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The 'Wise List' – A Comprehensive Concept to Select, Communicate and Achieve Adherence to Recommendations of Essential Drugs in Ambulatory Care in Stockholm

Lars L. Gustafsson[1,2], Björn Wettermark[1,3], Brian Godman[1], Eva Andersén-Karlsson[3,4], Ulf Bergman[1,2], Jan Hasselström[5], Lars-Olof Hensjö[6], Paul Hjemdahl[2,7], Ingrid Jägre[3], Margaretha Julander[3], Bo Ringertz[8], Daniel Schmidt[9], Susan Sjöberg[3], Folke Sjöqvist[1], Carl-Olav Stiller[2,7], Elisabeth Törnqvist[3], Rolf Tryselius[3], Sigurd Vitols[2,7] and Christer von Bahr[10], for the Regional Drug Expert Consortium*

[1]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [2]Clinical Pharmacology Services, Karolinska University Hospital, Stockholm, Sweden, [3]Regional Drug and Therapeutics Committee, Medical Knowledge Centre, Stockholm County Council (Healthcare Region), Stockholm, Sweden, [4]Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden, [5]Storvreten General Practice Centre, Tumba, Sweden, [6]Inera Ltd, National Information Services for Swedish Healthcare, Stockholm, Sweden, [7]Clinical Pharmacology Unit, Department of Medicine, Karolinska Institutet at Karolinska University Hospital Solna, Stockholm, Sweden, [8]Division of Rheumatology, Department of Medicine, Karolinska Institutet at Karolinska University Hospital Solna, Stockholm, Sweden, [9]Department of Internal Medicine, St Göran Hospital, Stockholm, Sweden, and [10]Section of Clinical Pharmacology, Department of Internal Medicine, Södersjukhuset, Stockholm, Sweden

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Abstract: The aim was to present and evaluate the impact of a comprehensive strategy over 10 years to select, communicate and achieve adherence to essential drug recommendations (EDR) in ambulatory care in a metropolitan healthcare region. EDRs were issued and launched as a 'Wise List' by the regional Drug and Therapeutics Committee in Stockholm. This study presents the concept by: (i) documenting the process for selecting, communicating and monitoring the impact of the 'Wise List'; (ii) analysing the variation in the number of drug substances recommended between 2000 and 2010; (iii) assessing the attitudes to the 'Wise List' among prescribers and the public; (iv) evaluating the adherence to recommendations between 2003 and 2009. The 'Wise List' consistently contained 200 drug substances for treating common diseases. The drugs were selected based on their efficacy, safety, suitability and cost-effectiveness. The 'Wise List' was known among one-third of a surveyed sample of the public in 2002 after initial marketing campaigns. All surveyed prescribers knew about the concept and 81% found the recommendations trustworthy in 2005. Adherence to recommendations increased from 69% in 1999 to 77% in 2009. In primary care, adherence increased from 83% to 87% from 2003 to 2009. The coefficient of variation (CV%) decreased from 6.1% to 3.8% for 156 healthcare centres between these years. The acceptance of the 'Wise List' in terms of trust among physicians and among the public and increased adherence may be explained by clear criteria for drug recommendations, a comprehensive communication strategy, electronic access to recommendations, continuous medical education and involvement of professional networks and patients.

Inappropriate use of drugs causes increased morbidity, mortality, adverse drug reactions, therapeutic failures and drug resistance as well as wasting valuable resources [1–6]. This recognition was a driving force behind the birth of Drug and Therapeutics Committees (DTC) [7–9] and the Essential Drug concepts [10] by WHO in the late 1970s. However, adherence to drug recommendations from DTCs varies markedly among prescribers [11–14].

Stockholm Healthcare Region with approximately 2 million inhabitants consists of 209 Primary Healthcare Centres, seven emergency hospitals as well as private specialists, nursing homes and other healthcare providers [15], with all healthcare financed through public taxation with co-payments for prescribed drugs [15]. A new Swedish law in 1996 made it mandatory for each Healthcare Region to have at least one DTC jointly for in- and outpatient care [8]. As a result, new ways were needed to develop and communicate independent drug recommendations to promote the rational use of drugs (RUD). Therefore, the 'Wise List' concept was introduced in Stockholm, based on the understanding that drug recommendations should be issued in one version for the whole region by respected drug experts to enhance quality of care. The 'Wise List' was designed knowing that multifaceted contextualized methods are needed to enhance adherence to drug recommendations including professional ownership, continuous medical education, active dissemina-

Author for correspondence: Lars L. Gustafsson, Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden (fax +46 858581070, e-mail lars-l.gustafsson@ki.se).

Please contact the corresponding author on questions related to a tentative English version of the Wise List 2010.

*The Regional Drug Expert Consortium also includes Peter Aspelin, Jonas Bergh, Peter Ekman, Carl-Gustaf Elinder, Johan Franck, Urban Hellgren, Angelica L. Hirschberg, Seher Korkmaz, Michael Lagerkranser, Gerd Lärfars, Lena Lundeberg, Rickard Malmström, Åke Örtqvist, Marie-Louise Ovesjö, Georgios Panagiotidis, Jan Persson, Peter M. Persson, Michael Runold, Gunilla Sundelin, Leif Tallstedt, Matti Viitanen, Mia von Euler, Katarina Wide.

tion as well as feedback of prescribing patterns to physicians [11,12,16–20]. The first version of the 'Wise List' was published in 2001 and subsequently developed in a stepwise manner.

This paper describes the 'Wise List' concept and analyses the variation in the number of recommended drug substances during a 10-year period. In addition, the attitudes to the 'Wise List' among prescribers and the public are evaluated as well as adherence to recommendations to provide guidance to other regions and countries seeking to enhance their RUD.

Materials and Methods

Selecting, communicating and monitoring the impact of the 'Wise List'. The 'Wise List' is issued by the regional DTC. All principles for selecting drugs, communicating pharmacotherapeutic recommendations and monitoring the impact of the 'Wise List' on prescribing were documented in the protocols and the guidelines from the regional DTC. Our presentation is based on such data from 2000 to 2010.

The number of drug substances recommended 2000–2010. We analysed the total number of substances recommended each year as well as the number of annual changes of the 'Wise List'. Data are presented by therapeutic area [Anatomic Therapeutic Chemical (ATC) 1st level] for the period of 2000–2010 [21], and 2000 was chosen as the first year with common drug selection throughout the region, although the name 'Wise List' was launched in 2001 (fig. 1).

Assessing attitudes and knowledge among prescribers and the public. Five surveys were undertaken between 2000 and 2005 investigating the attitudes to the 'Wise List' among prescribers and the public. All surveys were carried out by commercial marketing companies (Effekt Marketing Intelligence Ltd and Navigare Ltd, Stockholm Sweden). This was part of the early development of the concept to proactively guide the development of the 'Wise List' concept to maximize its acceptance and utility in clinical practice.

1. *Attitude surveys among prescribers* were performed in December 2000 and in June 2005, respectively. Telephone interviews were conducted among a randomly selected sample of general practitioners at public and private primary healthcare centres and among specialists in internal medicine. In 2000, 132 general practitioners were interviewed, and in 2005, 50 general practitioners and 25 specialists in internal medicine. The questions were designed to investigate the prescribers' recognition of the 'Wise List', the extent of trust with the concept and the main reasons why they either felt or did not feel comfortable with the recommendations.

2. *Attitude surveys* to monitor the effects of the marketing campaigns *among the public* were performed in 2001 and 2002. A baseline survey was undertaken in February 2001 before the 'Wise List' was launched among the public and patients. The survey was repeated in May 2001 and in March 2002, respectively (fig. 1). Each telephone survey was conducted among 400 randomly selected individuals above the age of 15 living in the Stockholm region. The questions focused on the respondents' knowledge about drug expenditure and their attitudes to the recommendations on the 'Wise List'. In addition, their drug consumption, the ways they search for drug information as well as their views regarding physicians' commitment to prescribing evidence-based and cost-effective drugs were investigated.

Adherence to recommendations 2003–2009. The impact of the 'Wise List' recommendations on drug prescribing was evaluated using complete data on dispensed drugs collected from all pharmacies in the country [13]. Data were analysed by ATC using defined daily doses (DDDs) adjusted to correspond to the DDD for the year 2010 [21,22]. Expenditure was measured in Swedish Crowns (SEK and with €1 = 9.5 SEK, June 2010). The time periods for analyses were between 1999 and 2009 for prescriptions dispensed to the population in the region and between 2003 and 2009 when evaluating adherence by prescriber categories; 1999 was chosen as baseline because this was before the first edition of joint recommendations was published (fig. 1). During 2002, a major pharmaceutical reform of mandatory generic substitution was instigated resulting in substantial price reductions for off-patented drugs [15,23]. To ascertain that the utilization changes were likely due to the regional DTC activities, we restricted the analysis period from 2003 to 2009. During the period 2003–2009, no major changes in the legislation or reimbursement of drugs were implemented. Another reason behind restricting the analyses to the period from 2003 was that complete data on prescriber categories only became available from late 2002 when workplace codes became mandatory for all redeemed prescriptions to be reimbursed. Drug utilization analyses focused on:

1. *Drug utilization 90% (DU 90%) adherence* to the 'Wise List' for dispensed prescriptions in ambulatory care to the whole population in the region in 1999 and 2009, respectively [24]. The DU 90%

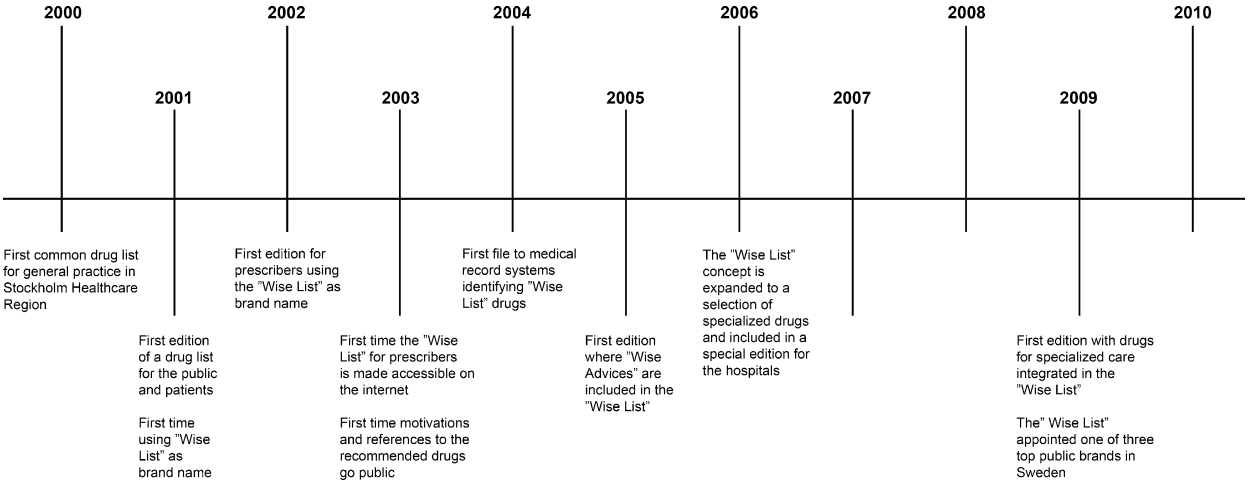


Fig. 1. Overview of the development of the 'Wise List' concept in Stockholm Healthcare Region. The first drug formulary in Stockholm was issued for hospital care in 1963. The regional Drug and Therapeutics Committee with expert groups was strengthened in 1996 and onwards by a dedicated annual budget.

method is recommended by WHO for drug utilization studies and defines the number of different substances (ATC 5th level) constituting 90% of the volume expressed in DDDs and the adherence to recommendations within this segment [24,25]. This method is routinely used in the region to monitor the adherence to the 'Wise List' recommendations as well as to provide feedback to prescribers forming the basis for local quality work and continuous medical education [6,13,15,26].

2. *Total adherence* was measured as the proportion of DDDs prescribed by different caregivers and dispensed between 2003 and 2009 representing the drugs included in the 'Wise List' in any of these years.

3. *The variation in adherence to the* '*Wise List*' by Primary Healthcare Centres each year between 2003 and 2009. Adherence was measured by calculating the DU 90% adherence for each practice with the practice variation measured by the coefficient of variation [CV% = 100 × (Standard deviation S.D./mean)] for the DU 90% adherence.

4. *Adherence to* '*Wise Advice*' *recommendations* between 2003 and 2009 was also analysed for Primary Healthcare Centres using ratios of recommended substances to all drugs within a selected pharmacological group (table 1). The drugs selected were included in prescribing indicators for those 'Wise Advice' recommendations that had been approved by the regional DTC for all years between 2003 and 2009. All ratios except for drugs used for urinary tract infections (UTI) were calculated using DDD as the volume measure. For UTI, the measure was dispensed number of prescriptions to get a minimum influence of the large volumes of quinolones dispensed for other conditions.

Results

Selecting, communicating and monitoring the impact of the '*Wise List*'.

Fig. 1 documents the step-wise development of the 'Wise List'. Table 2 summarizes seven key elements of the concept. A prerequisite for developing and implementing the 'Wise List' supporting RUD throughout the region was access to a comprehensive DTC organization (fig. 2, table 2). Physicians with excellent pharmacotherapeutic knowledge, drug evaluation skills [8,27] and many with research and teaching experiences were recruited as members from the Healthcare Region and Karolinska Institutet. The regional DTC and its expert groups included medical opinion leaders to increase the credibility of the 'Wise List'. All experts adhered to a strict policy for annual declarations of potential conflicts of interest

Table 1.
'Wise Advice' recommendations[1] being unchanged in Stockholm 2003–2009.

'Wise Advice'	Indicator	ATC codes	Rationale
Restrict the use of ARBs to patients intolerant to ACE inhibitors.	ACE inhibitors of all RAAS drugs	(C09A + C09B)/C09	ACE inhibitors are recommended as first-line choice in hypertension and to treat heart failure. Heavily marketing of ARBs during the period 2003–2009. The Swedish reimbursement agency (TLV) restricted reimbursement of ARBs in 2007.
Choose simvastatin for the prevention of cardiovascular disease in high-risk patients with ordinary or moderately elevated levels of cholesterol.	Simvastatin of all statins	C10AA01/C10AA	Simvastatin is first-line recommendation in the 'Wise List' for the whole period 2003–2009. Intense promotional activities by the pharmaceutical industry for other statins including rosuvastatin launched in 2003.
Avoid use of quinolones in the treatment of uncomplicated cystitis in women.	% of all UTI antibiotics	(J01CA08 + J01EA01 + J01XE01)/ (J01CA08 + J01EA01 + J01XE01 + J01MA)	High use of quinolones has been under debate because of resistance (3) and environmental problems. Trimethoprim, nitrofurantoin and mecillinam recommended in the 'Wise List' 2003–2009.
If PPIs are needed, prescribe generic omeprazole avoiding more expensive branded products.	Omeprazole of all PPIs	A02BC01/A02BC	Lansoprazole recommended in the 'Wise List' 2001–2003. Omeprazole recommended since 2004 because of patent expiry, introduction of generics and subsequent price reduction. Esomeprazole was launched in 2005.
For mild to moderate severe depression, start with citalopram or sertralin	Citalopram or sertralin of all SSRIs	(N06AB04 + N06AB06)/N06AB	Citalopram recommended in the 'Wise List' 2003–2009. Sertralin added in 2006 after patent expiry. Escitalopram was launched in 2006.

Summary of the used specific indicators for follow-up of adherence.
PPI, proton pump inhibitors; RAAS, renin-angiotensin system; ARB, angiotensin receptor blocker; UTI, urinary tract infection; SSRI, selective serotonin reuptake inhibitor.
[1]'Wise Advice' recommendations were chosen in therapeutic areas where either the quality in prescribing could be improved substantially or become more cost-effective. The recommendations were preferably selected in areas where it was possible to define indicators and set targets to monitor the adherence. 'Wise Advice' recommendations should be short, easily communicated and aimed for long-term use.

Table 2.

Seven key elements of the 'Wise List' concept.

1. Independent drug expert organization with network

- Regional DTC with expert groups and local DTCs with shared values and policy for declaring and managing potential conflicts of interest – in particular with the pharmaceutical industry. The policy is known, communicated and followed. This policy is fundamental for the DTC system and for trust to its experts [28].
- General practitioners, hospital-based specialists, clinical pharmacologists and pharmacists from major healthcare providers in the region are members of the regional DTC. They participate in selection of drugs in the 'Wise List'.
- Training of members of the regional and local DTCs in the principles of critical drug evaluation by clinical pharmacologists [27]. This helps to maintain high quality of drug selection principles across expert groups.

2. One 'Wise List' for ambulatory and hospital care

- *For basic care*, about 200 recommended drug products (205 in 2010) covering about 80% of common diseases in primary care and used as basic treatment for in- and outpatient hospital care. If necessary, second- or third-line choices.
- *For specialized secondary care*, an additional 97 recommended drugs (2010), if necessary as first-, second- or third-line choices.
- *Concise texts* explaining treatment strategies including preventive measures in important therapeutic areas.
- '*Wise Advice*' recommendations inserted in each of the pharmacotherapeutic areas. A focus on guidelines for use of antibiotics in accordance with recommendations from network for Rational Use of Antibiotics STRAMA [3].

3. Strict criteria for essential drug recommendations with motivations

- *Medical suitability* based on:
  a. parameters (solid study end-points) of relevance to evaluate the effects of a drug such as mortality, morbidity and hospital care.
  b. expected patient value.
  c. reference to minimum one published pivotal study. Only one drug is recommended first line in a class of drugs.
- *Safety*: Normally, a drug should have been registered for two years. Safety and adverse effects data should be based on pivotal studies.
- *Pharmaceutical suitability:* The recommended drug should be:
  a. available in a wide range of strengths and package sizes
  b. in packages easily handled and readable by patients and hospital staff
  c. delivered without interruption
- *Cost-effectiveness*: Highly relevant for primary care where a number of cost-effective generic drugs are available. The generic name (INN) is given in the 'Wise List' for ambulatory care.
- *Environmental and gender aspects* are considered if relevant. The acute risk to the aquatic environment is considered (insignificant, low, moderate or high) [40].

4. A comprehensive communication, branding and marketing strategy with a key role for experts

- From 2001 and onwards, the 'Wise List' was marketed as a brand name for essential and safe recommended drugs. Good knowledge about the 'Wise List' was created among health professionals and the public in Stockholm using respected drug experts and opinion leaders. Established marketing strategies were used including annual advertisements in specialized medical and public press since 2000 yearly [18].
- The owl was used as the branding symbol for independent, reliable and trustworthy information and for identification of different editions.
- Access for healthcare staff to the official independent website of the DTC organization (www.janusinfo.se) with all recommendations, detailed information about them and justifications also available as a web-based application (Janus toolbar) integrated into electronic health record (EHR) systems.
- Since 2005, an annual 'Wise List' Forum for prescribers with the involved experts as keynote speakers explaining the background to the recommendations.
- Launching of each new version of the 'Wise List' with press releases and providing drug information to medical journalists.
- Collaboration with respected partners such as pharmacies distributing the 'Wise List' to the public and to patients.
- Long-term training of members of the regional DTC system (approximately 400) in mass media contacts and discussion of risk of conflict of interests.

5. Targeted 'Wise List' editions for professional and public needs

Three printed editions of the '*Wise List*'. They are also available for healthcare staff at a producer-independent website www.janusinfo.se, *as digital files for EHR systems and accessible as a public version for laymen at www.vardguiden.se.*

a. *The* '*Wise List*' *with recommended drugs for prescribers* both for common diseases in primary and specialized care (a) and for widely used drugs in specialized care (b) (joint edition since 2009). 30,000 printed copies of the 'Wise List' distributed to healthcare staff in 2010.
b. *A special edition to help ordering procured drugs* in hospital wards across Stockholm healthcare institutions since 2003.

6. Feedback to prescribers and chief physicians of prescribing patterns

- *Feedback on prescribing patterns* and adherence to the 'Wise List' recommendations to all primary healthcare centres and hospital clinics in Stockholm by user-friendly internet tools (www.janusinfo.se) with standardized tables and graphs. Possibilities for bench-marking using drug utilization 90% profiles for follow-up [24,25].

Table 2. (Continued)

c. *A* '*Wise List*' *edition for patients and for the public* containing recommended drugs for common diseases in primary and specialized care. 300,000 copies distributed of the 2010 edition. d. *The* '*Wise List*' *for prescribers and healthcare staff available electronically (www.janusinfo.se)* as a pdf-file and in html-format since 2001. e. Delivery of a *digital file of the* '*Wise List*' recommendations for common diseases to be integrated in EHR systems since 2003. About 7000 prescribers have access to the 'Wise List' at point-of-care [30].	• '*Wise Advice*' *recommendations* available as tools for cross-practice learning across Stockholm Healthcare Region. These are used within the DTC system as they are increasingly marketed, combined with indicators and targets for improvements. • Health authorities have linked quality bonuses to adherence rates to the 'Wise List' for general practice [26].
7. Medical leadership and operative resources • Open long-term leadership with vision, continuous learning, shared values and internal communication with involvement of medical opinion leaders in Stockholm. • Operative resources for managing secretary of the regional DTC, for clinical pharmacologists, pharmacoepidemiologists, administrative staff, IT experts, medical editors and communication specialists.	

DTC, Drug and Therapeutics Committee; EHR, Electronic Health Record; 'Wise Advice', advice on how to select and use drugs or preventive measures in areas where major quality improvement of drug therapy can be achieved.

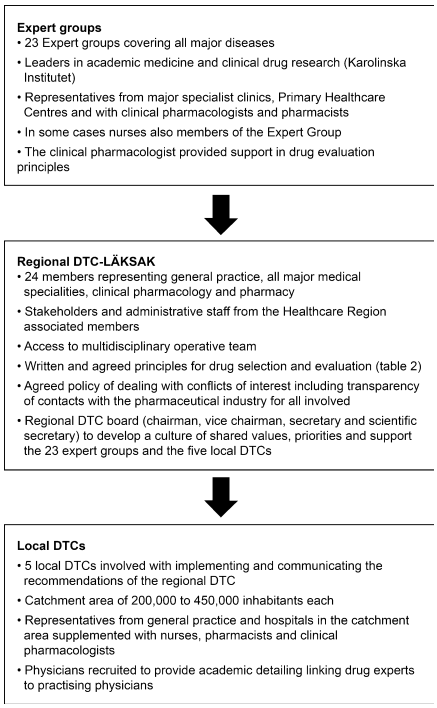


Fig. 2. Organization of the Drug and Therapeutics Committee (DTC) system in Stockholm Healthcare Region 1996–2009.

(table 2) [28]. The expert groups suggested recommendations in the 'Wise List' and the regional DTC approved these (fig. 2, table 2).

Local DTCs also recruited physicians and pharmacists as ambassadors for the organization and provided academic detailing to physicians [8,16]. These information physicians and information pharmacists helped to market the 'Wise List' recommendations and gave prescribing information in a consultative manner [16]. As such, they have become critical to the strategy linking drug experts with practicing physicians with approximately 900 visits at clinics and healthcare centres in 2009 alone. Marketing and distribution of a special edition of the 'Wise List' aimed at the general public was also part of the concept. The goal was to increase awareness of the benefits and risks of drugs among the general public as well as how diseases should be treated based on solid scientific principles counteracting pressures from pharmaceutical companies (table 2). The 'marketing' of the 'Wise List' was supported by the 'Wise List' owl logo on pens, memory sticks and other 'branding' materials, which were provided in considerable quantities to prescribers. As summarized in table 2, the communication strategy was initiated

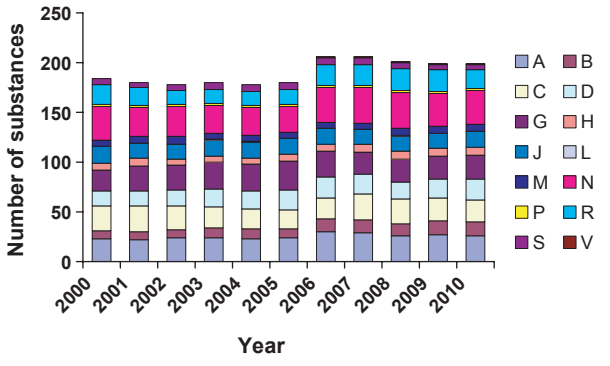


Fig. 3. The number of substances included in the 'Wise List' in Stockholm summarized by ATC groups 2000–2010. From 2009, 100 additional substances were added for specialist care (not shown). ATC group A = alimentary tract and metabolism, B = blood and blood forming organs, C = cardiovascular system, D = dermatology, G = genitourinary system and sex hormones, H = systemic hormonal preparations, J = anti-infectives for systemic use, L = antineoplastic and immunomodulating agents, M = musculoskeletal system, N = nervous system, P = antiparasitic products, R = respiratory system, S = sensory organs, V = various.

in 2000 and included annual advertisements of the 'Wise List' to the prescribers and to the public.

A key principle for drug selection was to recommend well-documented and cost-effective drugs (table 2, point 3 drug selection criteria). The 'Wise List' included first-line drug recommendations for common diseases typically treated in primary care. These were often generic drugs. In 2009, drug recommendations for specialized care were included in the 'Wise List' enhancing the provision of trust to the concept among hospital physicians (table 2).

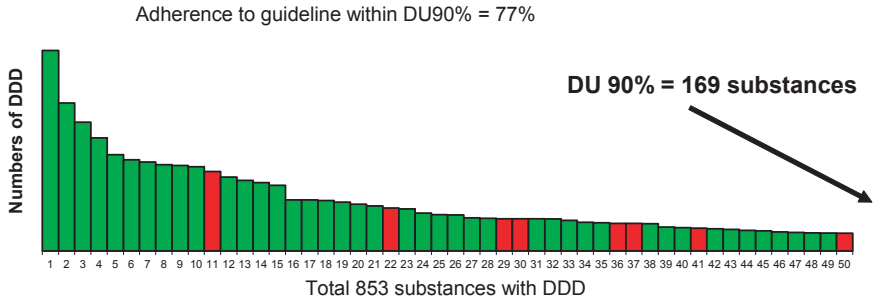
The number of drug substances recommended 2000–2010.

The 'Wise List' has included typically around 200 substances each year (table 2, fig. 3). Over the years, there has been little variation in the number of drugs with between 1 and 15 substances being changed annually. The highest number of recommended substances includes the cardiovascular, gastrointestinal and central nervous system disease areas (fig. 3). Further 100 substances were recommended for specialized care integrated in the list from 2009.

Attitude surveys.

All prescribers surveyed in 2005 were familiar with the 'Wise List' and 81% found the recommendations trustworthy. The main reasons reported for the trust in the 'Wise List' were high-quality information, confidence in the gathered expertise within the DTC organization and the principles of evidence-based medicine, prescribing information being considered unbiased and uninfluenced by commercial interests. Reasons for lack of trust were a too strong focus on drug expenditures and unsatisfactory quality of inserted information provided directly in the 'Wise List'. In 2005, 96% of the physicians were aware of the regional DTC and 81% expressed confidence in the organization.

In the first survey to the public in 2001, 76% reported that they were aware of the increasing drug expenditures. This figure was unchanged in the follow-up surveys in 2001 and in 2002. For the majority, mass media was the main source of information about drug expenditures. In the first survey, only a few respondents were familiar with the 'Wise List' concept. This proportion increased to one-third of the



	SUBSTANCE	(DDD)	DDD	% TOT	Rx	COST	COST/DDD
1	**Acetylsalicylic acid**	1 tablet	39 894 782	4,9%	650 808	22 995 814	0,58
2	**Simvastatin**	30 mg	29 455 125	3,6%	438 802	26 731 380	0,91
3	**Enalapril**	10 mg	25 632 413	3,2%	296 329	18 111 103	0,71
4	**Furosemide**	40 mg	22 513 352	2,8%	409 630	18 091 910	0,80
5	**Omeprazol**	20 mg	19 140 338	2,4%	399 298	30 122 076	1,57
6	**Cyanocobalamin**	1 mg	18 125 259	2,2%	319 737	11 711 704	0,65
7	**Amlodipine**	5 mg	17 685 421	2,2%	165 634	10 209 168	0,58
8	**Metoprolol**	0.15 g	17 160 653	2,1%	498 845	72 421 602	4,22
9	**Levothyroxine sodium**	0.15 mg	17 030 980	2,1%	405 353	23 094 330	1,36
10	**Ramipril**	2.5 mg	16 743 688	2,1%	95 412	8 323 952	0,50
11	Felodipine	5 mg	15 807 331	2,0%	177 725	13 901 701	0,88
12	**Candesartan**	8 mg	14 695 169	1,8%	118 979	59 427 671	4,04
13	**Zopiclone**	7.5 mg	14 059 603	1,7%	426 875	16 073 585	1,14
14	**Paracetamol**	3 g	13 597 335	1,7%	621 717	35 916 832	2,64
15	**Citalopram**	20 mg	13 065 325	1,6%	266 993	12 672 896	0,97
16	**Sertraline**	50 mg	10 178 236	1,3%	119 262	11 241 414	1,10
17	**Hydroc.thiazide + amiloride**	*	10 145 923	1,3%	120 927	5 066 822	0,50
18	**Calcium combinations**		10 047 562	1,2%	206 568	24 983 957	2,49
19	**Propiomazine**	25 mg	9 729 948	1,2%	174 248	12 173 527	1,25
20	**Metformin**	2 g	9 297 143	1,2%	152 190	18 415 868	1,98
...							
169							
DU 90%	**1 - 169**		727 456 526	90,0%	14 034 056	2 648 199 198	3,64
170 - 853			80 552 999	10,0%	2 699 117	2 370 147 348	29,42
TOTAL	**1 - 853**		**808 009 524**	**100,0%**	**16 733 173**	**5 018 346 546**	**6,21**

Bold = in guideline
**** = Different DDD's for various routes of administration***
Medicines without DDD excluded (455, corresponding to 511 million SEK)

Fig. 4. DU 90% (number of substances accounting for 90% of the volume in DDDs) in Stockholm Healthcare Region in 2009. Red = non-recommended drugs; DDD = defined daily dose; DU = drug utilization.

respondents in the survey performed in 2002 after marketing campaigns in the underground, buses and in mass media in 2001. Approximately 90% of those interviewed in all surveys wanted to have access to the list and a majority claimed that they were positive towards asking their doctor to follow the recommendations of the 'Wise List'.

Adherence to recommendations 2003–2009.

Total adherence to the 'Wise List' was 77% by substance in 2009 (fig. 4) increasing from 69% in 1999. In 2009, 169 substances accounted for 90% of the volume in DDDs (DU 90%) when compared to 166 in 1999. Acetylsalicylic acid was the most commonly used substance both years. Nine drugs including enalapril, furosemide, omeprazole and metoprolol were among the 'top-20' most used drugs both in 1999 and in 2009. In 1999, some contraceptive products and hormone replacement therapy were included in the 'top-20' group. By 2009, many different brands of contraceptives had become available resulting in no single drug dominating the market as much as in 1999. Furthermore, the use of hormone replacement therapy decreased markedly after two pivotal studies published just after 2000 [29] documented the risks with such therapy. Four new cardiovascular drugs, simvastatin, ramipril, candesartan and amlodipine, appeared again in the 'top-20-list' in 2009 (fig. 4).

Adherence to the recommendations was 87% for the 209 Primary Healthcare Centres, 77% for 7 hospitals and 73% for the private specialists in 2009 when comparing with a total list of all drugs recommended between the years 2003–2009. In primary care, the adherence increased by 0.5–1% annually from 83% in 2003 but remained unchanged for hospitals and for other prescribers. For the 156 Primary Healthcare Centres, adherence to the 'Wise List' within DU 90% segment varied between 71% and 92% in 2009 (fig. 5). Between 2003 and 2009, the practice variation decreased from CV 6.1% to CV 3.8%. For the 'Wise Advice' recommendations, the most rapid increase was for the ratio of omeprazole to all proton pump inhibitors (PPI) changing from 35% to 80% between 2003 and 2009 (table 1, fig. 6). Also, the ratio of statins and the ratio of the recommended

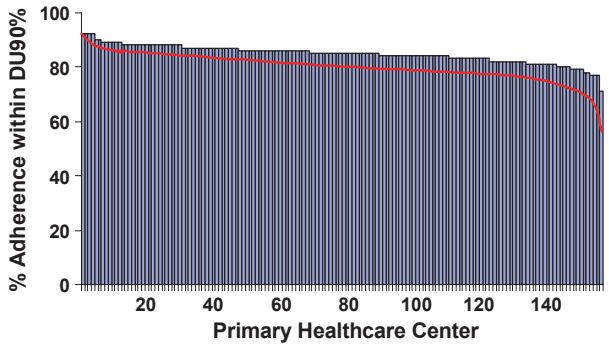


Fig. 5. Adherence to 'Wise List' recommendations for 156 primary healthcare centres for prescriptions dispensed in 2009. Red line equals the adherence range for the same practices in 2003. Observe that the order of the practices may differ between the 2 years.

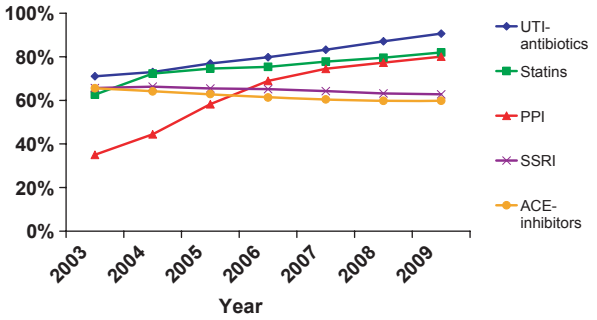


Fig. 6. Adherence to 'Wise Advice' recommendations in primary healthcare centres in Stockholm 2003–2009. Ratios of recommended drugs. Urinary tract infection (UTI) antibiotics = ratio of trimetoprim, nitrofurantoin and pivmecillinam of all UTI antibiotics in number of prescriptions, statins = ratio of simvastatin of all statins in DDDs (defined daily dose), PPI = ratio of omeprazole of all proton pump inhibitors in DDDs, SSRI = ratio of citalopram and sertralin of all selective serotonin reuptake inhibitors (SSRI) in DDDs, ACE inhibitors = ratio of ACE inhibitors of ACE inhibitors and angiotensin receptor blockers (ARB) in DDD.

antibiotics to treat UTI increased during the period. The ratio of recommended selective serotonin reuptake inhibitors (SSRI) remained stable, despite the introduction of escitalopram in 2002, and can be explained by a decreased utilization of paroxetine and fluoxetine. In 2009, escitalopram accounted for 10% of total DDDs for SSRI. The adherence to the 'Wise Advice' recommendation to use ACE inhibitors instead of angiotensin receptor blockers (ARB) decreased slightly from 2003 and the ratio of ACE inhibitors to all renin–angiotensin drugs was 60% in 2009 (fig. 6).

Discussion

The power of the concept is the combination of clear principles for drug recommendations, involvement of medical opinion leaders, comprehensive communication, an educational approach using recognized experts and easy access to the 'Wise List' at point-of-care [30]. The regional DTC has kept the number of recommended drug substances around 200 during 10 years demonstrating that it is feasible to maintain similar drug selection principles over time. We decided to target our activities both at the physicians and the patients. Based on feedback from the prescribers, we found that the patient version facilitated communication between the physician and patient around the most appropriate treatment. Examples of combined communication approaches towards patient and physicians include guidelines produced in Austria for a specific disease area with a patient version that is distributed in pharmacies and surgeries [31] as well as the SIGN guidelines in Scotland [20]. Combined approaches have also been used to raise awareness of antibiotic resistance issues among prescribers and the public [32]. However, all these initiatives are for individual diseases rather than providing prescribing recommendations across a wide range of common diseases seen in ambulatory care [20,31,32].

The results from the attitude surveys support the acceptance of the 'Wise List' concept by both physicians and patients. However, we acknowledge the weaker evidence of this material. It is interesting that already in 2005, all physicians surveyed were familiar with the 'Wise List' concept and 81% considered the recommendations trustworthy. This confidence in the 'Wise List' concept is illustrated by the 'Wise List' being ranked as one of five top-branded public concepts in Sweden by Swedish Television Culture Department late 2009 (http://svt.se/2.27170/1.1745034/listan_-_en_livlina_i_kaoset). This trust has been helped by the involvement of respected medical opinion leaders in the process of drug selection, the long-term strategic medical professional leadership (fig. 1, table 2) as well as the comprehensive communication strategy [18] including a wide range of activities from academic detailing to prompt electronic access to recommendations (table 2) [30]. Such key characteristics for achieving high acceptance to recommendations were described by Rucker and collaborators 20 years ago [33]. The success of such a strategy has been supported by others recently [34,35]. To the best of our knowledge, the present study is the only one where these principles have been tested over a long time period and on a large scale also showing increased adherence to recommendations over time.

The impact of the 'Wise List' on drug utilization is demonstrated by increased adherence to the recommendations over time among the Primary Healthcare Centres and a decreased variability between them (fig. 5). Increased adherence can also be attributed to provision of economic incentives to those healthcare centres achieving high adherence to 'Wise List' recommendations [15,26]. Improved adherence to 'Wise Advice' recommendations was strongest for the PPIs and antibiotics for UTI (fig. 6). We are not surprised by this because these drugs are mostly prescribed for short-term treatment courses with a higher rate of treatment initiations. There were, however, modest increases in the utilization of atorvastatin, rosuvastatin and esomeprazole, which are currently not recommended in the 'Wise List'. We are convinced that our comprehensive strategy including active involvement of medical networks and communication of the 'Wise List' recommendations of generic simvastatin and generic omeprazole explains the limited use of expensive patented statins in our region. This is in marked contrast to the findings in other countries lacking demand side measures including DTC activities to counteract commercial marketing pressures [36]. At the time of the study, there was also a substantial room for improvement in the utilization of ARBs which also was addressed recently by a national decision to reimburse ARBs only for patients intolerant to ACE inhibitors [37]. This decision resulted in an initial 20% reduction in the initiation of ARBs as first-line treatment in Sweden [37]. After patent expiry in April 2010, the price for losartan has now reached the same level as for ACE inhibitors. Consequently, the high prescribing rates of ARBs in the region is not an issue anymore. From 2011, the 'Wise Advice' promoting ACE inhibitors has been abandoned.

Few studies have reported on whether the benefits and savings achieved with intervention strategies to improve RUD outweigh the costs of performing the intervention [11]. Recently, we assessed that an annual increase in adherence by 1% in primary care in Stockholm is equivalent to €0.47 lower cost/prescription item [26]. This corresponds to *annual additional savings* in primary care in Stockholm of €4 million or more, and as a consequence, the total annual savings accelerate over time. This is in addition to improved care through increased prescribing of drugs with proven outcomes as opposed to newly registered drugs with as yet unknown long-term benefits. In contrast, we estimated annual costs to run the local and regional DTC organization including academic detailing at approximately €3 million excluding the time of the experts recommending the drugs. Consequently, the savings outweighed the cost for the comprehensive intervention already after the first year, with additional benefit over time. Recommended drugs in the 'Wise List' are often available as low-cost generics with proven outcomes in contrast to unproven surrogate outcomes typically associated with new drugs [10,15]. In a recent observational study of Primary Healthcare Centres, we have demonstrated that adherence to antidiabetic, antihypertensive and lipid lowering 'Wise List' recommendations, based on low-cost generics to a large extent, gave similar clinical outcomes as when physicians prescribed expensive non-formulary drugs [6].

There are limitations in our observational approach. A randomized, controlled intervention study could not be performed in view of multiple simultaneous interventions targeted at all healthcare providers in the region over this long period of time [11]. Furthermore, a control group outside the region would have been of limited value because DTCs are operated in all regions combined with other activities such as budget devolution as potential confounders. Possible other factors influencing the prescribing patterns are the continuous introduction of new drugs and changes in treatment policies, marketing activities from pharmaceutical companies and changes in regulatory policies. Despite these limitations, we are confident that our model can serve as an example to others to improve the quality of drug use. The 'Wise List' concept can be applied to other countries and regions to help balance against pharmaceutical company activities that are too often the sole source of information of new and existing drugs [38,39]. When considering implementation of the concept elsewhere, the seven key elements (table 2), long-term goals, recruitment of committed experts and a policy for handling potential conflicts of interest are essential. Recently, our concept has been quoted as an important tool for the achievement of RUD [9].

Conclusion

No comprehensive model exists for selecting and communicating essential drug recommendations to all categories of physicians and to the public in a healthcare region to enhance adherence. This study shows that:

• the number of drug substances recommended for common diseases can be kept around 200 with few annual changes during 10 years. After 5 years, the 'Wise List' concept was well known among all surveyed prescribers and 81% found the recommendations trustworthy. Among the public, only a few respondents were familiar with the 'Wise List' concept before launching annual marketing campaigns in 2001. This figure increased to one-third in a survey in early 2002.

• adherence to the 'Wise List' was 77% by substance in 2009 increasing from 69% in 1999. During 2003–2009, adherence to recommendations increased steadily from 83% to 87% for the primary healthcare centres. This resulted in substantial cost savings because cost-effective generic drugs were commonly first-line recommendations in the 'Wise List'. Savings were enhanced by continuously reduced variations in adherence between healthcare centres to drug recommendations.

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Conflict of interest

Jonas Bergh has participated in advisory boards to pharmaceutical and diagnostic companies and to consulting companies. He has acted as chairman and lectured and been remunerated for these tasks. Mia von Euler is married to a scientist working with development of Alzheimer drug therapy at Astra-Zeneca Ltd. She abstains from being involved in decisions about drug recommendations related to this company. No other conflict of interest was declared by any of the other 40 authors.

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Editorial

The 'Wise List' – A Comprehensive Model for Drug and Therapeutics Committees to Achieve Adherence to Recommendations for Essential Drugs Among Prescribers?

In this issue of the journal, Gustafsson *et al.* [1] describe the history and key policy elements of the Stockholm County Council's approach to achieve adherence to independent essential drug recommendations by branding and marketing a booklet called the 'Wise List', directed to prescribers (general practitioners and specialists) and the public.

For the Swedish capital region (2 million inhabitants), the concept includes a coherent policy for selection of just over 200 cost-effective essential drugs to be used for primary and hospital in- and outpatient care. The 'Wise List' concept has been consistently developed and expanded during the last 20 years. It is combined with continuous medical education, electronic access to recommendations, follow-up of adherence as well as with financial incentives. Most importantly for the success of this concept is the involvement of the prescribers, respected and independent drug experts and the public. In addition, the access to recommendations has been provided at point of care by using emerging information technology tools such as decision-support systems [2].

The approach is centered around the 'Wise List' (Kloka Listan in Swedish), a drug formulary of essential medicines published as a booklet for patient care in the whole Stockholm health care region and accessible for prescribers in electronic health records and at the independent and regional website for drug information.

Behind this publication stand regional and local multidisciplinary teams of participating physicians, pharmacists and clinical pharmacologists. The power of the concept of the 'Wise List' stems from the development of a consistent and transparent procedure for recommending drugs across pharmacotherapeutic areas by involving clinical pharmacologists, competent in critical drug evaluation, and taking the leadership to assure trust in the quality and the independence of the selection of drugs [3]. There is a strong emphasis on implementation including academic detailing programmes and reaching out to practising physicians. Through public information campaigns, the patients are informed of the existence and the value of the 'Kloka Listan'.

This work shows that it is feasible to change prescribing habits to reach as much as 87% adherence to recommendations in the 'Wise List' among primary health care centres in 2009. The lesson is that a comprehensive approach with a 10-year perspective is needed. The addition of knowledge databases on drug-drug interactions and dosage instructions increased the power of this concept, as computerised information is now widely accessible at the point of care in the form of decision support systems to further enhance adherence.

The approach of the Swedish Stockholm County Council has been implemented in most of the other health care regions of Sweden, albeit sometimes only partially. Other

European countries have also Drug and Therapeutics Committees or independent Drug Information Centres with or without a formal national mandate to provide impartial, evidence-based, point-of care drug recommendations.

Some countries in Europe and most countries in the rest of the world do not have access to such services and rely on limited information activities of the registration authorities, or on Physician Desk Reference services, provided by publishers and/or the pharmaceutical industry.

Is the quality of prescribing worse in countries where such Drug and Therapeutics Committees or independent Drug Information Centres do not exist, are weak or not sustained by implementation programmes?

From the European Surveillance of Antibiotic Consumption [4], we know that in France, Greece and Spain, consumption of antibiotics on a daily basis is up to three times higher than in The Netherlands and in Scandinavian countries. Apparently, these latter countries have deployed successful nation-wide strategies to enhance rational prescribing, and the former countries have not [5,6].

From the Effective Practice and Organisation of Care review group of the Cochrane Collaboration, we know that there are no simple effective interventions [7]. Multifaceted approaches on local levels are needed to improve the quality of drug prescribing and to assure the consistent choice of effective, safe and cost-effective drugs [8]. It is my opinion that the presence of strong independent Drug Information Centres and Drug and Therapeutics Committees is also a prerequisite for the success of targeted campaigns to improve prescribing in specific pharmacotherapeutic areas.

The organisation of the health care systems evolves from public to private governance, from national to small health care area approaches. The pharmaceutical industry, too, will discover and apply the power of information technology to market their drugs. Health policy-makers are pushing the wide spread use of electronic health care records and of electronic prescribing.

Hence, the question can be posed: Will the proposed 'Wise List' concept by the Drug and Therapeutics Committees be sustainable in future?

The publication of Gustafsson *et al.* [1] demonstrates that their 'Wise List' approach along with the electronic support systems in Stockholm County can be achieved economically and will lead to improved quality of care alongside potential savings. They suggest their model to be implemented across Europe and globally, provided the key characteristics are preserved. To make this happen, intense international collaboration between Drug and Therapeutics Committees, independent Drug Information Centres and Clinical Pharmacology Departments will be needed to face the tremendous challenges posed by innovations in information technology [9–11].

Robert Vander Stichele
Heymans Institute of Pharmacology, Ghent University, Belgium

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Feature Article

Drug and therapeutics committees: a Swedish experience

The development of drug and therapeutics committees (DTCs) in hospitals and for primary health care varies markedly from one country to another within Europe (1) but has been particularly strong in the Nordic countries. Since 1997, Swedish law requires that all twenty-one regions have a drug and therapeutics committee. These committees have played an increasingly important role in implementing the rational use of drugs.

For 40 years, hospital drug formulary committees have existed in Sweden to develop guidelines for the selection of the pharmacotherapeutic armamentarium. Committees were primarily established to evaluate drugs available for use in routine care and to recommend drugs of choice for common diseases. Selection was based on therapeutic value, therapeutic tradition, and price. The right of an individual physician to prescribe according to his own judgement was fully recognized as a fundamental element of health care delivery, but the difficulty of maintaining oversight of the increasing number of drugs on the market was also acknowledged (2). The committee's primary objective was thus to improve rational use while decreasing the cost of drug treatment.

Four important prerequisites relating to the work of the committee were emphasized (2):

- Work should be a collaborative effort between clinicians, pharmacists and clinical pharmacologists.
- Selection of recommended drugs should be based on relevant statistics on the use of drugs in a hospital setting.
- The committee should work through "ambassadors" to inform prescribers about committee evaluations and conclusions.
- The drug committee should inspire a sophisticated and intense pharmacotherapeutic debate in hospitals.

Folke Sjöqvist, Ulf Bergman, Marja-Liisa Dahl, Lars L. Gustafsson, and Lars-Olof Hensjö, Department of Medical Laboratory Sciences and Technology of the Karolinska Institute (Division of Clinical Pharmacology), WHO Collaborating Center for Drug Utilization Research and Clinical Pharmacological Services, Huddinge University Hospital, Stockholm, Sweden, and the Regional Drug Committee (LÄKSAK), Stockholm (correspondence: Folke.Sjoqvist@labtek.ki.se)

The success of the first committees within university hospitals was instrumental in extending rational use throughout the country. As a result of initial work, the number of standard solutions for infusion was reduced from 25 to four, and the number of pharmacotherapeutic hypnotics from 37 to six (2). During the early seventies, follow-up of the outcome of drug recommendations through drug utilization statistics was emphasized, and educational initiatives were implemented when prescribing was found to deviate from recommendations (3). By 1975, the concept of generic substitution had been successfully introduced in Stockholm hospitals. Major events in the development of drug selection are summarized in Table 1 on page 208.

In the 1980s, a special guideline focusing on drug choices in primary health care was developed to increase the commitment of general practitioners. In 2000, a single guideline with some 200 recommended first-line drugs for the most common diseases was agreed upon for the entire population of 1.8 million inhabitants in Stockholm. During the early 1990s, the scope of the committees was broadened to include drug information and education of prescribers. The number of committees in Sweden now reached almost one hundred.

In 1997, drug and therapeutics committees became obligatory under law and instructions were issued (see Table 2 on page 208). Counties now had to provide a budget to support committee activities. The number of coordinating DTCs was reduced to 21 regional committees, performing their work through expert groups on different diseases and through local committees.

Functions of drug and therapeutics committees

Since the 1997 Swedish Drug Reform Act, the function of drug and therapeutics committees has

Table 1. Major development of drug and therapeutics committees in Sweden

1961	First committee set up at the Karolinska Hospital, Stockholm.
1970s	Follow-up of the impact of drug recommendations on prescribing. Drug utilization statistics.
1975	Generic substitution encouraged.
1980s	Committees for primary health care and hospitals join forces. Stronger influence from primary health care. Newsletters.
1986	"Drug watcher" – drug bulletins and academic detailing.
1990s	Broadened scope towards drug education and problem-oriented drug information – 100 committees in Sweden.
1997	Drug and therapeutic committees required by law. Instructions issued, budget provided. Number of committees reduced to 21 regional committees.
2000	Information campaigns to public about recommended drugs of choice.

been regulated by the local county councils as the main providers of public health care. As the principal source of expertise, the overall aim of the committees is to promote the rational use of drugs at all levels of the health care system, whether at specialized clinics or primary health care centres. The committees have become a core facility for evidence-based principles of drug therapy within the health care system. Clinical pharmacologists, pharmacists, and district nurses (who have restricted prescribing rights in Sweden) are also represented. Members must declare any conflict of interest and acting as a consultant to industry is not allowed if this would lead to the promotion of an individual drug product. However, scientific collaboration at the institutional level is acceptable and even desirable.

Regional DTCs gather and evaluate knowledge on drugs and drug therapies through screening of scientific documentation systematically retrieved from the literature. Local networks of experts representative of the various health care levels are responsible for implementation of the recommendations. The committees are urged to improve the quality of drug therapy at all levels of health care within a given county, including the private sector, and collaborate with other experts from regional

Table 2: Swedish law concerning drug and therapeutics committees (28 November 1996)

1. There shall be one or several drug committees in each county.
2. Each drug committee shall engage medical and pharmaceutical expertise.
3. A drug committee shall work towards the rational use of drugs through its recommendations to health care personnel. The recommendations should be based on scientific evidence and well-tried experience.
4. The National Corporation of Swedish Pharmacies shall provide drug committees with drug utilization statistics. If the committee realizes that there are shortcomings in the use of drugs it should provide education to prescribers.
5. Each committee shall, when required, collaborate with other committees and with relevant authorities and universities.
6. The County shall issue an instruction for the drug committee.

clinical pharmacology departments, telepharmacological services, local pharmacies, the Medical Products Agency, the pharmaceutical industry, and drug formulary committees. Other important functions are to provide the county council administrations with medical expertise in drug purchasing, develop policy documents for drug information, and provide education and follow-up on drug utilization and prescription patterns.

Selection of recommended drugs

Selected drugs should be well documented and appropriate from the pharmaceutical, pharmacological and therapeutic point of view, and considered essential in the treatment of common diseases. Evaluation of documentation follows the principles of evidence-based medicine. In order to gather experience about the safety of the compound, a new drug should have been registered and available on the market for at least two years. However, there is a trend towards quicker decisions and earlier acceptance of new drugs if they have shown potential to improve therapy.

Treatment costs are taken into account and an economic evaluation is demanded both for initial drug cost and the total treatment schedule. Recommended drugs should have high delivery guarantees from the producer/distributor, with relevant and up-to-date product information. Maintaining drug selection requires continuous follow-up of newly registered drugs, evaluation of the literature with respect to new guidelines, clinical trials and reports on adverse reactions. Expert groups are expected to stay in touch with specialist organizations preparing national treatment guidelines as well as with the Medical Products Agency, which regularly initiates and coordinates workshops.

Education and information

The rapidly expanding number of new drugs and treatment principles has created an increased need for independently evaluated drug information and education. The drug and therapeutics committee plays a central role here and supports a bilateral exchange of information with prescribers. Education is mostly problem-oriented, being initiated and organized by the medical community based on the needs of prescribers. Different models are being tested and an important idea is "drug education by prescribers for prescribers". Primary health care physicians in academic drug detailing have been engaged at primary health care centres as "Drug Watchers" (4).

Regional drug information centres based within clinical pharmacology departments provide independent and evaluated problem-oriented drug information to prescribers (5) through a database — *Drugline* — containing more than 10 000 evaluated documents on drug-related issues (6).

In several counties, DTCs regularly inform the public of their recommendations. In Stockholm, mass media campaigns focusing on the list of recommended drugs have been directed at prescribers and their patients. The campaigns have helped to establish the regional committee as an independent and reliable expert organization. Both DTCs and the regional drug information centres collaborate actively with the Medical Products Agency, which publishes excellent monographs on individual drugs and reviews on the treatment of different diseases.

Electronic prescribing

In Stockholm, a computer-based prescription support system, JANUS telepharmacology, has been developed (http://www.janusinfo.org) aimed at providing all prescribers within a county with easily accessible, clinically relevant and updated information on drugs. The system includes (mainly in Swedish):

- information and recommendations from the regional and local drug committees in the county;
- recent guidelines from the Medical Products Agency;
- links to the Physicians Desk Reference (FASS) and *Drugline*; and
- recent drug news with comments and evaluations by specialists.

JANUS also provides access to information on drug interactions, with evaluated literature references to each interaction (7). The key objective is to provide appropriate information and prescribing tools to simplify the selection and dosage of drugs.

Graphic presentations of local drug prescription patterns are also included to allow quick feedback to and between prescribers. Within the next few years, electronic prescribing is expected to replace old-fashioned prescriptions, and the prescriber will then have access to real time information while prescribing. Integrated into the JANUS prescription

system is a website (http://www.janusinfo.org) that serves as the electronic channel for all DTCs in Stockholm. Representative examples of the site pages in JANUS are set out in Figures 1 and 2.

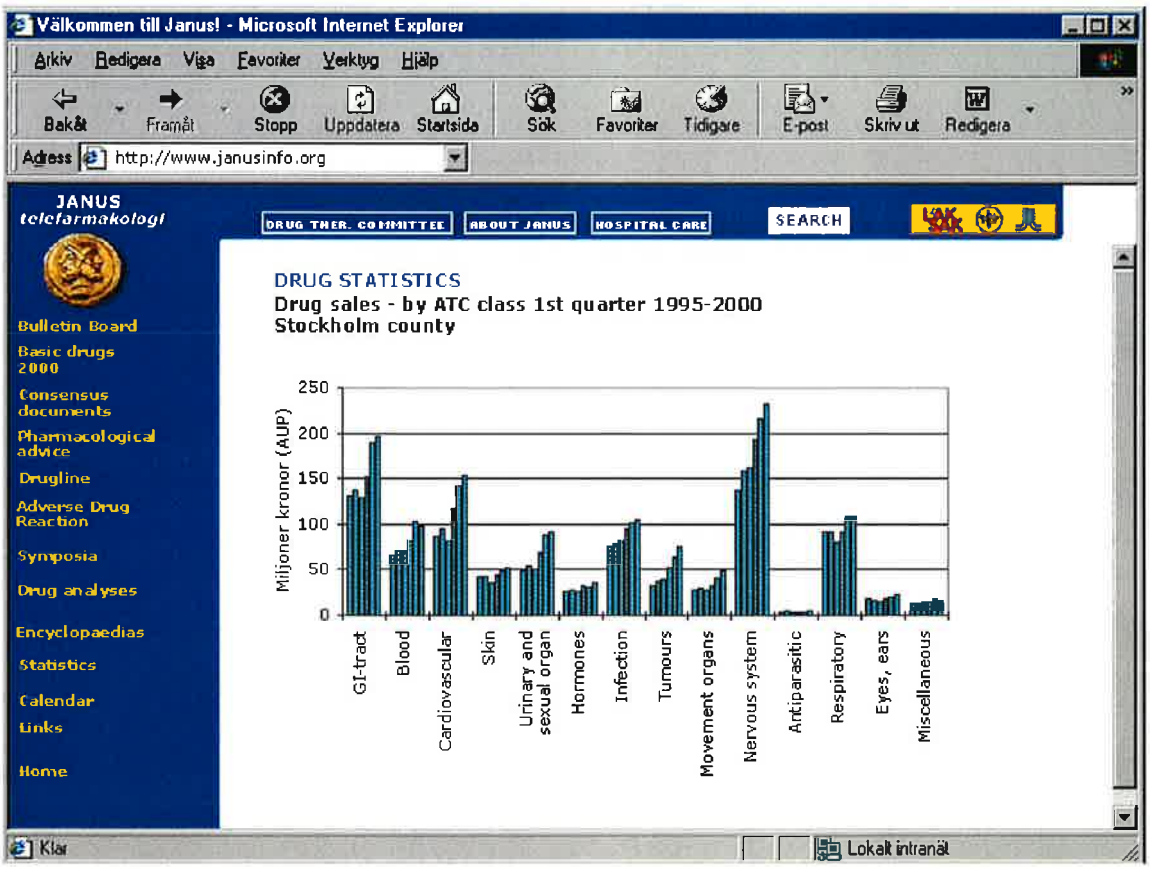
Follow-up and feedback of drug utilization

Increasing drug costs, together with the transfer of the drug budget from the government to the county councils, emphasizes the need for follow-up of drug use, prescription patterns and cost trends. Drug committees play a key role in developing pharmacoepidemiological tools. The 1997 Drug Reform Act required bar codes for prescriptions, indicating workplace and prescriber identity. The feedback provided serves as an ideal self-audit system for primary health care centres, clinics, and individual prescribers (10).

Local auditing of prescription patterns and cost development in relation to the committee's recommendations is an important strategy and stimulates feedback on rationality, prescribing and cost-awareness. Such data also form the basis for revision of drug recommendations, educational and informational activity needs, or intervention studies. Before drug reform, physicians were relatively unaware of the costs that prescribing generated, since the government paid the bill. This will now change dramatically and drug costs will become an integrated and visible part of the entire budget for a clinic or primary health care centre.

A new indicator of the quality of drug prescribing has recently been introduced in Stockholm County (8): Drug Utilization 90% (DU90%). The term refers

Fig. 1. JANUS prescription system:

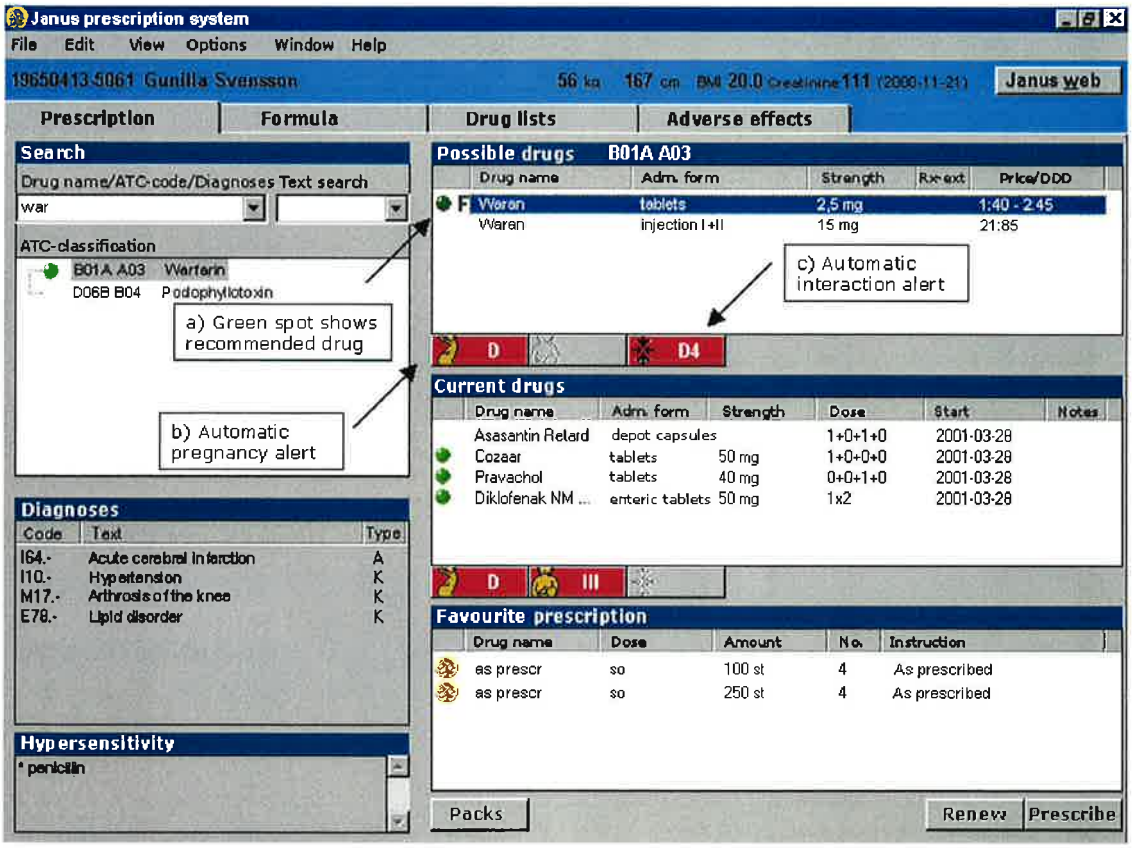


Drug statistics:
Drug sales (1 million Swedish Kroner= 0.1 million Euros) by ACT class for 1st. quarter 1995–2000 in Stockholm. This function is updated monthly at the webiste: http://www.janusinfo.org

to the number of drugs accounting for 90% of drug use, measured in defined daily doses (DDDs). The Swedish Medical Quality Council (9) has suggested using the DU90% as a general quality indicator of drug prescribing, and this has also been adopted in Stockholm (10). Adherence to guideline recommendations or other consensus documents is reflected by the percentage of recommended drugs within the DU90% segment. This measure can easily be used for comparisons over time between hospitals, clinics, primary health care centers and geographical regions and may identify problem areas where educational interventions are required. The method can be applied to all drugs or to different therapeutic classes (ATC groups). It also provides data for economic follow-up and analysis, as the drug costs are also included. By sorting on "costs" the corresponding Drug Costs 90% – DC90% – profile is obtained.

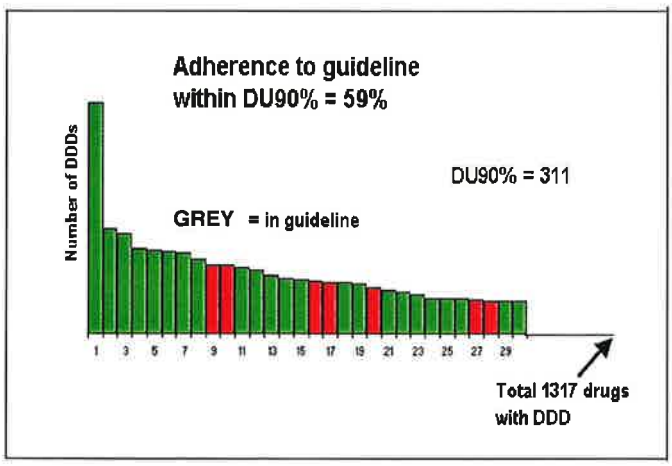
The combined DU90%/DC90% profile has turned out to be of considerable interest to prescribers and physicians responsible for health care costs, including drugs. Figure 3 on page 212 describes DU90% profile by brand name based on prescriptions dispensed to the population of Stockholm during the three months of October–December 2000 ranked by number of defined daily doses (DDD), according to the recommendations by the Swedish Medical Quality Council (9). The drug utilization 90% (DU90%) segment (the area below the curve) corresponds to 311 of a total of 1,317 brand names with DDDs dispensed at pharmacies. Adherence to

Fig. 2. JANUS prescription system:



The JANUS prescribing tool contains 24 different drug information databases. Patient data are automatically retrieved from electronic records. A bullet shows that the drug is recommended by the drug and therapeutics committee (arrow a). Arrow b indicates an automatic pregancy alert for drugs with potential effects on the foetus. Arrow c shows an automatic interaction alert for warfarin. http://www.janusinfo.org

Fig. 3. DU90% Drug use profile



1. (Trombyl = ASA; 2. Levaxin = levothyroxine; 3. Zocord = simvastatin; 4. Plendil = felodipine; 5. Cipramil = citalopram; 6. Renitec = enalapril; 7. Seloken ZOC = metoprolol; 8. Imovane = zoplicone; 9. Lasix Retard = furosemide; 10. Lipitor = atorvastatin; 11. Furix =f urosemide; 12. Pulmicort Turbuhaler = budesonide; 13. Propavan = propiomazine; 14. Triatec = ramipril; 5. Furosemid NM = furosemide; 16. Imdur = isosorbide mononitrate; 17. Losec MUPS = omeprazole; 18. Behepan = cyanocobalamin; 19. Zoloft = sertraline hydrochloride; 20. Tenormin = atenolol; 21. Stilnoct= zolpidem; 22. Bricanyl Turbuhaler = terbutaline; 23. Desolett = desogestrel; 24. Lanzo= lansoprazole; 25. Citodon = paracetamol; 26 Atrovent = ipratropium bromide; 27. Calcichew-D_3=calcium carbonate; 28. Fludent = sodium fluoride; 29. Alvedon = paracetamol; 30. Laktulos P&U = lactulose)

PHARM. PRODUCT	(DDD)	DDD	%	Rx	COST (SEK)	SEK/ DDD
1. TROMBYL	1 tabl.	6,569,005	4.5%	64,425	2,186,994	0.33
2. LEVAXIN	0.15 mg	2,952,441	2.0%	41,535	3,059,630	1.04
3. ZOCORD	15 mg	2,816,558	1.9%	24,749	25,618,330	9.10
4. PLENDIL	5 mg	2,409,584	1.7%	23,319	11,072,443	4.60
5. CIPRAMIL	20 mg	2,372,289	1.6%	27,362	19,325,240	8.15
6. RENITEC	10 mg	2,335,146	1.6%	18,642	9,841,277	4.21
7. SELOKEN ZOC	0.15 g	2,304,272	1.6%	47,073	12,493,554	5.42
8. IMOVANE	7.5 mg	2,097,315	1.4%	42,237	4,831,678	2.30
9. LASIX RETARD	40 mg	1,957,065	1.4%	19,505	2,666,956	1.36
10. LIPITOR	10 mg	1,935,550	1.3%	12,783	13,528,542	6.99
11. FURIX	40 mg	1,863,001	1.3%	10,919	751,774	0.40
12. PULMICORT TURBUH.	0.8 mg	1,779,825	1.2%	22,903	11,065,400	6.22
13. PROPAVAN	25 mg	1,640,487	1.1%	20,353	1,791,482	1.09
14. TRIATEC	2.5 mg	1,558,301	1.1%	6,778	4,615,226	2.96
15. FUROSEMID NM	40 mg	1,525,293	1.1%	7,629	549,500	0.36
16. IMDUR	40 mg	1,498,186	1.0%	11,996	3,645,951	2.43
17. LOSEC MUPS	20 mg	1,464,548	1.0%	23,961	23,312,114	15.92
18. BEHEPAN TABL.	1 mg	1,445,912	1.0%	13,635	2,106,438	1.46
19. ZOLOFT	50 mg	1,404,284	1.0%	15,813	13,158,324	9.37
20. TENORMIN	75 mg	1,303,954	0.9%	19,172	1,863,095	1.43
21. STILNOCT	10 mg	1,234,150	0.9%	27,991	3,918,260	3.17
22. BRICANYL TURBUH.	2 mg	1,179,700	0.8%	22,369	3,696,018	3.13
23. DESOLETT	*	1,114,876	0.8%	6,255	1,182,517	1.06
24. LANZO	30 mg	1,005,654	0.7%	23,132	10,677,362	10.62
25. CITODON	3 t/supp	985,687	0.7%	33,107	3,013,438	3.06
26. ATROVENT	*	971,489	0.7%	10,421	3,914,818	4.03
27. CALCICHEW D3	2 tabl	953,640	0.7%	12,257	2,963,622	3.11
28. FLUDENT	1.1 mg	925,260	0.6%	4,564	411,151	0.44
29. ALVEDON	3 g	922,590	0.6%	34,307	2,247,339	2.44
30. LAKTULOS P&U	6.7 g	919,890	0.6%	8,732	909,068	0.99
DU90% 1-311		130,278,408	90.0%	2,022,457	555,509,919	4.26
312-1317		14,464,452	10.0%	439,649	282,849,843	19.55
TOTAL 1-1317		**144,742,860**	**100.0%**	**2,462,106**	**838,359,762**	**5.79**

Guideline 2000 issued in January 2000 was 59% in the DU90% segment. The technical unit of comparison (DDD) is given in mg, or number of tablets, etc. Rx = number of prescription items. Cost (SEK) in Swedish kronor. Corresponding ranking by cost provides a drug cost 90% profile – DC90%. SEK/DDD is the actual costs per DDD.

Resources

The drug and therapeutics committees have an annual budget which varies between the 21 regions. In the most progressive counties it has been considered appropriate to invest a sum corresponding to 1% of the total drug expenditure. The annual budget for the DTCs in Stockholm is about 4 million Euros, with drug expenditure about 0.4 billion Euros annually.

In Stockholm, the budget is spent on salaries and for engaging clinical expertise. With the existing financial system for the health care budget it is impossible to engage clinical experts for this intellectual work unless they can have leave of absence from their pressing daily work with patients. Much of the budget is spent on continuing education of prescribers and to implement the recommendations of the drug committee.

The committees can also use the competence of existing units in clinical pharmacology as well as regional and local pharmacies. The regional drug information centres (6) offer a service to retrieve, evaluate and summarize the documentation of different drug products.

The future of drug and therapeutics committees

A number of circumstances make it clear that the individual prescriber will be in great need of unbiased, consultative support in the selection and use of drugs in the future. The aims of drug treatment should be that the right drug is prescribed to the right patient in the right dose with the right information and at the right (affordable) cost (11). This implies competence, integrity and cost-awareness on behalf of the prescriber.

Prescribers, then, will accept advice from the organization paying the drug bill and not from the manufacturer alone, while providers of health care have to take responsibility for the continued drug education of the prescribers. This will probably be an invaluable investment in view of the alarming annual increase of expenditure for drugs, and adverse drug effects now reported worldwide.

For drug and therapeutics committees to be effective, it is vital to broadly engage the prescribing professions in the work and to base the selection of the therapeutic choice on advice from the most competent experts in pharmacotherapeutics.

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Stockholms läns landsting
Stockholm County Council

Karolinska Institutet

Welcome to a three-day workshop and site visit on

Interface Management of Pharmacotherapy

Promoting Hospital-Primary Care Collaboration for Rational Use of Medicines – Workshop and Site Visit

September 11–13, 2012, Stockholm, Sweden
Stockholm Health Care Region

Aims: To understand how multifaceted models can improve adherence to drug recommendations and quality of drug use across primary and hospital care. This will be achieved by:

A: International speakers and experts from WHO, Norway, Spain and the United Kingdom, as well as from the Drug and Therapeutics Committee Stockholm County Council and the Department of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden.

B: Presentation of different "Interface Models" including the Stockholm Model for the "Wise Use of Medicines". The Stockholm Model will be supplemented by site visits with key personnel involved with the development, dissemination and implementation of this approach to gain practical experiences.

C: Participants exchanging experiences and discussions how the Rational Use of Medicines including Interface between hospitals and primary care can be improved in their countries with ever growing pressure on resources.

Target groups of participants:

– senior medical and administrative managers and their advisors at hospitals, primary care boards, Ministries of Health, health authorities, health insurance agencies, in National Drug Policy programmes and researchers in the field

– chief physicians, hospital pharmacists, clinical pharmacologists and leaders of Drug and Therapeutics Committees

Stockholms läns landsting
Stockholm County Council

Karolinska Institutet

Stockholm Model for Wise Use of Medicines:

A comprehensive approach for improving the quality of drug use in a metropolitan healthcare region including:

– "Wise List" recommendations of medicines jointly for primary and hospital care

– Medicines policy strategy

– independent Drug and Therapeutics Committee with key role for respected drug experts with policy for "interest of conflicts"

– communication strategy with continuous medical education

– methods and tools for follow-up of medicines use

– systematic introduction of new expensive medicines

– operative resources

– e-pharmacological support at "point of care"

Application: The course/site visit is open to 25–30 participants from all over the world. Participants should apply for the course electronically to wiselistmeetstockholm@sll.se where you also can ask for the application form. The application should contain information about:

– Personal details, including address, telephone and e-mail

– Rationale for attending

– Brief CV

– How the participant envisages coverering his/her costs

– Any other important issues for consideration

Our ambition is to get back to those applicants who have been accepted as participants for the course by the beginning of August 2012. We will keep a waiting list for the course. Participants will be admitted to the course when the course fee has been paid.

Course fee: 500 Euro. International participants pay to account holder Karolinska Institutet Bank:
SEB, KG2 Team Staten, S-106 40 Stockholm, Sweden
IBAN NO: SE15 5000 0000 0543 9102 8247 SWIFT: ESSESESS
The course fee covers all course material as well as transport for the site visits.

Swedish participants pay to account holder Karolinska Institutet BG 5310-6654

Host: The Drug and Therapeutics Committee in Stockholm in collaboration with Department of Clinical Pharmacology at Karolinska Institutet and Karolinska University Hospital

Accommodation: Participants must cover their own accommodation costs. Hotel information will be provided on request.

Scholarships: Scholarships may be provided for participants from developing and emerging countries.

International organizing group: Lars L Gustafsson Stockholm (chair), Richard Laing WHO Geneva, Eva Andersén Karlsson Stockholm, Brian Godman Stockholm/Liverpool, Oyvind Melien Oslo, Sabine Vogler Vienna.

Contact information: Practical/organizational through Executive Secretary Paula Nordahl (paula.nordahl@sll.se) and scientific through Associate Professor Eva Andersén Karlsson (eva.andersen-karlsson@sll.se) and Professor Lars L Gustafsson (lars-l.gustafsson@ki.se).

Stockholms läns landsting
Stockholm County Council

Karolinska Institutet

Interface Management of Pharmacotherapy

Promoting Hospital-Primary Care Collaboration for Rational Use of Medicines

Workshop and Site Visit

September 11–13, 2012
Stockholm, Sweden

Organized by

Drug and Therapeutics Committee, Stockholm County Council, Stockholm,
Clinical Pharmacology at Karolinska Institutet and
Karolinska University Hospital in collaboration with
WHO Essential Medicines and Health Products

Workshop and study visit to Stockholm

WHO realizes that new methods and models are needed across healthcare systems to improve the quality of drug therapy. Medicine selection and collaboration between primary and hospital care on Rational Use of Medicines (RUM) needs to be improved through shared recommendations of essential medicines. The aim is that pharmacotherapy should be rational for patients regardless of whether they are treated in ambulatory or in hospital care.

1. This 3-day study visit to Stockholm Healthcare Region will show a new model for improving quality of medicine use in the 2-million Stockholm metropolitan area. The *"Stockholm Model for Wise Use of Medicines"* is multifaceted with involvement of medical, clinical pharmacological, pharmaceutical and administrative staff. The focus is to improve *adherence to essential medicine recommendations* and strengthen the impact of the Drug and Therapeutics Committee using a "Wise List" of recommendations of essential medicines valid both for primary and hospital care provided for all healthcare providers in metropolitan Stockholm.

2. Healthcare providers and scientists around the globe are interested in evaluating what is known about models, experiences and effects of interface cooperation between primary and hospital care to improve the Rational Use of Medicines.

3. New initiatives for "Interface management of pharmacotherapy" will benefit from being shared at a "workshop"-like study visit.

Stockholm Model for Wise Use of Medicines

Stockholm County Council (Healthcare region) has developed and implemented a comprehensive way to improve quality of pharmacotherapy in the 2-million metropolitan capital of Sweden during the past 15 years, building on:

- The "Wise List" of recommendations of essential medicines jointly for primary and hospital care
- Medicine policy strategy
- Independent Drug and Therapeutics Committee with key roles for respected drug experts with a policy for "conflict of interest"
- Communication strategy with continuous medical education
- Methods and tools for follow-up of medicine use
- Systematic introduction of new expensive medicines
- Operative resources
- E-pharmacological support at "point of care"

Target group of participants

The target group for this study visit consists of 25 medical executives, advisors and researchers around the globe for this study visit in charge of enhancing the quality and efficiency of medical prescribing and medicine use in healthcare institutions, in particular at the interface between hospitals and primary care.

Target groups include:

- Senior medical and administrative managers and their advisors at hospitals, primary care boards, Ministries of Health, health authorities, health insurance agencies, in national medicine policy programmes and researchers in the field.

- Chief physicians and hospital pharmacists as well as pharmacotherapeutic, clinical pharmacological and pharmacist leaders of Drug and Therapeutics Committees.

Time for workshop and study visit

The workshop will last three full days September 11-13, 2012 including opportunities for extended discussions and in depth-studies with participating and organizing experts.

Application

Apply to wiselistmeetstockholm@sll.se. Please pay the course fee upon receipt of information on acceptance to the course. Fellowship may be provided for participants from developing and emerging countries.

Course fee

The course fee is €500 per person.

The fee includes reception, lunches, coffees and one dinner during the workshop. Each participant covers their own accommodation and travel costs. A list of recommended hotels can be provided.

International participants pay to account holder
Karolinska Institutet
Bank: SEB, KG2 Team Staten, S-106 40 Stockholm, Sweden
IBAN NO: SE15 5000 0000 0543 9102 8247
SWIFT: ESSESESS

Swedish participants pay to account holder
Karolinska Institutet
BG 5310-6654

Programme

Monday evening prior to start, September 10

Welcome reception in downtown Stockholm together with invited guests.
Hosts: Karolinska Institutet and Stockholm County Council

Day 1 – Tuesday, September 11
9.00 am-5.45 pm

Coordinating chair: Eva Andersén Karlsson

I: Welcome, aims and presentation of participants and organizers
Chair: Eva Andersén Karlsson

9.00-9.15 am **Welcome and aims of workshop and study visit**
Dr Richard Laing, WHO Geneva
Executive Head, Dr Catarina Andersson-Forsman, Stockholm County Council Public Healthcare Services Committee

9.15-9.30 am **Details of study visit, presentation of organizers**
Associate professor Eva Andersén Karlsson, Chairperson, Drug and Therapeutics Committee (DTC), Stockholm County Council and
Professor Lars L Gustafsson, Karolinska Institutet and Karolinska University Hospital, Stockholm

9.30-9.50 am **Presentation of participants and review of expectations**
All participants

II: Rational use of medicines: The challenge of interface collaboration between ambulatory and hospital care
Chair: Lars L Gustafsson

9.50-10.00 am **International perspective**
Richard Laing, WHO Geneva
(10 min presentation)

10.00-10.35 am **European perspective**

a. Scottish country-wide collaboration to integrate medicine therapy between primary and hospital care
Professor Ken Paterson, University of Glasgow, Glasgow
(25 min presentation, 10 min comments)

10.35-10.55 am **Tea/Coffee break**

II: continuation

10.55-11.30 am ***b. Catalonian country-wide collaboration to integrate medicine therapy between primary and hospital care***
Dr Eduardo Diogene,
Catalonian Healthcare Region, Barcelona
(25 min presentation, 10 min comments)

11.30-12.05 am ***c. Interface management in Norway-***
status and initiatives at national and regional levels
Senior advisor Dr Oyvind Melien,
Norwegian Directorate of Health, Oslo
Dr Jan-Henrik Lund, Chairman Drug and Therapeutics Committee, Health Region South East, Oslo
(25 min presentation, 10 min comments)

12.05-12.15 am **Summing up, key conclusions module II**

12.15-1.15 pm **Lunch**

III: Stockholm Model and literature review on interface management of phamacotherapy
Chairs: Professor Carl-Gustaf Elinder and Ken Paterson

1.15-1.45 pm **Swedish and Stockholm healthcare including pharmaceuticals scenery**
Associate professor Rickard Malmström,
Karolinska Institutet and Karolinska University Hospital
Associate professor, pharmacist Björn Wettermark,
Stockholm County Council and Karolinska Institutet
(20 min presentation, 10 min discussion and comments)

1.45-2.35 pm **Presentation of Stockholm Model focusing on "Wise List"**
Lars L Gustafsson and Eva Andersén Karlsson
(40 min presentation, 10 min questions and discussions relating to experiences across the globe)

2.35-2.40 pm **5 min break**

2.40-3.10 pm **Summary of literature review on interface management of pharmacotherapy (collaboration between primary and hospital care)**
Dr Sabine Vogler,
WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Austrian Health Institute

3.10-3.30 pm **Tea /Coffee break**

3.30-5.20 pm **Hearing on the "Wise List": Panelists include DTC-members, officers and stake-holders**

Chairs: Lars L Gustafsson/Senior researcher Brian Godman, Karolinska Institutet, Stockholm

Initial short presentations on key parts of the "Wise List" concept.

a. ***The "Wise List" – role of experts and critical medicine evaluation***
(20 min presentation, 5 min questions)
- The key role of experts and opinion leaders
- Handling conflict of interest
- Medicine evaluation

Eva Andersén Karlsson
Professor Paul Hjemdahl, Karolinska Institutet Stockholm
Rickard Malmström, Karolinska Institutet, Stockholm

b. ***The work process for selection of medicines in various editions of the "Wise List"***
(15 min presentation, 5 min questions)
MD PhD Marie-Louise Ovesjö

c. ***Comprehensive communication of the "Wise List" recommendations including continuous medical education***
(15 min presentation, 5 min questions)
Information officer Malena Jirlow and GPs Christer Norman and Jan Hasselström, Stockholm

40 min general discussion and 5 min for a summary of key points by participants.

5.20-5.45 pm **Aims and planning of site visits on day 2**
Chair: Pharmacist Kristina Johansson, Stockholm County Council

5.45 pm **Closure**
Free evening

Day 2 – Wednesday, September 12
9.00 am–5.30 pm

Coordinator of site visits: Kristina Johansson

Startplace: Magnus Ladulåsgatan 63 A, at 9.00 am

IV: Site visits to practices, hospitals and institutions to study experience and application of the "Stockholm model"
Each group with 4 to 5 members will make two visits (one in the morning and one in the afternoon). Total 12 site visits. One officer guides at each visit

Visit 1: Morning – *between 9.00 am to 1 pm (including lunch)*
Transport maximum 1 hour

Visit 2: Afternoon *– between 1.30 / 2 pm to 5.30 pm*

Group A

Morning:	*Unit for monitoring of medicine use and adherence*. Host: Björn Wettermark et al
Afternoon:	The ”Wise List” and the Stockholm Model at *Karolinska University Hospital*. Host: Associate professor, chief physician Johan Bratt

Group B

Morning:	*Clinical pharmacology medicine evaluation group*. Host: Rickard Malmström et al
Afternoon:	*General practice visits*. Host: Jan Hasselström et al, *Storvretens Practice Centre*

Group C

Morning:	*Healthcare management board*, Stockholm County Council. Host:Dr Henrik Almkvist
Afternoon:	*General practice visits*. Host: Dr Marianne Jägestedt et al, *Stureby Practice Centre*

Group D

Morning:	The ”Wise List” and the Stockholm Model at *St Göran, privately managed hospital.* Host: Chief physician and chief pharmacist Peter Persson
Afternoon:	*Unit for monitoring of medicine use and adherence*. Host: Björn Wettermark et al.

Group E

Morning:	The ”Wise List” and the Stockholm Model at *Södersjukhuset*. Host: Marie-Louise Ovesjö
Afternoon:	*Clinical pharmacology services*. Host: Professor and managing medical director Marja-Liisa Dahl

Group F

Morning:	The ”Wise List” and pharmacies, *Apoteket AB*. Hosts: Lars-Åke Söderlund and Karin Söderberg
Afternoon:	”Wise List” and Stockholm Model at *Danderyd Hospital*. Host: Professor Thomas Kahan

7.00 pm **Invited dinner hosted by Stockholm Healthcare Region in collaboration with Karolinska Institutet**

Day 3 – Thursday, September 13
9.00 am–5.30 pm

Coordinating chair: Eva Andersén Karlsson

9.00-10.30 am ***V: Site findings and way forward for Interface Management. Reports of findings at site visits with discussions***

Chairs: Eva Andersén Karlsson and Ken Paterson

Each of the six groups report key findings using one slide for 7 min followed by 2 min of discussion. Summing up with 30 min of general discussion and concluding remarks.

10.30-10.50 am **Tea/Coffee break**

10.50-11.20 am **Continued discussion of findings of site visits**

11.20am-2.00 pm **Group work on "Interface Management"**

Lunch included Group work based on the "Wise List" and other models. Each group summarizes key suggestions on how to improve interface management to be discussed in plenary.

2.00–4.00 pm **Feedback of groups, discussions and conclusions**

Chairs: Eduardo Diogene and Eva Andersén Karlsson

Executive managers of healthcare, responsible politicians and researchers participate

4.00-4.45 pm **Main findings and future steps**
Richard Laing and Rickard Malmström

4.45-5.15 pm **Evaluation of course**
Eva Andersén Karlsson
Pharmaceutical advisor Klara Tisocki, WHO Manila
Oyvind Melien

5.15-5.30 pm **Final remarks**
Carl-Gustaf Elinder

7.00 pm **Informal dinner for people staying over**
(at their own expense)

Day 4 – Friday, September 14

Optional

In-depth discussions, consultations and site visits can be organized with participating and organizing experts related to Rational Use of Medicines, in particular hospital-primary care "interface management" in medicine therapy, and on the "Stockholm Model for Wise Use of Medicines". The Swedish Drug Registration Body, Medical Products Agency, is in Uppsala close to Arlanda Airport. Karolinska Institutet is an internationally leading medical University with

strong research groups in several pharmacotherapeutic areas and with an internationally recognized centre for education and research in clinical pharmacology.

Organizing group, Stockholm
Chairperson DTC Stockholm, associate professor Eva Andersén Karlsson (chair), associate professor Johan Bratt, professor Carl-Gustaf Elinder, professor Lars L Gustafsson, communication officer Malena Jirlow, pharmacist Kristina Johansson, associate professor Rickard Malmström, executive secretary Paula Nordahl, executive secretary Anna-Lena Forssén, graphic designer Magnus Edlund.

International organizing group
Lars L Gustafsson Stockholm (chair), Dr Richard Laing, WHO Geneva, Eva Andersén Karlsson, Stockholm, Dr Brian Godman, Stockholm/Liverpool, Dr Oyvind Melien, Oslo, Dr Sabine Vogler, Vienna.

Welcome to Stockholm!

ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Potential savings without compromising the quality of care

C. Norman,[1] R. Zarrinkoub,[1] J. Hasselström,[1] B. Godman,[2] F. Granath,[3] B. Wettermark[1,3]

[1]Southwest Drug and Therapeutics Committee and Department of Drug Management and Informatics, Stockholm County Council, Stockholm, Sweden
[2]Institute for Pharmacological Research 'Mario Negri', Milan, Italy
[3]Karolinska Institutet, Centre for Pharmacoepidemiology and Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden

Correspondence to:
Björn Wettermark,
Department of Drug Management and Informatics, Stockholm County Council, Box 17533, SE-118 91 Stockholm, Sweden
Tel.: + 46 8 737 40 81
Fax: + 46 8 7374010
Email: bjorn.wettermark@sll.se

Disclosures
No.

SUMMARY

Aims: This study was designed to analyse the association between adherence to guidelines for rational drug use and surrogate outcome markers for hypertension, diabetes and hypercholesterolaemia. **Methods:** The study used a cross-sectional ecological design. Data from dispensed prescriptions and medical records were analysed from 24 primary healthcare centres with a combined registered population of 330,000 patients in 2006. Guideline adherence was determined calculating the proportion of the prescribed volume of antidiabetic agents, antihypertensives and lipid-lowering agents representing the 14 different drugs included in the guidelines for these three areas. Patient outcome was assessed using surrogate marker data on HbA1C, blood pressure (BP) and s-cholesterol. The association between the guidelines adherence and outcomes measures was analysed by logistic regression. **Results:** The proportion of guideline antidiabetic drugs in relation to all antidiabetic drugs prescribed varied between 80% and 97% among the practices, the ratio of angiotensin converting enzyme (ACE)-inhibitors to all renin–angiotensin drugs 40–77% and the ratio of simvastatin to all statins 58–90%. The proportion of patients reaching targets for HbA1C, BP and s-cholesterol varied between 34% and 66%, 36% and 57% and 46% and 71% respectively. No significant associations were found between adherence to the guidelines and outcome. The expenditures for antihypertensives and lipid-lowering drugs could potentially be reduced by 10% and 50% respectively if all practices adhered to the guidelines as the top performing practices. **Conclusion:** A substantial amount of money can be saved in primary care without compromising the quality of care by using recommended first-line drugs for the treatment diabetes, hypertension and hypercholesterolaemia.

What's known
- There are substantial price differences between branded and off-patent drugs for the treatment of diabetes, hypertension and hypercholesterolaemia.
- There is a wide variation in adherence to prescribe targets in primary healthcare.
- There is a limited knowledge on the relation between adherence to prescribing targets or guidelines, patient outcomes and potential savings that could be achieved.

What's new
- No significant associations were found at a practice level between adherence to the guidelines and outcomes in terms of patients reaching target levels for surrogate markers.
- A substantial amount of money can be saved in primary care without compromising the quality of care by using recommended off-patent drugs for the treatment of diabetes, hypertension and hypercholesterolaemia.

Introduction

A considerable number of guidelines and treatment recommendations are being developed by professional organisations, healthcare providers and authorities. In Stockholm, Sweden, regional guidelines for drug prescribing are developed by the Drug and Therapeutics Committees (DTCs) (1–3). These guidelines, called 'The Wise List', are produced by 20 expert groups with specialists in family medicine, hospital specialists, pharmacists and clinical pharmacologists. They consist of diagnosis-specific evidence-based recommendations with some 240 pharmaceutical products suggested as first-line choices for outpatient treatment of common diseases. The drugs in the Wise List are selected based on medical efficacy and safety preferably with data from randomised-controlled studies, pharmaceutical suitability, comparative cost-effectiveness, experience and environmental aspects (2,3). Substantial savings can be achieved using the drugs recommended in the guidelines, instead of the more expensive branded alternatives. Some examples include replacing atorvastatin with simvastatin for the treatment of hyperlipidaemia and replacing angiotensin receptor blockers (ARBs) with ACE-inhibitors (ACEi) for the treatment of hypertension and heart failure (4,5). Although certain differences in documentation and pharmacokinetic properties, these drugs have shown to be equally effective for a vast majority of all patients with hypertension and hyperlipidaemia respectively (6–12).

However, guidelines are poorly adopted in healthcare because of various barriers at an organisational and professional level (13). Furthermore, many physicians are facing the challenge to comply with an

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ever increasing number of different guidelines (14). Consequently, guideline implementation needs to be supported by the use of indicators to monitor healthcare performance against agreed targets. Traditionally, these indicators focused on quality and were developed by professional organisations to stimulate learning and promoting adherence to guidelines (15–17). In recent years, there has been an ongoing trend in many countries towards linking quality indicators to financial incentives and paying the doctors for reaching certain targets (17–21). The most comprehensive system is probably the Quality and Outcomes framework in the UK, whereby 30% of the payment in general practices is linked to a sophisticated system of quality indicators covering different aspects of care ranging from practice management, record keeping and continuous education to patient satisfaction, clinical outcomes and adherence to guidelines for the treatment of 10 common chronic diseases (17–19). Similar programmes have also been introduced in Germany where physicians receive payment for monitoring patients with chronic illnesses using specific forms including outcome measurements under the Disease Management Programme initiative (20,21).

Indicators can be classified in structure, process or outcome depending on which aspect of care is being assessed (22). The structure comprises the organisational factors that define the health system under which care is provided; the process is the interaction between users and the healthcare structure; and the outcome is the consequences. Although outcome measures are important as they reflect all aspects of care, they are difficult to apply in quality improvement activities (23,24). Healthcare is only one determinant of health and differences in outcome may be because of case mix, how the data were collected, chance, or quality of care. Process measures are more sensitive to differences in the quality of care. They are readily measured and they can directly indicate deficiencies of care which need to be remedied (23,24). However, concern has been raised that a too strict focus on performance measures and prescribing guidelines as currently being undertaken in many countries may have negative effects on the quality of care provided. We therefore analysed to what extent our DTC guidelines were followed in primary healthcare and the potential association between adherence to guidelines and the surrogate outcome markers – blood pressure (BP), HbA1C and s-cholesterol.

Methods

This cross-sectional, ecological study was undertaken in 24 primary healthcare centres (PHCs) in the south-western part of Stockholm County, Sweden. Primary healthcare is the basis of the Swedish healthcare system, although PHCs lack a gatekeeper function and patients are generally allowed to seek care from specialists without referral. All the participating PHCs were group practices of varying size from five general practitioners up to 20. The combined registered population was 330,000 patients in 2006. All the PHCs are part of a voluntary quality collaboration administered by the south-western DTC. This collaboration has included agreements on how to register diagnosis and quality parameters in the electronic medical records.

'Adherence to guidelines (drug formulary recommendations)' was determined using data on dispensed prescriptions collected from the Swedish National Prescription Register administered by the National Corporation of Swedish Pharmacies. The register was introduced in 1997 and consists of aggregate data from all prescriptions dispensed at Swedish pharmacies regardless of reimbursement status. We included all prescriptions dispensed in 2006 issued from the participating PHC centres. As all prescriptions are valid for 1 year, the dispensing data reflected the prescribing for a period up to 1 year before the dispensing.

Drug utilisation (DU) was expressed in defined daily doses (DDDs) (25) and expenditure in Swedish Crowns – SEK; 100 SEK = 10.4 Euro (10 February 2009). The extent of potential savings with physicians switching to less expensive but similarly effective choices such as generic simvastatin vs. atorvastatin and an ACEi vs. ARBs was calculated on a DDD basis assuming all practices could adhere similarly to the guidelines as the top performing practices. The average cost/DDD for simvastatin and atorvastatin was 0.72 and 5.90 SEK/DDD (0.075 and 0.61 €/DDD) respectively in 2006. The average cost for ACEi and ARB was 0.84 and 6.77 SEK/DDD (0.087 and 0.70 €/DDD) respectively.

The global adherence to drug recommendations (not capturing data on diagnosis) was determined for antidiabetic drugs (ATC A10), antihypertensives (C03, C07, C08 and C09) and lipid-lowering agents (C10A) using three different drug-specific indicators (15,16):

- Proportion of the overall volume in DDDs representing drugs included in the guidelines – antidiabetic agents and lipid-lowering drugs.
- Drug Utilisation 90% focusing on the number of drugs constituting 90% of the volume expressed in DDDs and the adherence to recommendations within this segment (26) – antihypertensive agents.
- Ratios between different treatment alternatives (share of recommended drugs in DDD within a

pharmacologic group) – % of simvastatin of all statins and % ARBs of all renin–angiotensin drugs.

The chosen guideline for comparison was the list of drugs recommended in the county of Stockholm 2006 (Kloka Listan – 'the wise drug list') (1–3). The drugs recommended in diabetes, hypertension and hyperlipidaemia are listed in Table 1. They are selected on the basis of medical efficacy, safety and comparative cost-effectiveness. A high proportion of these drugs or a high proportion of low cost generic ACEi compared with expensive brand ARBs is considered to be legitimate targets to enhance prescribing efficiency based on their current acquisition costs vs. alternatives and the wealth of available published evidence reviewed by the expert groups.

Patient outcome was assessed using surrogate marker data captured from electronic medical records. We included all patients who visited any of the 24 PHC centres between 1 January 2005 and 31 December 2006. A 2-year period was selected to include also those patients visiting the practice once a year being prescribed a sufficient supply of drugs for 1 year. All patients with recorded diagnoses of hypertension (ICD-codes I10-, I13-P, I15-) diabetes mellitus (E108P, E109, E118P, E119 and E14-P) and/or ischaemic heart disease (IHD) (I200, I209P, I21-P and I25-P) were included. Data on age, systolic and diastolic BP, HbA1C and s-cholesterol were analysed with the outcomes indicators below, each of them based on last recorded value during the period for each patient. The targets include the:

- Proportion of patients with diabetes mellitus with an HbA1C ≤ 6.
- Proportion of patients with hypertension having a recorded BP ≤ 140/90.
- Proportion of patients with IHD with s-cholesterol ≤ 5 mmol/l.

Table 1 Drugs included in the guidelines (the Wise Drug List)

Antidiabetic agents	Antihypertensives	Lipid-modifying agents
Metformin	Hydrochlorothiazide	Simvastatin
Glibenclamide	Bendroflumethiazide	
Insulin (human)	Enalapril	
Insulin lispro	Ramipril	
Insulin aspart	Amlodipine	
	Metoprolol*	
	Losartan*	
	Candesartan*	

*Recommended as second-line drugs in the guidelines.

These targets were chosen from 'The Wise List 2006' and from national guidelines for the prevention of IHD and diabetes from the National Board of Health and Welfare (27,28).

All data were extracted using RAVE software (Stockholm, Sweden) (29). The RAVE software extracts data from the medical record database in a reliable and systematic way making it possible to link most of the recorded data such as diagnosis, laboratory findings and text registered in the medical record. If quality parameters are recorded under specific key words, they will be found in the extraction and included. There is no regulation in Sweden requiring diagnoses to be recorded at the consultation. Nevertheless, in 85% of all consultations performed in these PHCs in 2006, a diagnosis had been registered in the medical record following established standards (30).

The association between the proportion of patients reaching target levels in each age group in different PHCs and the proportion of DDDs following recommendations in the corresponding groups was analysed by logistic regression. The models including the proportion following recommendations divided by age groups (40–64, 65–79 and 80+) displayed substantial over-dispersion; consequently, the p-values and confidence intervals were subsequently adjusted by scaling for heterogeneity. Results were presented as odds ratios per 10 percentage units of the 'prescriptions' following recommendations together with 95% confidence intervals and p-values for a log-linear trend.

Results

A total of 1.3 million prescriptions (all drugs) were dispensed in 2006 that had been issued by the 24 PHCs. The total drug expenditures were 243 million SEK (25.3 million €).

The mean number of prescriptions per practice was 54,000 (variation 24,000–118,000) with a mean total cost of 10.1 million SEK (1.05 million €) (variation 5.3–20.4 SEK, 0.55–2.12 €).

The total number of DDDs dispensed for antidiabetics, antihypertensives and lipid-lowering agents during the year was 2.9, 16.4 and 5.1 million respectively (Table 2). In 2006, metformin and glibenclamide were recommended as first-line peroral agents, while various fast- and intermediate-acting insulins were recommended for parenteral use. The average adherence to the DTC guidelines was 91%, with variation seen between practices (Table 2).

A total of seven different antihypertensive agents were recommended in the DTC guidelines – hydrochlorothiazide, bendroflumethiazide, enalapril, ramipril, amlodipine, metoprolol, losartan and candesartan

(Table 1). The range of drugs used varied between the practices with on average 16 drugs accounting for 90% of the volume, i.e. DU90% (Table 2). The adherence varied between 64% and 81%. There was a wide variation in the use of ARBs, and the proportion of ACEi to all renin–angiotensin drugs varied between 40% and 77% (Table 2).

The DTC guidelines included only one lipid-lowering agent, simvastatin, recommended for cardiovascular prevention after IHD, stroke and for patients with a high cardiovascular risk. The ratio of simvastatin to all statins varied between 58% and 90% among the practices (Table 1).

The number of patients with diagnoses of diabetes, hypertension or IHD who had visited the practices in 2005–2006 was 9150, 21,175 and 4449 respectively. However, data on surrogate outcomes markers were not recorded for all patients. Information about HbA1C was recorded for 92%, BP for 87% and s-cholesterol for 69% of all patients with a diagnosis of diabetes, hypertension and IHD respectively.

The proportion of patients reaching targets for the surrogate markers HbA1C, BP and s-cholesterol varied among the practices between 34% and 66%, 36% and 57% and 46% and 71% respectively. The variation is illustrated by age in Figure 1.

No significant associations were found between the process indicators measuring adherence to the guidelines (or guidance) and the outcome indicators measuring the proportion of patients reaching surrogate targets (Figure 2 and Table 3).

The total expenditures in 2006 for the prescribing of antidiabetics, antihypertensives and lipid-lowering agents from the 24 PHC centres were 14, 35 and 10 million SEK (1.46, 3.64 and 1.04 million €) respectively. The renin–angiotensin drugs accounted for 15 million SEK (1.56 million €) of the total expenditures for antihypertensives. The estimated savings if all practices adhered to the guidelines as the top performing practices were 3.6 million SEK (0.37 million €) by increasing the proportion of ACEi to 77% and 5.4 million SEK (0.56 million €) by increasing the proportion of simvastatin to 90%.

Table 2 Total volumes (DDD) and adherence to DTC guidelines

Indicator	Total	Mean/practice	Variation
Antidiabetic agents			
Number of DDDs × 1000	2900	121	56–292
% Recommended drugs	91	91	80–97
Antihypertensives			
Number of DDDs × 1000	16,400	684	343–1267
DU90% (no of drugs)	–	16	13–20
DU90% adherence	–	75	64–81
DDD ACEi/ARB × 1000	5600	234	112–441
Ratio of ACEi to ACEi/ARB (%)	66	66	40–77
Lipid-lowering agents			
Number of DDDs × 1000	5100	213	110–394
% Recommended drugs	78	78	54–90
Ratio of simvastatin to statins (%)	79	79	58–90

Prescriptions dispensed in 2006, issued from 24 PHC centres in south-west Stockholm. DDD, defined daily dose; DTC, Drug and Therapeutics Committee; PHC, primary healthcare centre; DU90% drug utilisation 90%; ARB, angiotensin receptor blocker; ACEi, ACE-inhibitors.

Table 3 Association between the adherence to guidelines and the proportion of patients reaching target levels in each age group in different primary care centres

Effect	OR	Low 95% CI	Up 95% CI	p-Value
% Recommended antidiabetic agents	1.03	0.84	1.26	0.79
% Recommended lipid-lowering agents	1.02	0.92	1.12	0.75
% Simvastatin to all statins	1.00	0.91	1.10	0.99
% ACE-inhibitors of all RAAS	0.95	0.90	1.01	0.07
DU90% adherence antihypertensives	0.94	0.84	1.05	0.31

Presented as odds ratios (OR) per 10 percentage units of the 'prescriptions' following recommendations with 95% confidence intervals (CIs) and p-values for a log-linear trend. RAAS, drugs acting on the renin-angiotensin-aldosteron system; ACE, angiotensin converting enzyme.

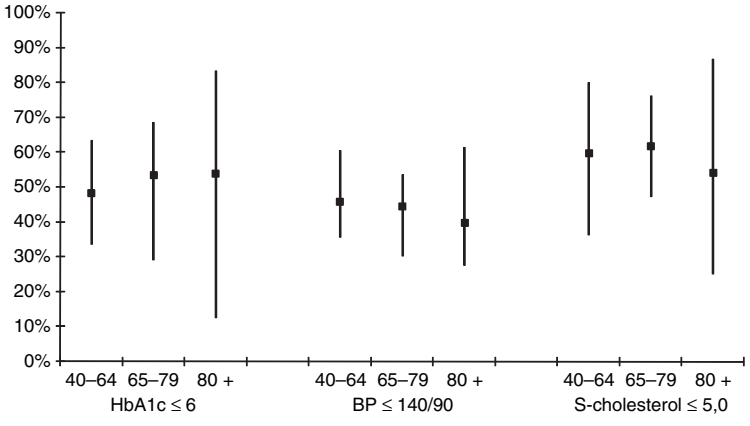

Figure 1 Proportions of patients with diabetes, hypertension and ischaemic heart disease reaching targets for HbA1C, blood pressure (BP) and s-cholesterol broken down by age group. Mean and range depicted between practices (n = 24)

Discussion

We found a wide variation between different primary care practices in quality of prescribing, both measured as attaining targets for cost-effective drug treatment of diabetes, hypertension and hyperlipidaemia and outcomes measured by surrogate markers BP, HbA1C and s-cholesterol. This is in agreement with several studies showing a wide variation in practice performance, only to some extent explained by

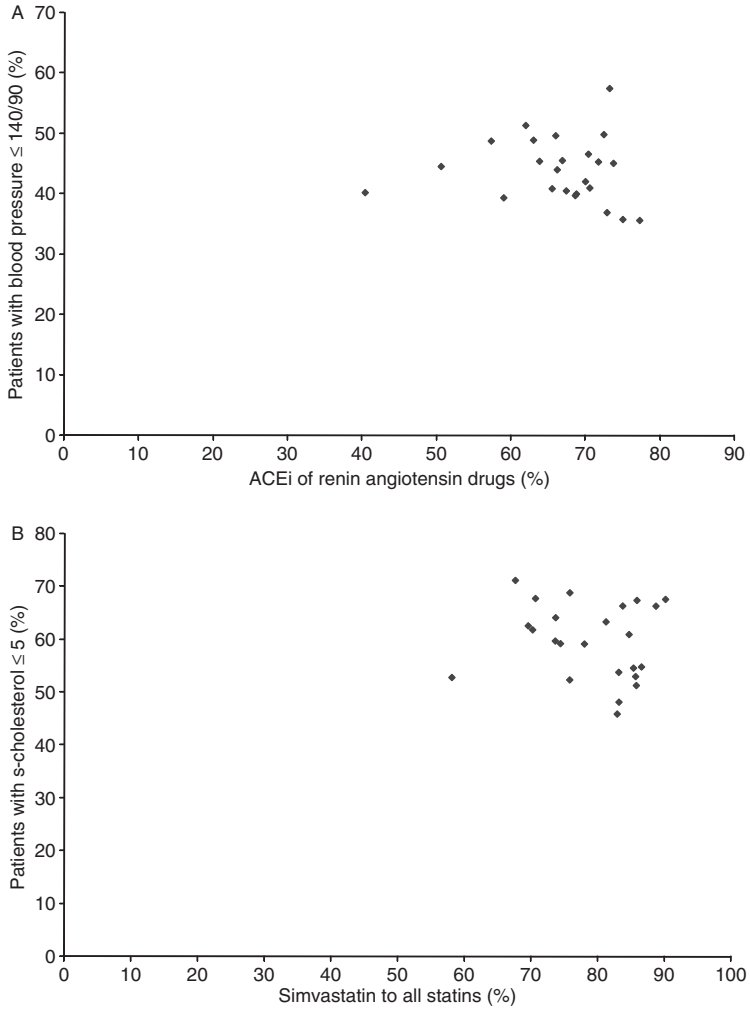

Figure 2 (A) Ratio of ACEi to all renin–angiotensin drugs compared with % patients with hypertension reaching targets for blood pressure (BP) (n = 24 practices). (B) Ratio of simvastatin to all statins compared with % patients with ischaemic heart disease reaching targets for s-cholesterol (n = 24 practices)

differences in patient or prescriber characteristics (5,26,31–35).

No correlation was found by between adherence to the recommendations on drug choice and patient outcome. A limitation with the study was the ecological study design with no record linkage at the patient level between exposure and outcome. There are several reasons why the overall prescribing of these drugs does not completely represent the same population as the patients studied with data from the electronic records. Some reasons include the time lag between consultations and (repeat) dispensing as well as the time lag between initiation of therapy and expected outcome. Furthermore, the dispensing data consisted of all prescriptions dispensed regardless of the diagnoses registered in the medical records. There is also room for improvement in the accuracy and validity of data derived from medical records (36–38). In our study, laboratory analyses on HbA1C and s-cholesterol were performed in a few central laboratories for all participating practices. Routines for measuring BP may vary between practices. However, there were common rules for registration and record keeping among the practices and it is not likely that this will have introduced any systematic error. It is also important to emphasise that outcomes are influenced by a many other factors ranging from compliance to life style factors and concomitant diseases. Consequently, there is probably no association between which specific drugs are prescribed and patient outcomes assuming the drugs prescribed have been shown in clinical trials to improve outcomes.

Our study indicates that a substantial amount of money can be saved in primary care without compromising the quality of care. The estimated savings

were 9 million SEK (0.94 million €), in the same magnitude as the total annual expenditure for all drugs prescribed at one PHC. The substantial savings in reality are likely to be higher than this as the prices for generic drugs in Sweden have been decreasing since the study was undertaken (3). There is also empirical evidence from other settings to support switching statins to save considerable resources. In a recent UK study carried out in a primary care practice, no significant change was observed in mean total cholesterol levels 2 years after the switch from atorvastatin to simvastatin (39). No adverse events attributable to the switch were reported, and substantial savings were achieved (4,39). The resources saved by more cost-effective drug selection could for instance be re-directed to interventions to improve patient compliance as this has been shown to be a significant problem for these disease areas (40).

It has been suggested that proposed process quality indicators must be linked to at least one outcome subcomponent (e.g. morbidity, mortality or quality of life) to be called a quality indicator (41). Quality indicators that lack this evidence should only be called 'putative' or 'aesthetic' (41). However, factors including the data availability and time delay between process and outcome make it very difficult to demonstrate the existence of such a link. Consequently, the way forward is to only recommend drugs in DTC guidelines that have been shown to improve outcomes in the long-term and monitor their utilisation by means of surrogate markers. For instance, there is evidence that lowering HbA1C by using metformin, sulphonylurea or insulin correlates to better clinical outcomes (42,43). Alongside this, drugs should not be recommended which improve surrogate markers, but as yet either have shown no beneficial impact on outcomes or have a detrimental impact on outcomes in reality. For example, the thiazolidinediones lower HbA1C but appear to worsen clinical outcomes (44) Similar findings were shown in the Illuminate study in which torcetrapib was added to atorvastatin for patients at high risk for coronary events (45). The number of adverse cardiovascular events increased significantly despite a 25% decrease in LDL and a 72% increase in HDL, for the patients additionally treated with torcetrapib.

The growing interest in cost-effective use of drugs has increased the need for observational studies. It is well known that patient compliance may be as low as 50% in clinical practice and patient recruitment in randomised clinical trials is regularly skewed (46,47). Consequently, there is an urgent need for the pharmaceutical industry, regulatory agencies and healthcare providers to assess which drugs are prescribed to which patients and what are the effects in real life on morbidity, mortality and quality of life. The ecological study design used in our study has several shortcomings, but may be useful to generate hypothesis to be analysed more in depth using record linkage between exposure and outcome. In Sweden, these studies have been facilitated with the establishment of a nationwide patient identity register on dispensed prescriptions (48), and further studies are now being planned.

Acknowledgements

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Knowledge Bases for Clinical Decision Support in Drug Prescribing – Development, Quality Assurance, Management, Integration, Implementation and Evaluation of Clinical Value

Birgit Eiermann[1,2], Pia Bastholm Rahmner[1], Seher Korkmaz[1], Carina Landberg[1], Birgitta Lilja[1], Tero Shemeikka[1], Aniko Veg[1], Björn Wettermark[1,2] and Lars L Gustafsson[1,2]
[1]Departmentof Drug Management and Informatics, Stockholm County Council
[2]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

1. Introduction

The access and use of information technology is increasing in all parts of society and in particular in the health care sector in developed and developing countries (Bates & Gawanda, 2003; Lucas, 2008). The integration of health information technology into health care institutions governs the agenda in most countries presently (Lucas, 2008; Gustafsson et al. 2003). The US has recently enacted a $ 19 billion program to promote the use and adoption of health information technology (Blumenthal, 2009) and information systems including electronic health records (EHR). This program is seen as an essential component to improve the health of every American. Challenges discussed span over the whole area of installing electronic health records, supporting and updating the systems, assistance with the interoperability, training the personal, and implementation of the systems as well as medical education (Blumenthal, 2009). Information technology, in particular computerized decision support systems, is also seen in the recent report by the Institute of Medicine in the US as a key way to address the identified great risk of medication errors in American health care institutions (Aspen, 2006).

A recent European report published by the Swedish government analyses health care in 6 European member states. The report describes the impact of health technology on several political goals such as increasing the availability of health care, continuity, empowerment of patients, patient safety and quality of care. It states that in the 6 European member states studied, 100 000 yearly inpatient adverse drug events (ADE´s) could be avoided through usage of computerised physician order entry systems (CPOEs) with clinical decision support (CDS), which would correspond to a yearly saving of 300 million € (Gartner, 2009). This report combined with other studies and reviews (Sjöborg et al, 2007; Kelly et al., 2006) underlines the complexity of integration and implementation, including local conditions, the involvement of stakeholders and adoption and measurements of changes, all of which have

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to be tackled for a beneficial usage of the technology. The Gartner report envisages that increasing costs within the health care sector will accelerate the efforts to develop new technologies as well as lead to a beneficial usage of existing systems.

Computerised physician order entry systems (CPOEs) are one step towards increased safety in patient safety. They allow physicians and other health care staff to prescribe patient medication directly by using a computer, replacing hand-written orders, and thereby eliminating possible interpretation and transcription faults. Transcription and/or interpretation errors have been shown to cause 11% of all medication errors resulting in adverse drug events in hospitals (Krahenbuhl-Melcher et al., 2007). An additional step to improving patient safety and efficacy in the prescribing process is the integration of clinical decision support systems (CDS systems) within the CPOEs. This allows physicians to retrieve up-to-date medical knowledge of the optimal/recommended management of the diseases and drugs, thereby improving patient care through enhancing compliance with recent guidelines and recommendations. CDS systems deliver their information through knowledge bases (e.g. drug-drug or drug-food interactions, drugs & pregnancy, drugs & lactation, drug dosage according to kidney function and genotype and in risk groups), which are integrated through software algorithms, that will generate alerts, warnings and recommendations during drug prescribing. For optimisation of the effect of CDS systems, they should be integrated into EHRs´ resulting in patient specific recommendations and alerts using patient characteristics available in the EHRs.

Numerous studies have demonstrated positive effects of CDS systems in various settings including hospital or ambulatory care, intensive care units and in pediatric care (Ammenwerth et al. 2008, Eslami et al. 2008, Wolfstadt et al. 2008, van Rosse et al. 2009). Areas of improvement identified include costs, safety, adherence, alerts, user satisfaction and time. Reduction of medication errors have been demonstrated with the introduction of CDS systems as well as reduction of ADE´s. However, further studies are needed which focus directly on patient outcomes rather than the surrogate outcome such as "practitioners' performance" to further accelerate their introduction (Garg et al., 2006). Many studies pinpoint improvements of the knowledge bases or CDS systems including optimization of the content (Luna et al. 2007), introduction of classification systems to knowledge bases (Böttiger et al., 2009), and tiering alerts through introduction of severity levels (Paterno et al., 2009). Their introduction is likely to further improve CDS systems.

Evidence is growing though that CDS systems might not only lead to improved quality in health care but they can themselves create unintended errors jeopardizing patient safety (Ash et al., 2004). Introduction of CDS systems might cause diminished medical judgement, letting the computer overrule physicians´ own professional knowledge. Additional work tasks might create disturbances in the already burdened physicians work flow resulting in inefficiencies of the systems. Also the complexity of the systems increases the potential in design flaws thereby actually introducing new errors rather than preventing them (Bates et al. 2001). Therefore, the implementation and use of any CDS system should be linked to the establishment of a medical management, maintenance and quality assurance system, which leads to discovering, analysing and foreseeing possible errors.

Being responsible for paying the drug bill Stockholm County Council, the largest health care provider in Sweden, implemented a health care strategy in 1997 including the development of an IT architecture (Sjöborg et al., 2007). The aim was to provide numerous services to the prescribers to ensure safe and effective drug prescribing. Additional initiatives where

started, like the formation of drug expert groups providing a Wise Drug List, which contains a list of about 240 first line drugs for common diseases incorporating therapeutic ladders or guidelines. Recommendations from 23 expert groups and 5 local drug and therapeutic committees are used to produce and refine the guidance. On the IT site Stockholm County Council in collaboration with Karolinska Institutet and other academic partners has designed, developed and implemented a prescribing tool (Eliasson et al., 2006) and the content for medical knowledge bases for drug-drug interactions, Sfinx (**S**wedish **F**innish **In**teraction **X**-Referencing), drugs & pregnancy, and drugs & breast feeding (Nörby et al., 2006, Böttiger et al., 2009). The knowledge bases are integrated into clinical decision support tools (Janus toolbar described below) or are accessible through the web (www.janusinfo.se). This strategy has been combined with a range of initiatives to promote rational use of drugs as described by Godman et al., (2009). The different knowledge bases and their life cycle from development to evaluation are used as examples for our own experiences in the following parts.

The review is based on more than 10 years experiences from joint efforts to develop, implement and evaluate user friendly and effective decision support systems for drug prescribing in Stockholm. It summarizes state-of-the art knowledge on development, integration, maintenance, implementation and evaluation of knowledge bases and CDS systems used for rational drug prescribing. Consequently, we see this review as a first step in the process of creating robust future models and international standards for the retrieval of medical and pharmacological knowledge, its conversion and organisation into knowledge bases, as well as their integration into CDS systems, their management and evaluation of user satisfaction and treatment outcome.

2. Development of knowledge databases

Why are knowledge bases needed and what advantages do they offer compared to other sources like e.g. the official product SPC (summary of products characteristics) issued as part of the registration of a drug product? One advantage with knowledge bases is the standardisation of information for all drugs containing the same substance. For instance the content of individual SPCs or physician desk references may vary considerably between drugs containing the same substance and with identical drug formulations produced by different pharmaceutical companies. This can cause confusion for the prescribing physician. For example information about drug-drug interactions can be found in the SPC for drug A from provider 1 but is missing in the SPC for the same product from provider 2. Alternatively, the drug-drug interaction between drug A and B can be found in the SPC text for drug A but not for drug B (Bergk et al., 2005). Another example for inconsistencies is the classification for drug and pregnancy alerts for pharmaceutical products. One provider may state, that the drug should be avoided during pregnancy, but another drug company may state, that the drug can be used without any problems. Other examples are variations in dosing information (maximum recommended therapeutic dose) between SPCs´ from different providers or in information published by the US Food and Drug Administration (Seidling et al., 2007). Consequently, knowledge bases should help by providing more consistent information about the substances and drugs related to that substance.

The starting point for development of any knowledge base is the analysis of the perceived needs of the potential users in the health care system (Revere et al., 2007). Likewise it is important to assess the potential of a new knowledge base to improve efficacy and safety in

drug prescribing (Gustafsson et al., 2003; Schiff & Rucker, 1998). We believe the formation of user groups should be mandatory to explore the functional and content needs for a knowledge base and decision support system before other activities are undertaken (Eliasson et al., 2006). Consequently, a multidisciplinary group of clinical experts within the medical field the knowledge base should be aimed for (e.g. nephrologists for a database about drug dosage in patients with reduced kidney function) together with drug experts (e.g. clinical pharmacologists specialised on drug dosage, drug-drug interactions or drugs & lactation depending on the knowledge base), future users, experts within existing drug registries and software developers, should be convened to discuss the potential and obstacles for the knowledge base (Ash et al., 2004). Our own experience is that there often is a mismatch between users' expectations and the clinical and medical research basis or the availability of certain parameters or features within existing registries. For example, the clinical specialists will focus on one specific recommendation for the most common indications for both drugs for a certain drug-drug interaction. However, this recommendation might not fit all patient cases for which this pertinent drug-drug interaction alert will be shown, leading sometimes to suboptimal recommendations.

Another example is that the recommendation to achieve a certain therapeutic drug concentration interval can only be given, if there is scientific evidence. In addition, even though the potential user of a knowledge base (the general practitioner or any other physician) and the drug expert have the same basic medical education, they do not "talk the same language" and medical and clinical expertise differs, with clinical experts having more knowledge about patient treatment while drug experts possess more information about the properties of the drugs used. Medical advice given by the drug expert might not suit the practical needs of the physician and on the other hand the specialist physicians´ needs may not be fulfilled due to missing medical evidence.

It is also very important to clarify when CDS systems or knowledge bases can help and when they can't. For example, during the development of the drug-drug interaction database Sfinx one of the future users mentioned, that he now finally can detect all the drug interactions for herbal drugs his patients always take. But since this physician never enters herbal drugs to the patient's drug list, because he is not prescribing them, he will never get a warning for these drugs.

Prior to the development of the content of a knowledge database the multidisciplinary group needs to define its structure. For example developing the drug-drug interaction database (DDI db), Sfinx, physicians wished not only to receive warnings on certain drug interactions, but also recommendations on how to avoid and handle this interaction (Böttiger et al., 2009). The recommendation part is extremely important, since physicians do not only want warnings on avoiding certain drug combinations, but would like a recommendation how to handle the situation. In a survey among prescribers and pharmacists in the US both groups demanded that drug-drug interaction alerts should be accompanied by management options of the DDI (Ko et al., 2007). In a recent Australian study (Sweidan et al., 2009) recommendations for handling of drug-drug interactions were seen as a quality measure for the DDI databases. However, comparing 9 drug interaction systems used in primary care only 1 out of 9 systems provided useful management advices.

A number of studies have demonstrated, that physicians need timely, easy to digest and up-to-date information, which is filtered, summarized, and synthesized from reliable sources by clinical respected experts (Revere et al., 2007; Grol & Grimshaw, 2003; Schiff & Rucker,

1998). The expert group needs to define the relevant sources to be used for the knowledge base, which might consist of recent research publications, legal documents, information from pharmaceutical companies, textbooks, and other databases. It is critical for the integrity of the knowledge base to use scientifically rigorous methods for evaluation of scientific data by applying critical drug evaluation principles (Godman et al., 2009). Search strategies have to be developed and documented in standard operation procedure protocols (SOP´s) to assure reproducibility of the search results (Böttiger et al., 2009). This is critical in all cases but especially if different people are executing the same task or if expert groups are located in different places and can not communicate with each other on a daily basis.
Figure 1 describes the process from filling a knowledge base with data to providing it to the end user. Literature searched will be evaluated by different experts regarding their clinical relevance and their level of documentation according to standardised rules. It will then be synthesized into short text messages, according to a predefined structure (Böttiger et al., 2009). Different content providers have to use the same tool for data entrance. It is advisable

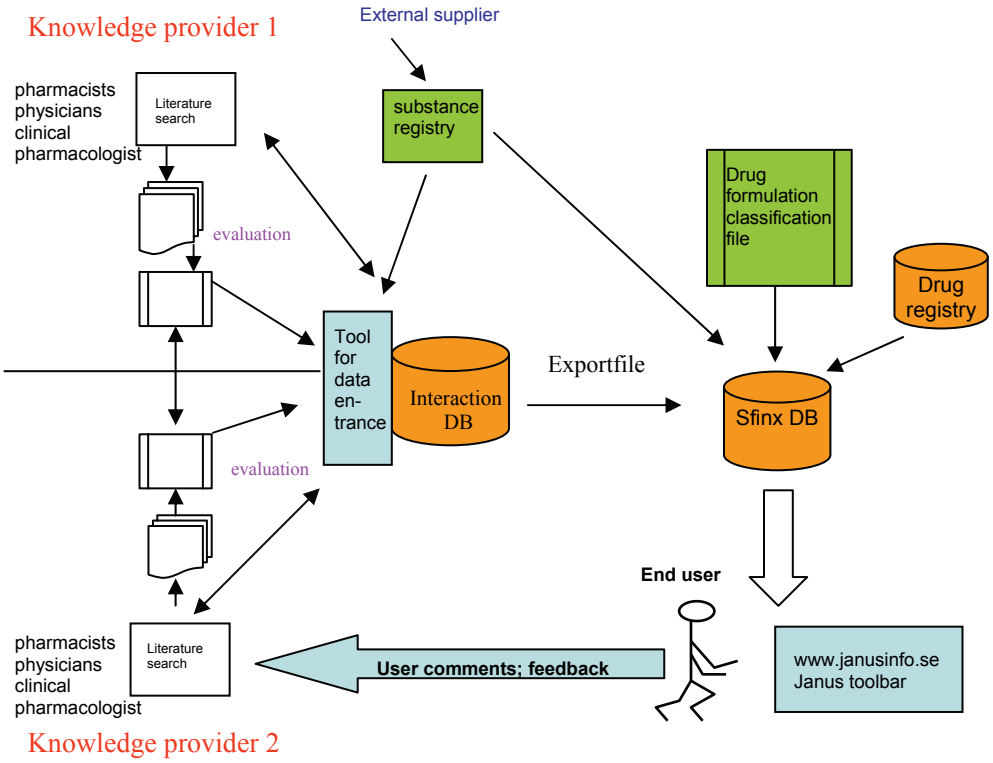

Fig. 1. The design and process of building and maintaining a knowledge base to be integrated into CDS systems for drug prescribing at point of care or accessible through the web. User feed back triggers new literature searches and improves the quality of the knowledge base. This figure outlines the data management process for the drug-drug interaction database Sfinx (Böttiger et al., 2009).

to define in advance certain standard terms for the text messages to avoid heterogenicity in the text content. It is easier for the end user to recognise standard phrases for certain conditions or recommendations.

Data are entered into the knowledge base and connected to various other registries or databases to assure optimal usage in the CDS system used by the prescribers. We have experienced, that access to experts is always the bottleneck in the production of knowledge bases, which agrees with the experiences by Kuperman et al. (2006). Consequently, data entrance into the knowledge base has to be simplified to save valuable expert time. For example through an easy text sharing function the experts should be able to reuse the same texts in different documents (e.g. interactions), which follow the same interaction mechanisms and rules, as a result reducing both the time for entering data and the size of the database. We have developed a terminology model for substances so that substances within a class such as different salts of the same substance belong to the same mother substance, if they react in the same way (Böttiger et al., 2009). The grouping of substances and text sharing function results in an effective and easy way to use the tool which simplifies data entrance and database updates.

Knowledge bases need to be connected to certain registries through software algorithms for their optimal use (see Fig. 1). Because texts in knowledge bases usually are written on a substance basis they need to be linked to specific drugs which contain the substance. This linkage can be done using substance registries, which contain substance names and drugs connected to the substance. Key fields for the linkage can be:

- ATC (Anatomical, therapeutic, chemical classification) codes
- CAS (Chemical Abstract Service) numbers
- other nationally available unique identifiers (Böttiger et al. 2009).

All systems have advantages and disadvantages. The ATC code system is valuable since it takes indications of drugs into account. This can be used to link or exclude drugs containing the same substance, but with different formulations or used in different strengths. A disadvantage of the ATC code system is the handling of combinational drugs, where the content of the drug most often is not specifically defined by the code. CAS numbers identify each substance in a unique way, which allows correct linkage. Problems within the system are its complexity. For example a substance which appears to be the same might have a different CAS number due to its varying content of crystal water, which is not obvious from the description of the drug. Another disadvantage is the limited use of CAS numbers in national registries. National identifiers might be the optimal way for linkage of knowledge bases to drug registries. However, substance based national identifiers do not take drug dosages into account. A substance can have a different interaction profile due to variations in dose (for example: high-dose versus low-dose acetylsalicylic acid). Consequently linkage just by a substance identifier would lead to wrong interactions alerts. Another disadvantage of national identifiers is, that the national identifier can't be used across nations, a problem we faced for the Sfinx database distributed in Sweden and Finland. Whatever registry or system is used for linkage it is of great importance to ensure correct update and maintenance of the registries as described in the next chapter.

If drug formulations are relevant for the triggered alert, these should be taken into account. Even here it is important to simplify matters for the knowledge expert and create drug formulation groups (e.g. all sorts of tablets, capsules or oral solutions should be grouped under the term "peroral"). The Swedish drug registry contains about 650 different drug formulations, which we have grouped into 5 different groups in the "drug formulation

classification file" (Fig.1) to support data entrance. International standard terms are needed to reduce the work load for a single country and to facilitate the integration with other drug registries from other nations. To our knowledge there is no European or worldwide registry with standardised drug formulations available, which could facilitate integration of knowledge bases across countries.
Finally database updates have to follow the same procedures and rules as defined for the starting phase. Ideally, they should include incorporating the handling of end user comments and feedback for further improvement and refinement (Böttiger et al., 2009). Each specific update should be tested, documented and saved in order to be able to trace back incorrect alerts reported by the end users.

3. Combined quality assurance for knowledge bases and linked registries

Quality assurance of the knowledge bases and their linkage to other registries is an essential task often forgotten as it is time consuming, labour-intensive and requires significant effort and expertise. Quality assurance does not only refer to the medical content in question but stretches over the whole procedure from literature searches, the evaluation process to the linkage of the knowledge base to local or national registries and thereby requires experienced multidisciplinary staff.
Literature about quality assurance processes within clinical databases is limited. Quality assurance papers in medicine mainly deal with securing the quality for a certain medical treatment or procedure, but are not extended to databases and CDS systems. It is amazing that still today EHRs or CDS systems do not need to be certified by health or medical agencies. However, due to the increasing awareness of the possibility that information technology implemented into health care can actually increase the error rate even with risk for higher mortality rate (Han et al. 2005), changes are on their way both in the US (Blumenthal, 2009) and Europe (EU directive; 2007/47/EC;2007). Certification should cover not only the technical part of these systems, but should include even the medical content of knowledge bases integrated into CDS systems and implementation of the systems.
Quality assurance is mostly self evolving during the development phase of any database system including the handling of external registries for linkage purposes. Baorto et al. (2009) describe the experiences they made with the maintenance of a large medical ontology at one of the larger hospitals in New York. They state that the methods described even though developed specifically for their system can be used for carrying out similar tasks at other institutions. Many of the problems and procedures mentioned mirror exactly the situation with the development of our knowledge base systems. In our mind resources and expertise for quality assurance processes are needed for integration and maintenance of high quality knowledge bases. Standards need to be developed in this area.
Combining different registries or other knowledge sources has to be performed using "key fields" like ATC codes, specific identifiers, or CAS-numbers. We were surprised though when comparing different registries that the information in key fields could vary. For example a drug could be assigned to a specific ATC code in one registry and this could vary from the code in another registry. This could be due to simple typing mistakes, system requirements of the registry owner, delays in the update process or other possibilities. We, like Baorto and colleagues (2009), used the "diff approach" for detection of theses variations, where you compare two registries regarding the information in predetermined fields using the information in key fields to link the registries. For example we assume that a drug with a

specific registration number has to have the same name, ATC code and drug formulation in all registries. Another approach to detect variations is to compare an older version of the same file with the newer one discovering changes for already existing fields, and new posts entered to the file. Logs are produced during the comparison process, which mainly have to be evaluated manually. Possible mistakes are corrected in the registries and reported to the source owners for correction in the original source.

Over the years we have discovered many mistakes at the point of acquisition of the data including missing information in essential fields (they were either completely empty or omitted), changes in the meaning of existing codes, existence of wrong characters in the master file or creation of redundant terms. The "diff approach" is also used for updating the knowledge base system, e.g. to identify new substances on the market, which will then be added and grouped into the mother child terminology, to discover new drug formulations, which have to be included into the drug formulation file, or to seek for new drugs on the market, which have to be linked to certain knowledge bases. The linkage has to be correct both technically and content wise else care will subsequently be compromised. For example, you can't link some new ear drops, containing a substance you already have in your knowledge base, to that base, if the text document is irrelevant for this new drug.

Auditing terminology and data structure of the registries linked to the knowledge base is mainly performed manually through reviewing log files created during the import process, which flag for changes and differences. These processes are labour-intensive and time consuming. Some of these audit processes though can be automated or at least semi-automated to save time and resources. For example, if you want to add a new substance child to the registry the hierarchy principle within your database requires the existence of the mother substance to be consistent with previously existing structures. Other examples are rules you create for maintenance purposes, like no two medications with the same registry number are allowed with different names.

As Baorto et al. (2009) stated quality assurance and maintenance of the knowledge base and its linked registries is a "mission critical" task that cannot tolerant errors. If we do not add one specific, new ATC code to a document the new drug assigned to that code will fail to be considered by the alerting system. It must be recognised though that all quality assurance processes rely at least partly on human surveillance so they are inevitably prone for mistakes. One can never be sure, that the knowledge base is completely correct. However, we can increase our confidence in the database through implementation of audits, rules and log files. This will help to create a system, which is detecting and minimising a large percentage of potential errors.

Any errors that occur through the usage of the knowledge base have to be handled by the medical management and maintenance system in a systematic way to enhance the utility of the database. This is described below.

4. Medical management and maintenance system for knowledge bases and CDS systems

The development and implementation of several knowledge bases, CDS systems and other IT applications within health care required the introduction of a surveillance system for possible errors introduced by its applications as an essential pre-requisite for the management of these systems. Our department has implemented a maintenance system, which allowed smooth handling of all procedures linked to its databases and depending

registries e.g. regular update processes of the medical content, improvements or changes in the graphical interface and IT structure or adapting to new external registries. At the same time the EU Directive, 2007/47/EC, amending among others the Directive 93/42/EEC (http://Eur-Lex.europa.eu) concerning medical devices is under implementation in Sweden, and supports the process by raising the requirements for software and information systems used for clinical decisions regarding individual patients.
Important parts for the function of knowledge bases and CDS systems are management, maintenance and quality assurance of these applications after their implementation, together with handling of possible errors introduced by the systems, which could be of either technical or medical nature. Clinical, medical, and pharmaceutical competences, as well as competences in various IT-areas and in implementation are needed. Additionally, complete technical documentation of the knowledge base and the CDS system as well as guidelines (standard operation procedures = SOPs´) for producing their content and its distribution have to be part of the management plan to secure standardized procedures and avoid occurrence of mistakes.
Documented incidents include all kinds of subjects i.e. requests for further information, e-services, training, as well as reporting of major or minor errors. Minor or major errors include discussions of diverse opinions about recommendations or conclusions in the knowledge base, wishes for changes in classification levels or inclusion criteria. Technically it could be problems in the applications, or its documentation, or errors regarding the technical integration including design and functionality of user interfaces. All incidents are documented in the management system. Within the management and maintenance system the experiences we have made through real incidents and errors enable us to perform risk analysis on a regular basis. This helps us to foresee and judge possible incidents, which might occur through changes in the content, the graphical interface or the technical solution of our systems.

4.1 Management of errors using root cause analysis

The medical management of incidents or errors involves the processes of discovering the incidents, collecting documentation, performing event analysis and, if required, reporting of the error as a medical event - named Lex Maria - to the authorities in Sweden (Shemeikka et al., 2008). Root cause analysis (RCA) is a technique originally developed in psychology and systems engineering to identify "the basic and casual factors that underlie variation in performance". We use RCA to investigate errors after they are discovered. It involves critical incident reporting followed by self-managed investigation of the event involving all staff in charge. It should answer three basic questions:

- what happened?
- why did it happen?
- what could be done to prevent it from happening again?

The investigation team consists of colleagues from the department and includes everybody involved in the processes related to the incident.
In the US root cause analysis for investigations of medical errors became mandatory in 1997 for hospitals accredited by the US Joint Commission on Health Care Safety. Models used for RCA were further developed and adopted for by health care systems in other countries like Australia (Iedema et al., 2005). Though RCA used in the US and other countries only included medical procedures and not handling of errors introduced by decision support

systems, we have applied the technique for handling of our knowledge bases and decision support tools as well as the e-prescribing system. We have relied on experiences by team members from using the method in pharmaceutical companies to handle reports on adverse drug reactions, and from the health care system reporting events when harm or risk of harm for the patient has occurred during medical treatment.

Once an error of the CDS system is reported an initial rapid assessment is performed of the potential immediate and long term clinical consequences. If there is any risk for the safety of the patient or other patients due to the error, a decision is taken to shut down the e-services or keep it going whilst performing immediate changes. In these cases a report is sent to the national authorities in charge of monitoring and guarding patient safety during clinical care. The error is documented in detail often by requesting additional information from the reporter. The next step is to perform RCA to investigate the reason for the error (Iedema et al., 2005) and to suggests changes in for example the system, content, procedures or technical and user interfaces.

Incidents can be due to medical (e.g. wrong medical recommendation), pharmacological (e.g. wrong pharmacological mechanism thought to be cause for a DDI) or pharmaceutical (e.g. drugs with wrong formulations can be linked to a text) errors in the content of the knowledge base, or due to an unclear text, leading to misinterpretation. Errors in drug linkage can result in wrong alerts for a certain drug or missing alerts. The reason for the error could also be of technical nature. RCA may lead to organisational changes like education of the personal or policy changes, though they have a lower probability of reducing risk (Wu et al. 2008). It may also lead to changes of the content or processes for producing the knowledge bases or CDS systems or in redesign of the product or processes linked to knowledge base or CDS system, which are actions with a high probability of reducing risk (Wu et al., 2008). Procedural changes may lead to updates in the documentation or SOPs´ for the knowledge bases. Any changes in the device will be followed by extensive tests of the modified application before reintegration into the work environment. If the incident does not depend on one's own systems but on the EHR the CDS system is implemented in, the health record system owner has to solve the problem and document and proof changes. These changes are performed in close contact with vendors and producers of electronic health record systems.

Other incidents like inappropriate handling of the CDS system by the user may lead to a modification of the system and if necessary, user training must be performed. An example of a RCA is shown in figure 2 and 3. It describes an incident, where an ATC code was connected to a medical document by mistake. Drug name and ATC code was incorrectly send to the authors of the knowledge base. This led to the addition of the code to the document by the authors and a wrong linkage of drugs to the document. Processes for quality assurance of linkage of drugs to documents failed due to various reasons (technical equipment; frequent change of personal involved in the process). Consequently, users searching on the web for one of these drugs in one of our knowledge bases ended up in a document which had nothing to do with the drug searched for. Even if RCA has some benefits, including increased awareness of faulty processes and fixes to specific problems, more emphasis should be placed on drawing lessons across investigations rather than to approach each RCA independently. Most important, follow-up for implementation and outcome of each RCA and its actions should become a standard element of the process (Wu et al. 2008)

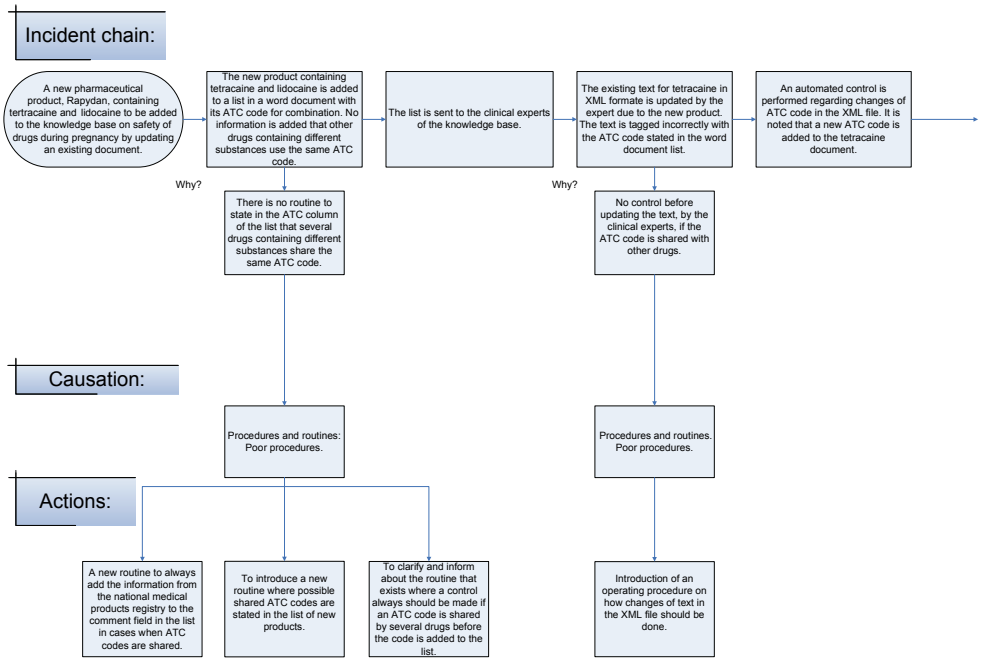

Fig. 2. RCA part 1: On the top of each RCA the incidents following each other and leading to the mistake are stated. Next line gives the reasoning for each incident. These are followed by the causes, grouping the reasons into categories. Each reason is followed by one or several actions suggested.

4.2 Analyses of risks

Risk analyses are also included into the management and maintenance system. Using the experiences made with existing systems we apply this knowledge to other parts of the knowledge base and the CDS system to foresee possible risks. On a regular base we perform preventive risk analysis to identify and classify different kinds of risks. The method has been adapted and is now used even during development of new CDS systems or knowledge bases in our setting in Stockholm. It improves our possibilities to evaluate the costs, risks, and improvements made with the implementation of new knowledge bases or decision support tools. For example when the graphical interface of the decision support system is changed risk analysis can be performed on possible effects for end user performance.

5. Providing medical knowledge bases at point of care

The knowledge base can either be provided:

- as a website solution
- integrated into EHR systems
- used in learning tools.

The integration into EHR systems facilitate the exchange of patient-specific data with the knowledge base, thereby creating patient-specific alerts or reminders during the process of

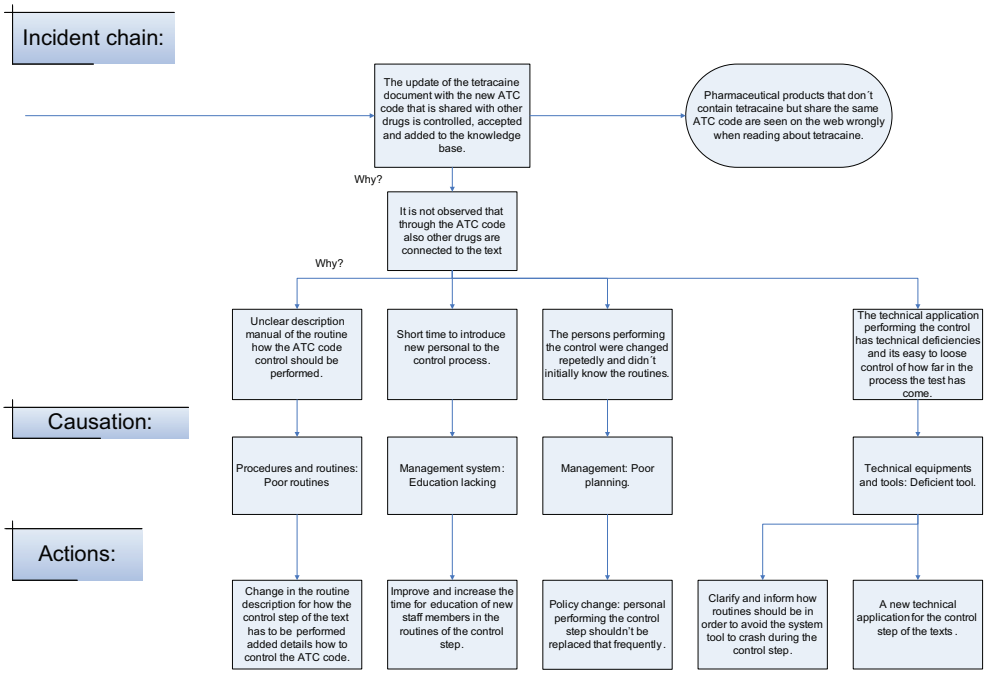

Fig. 3. RCA part 2: the second part of the incident chain explains, how the document with the wrong ATC code was added to the database without proper controls of the document and the effect it had on the linkage of drugs to the document. Actions suggested include changes in routines and policies, education and even changes in the technical tools used.

drug prescribing. The integration into an EHR system should be performed in collaboration between the providers of the knowledge base and the owners of the EHR systems. Contracts should specify the implementation of the database and how it is to be used and presented to the end user. The organizations implementing CDS systems must have detailed knowledge of the structure of the knowledge base and the architecture of the CDS system so that it is clear, how the systems interact (Kuperman et al.2006). Intensive testing of its integration following predefined protocols should be required to avoid unintended errors or mistakes due to lack of experiences and knowledge of the product. One must be sure that the knowledge base is behaving as intended (Kuperman et al. 2006).

The knowledge bases for drug-drug interactions, Sfinx, drugs & pregnancy and drugs & lactation produced by Stockholm County Council are provided free of charge through the county website on www.janusinfo.se. The website is aimed at health care personal. Physicians or nurses can search various knowledge bases by typing in the patient's medication and receive advice, whether specific drugs can be used during pregnancy or breast feeding or should be avoided (Norby et al., 2006). Drug-drug interactions can be searched for in Sfinx by either substance or drug names.

However, for optimal use knowledge bases should be implemented into a CDS system linked to an EHR, which will send patient specific data such as age, sex, height, weight, parameters for kidney function and the current drugs a patient is being prescribed to the

knowledge base. Through certain software algorithms an alert or reminder could then be triggered or not, providing patient specific warnings for e.g. drug-drug interactions, drugs & lactation or drugs & breast feeding.

The DDI database Sfinx is integrated into the CDS system Janus toolbar, providing patient specific automatic alerts during drug prescribing (Sjöborg et al., 2007). In figure 4 we describe an example of the decision support system provided through Janus toolbar integrated into one EHR system in Stockholm County Council. The patient's name, sex and age can be seen at the top of the screen. The prescribing module within the EHR contains the current drug list, consisting of 4 different drugs. Sending those data to the knowledge base for DDIs´, pregnancy and breast feeding the alert buttons will be illuminated, if there is any information to be retrieved (Eliasson et al., 2006, Sjöborg et al., 2007). It is of great importance that the EHR and the knowledge base interact in an optimal and correct way. For example in a survey among ambulatory care clinicians in Massachusetts it was observed, that the local CDS system often delivered alerts with out-of-date medications, which led to scepticism towards the system among users (Weingart et al. 2009).

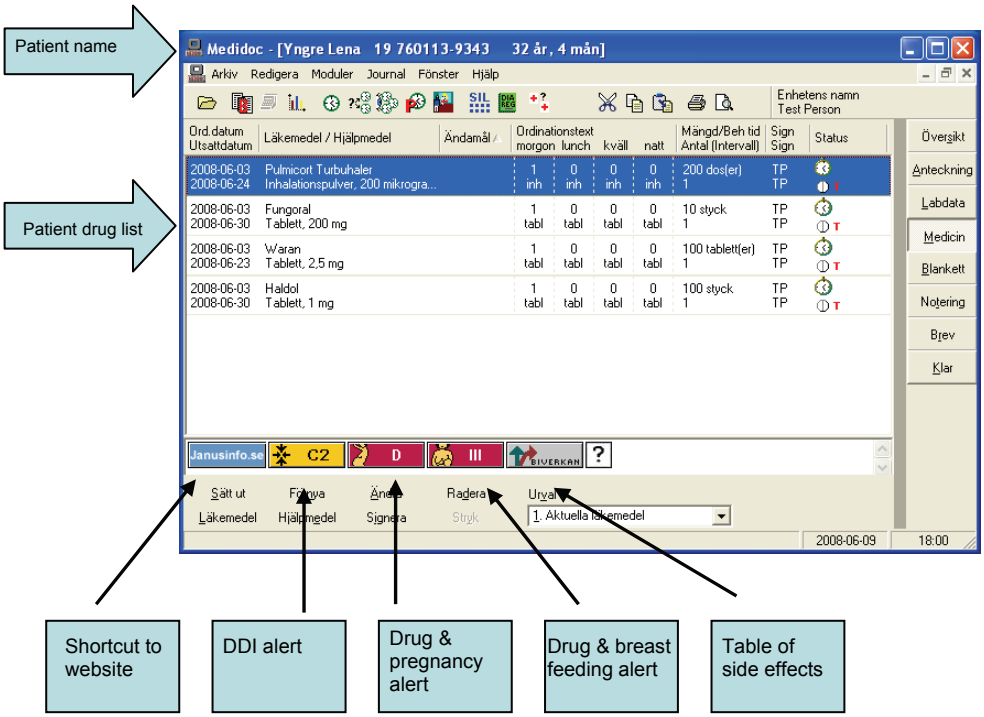

Fig. 4. Implementation of Janus toolbar into an EHR. Patient specific alerts are illuminated related to the patient's age, sex and current list of drugs. Several different knowledge bases are the basis of the decision support system. For every new order of medication a new drug list will be send to the knowledge base, evaluated and may lead to changes in the alerts.

To further improve user friendliness, accessibility, and speed of the CDS system the most important information of the knowledge base should be short and concise only one click away. This principle is implemented into the Janus toolbar with the most important message

being provided immediately, while for information about possible mechanisms, background studies for the statement and references users have to click further (Eliasson et al, 2007, Böttiger et al. 2009). We believe this quick access to pertinent information enhances the utilisation of the support tool. Even other surveys have shown that important information should be easily accessible and speed of use is a critical factor for the successful use of medical information systems (Dawes & Sampson, 2003; Bates et al., 2001).
Figure 5 shows the information provided by the knowledge base for drug-drug interactions, - Sfinx. Sfinx was developed by us together with partners from clinical pharmacology in Finland and in Sweden (Böttiger et al., 2009). Clicking on the yellow alert button, which is illuminated according to the patients' drug list, short and concise information about the medical consequence and recommendations can be seen immediately. Additional more educational information is available through clicking on the "read more" button.

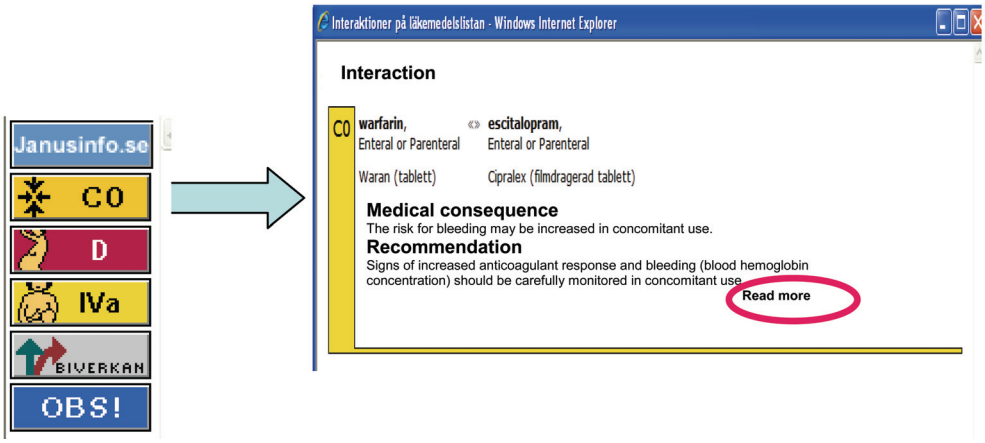

Fig. 5. Warning texts of the drug-drug interaction database, Sfinx. The yellow colour code is used for interactions classified as "C" which means, that the interaction is clinical relevant but the drug combination can be handled by for example dose adjustment (Böttiger et al., 2009). A short consequence text describes, what can be expected medically. This is followed by a recommendation part, stating how to handle the interaction.

The Janus toolbar alert system delivers non-intrusive reminders. This means that the illuminated warnings are optional not forcing the physician to take any action and not disturbing the workflow for the practitioners. Shah et al. (2006) showed that acceptance of drug alerts was improved by minimizing workflow disruptions, designating only high severity alerts to be interruptive to clinicians work. Disadvantages with intrusive alerts are disruption of physicians' workflow and increased tendency to ignore, work around or override these warnings. In a survey by Krall & Sittig (2001) physicians indicated that intrusive or active alerts might be more useful but less easy to use. It was also stated that another important factor for increased compliance and effectiveness of a CDS system is the interface design in relation to the workflow process. Alerts showing up too early or too late in the workflow process might lead to decreased compliance and reliability of the users in the system or even worse, lead to errors and harm for the patient (Krall & Sittig, 2001; Khajouei & Jaspers, 2008).

Studies on the effectiveness of non-intrusive versus intrusive alerts are contradictory. One study (Palen et al., 2006) showed no significant difference between control and intervention groups in the overall rate of compliance to ordering certain laboratory monitoring values when prescribing certain medications. They used non-intrusive alerts in their intervention group. Another study (Tamblyn et al., 2008) compared the effectiveness of on-demand versus computer triggered decision supports regarding dosing information, drug-drug, drug-age, -allergy and -disease interactions. They found that physicians in the computer-triggered group saw more alerts, and made more changes. However, they also ignored more of the alerts shown (87.8%). The on-demand group requested less than 1 % of all alerts provided by the CDS, but ignored only 24.4%. There was no difference in the overall result of existing prescribing problems after intervention between both groups.

We believe that CDS systems need to keep a balance between producing too many alerts and reminders and delivering the message in a straight-forward manner. Too many alerts are likely to be overridden and cause "alert-fatigue", which leads to underestimation of the CDS systems as useful tools in the daily practice (Shah et al. 2006). To avoid too many uncritical alerts classification of the content of knowledge bases regarding clinical significance is of great importance. Numerous studies have shown that compliance to CDS systems and user satisfaction is related to the balance between useful alerting and overalerting (Paterno et al. 2009; Shah et al. 2006). Therefore, we have implemented classification systems in all our knowledge bases. Classification is performed regarding the clinical significance of the content and the level of documentation for the alerts. Colour codes are provided additionally to knowledge base specific classifications (letter or number codes) thereby supporting the prescriber, to identify the urgency of the information retrieved from the knowledge base. The red colour signalises very important messages (e.g. for drug- drug interactions it means: avoid combination) (Böttiger et al., 2009). A yellow colour code indicates information, which should be retrieved and could influence the prescribing (e.g. dose adjustment for a DDI warning). White colour means that information of more theoretical value is available but it has no clinical relevance which has to be considered during prescribing.

Isaac and colleagues (2009) recently showed, that physician's tendency to override alerts was less pronounced for the alerts with high-severity / high risk compared to medium or low severity alerts. Tiered alerting for severity for drug-drug interaction information, like in Sfinx, is one possibility to increase compliance rates for interaction warnings. That was confirmed in a study by Paterno et al (2009), where compliance in the tiered DDI alert group was significantly higher than in the non-tiered group (29% vs. 10%). Additionally, the most severe alerts were accepted to 100% in the tiered group while only 34% in the non-tiered group.

Commercially available DDI databases tend to put more emphasis on covering the whole medical domain rather than differentiating between clinical important and non-important messages. So there is a need for increased specificity to reduce extraneous workload and reduce "alert-fatigue". Luna et al. (2007) described the need to "clean" the content of their commercially purchased knowledge base according to the clinical significance of drug-drug interactions. By creating a classification for DDIs in the system they customized the knowledge base for their organisation.

Spina et al. (2005) investigating the usefulness of different types of alerts in a CDS system in a group of primary care physicians stated that more tailored systems are needed, where DDI

warnings on topical drugs should be avoided, when not relevant. Therefore drug formulations should be taken into account in a DDI knowledge base (Böttiger et al., 2009). Also interaction warnings should be suppressed, when drug monitoring is already in place.
Another option can be to suppress warnings on reorders for patients' medications as shown by Abookire et al. (2000). They found that overriding rates for drug allergy warnings increased from 48% to 83% for drugs being reordered for a single patient over a certain time period, suggesting that physicians tend to ignore warnings for the patients permanent medications, since they have handled and considered these alerts already once before. Consequently, tailoring systems focussing more on new ordered medications rather than on drug renewals would be another possibility to increase usefulness of CDS systems.
However, it will not be possible to develop knowledge bases and CDS systems fitting all needs. Personal adjustments seem to be necessary since physicians´ needs and their varying level of knowledge result in different perceptions of any CDS system.

6. Implementation of CDS systems

Healthcare agencies spend significant amounts of money on the development of clinical information systems, though often failing with successful implementation. Designing an effective approach for increasing end-user acceptance and subsequent use of IT- systems is a fundamental challenge. Successful implementation needs comprehensive approaches tailored to clinical settings and target groups taking individual, health care team, and organizational variations into account.
Wears & Berg (2005) described how implementation of any new technology into a clinical workplace triggers both changes in the workplace and in the use of technology, which itself triggers development of the technology (Figure 6). A workplace is described as a field where social behaviour meets technology and both influence each other.
It is also of great importance to consider the different interests in and views on a CDS system from users, administrators and vendors. Ash and colleagues (2003) described the complex interplay of physicians, administrators and IT- staff when implementing a computerized physician order entry (CPOE) system into a hospital setting. They looked at three important parts, which are always influenced by an implementation: the technical, organizational and personal part. Physicians thought the CPOE as technically cumbersome and time-consuming, forcing them to think like computers and click through various screens. They also felt that the CPOE was "forced" on them by hospital administration not taking into account the work situation which they believed was already overburdened. However, on a personal note they felt a need to master the system. The hospital administration thought the system technically to be cost-effective and delivering great statistics. People in the organisation felt pride in being at the forefront of technology. Personally they felt pride in having overcome the clinicians' resistance. The information technology staff perspective on the technical system was the urge and tendency to make the system even more useful, train the users and fulfil and develop the system according to the users wishes. Organisationally they tried to identify the right staff members for the implementation to reach everybody in the hospital. Personally they described enthusiasm for the benefits of the system, but at the same time they felt implementation as difficult and painful but useful in the long run. This study reflects the difficulties of a successful implementation taking into account the various expectations of different "interest groups".

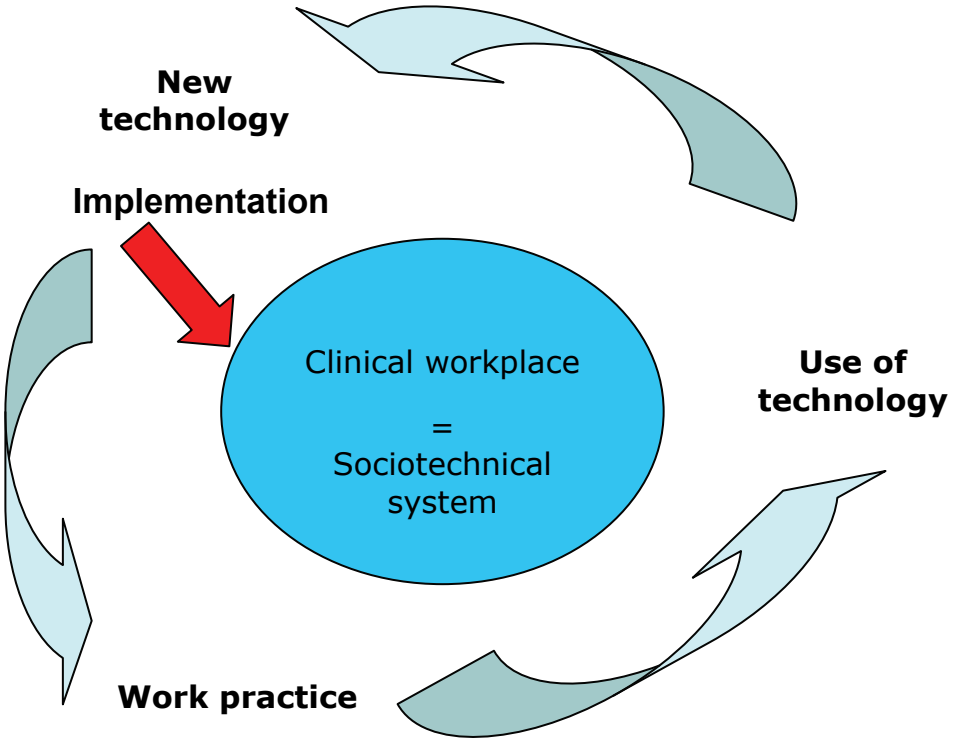

Fig. 6. Influences of technology in a clinical workplace environment. This figure shows that any new technology integrated into a clinical workplace will change work practice, which then will result in use of the technology different as planned from the beginning. This will trigger the development and change of the technical tool implemented (Wears & Berg, 2005)

Ash and colleagues (2003) derived four categories of principles for a successful implementation:

- computer technology
- personal principles
- organizational principles
- environmental issues.

These principles reflect the need to consider multiple issues during implementation and they highlight the relationship between technology, clinical information, people and organizational issues. Callen et al. (2008) described a Contextual Implementation Model (CIM), which is based on data from sites, where physicians use an existing CPOE system. The model acknowledges the complexity of the clinical environment and the requirements of the users. They concluded that implementation should start with a thorough analysis of the context where the CDS system will be implemented into. This analysis should include all three levels namely organisational, departmental and individual. Work practices have to be studied on an individual and department level. Computer literacy and keyboard skills have to be investigated among potential users and work requirements between departments have to be clarified to take the differences between organizations into account. Requirements of

the CDS systems on individual and workplace level have to be investigated and differences can be included in the implementation plan so that during implementation one can accommodate the different needs. Targeted training programs can eliminate the problem with different keyboard skills and computer literacy. Analysis of organizational and team cultures will assist with modifying the cultures to increase receptiveness. They concluded that using the CIM model for implementation will facilitate the usage and benefit of any CDS system.

In a systematic review (Gruber et al., 2009), it was stated, that no single implementation strategy has proved to be completely effective. The authors defined a theoretical model for a computerised decision support system including five major steps in the life cycle of any CDS system (= Expanded Systems Life Cycle = ESLC):

- planning
- analysis
- design
- implementation
- maintenance

They identified risk zones for each phase and corresponding risk factors. Their analysis revealed that the highest number of failure and success were in the implementation zone focusing on preimplementation and "go-live" of the system. They also identified that training and education, attention to training, policy, process changes, and training to clinical content are key factors influencing the success or failure of a CDS system.

However, more research is needed to avoid costly errors in implementation. Studies focussing on barriers and incentives for changes should be performed focussing on various levels (namely the innovation itself, the professional, the patient, the social context, the organisational context, and the economic and political context) as suggested (Grol & Wensing, 2004).

7. Evaluation

Rigorously designed evaluations and research on the effectiveness of decision support systems are needed to assess their value in clinical practice and to identify areas for improvement in design and implementation. Kirkpatrick described four levels of evaluation in which the complexity of the behavioural change increases as evaluation strategies ascend to each higher level (Kirkpatrick, 1967). The four levels measure

- reaction to information
- learning
- behaviour
- results

Studies assessing effects of CDS systems on patient outcome are urgently needed. They are difficult to perform due to the length of time needed for the evaluation, the lack of reliable objective measures, and the number of potential confounding factors.

The selection of methodology to investigate an implementation of decision support systems is no different from choosing methods in any other type of research. A variety of study designs can be used to evaluate if decision support systems influence prescribing behaviour and patient outcomes. These studies include quasi-experimental designs (uncontrolled or controlled before-and-after studies and interrupted time series) and randomized controlled trials (RCTs) (Grimshaw et al., 2000). The RCT has the highest degree of evidence as non-

randomized designs might introduce selection bias by including in the intervention group doctors or clinics that favour the particular intervention (Grimshaw et al., 2000, Stephenson & Imrie, 1998). The control group design considers other factors influencing the prescribing pattern such as seasonal variations in disease patterns, the introduction of new drugs and changes in treatment policies, the marketing activities of pharmaceutical companies and changes in regulatory policies (Grimshaw et al., 2000). However, due to ethical, practical and methodological reasons, they are seldom possible to apply when evaluating the impact of decision support systems. Therefore, well-designed quasi-experimental studies may be the method of choice.

Alternative research strategies include qualitative research methods to provide a deeper understanding of the subjective aspects of the interaction between healthcare professionals, patients and the electronic tools. The common feature of qualitative studies is that they do not primarily seek to provide quantified answers to research questions. The goal of qualitative research is the development of concepts which can help us to understand social phenomena in natural rather than experimental settings, giving due emphasis to the meanings, experiences, and views of all the participants (Pope & Mays, 1995). Examples of qualitative methods include in-depth interviews, focus group discussions, observations and various consensus methods.

Development and evaluation of a complex system, such as a CDS system and implementing it into the health care organisation require a multiple research approach i.e. method triangulation. The evaluation of the pilot study of the Janus decision support system had primarily a qualitative approach with focus on user satisfaction. Semi-structured qualitative interviews were performed with all users before, during and after the pilot study. By concentrating the evaluation on user satisfaction we gained data both on the technical failures as well as the physicians' attitudes to medical content and usefulness of the system and acceptance in clinical work. The evaluation and implementation were carried out by a multidisciplinary team within a small scale user clinic in order to be able to easily detect technical and practical obstacles (i.e. integration bugs) and even more serious potential quality problems of the pharmacological sources (i.e. pregnancy and breast-feeding alerts in the Swedish PDR) (Eliasson et al., 2006). Data and support were handled in a rapid way to be able to give direct feed-back to the user. Our experiences confirm that evaluations of small-scale pilot studies for proof of concept are important tools in the design of an optimal intervention that improves health care quality so that resources are used in an optimal way as stated by Harvey & Wensing (2003).

The results of the pilot study even helped us to identify factors, which have major impact on usefulness of the CDS system and user satisfaction and led to a two-part theoretical model for implementation and evaluation (Eliasson et al, 2006). This model considers both system-dependent and system-independent factors (Figure 7). The first part includes system-dependent factors, such as medical content, user friendliness and user support. The second system-independent part includes personal attitudes of the prescribers´ towards computer use as well as the attitude of the organisation towards implementing a CDS system.

Stockholm County Council conducts regular evaluations after pilot studies which we see as a cornerstone for development of successful electronic tools. The effectiveness of Janus toolbar and the frequency of its use, and users' characteristics are measured by questionnaires. Simultaneously, interviews are carried out to explore doctors' and other prescribers' experiences and perceptions of Janus toolbar. Those evaluations were used to

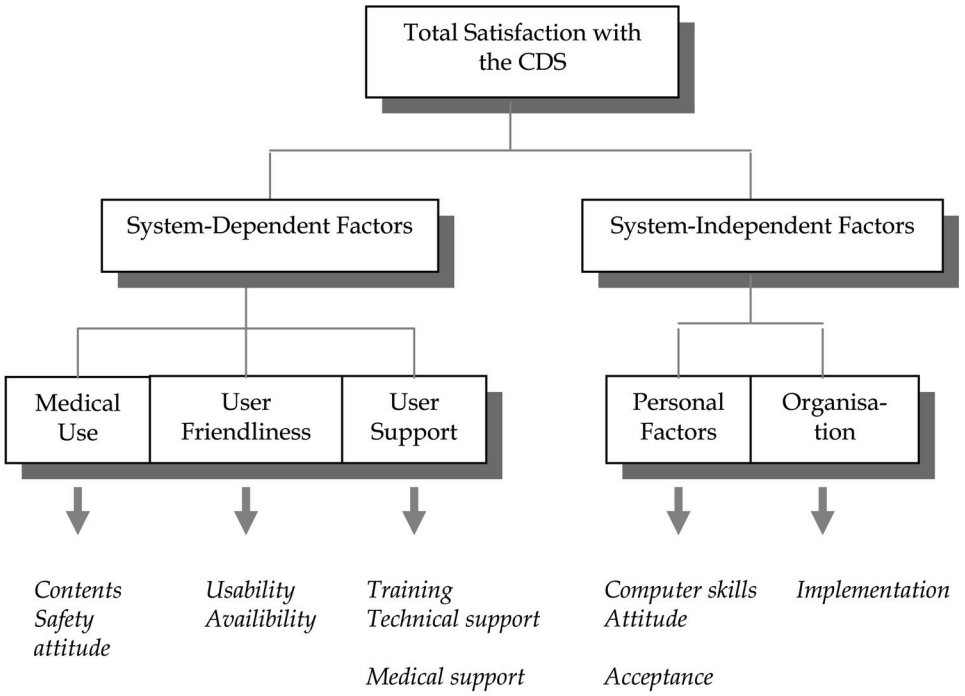

Fig. 7. A two-part theoretical model for evaluation of the CDS system taking system dependent (e.g. medical content, usability, support) and system independent factors (e.g. personal attitudes, organizational aspects) into account.

decide about the development of a new knowledge base for drug-drug interactions Sfinx, which is described above. The regular follow-ups over years showed results similar to the actual literature especially in terms of satisfaction, acceptance and intention to use (Krash, 2004, Ahearn & Kerr, 2003; Magnus et al., 2002). Physicians generally overrode the interaction warnings and expressed irritation on the irrelevant alerts, which often led to ignore them. Furthermore, physicians were dissatisfied with the usability, information and training of how to use the tool, and complained about technical barriers. Although physicians did not seem to use the tool in every day practice they underlined the clinical value and needs of it, i.e. being reminded of unknown /known drug-drug interactions and getting recommendations about how to avoid them. Prescribers were aware of the fact that the decision support system contributes to safer and more effective treatment of the patients. They were clear about their needs for the system and had good intentions to use it. However, even after thorough analysis of physicians' needs, we could observe that the system was not fully used after its implementation.

Some contributing factors are changes in expectations and intentions of the users from the initial discussion, to later implementation and the actual use at the work place when the database is integrated into daily work flow. Another influencing factor is that CDS systems integrated into daily practice suddenly offer more complete knowledge about patients' medications for the physicians, demanding new decisions and work tasks that GPs were not aware of. Physicians have different views on their responsibilities for diagnosis, drug

treatment and follow-up of a patient resulting in different actions and variations of handling the information provided. Recently we have highlighted that there is a need for common and understandable rules on prescribing physicians´ responsibility in handling the total patients' drug lists. These lists are made available to all prescribers through a newly implemented IT-tool (Rahmner et al., 2009). We can conclude that work flow, working environment and processes influence physicians' behaviour to a greater extent than expected.
Consequently, we still do not know how to design optimal CDS systems which affect and influence physicians' behaviour in drug prescribing. The challenge for the future development and implementation of a CDS system into health care is to find a method to achieve and maintain expected changes in prescribing behaviour.

8. Summary

Knowledge bases provide the contents for any clinical decision support system. In this review we characterize the life cycle of a knowledge database to be used in drug prescribing. The various phases and the important issues in each phase are summarized in table 1. Knowledge bases need to fulfil and be tailored to the needs of the users. The focus of the content should be on practical use in a clinical environment, rather than covering the whole scientific area of a medical speciality. Standards are needed to be able to use knowledge bases across different electronic health care systems and countries, since clinical expertise is often the bottle neck for any development.
Integration of knowledge bases into CDS systems implemented into electronic health record system optimises their effectiveness by delivering patient specific reminders and alerts. The linkage between knowledge bases and CDS systems needs to be quality assured. Knowledge bases and CDS systems need to be surveyed through a management and administration system handling incidents and errors due to system or its content. Though many studies have shown the positive influence of CDS systems on physicians' performance, there is still lack of understanding, when CDS systems improve performance. Outcome studies on patient care are lacking. Implementation of CDS systems has to be accompanied by staff education and training to assure acceptance and effectiveness even throughout the maintenance phase. More studies are needed with focus on actual improvement of patient safety and care instead of investigating physicians change in prescribing drugs.
With that in mind knowledge bases and CDS systems will prove to be helpful tools in the daily decision making process of any busy clinician when instituting and evaluating the drug therapy of a patient.

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Life cycle phase of a knowledge base	Important issues for each life cycle phase
Development	Thorough analysis of physicians needs Standardisation of data structure, implementation of classification system, optimal linkage to drug registries
Quality assurance	Control of quality in key fields for linkage Introduction of semi-automated and manual processes for data auditing
Medical management & maintenance	Well documented and standardized procedures for knowledge base maintenance Root Cause Analysis for analysis of mistakes and follow ups of the planned actions
Providing knowledge bases at point of care	Integration into electronic health records for patient specific alerts Tailored systems with fast data access to avoid overalerting and increase acceptance
Implementation	Consider interests of users, organizations and vendors within the implementation plan Education, personal training, attention to process changes are key factors
Evaluation	Evaluation of small scale projects as important tools in the design of optimal interventions Regular evaluations necessary to secure optimal use of knowledge base or CDS system

Table 1. Summary of important messages for each step in the life cycle of a knowledge base.

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Folke Sjöqvist, konsult inom läkemedelskontroll, professor emeritus i klinisk farmakologi, Karolinska institutet, Huddinge universitetssjukhus, t o m 1999 ordförande i LÄKSAK (Läkemedelssakkunniga i Stockholms läns landsting)

Skärpta krav på ojävig hantering vid val av läkemedel

Ledamöter i Stockholms läkemedelskommittéer lämnar årlig jävsdeklaration

SAMMANFATTAT

Läkemedelskommittéerna har i många landsting ett avgörande inflytande på bland annat upphandlingen av läkemedel. Kommittéerna måste därför agera på ett ojävigt sätt gentemot läkemedelsindustrin.

Sedan 1995 uppmanas medlemmar i Stockholms läkemedelskommittéer att avlämna årlig jävsdeklaration. Deklarationen och bedömningen av denna överensstämmer med vad som tillämpas inom andra läkemedelsmyndigheter, till exempel Läkemedelsverket.

LÄKSAK (Läkemedelssakkunniga i Stockholms läns landsting) anser att jäv föreligger då man har en konsultrelation till viss firma, andra personligt arvoderade uppdrag samt sådan verksamhet som kan leda till preparatlojalitet.

LÄKSAK skiljer mellan privatekonomiska relationer och forskningssamarbete, där den enskilde läkaren representerar sin institution/klinik i ett reglerat avtal med sponsorn.

I framtiden blir det nödvändigt för läkemedelsexperter att öppet redovisa för vem (vilka) man arbetar och undvika intressekonflikter, som kan äventyra sjukvårdens trovärdighet.

»Det börjar den första dagen i läkarutbildningen och varar fram till pensioneringen och är den enda pålitliga förmånen som läkare kan räkna med från vaggan till graven«. Detta konstaterar Lancet i en ledare om läkemedelsföretagens inflytande på medicinsk utbildning i USA [1]. Ledaren uttrycker stor oro för att så mycket av den amerikanska vidareutbildningen av läkare filtreras av industrin. I en översiktsartikel i JAMA förra året analyseras samspelet mellan läkare och den farmaceutiska industrin under titeln »Is a gift ever just a gift«. Här tas även de alldagliga kontakterna mellan industrins marknadsförare och läkarna upp, och det understryks att dessa interaktioner ofta leder till ändrade förskrivningsvanor och framstötar om att lägga till just den firmans preparat till läkemedelslistan [2]. En tung artikel i detta avseende publicerades redan 1994 i JAMA av Chren och Landefelt [3], som i en kontrollerad studie visade att läkare som krävde att vissa läkemedel skulle adderas till sjukvårdsinrättningens läkemedelslista hade haft mångdubbelt fler kontakter med tillverkaren av just dessa preparat än en kontrollgrupp (oddskvoter för olika slags kontakter såsom information och arvoden låg mellan 13 och 19). Intressant nog väcktes dessa förslag ofta oberoende av preparatets terapeutiska värde. Det torde vara ovedersägligt att de möten av olika slag som arrangeras mellan industrin och läkarkåren uppnår syftet att påverka läkemedelsförskrivningen. Det finns föga anledning att tro att situationen skulle vara väsentligt annorlunda (bättre) i Sverige.

Mot denna bakgrund är det angeläget att försöka undvika intressekonflikter som skulle kunna påverka det läkemedelsval som görs inom läkemedelskommittéerna. Från och med 1995 har LÄKSAK (Läkemedelssakkunniga i Stockholms läns landsting) genom sina expertgrupper spelat en avgörande roll vid upphandlingen av läkemedel för slutenvård, senare också vid ställningstagande till olika rabattavtal för läkemedel i öppenvård. Härigenom påverkar medicinsk expertis valet av läkemedelssortiment inom ett landsting på ett mer kraftfullt sätt än någonsin tidigare. Samtidigt har kraven skärpts på en ojävig hantering av läkemedelsvalet, inte minst med tanke på dess stora ekonomiska betydelse. Läkemedelsreformen innebar att Läkemedelskommittén fick ställning som myndighet och det tedde sig därför naturligt att man i likhet med andra myndigheter inom läkemedelsområdet (Läkemedelsverket, EU) började hantera jävsfrågorna på ett konkret och, som det heter, transparent sätt.

LÄKSAKs jävsdeklaration

Hösten 1995 ombads expertgrupperna för läkemedelsupphandling och medlemmarna i de fem läkemedelskommittéerna samt LÄKSAK att rapportera eventuellt jäv till sina respektive ordförande (beträffande definitionen av jäv se förvaltningslagen §11–12). LÄKSAK kom fram till att jäv föreligger då man har en konsultrelation till en viss firma, andra

Fakta 1

Offentlig jävsdeklaration för LÄKSAK och läkemedelskommittéer i Stockholm

Funktion inom landstingets läkemedelsverksamhet:

1. Redovisa Dina konsultuppdrag till läkemedelsindustrin.
a. Ev anställningar som konsult under de senaste två åren (arvodering).
b. Personliga ersättningar för läkemedelsprövningar i form av arvoden, resor m m.
c. Finansiella intressen i läkemedelsfirmor i form av aktieposter etc (aktiefonder undantagna).
d. Övrig information av intresse.

2. Redovisa Dina konsultuppdrag till Apoteket AB.

3. Redovisa forsknings- och utvecklingsprojekt tillsammans med Apoteket AB eller läkemedelsindustrin, där forskningsanslag till klinik/institution utgår (Bilaga kan lämnas).

Jag deklarerar härmed att de enda intressen som jag har i den farmaceutiska industrin eller Apoteket AB är de som deklarerats ovan samt förbinder mig att informera landstinget om ytterligare intressekonflikter skulle uppkomma.

Stockholm den Signatur

personligt arvoderade uppdrag samt sådan verksamhet som kan leda till »preparatlojalitet«.

Efter ingående debatt beslutade LÄKSAK 1996 att begära in offentliga jävsdeklarationer från medlemmarna i läkemedelskommittéorganisationen enligt ett formulär (Fakta 1) som har likheter med det som användes inom EU. Man skiljer i båda fallen mellan rent privatekonomiska relationer och forskningssamarbete, där den enskilde läkaren representerar sin institution/klinik i ett reglerat avtal med sponsorn.

Det ansågs vara påkallat att även få en redovisning av ledamöternas relationer till dåvarande Apoteksbolaget, numera Apoteket AB. Detta av två skäl. Det ena är att Apoteket AB utgör en samarbetspartner med landstingen, som till stora belopp upphandlar olika tjänster från bolaget, tjänster vars inriktning och volym inte sällan är svårgenomlysta av landstingens administratörer och kan behöva en bedömning inom läkemedelskommittén. Det andra är att den enskilde läkaren i samarbete med Apoteket AB (exempelvis inom läkemedelsinformation) kan binda upp sig i terapirekommendationer, som kommer nära preparatlojalitet.

När beslutet togs om en skriftlig redovisning av jävsfrågorna menade olyckskorparna att antalet för kommittéarbete tillgängliga läkare skulle reduceras avsevärt samt att de mest kompetenta skulle eliminera sig själva. Så blev inte alls fallet och bara ett fåtal föll ifrån, i allmänhet på grund av engagemang, direkt eller indirekt, i marknadsföringen av enskilt preparat eller preparatgrupp.

Vi tog tidigt ställning till att utvecklingsarbete i form av kliniska prövningar på intet sätt diskvalificerar från arbete inom läkemedelskommittéer, utan i många fall kan ses som en merit för den viktigaste uppgiften inom kommittén, det vill säga läkemedelsvärdering. Det är givetvis en klar skillnad i meritvärde mellan explorativa, innovativa samt randomiserade studier och rent kommersiella prövningar, till exempel vissa fas IV-studier, vars huvudsyfte kan vara att öka försäljningen av ett visst preparat. I samband med denna diskussion framkom att man inom vissa kretsar misstänker att läkemedelsprövningar ofta är ett förtäckt extraknäck snarare än seriös behandlingsforskning. Grundregeln vid Stockholms undervisningssjukhus är emellertid att inga personliga arvoden bör utgå utan att hela avtalet skrivs mellan landstinget/Karolinska institutet och respektive läkemedelsföretag. Prövningen blir således ett tjänsteuppdrag för huvudmannen, och bör därför inte diskvalificera från andra tjänsteuppdrag för samma huvudman. Majoriteten inom LÄKSAK förespråkar att all arvodering för arbetsinsatser i samband med klinisk prövning sker genom klinikchefen och inte direkt från enskild firma. Delikatessjäv kan givetvis uppkomma även vid »rena« avtal i form av ogrundad tilltro till det preparat som man själv har prövat.

Bedömning av jävsdeklarationer

Bedömning av potentiellt jäv har skett pragmatiskt, oftast i samråd mellan den enskilde kollegan och dennes ordförande, ibland i samråd med ansvarig administratör eller landstingsjurister. I stort har LÄKSAK tillämpat Läkemedelsverkets riktlinjer (1997-01-28) avseende industriuppdrag för vetenskapliga råd. Där skiljer man mellan enskilda ärenden och allmänna principer.

Om enskilt ärende sägs att: »Vetenskapligt råd är förhindrat att delta i nämndens handläggning av ett enskilt ärende rörande visst läkemedel beträffande vilket det vetenskapliga rådet i något avseende biträtt företaget under läkemedlets utveckling med råd och dåd. Samma gäller om rådet i övrigt kan anses ha en sådan relation till det i ärendet aktuella företaget att dennes objektivitet kan ifrågasättas (s k delikatessjäv)«.

Beträffande allmänna principer sägs: »För att den allmänna objektivitetsprincipen i regeringsformen skall tillgodoses bör dessutom ett vetenskapligt råd inte ha en alltför nära knytning till ett enskilt läkemedelsföretag. En sådan fastare knytning skulle kunna leda till att rådets objektivitet skulle kunna ifrågasättas.

Följande riktlinjer skall i allmänhet gälla:

Tillfälliga ad hoc-betonade industriuppdrag mot skälig ersättning bör i allmänhet anses godtagbart (se dock ovan om hinder mot att delta i enskilda ärenden).

En fastare knytning av mer permanent karaktär till ett visst företag gränsande till ett rent anställningsförhållande kan däremot inte anses acceptabelt från objektivitetssynpunkt. Det bör i detta sammanhang även framhållas att ekonomiska intressen i form av större aktieinnehav och dyl i läkemedelsföretag också torde vara att anse som en sådan fastare knytning.«

Hittills har få läkemedelskommittéer publicerat sin syn på jävsfrågorna. Ett undantag är Jämtland, vars policy i stort harmoniserar med Stockholms [4].

Ökande självrannsakan på väg

Det faktum att LÄKSAK lyft upp frågorna om jäv till ytan har stimulerat diskussionen om våra relationer till industrin. I september anordnade således LÄKSAK och södra läkemedelskommittén ett livligt symposium om ämnet med deltagande av Stockholms HIV-läkare [P Hedman, Stockholm, pers medd, 1999]. Flera yngre läkare framhöll vikten av att öppet diskutera kårens förhållningssätt till industrin, en fråga som sällan tas upp under läkarutbildningens olika faser.

De stora framgångarna inom läkemedelsbehandlingen av HIV/aids är resultatet av ett samarbete mellan läkemedelsindustrin och sjukvården, någonting som måste uppmuntras. Men samarbetet måste bedrivas på bådas villkor och med bibehållen integritet hos parterna samt på ett sådant sätt att lä-

karen känner sig komfortabel. Dennes viktigaste lojalitet är gentemot patienten eller patientgruppen. Enligt Helsingforsdeklarationen skall den främsta (enda!) anledningen till kliniska prövningar vara möjligheten att förbättra patientbehandlingen.

Våra relationer till läkemedelsindustrin är och kommer att förbli föremål för debatt såväl inom den egna professionen som i medierna. En ökande självrannsakan synes vara på väg. Två ledare i New England Journal of Medicine av Marcia Angell under sommaren 2000 analyserar problemen [5, 6]. Hon vill värna om forskningssamarbetet, men ställer sig kritisk till att professionen direkt eller indirekt medverkar i marknadsföringen av enskilda läkemedel. För medlemmar i läkemedelskommittéer är detta givetvis direkt olämpligt. Det hör till saken att gränsen mellan forskning och marknadsföring ibland kan vara flytande.

New England Journal of Medicine har profilerat sig som mycket sträng, näst intill fundamentalistisk, i kravet på att författarna skall redovisa sina industrikontakter och i något fall i efterskott tagit avstånd från en publicerad läkemedelskommentar, när det visade sig att författaren haft industrikontakter som bedömdes som olämpliga. Allt fler tidskrifter tillämpar numera liknande principer och vetenskapliga artiklar avslutas allt oftare med en deklaration av aktuella intressekonflikter. Ett ökande problem är »nonwriting author – nonauthor writing«-syndromet. Detta innebär att läkemedelsfirmor hyr in professionella skribenter, som sammanställer prövningsdata och serverar manus till prövarna, som sedan sätter sina namn på arbetet. Ibland förstärker man författarskaran med en känd »opinion maker« för att få kommersiellt genomslag av publikationen. I klartext rör det sig således om akademiskt fusk. Förslag har därför väckts att design av kliniska prövningar, implementering, dataanalys och publicering skall ske via oberoende akademiska centrum och inte via tillverkare eller prövningsföretag [7].

Utvecklingen innebär att man i framtiden som klinisk läkemedelsexpert får välja sida och öppet redovisa för vem man arbetar. Det blir omöjligt att sitta på flera stolar samtidigt utan att äventyra sin egen och sjukvårdens trovärdighet.

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RESEARCH ARTICLE Open Access

Forecasting drug utilization and expenditure in a metropolitan health region

Björn Wettermark*[1,2], Marie E Persson[1], Nils Wilking[3], Mats Kalin[1,4], Seher Korkmaz[1,5], Paul Hjemdahl[5], Brian Godman[2,6], Max Petzold[7], Lars L Gustafsson[1,2] for the Regional Drug Expert Consortium in Stockholm County Council

Abstract

Background: New pharmacological therapies are challenging the healthcare systems, and there is an increasing need to assess their therapeutic value in relation to existing alternatives as well as their potential budget impact. Consequently, new models to introduce drugs in healthcare are urgently needed. In the metropolitan health region of Stockholm, Sweden, a model has been developed including early warning (horizon scanning), forecasting of drug utilization and expenditure, critical drug evaluation as well as structured programs for the introduction and follow-up of new drugs. The aim of this paper is to present the forecasting model and the predicted growth in all therapeutic areas in 2010 and 2011.

Methods: Linear regression analysis was applied to aggregate sales data on hospital sales and dispensed drugs in ambulatory care, including both reimbursed expenditure and patient co-payment. The linear regression was applied on each pharmacological group based on four observations 2006-2009, and the crude predictions estimated for the coming two years 2010-2011. The crude predictions were then adjusted for factors likely to increase or decrease future utilization and expenditure, such as patent expiries, new drugs to be launched or new guidelines from national bodies or the regional Drug and Therapeutics Committee. The assessment included a close collaboration with clinical, clinical pharmacological and pharmaceutical experts from the regional Drug and Therapeutics Committee.

Results: The annual increase in total expenditure for prescription and hospital drugs was predicted to be 2.0% in 2010 and 4.0% in 2011. Expenditures will increase in most therapeutic areas, but most predominantly for antineoplastic and immune modulating agents as well as drugs for the nervous system, infectious diseases, and blood and blood-forming organs.

Conclusions: The utilisation and expenditure of drugs is difficult to forecast due to uncertainties about the rate of adoption of new medicines and various ongoing healthcare reforms and activities to improve the quality and efficiency of prescribing. Nevertheless, we believe our model will be valuable as an early warning system to start developing guidance for new drugs including systems to monitor their effectiveness, safety and cost-effectiveness in clinical practice.

Background

During the last decades of the 20th century, several new and effective drugs have gained widespread use in the treatment of major diseases such as cardiovascular diseases, depression and diabetes mellitus [1]. These drugs markedly decreased mortality, shortened hospital stay and improved the quality of life for large groups of patients. In recent years, science has witnessed breakthroughs in molecular genetics, proteomics and combinational chemistry [2-4]. These advances have triggered the development of biotechnological methods for the design and production of drugs to be used in the diagnosis or therapy of chronic diseases. Consequently many new "biological" drugs have been developed and presently account for 15% of all New Chemical Entities (NCE) or Biological Entities registered annually in US [5]. These

* Correspondence: bjorn.wettermark@sll.se
[1] Department of Drug Management and Informatics, Stockholm County Council, Stockholm Sweden
Full list of author information is available at the end of the article

drugs are usually considerably more expensive than traditional drugs.

The increasing expenditures for new drugs place considerable pressure on healthcare systems in their efforts to continue to provide comprehensive care [6,7]. As a result, new models for introduction of expensive medicines are urgently needed to avoid prohibitive increases in taxes or health insurance premiums. Such models should include early warning systems (horizon scanning), forecasting of drug utilization and expenditure, critical drug evaluation to help define which patient groups will benefit most from the new medicine, and follow-up to ascertain whether the new drugs are cost-effective in practice.

In the metropolitan health care region of Stockholm, Sweden, a new model to introduce new drugs in healthcare was established in 2007 [8]. The concept is operated through the Regional Drug and Therapeutics Committee (DTC) in Stockholm (LÄKSAK) and includes:

- Early detection (horizon scanning) of drugs to be launched during the coming years
- Forecasting of drug utilization and expenditure
- Critical drug evaluation
- Guidelines for the introduction of medicines, preferably including protocols to assess their value in practice (effect, safety and cost-effectiveness)
- Retrospective quality assessments using observational data
- Communication and involvement of DTC members and professional quality networks, prescribers, patients and other stakeholders at the regional, national and international level
- Continuous monitoring of utilization and expenditure for drugs in hospitals and ambulatory care
- If needed, further educational activities to enhance appropriate prescribing

This paper presents our forecasting model for drug utilization and expenditures, and the predicted growth in different therapeutic areas in the Stockholm region in 2010 and 2011. In addition, we present explanatory factors behind the predicted changes in expenditures. We believe this model will be of interest also for other regions and countries when planning for the future.

Methods

The forecasting included a prediction of future expenditure in all therapeutic areas based on a linear regression analysis applied to historical sales pattern, subsequently adjusted for factors likely to influence utilization and/or expenditure.

Linear Regression Analysis

Linear regression analysis was applied to aggregate sales data from the National Corporation of Swedish Pharmacies on hospital sales and dispensed drugs in ambulatory care, including both reimbursed expenditure and patient co-payment. The method of statistical analysis was chosen since the forecasting was based on annual data without seasonal dependencies. We had previously ascertained there were no long term cyclical patterns during few years included. In addition, the resulting residuals from the regression analysis did not show any particular patterns. Consequently, applying time series models without any such patterns would give approximately the same results since the auto-correlations will be estimated to about zero.

Annual expenditures and volumes for all pharmacological groups at the 3rd ATC (Anatomical Therapeutic Chemical Classification) level [9] between 2006 and 2009 were included in the analysis. Expenditure was measured in Swedish Crowns (SEK) (1 Eur = 10.0 SEK, March 2010) and volumes in Defined Daily Doses (DDD) [9]. A linear regression model was applied to each time series of four observations 2006-2009. The crude predictions for the coming two years 2010 and 2011 were based on linear extrapolation. These were then adjusted for factors likely to increase or decrease future utilization and expenditure, such as patent expiries, new drugs to be launched or new guidelines from national bodies or the regional Drug and Therapeutics Committee (Table 1, [10-15]). The individual impact of these factors in each pharmacological group is presented in the results section. No specific adjustments were made for the ageing of the population, population growth and financial incentives for drug prescribing since these changes were already covered by the original trends.

New Drug therapies or changed indications for old therapies

New therapies were identified through horizon scanning. This is a systematic process to identify new medicines or new indications of existing medicines that are expected to receive marketing authorisation from the Regulatory Authority in the near future and to estimate their potential impact on patient care [16]. Information on drugs likely to be launched during the coming two years was collected from a number of sources. These included published reports and websites from regulatory agencies, the European Commission and the FDA, the UK organizations for horizon scanning (National Horizon Scanning Centre in Birmingham and National Prescribing Centre in Liverpool) and the pharmaceutical industry through pipeline information on their public websites, as well as formal face to face meetings with different pharmaceutical companies.

Review and modification of forecasting based on expert input

All the information collected was discussed and prioritized in consultation with each of the 23 medical and sci-

Table 1: Factors likely to influence future utilization and expenditure considered in the forecasting model.

Factor	Estimated impact on expenditure	Comment
Decreasing expenditure		
Patent expiries and the subsequent introduction of generics	50-90% decrease	In Sweden, since generic substitution was introduced in 2002, reimbursed prices for generics have been decreasing down to 10 to 20% of the price of the original brand within a year after patent expiry [10,11]. Since it may take a year for the prices to decrease by 90%, we estimated expenditure for a drug on an annual basis to be reduced by 50% the first year after patent expiry. We have not applied the same estimates for biosimilars since these are not considered interchangeable and questions still remain about their clinical efficacy, safety, and immunogenicity [12].
Changes in prices and reimbursement status	0-20% decrease	All existing drugs are currently being reviewed by the Swedish Dental and Pharmaceutical Benefits Agency (TLV) (value-based pricing for existing drugs) [10]. Individual assessment was performed for each planned reimbursement review since the impact of them has been variable.
Increasing expenditure		
Likely new drugs to be launched and new indications for existing drugs	0-x% increase	The potential impact on the healthcare budget was assessed based on estimates of likely/anticipated price for each new product, target patient populations and time for diffusion. Target populations were estimated based on the prevalence and/or incidence of the diseases and conditions or procedures for which each new medicine was likely to be prescribed. Data on the prevalence and incidence were collected from various published and unpublished sources including the Swedish National hospital discharge register, the National prescribed drug register, databases from the County Council, and published scientific studies [13].
Variable impact		
New guidelines from national authorities or the regional DTC [11].	+/-5% annual change	Some guidelines were considered to increases in utilization, e.g. National Guidelines for diabetes suggesting stricter targets for HbA1c. Other guidelines were suggested to decrease utilization, e.g. regional guidelines for stricter management of infectious diseases. Overall, guidelines were predicted to have a limited impact during the first two years since prior studies have shown that guidelines are slowly adopted in the healthcare system [14].
Introduction of incentives and budgets for drug prescribing along with greater scrutiny of prescribing	+/-0	The regional budgetary model that had been applied for a number of years included voluntary financial incentives for primary care practices linked to the level of adherence to the DTC recommendations and local assessment of prescribing performance in a "prescribing quality report" [15]. A decision had been taken to allocate strict drug budgets for primary care in 2011. However, at the time when the forecasting was performed, it was not clear how it should be constructed. Budgets have also been introduced for ambulatory care prescribing from hospitals. These budgets are, however, only partly allocated and to certain drugs. Consequently, we have not predicted the change in budgeting system to have any impact on the overall trends for 2010-2011.
Major structural changes in healthcare provision, organization and reimbursement	0-3% annual increase	A number of structural changes were expected to take place during 2010-2011. A reform increasing patient access to primary healthcare was expected to increase the prescribing of antibiotics, analgesics and antiasthmatics by 3% while changes in access to community pharmacies (state monopoly for pharmacies replaced by new law opening up for private pharmacies) were not expected to influence net expenditure during 2010-2011.

entific expert groups belonging to the DTC system in the Stockholm County [10]. These expert groups cover diseases of organ systems e.g. cardiovascular, gastrointestinal and neurological disorders. Each group has members representing all major specialist clinics in the county as well as a general practitioner, a clinical pharmacologist and a pharmacist. All involved experts have to apply a strict policy for declaration of interests including contacts with the pharmaceutical industry [10]. Finally, the forecasting models were scrutinized and modified after input from joint workshops with expert groups and after final input and comments from the main authors, who have extensive clinical pharmacological and/or pharmacotherapeutic knowledge or experience. The final forecasting report for 2010-2011 was published in Swedish in March 2010.

Results

Overall forecasting results

In 2009, the total drug expenditure for the Stockholm County was 6.9 billion SEK, corresponding to 3.490 SEK or €349/inhabitant. This increased by 3.3% compared with 2008 (Figure 1). We predict that the total expenditure, including both ambulatory and hospital sales, will increase by 2.0% in 2010 and by 4.0% in 2011.

The expenditure is predicted to increase for all major therapeutic areas (Figure 2); most predominantly for antineoplastic and immunomodulating agents (ATC L) as well as drugs for the nervous system (ATC N), infectious diseases (ATC J) and blood-forming organs (ATC B).

In particular, large increases are expected for "biological" drugs, such as TNF-alpha inhibitors and monoclonal antibodies, and small molecules for targeted cancer therapy. We also estimate that expenditure will increase rapidly for some drugs used for common diseases, i.e. drugs prescribed for pain, asthma and diabetes, as well as anticoagulants. This is due to the launch of new medicines, as well as increasing overall volumes without expected savings from new patent expirations. Table 2 contains data on the changes envisaged for all therapeutic groups.

Alimentary tract including antidiabetic agents (ATC-group A)

We expect the expenditures for anti-ulcer drugs to decrease by 5% in 2010 and 3% in 2011 due to patent expiries and decreasing prices for proton pump inhibitors. The impact of lower prices on the overall expenditures will to some extent be counteracted by increasing volumes, although reimbursement restrictions by TLV (Table 1) may limit such an increase [10].

Considerable increases are expected for antidiabetic agents excluding insulin (13% in 2010 and 9% in 2011) due to the increased prevalence of type 2 diabetes [17], new National Guidelines suggesting stricter targets for HbA1c, and the introduction of several new drugs (the GLP-I agonists exenatide and liraglutide, as well as the DPP-4 inhibitors sitagliptin, vildagliptin and saxagliptin) [18]. We anticipate that the safety problems observed for glitazones in patients with ischemic heart disease [19] may contribute to a more rapid introduction of the DPP-IV inhibitors for add-on therapy in patients with type 2 diabetes not controlled on traditional sulphonyl ureas and metformin. On the other hand, there are also anticipated safety problems with these drugs [20]. There is a need for new antidiabetic drugs, but their place in therapy will depend on their long-term safety and effectiveness suggesting a need for the step wise introduction of these NCEs. It is likely that the net increase for all antidiabetic agents will remain at 4% due to the moderation in sales of long-acting insulin as a result of new recommendations in national guidelines and the observational studies demonstrating a potential association between insulin glargin and the development of breast cancer [21].

The ATC group A also includes orphan drugs for patients suffering from rare enzyme deficiencies, e.g. Gaucher's disease. In Europe, orphan drug status can be granted when the prevalence of the disease does not exceed 5 cases per 10 000 inhabitants [22]. Since 2000, when the ad hoc legislation came into force, up to 2007, out of 528 designated orphan indications related to 400 orphan medicinal products (OMP) only 45 (44 drugs) were approved (8.5%) [22]. Access to these drugs varies greatly both between and within countries, mainly because of the high annual cost of treatment (up to € 300 000 per patient) [22]. We predicted the expenditure for orphan drugs within ATC group A to increase by 10% in 2010 and by 9% in 2011.

Blood and blood forming organs (ATC B)

The expenditure for anticoagulants is likely to decrease by 9% in 2010 and increase by 17% in 2011. The decrease predicted for 2010 is explained by the patent expiry for clopidogrel in November 2009. In March 2010, the price for generic clopidogrel had fallen by 90% compared to the originator price before patent expiry. The subsequent increase in expenditure in 2011 is partly explained by the introduction of dabigatran, rivaroxaban and apixaban [23]. The clinical development of these new anticoagulants is following the well tested strategy of dose-ranging and registration studies for short-term use after major orthopaedic surgery, prior to the development for long-term use in atrial fibrillation. Phase III trials for stroke prevention in patients with atrial fibrillation (AF) are ongoing or recently presented (e.g. RE-LY, Aristotle, Rocket, Borealis and Averroes) [24,25]. Rapid increases in drug expenditure can be anticipated if these drugs will replace warfarin for large numbers of patients [24]. A potential argument for the new more expensive anticoag-

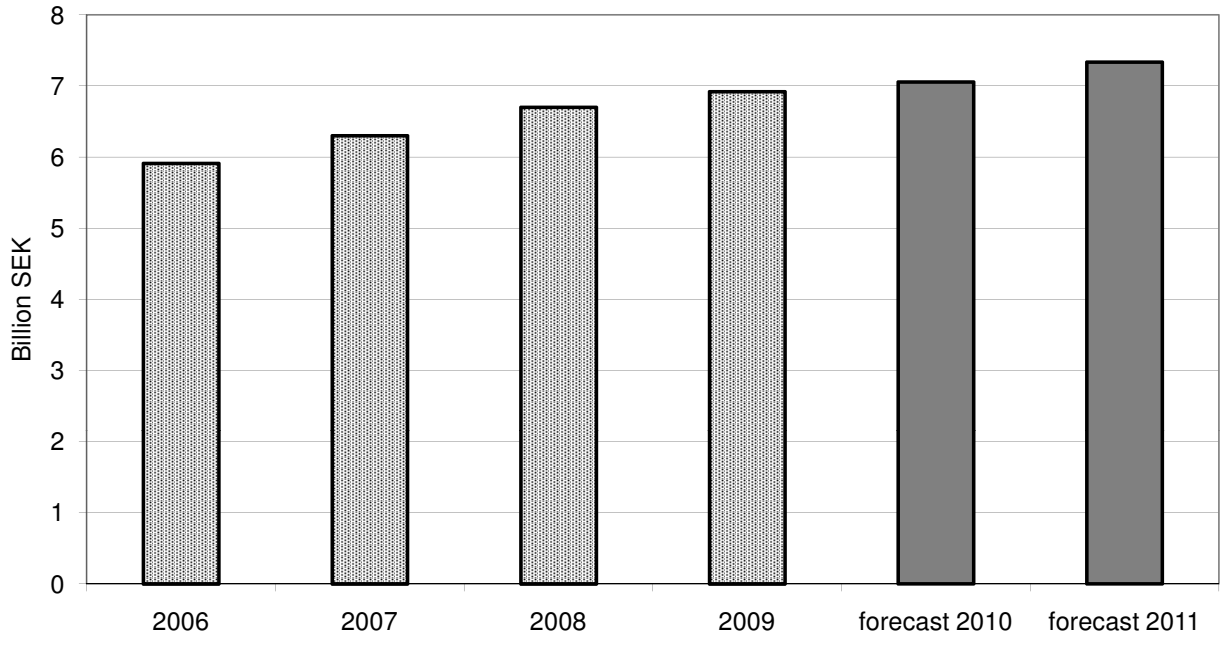

Figure 1 Historical (2006-2009) and predicted (2010-2011) drug expenditures for the Stockholm County Council. Hospital sales and dispensed drugs in ambulatory care, including reimbursed expenditure and patient co-payment.

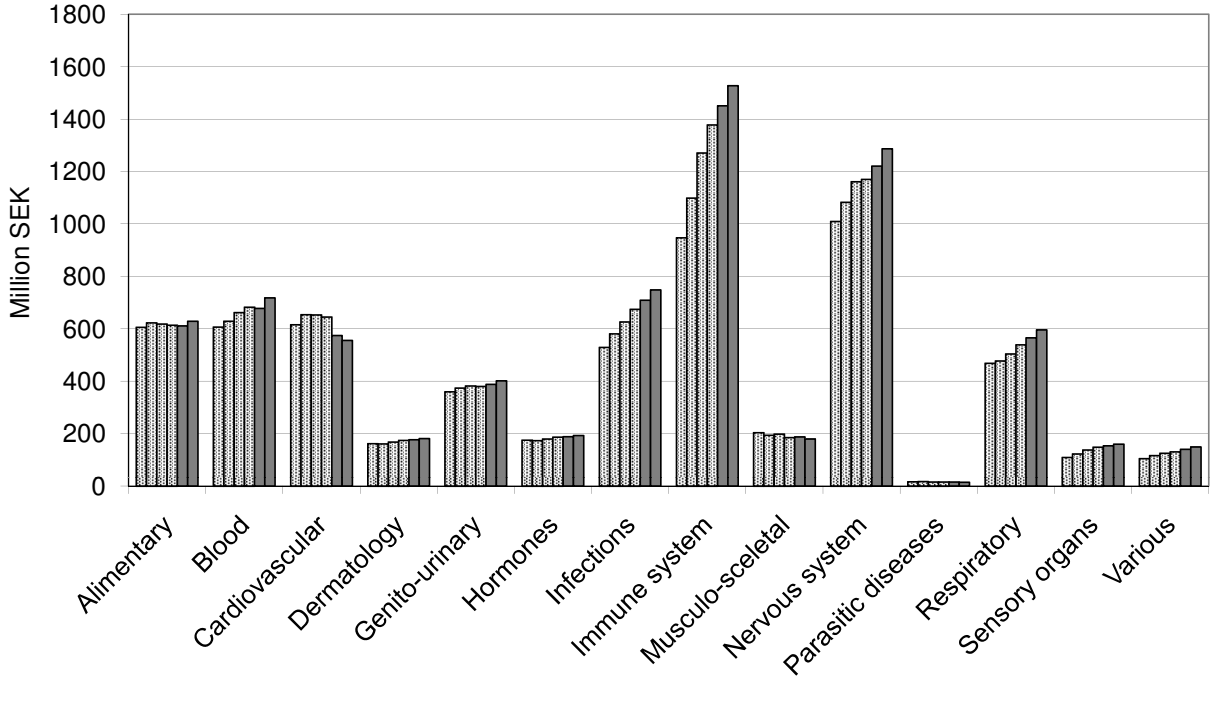

Figure 2 Historical and predicted drug expenditures 2010 and 2011 (forecast in February 2010) for all pharmacological groups (ATC 1st level) in Stockholm County Council.

ulant drugs is that increasing drug expenditure may be counteracted by substantial savings in other areas of healthcare if less coagulation control is needed. However, our current opinion is that these drugs also need to be monitored due to the narrow therapeutic margin of anticoagulants, and for the purpose of monitoring compliance. Another factor contributing to the expected increase in antithrombotic drug expenditure is longer treatment periods with clopidogrel in combination with low dose acetylsalisylic acid if the European Guidelines for cardiovascular prevention proposing 12 months treatment [26] are to be adhered to. However, our National Guidelines recommend 3 to 12 months co-treatment and most patients receive shorter co-treatment periods. Lastly, the introduction of prasugrel and tigacrelor may also influence expenditure. Prasugrel has been introduced at a 50% higher price than the original clopidogrel (Plavix), and has recevied reimbursement for treatment of patients with stent thrombosis despite clopidogrel treatment only; this restriction is challenged by the company. However, we do not anticipate that prasugrel will cause major expenses during 2010-2011. Ticagrelor was shown to be superior to clopidogrel in the PLATO study [27], and will presumably be launched in 2011. Its future place in the therapeutic arsenal is so far unclear.

Expenditure for erythropoietin may be reduced due to the introduction of biosimilars but we have not forecasted any major changes in drug expenditure for this group of drugs due to the ongoing uncertainty about differences in biological activity [12]. This may change as more data becomes available about the safety and efficacy of the biosimilars in practice, as well as any significant differences in price between biosimilars and originators in hospital or ambulatory care.

Cardiovascular drugs (ATC C)

The total expenditure for cardiovascular drugs has remained stable between 2002 and 2009 despite increasing volumes. This is mainly explained by patent expiries and generic availability for some high volume drugs such as simvastatin, amlodipine, enalapril and ramipril during a period when few new drugs were launched [10]. It is likely that expenditures will continue to decrease during the coming two years, mainly due to patient expiries for the angiotensin receptor blockers (ARB's).

As a result of a reimbursement review, ARB's are only reimbursed for patients intolerant to ACE-inhibitors (ACEi) since 2008 [28,29]. This restriction resulted in a 20% decrease in the initiation of ARB while at the same time the number of patients initiated on ACE-inhibitors and calcium channel blockers increased [29]. We believe this change in reimbursement status combined with DTC educational activities and patent expiry of losartan in early 2010 will decrease the expenditure for ARB's by 23% in 2010 and 12% in 2011 (Table 2).

Lipid-lowering agents are the most commonly used drugs in the population after the antiplatelet agents (i.e., mostly low-dose acetylsalicylic acid). In June 2009, the TLV decided on certain reimbursement restrictions, e.g. excluding atorvastatin 10 mg and rosuvastatin 5 mg from the reimbursement scheme [30]. This resulted in a 9% decrease in expenditures. We believe that the expenditures for lipid-lowering drugs will decrease by a further 6% in 2010, but remain stable after that since there is substantial pressure to treat to low cholesterol goals (which will require higher dosages) [31].

Few new cardiovascular drugs will be launched in 2010 and 2011. In 2010, a new antiarrythmic agent, dronedarone, will be introduced as an alternative to amiodarone for patients with atrial fibrillation. The drug has in a large trial (ATHENA) been shown to decrease morbidity and mortality compared to placebo and may, consequently, offer benefits for certain patients [32]. However, the greater tolerability of dronedarone compared to amiodarone is achieved at the expense of lesser efficacy [33], and the target population for dronedarone has not yet been defined.

Genito-urinary tract and sex hormones (ATC G)

This group is dominated by sex hormones for contraception and hormone therapy for climacteric symptoms. The prescribing of hormone therapy decreased substantially after publication of the randomized studies HERS and WHI in 2002 [34,35]. We predict that the use and consequently expenditure will remain stable during the next couple of years.

The expenditure for drugs for erectile dysfunction is expected to increase by 9% annually due to increasing number of men treated. Further increases in this category of drugs are expected following the launch of the first drug for premature ejaculation (PE), dapoxetin, in 2009. This is because PE is the most common male sexual disorder, estimated to affect up to 30% of men [36]. These "lifestyle" drugs have great potential for increased expenditure since an international comparison showed that Sweden had the most rapid diffusion of sildenafil [37]. However, since then, most drugs for erectile dysfunction have been excluded from reimbursement and there is also more structured diffusion of these drugs through active professional involvement, e.g. in DTC activities [10,38]. This has been factored into the forecast model.

Infectious diseases (ATC J)

Substantial increases in expenditures are expected for antiviral drugs - 9% and 10%, respectively in 2010 and 2011. We anticipate the expenditure for antiviral drugs will increase due to the continued launch of new drugs for the treatment of HIV and hepatitis B and C. The numbers of patients treated for HIV will increase due to improved survival and ongoing transmission [39]. Fur-

Table 2: Historical and predicted drug expenditures for 2010 and 2011 in different therapeutic areas.

ATC	Therapeutic area	Expenditures			Forecast		Change 2010		Change 2011	
		2007	2008	2009	2010	2011	MSEK	(%)	MSEK	(%)
A02	Drugs for acid related disorders	143	124	113	107	104	-5	-5%	-3	-3%
A10	Drugs for diabetes	194	209	214	223	231	9	4%	8	4%
A	Other therapeutic areas	286	286	287	280	293	-7	-2%	13	5%
B01	Anticoagulants	164	180	189	173	202	-16	-9%	29	17%
B02	Coagulation factors	197	212	225	238	249	12	5%	12	5%
B	Other therapeutic areas	267	269	268	267	266	-1	0%	-1	0%
C09C&D	Angiotensin receptor blockers	185	199	204	157	138	-47	-23%	-19	-12%
C10	Lipid lowering agents	145	149	140	131	131	-9	-6%	0	0%
C	Other therapeutic areas	323	305	301	286	287	-14	-5%	1	0%
D	Dermatologicals	161	168	174	177	181	3	2%	4	2%
G	Genito Urinary system	374	382	380	388	401	8	2%	13	3%
H	Hormones	173	179	186	188	192	2	1%	4	2%
J01	Antibiotics	230	243	250	248	250	-2	-1%	2	1%
J05	Antiviral drugs	205	233	270	294	322	24	9%	28	10%
J	Other therapeutic areas	146	151	154	166	175	13	8%	9	5%
L01 & L02	Oncology	521	584	592	591	583	-1	0%	-8	-1%
L04AB	TNF - alpha inhibitors	304	359	420	473	529	53	13%	56	12%
L	Other therapeutic areas	274	328	366	386	415	20	5%	29	7%
M	Musculo-skeletal system	194	198	185	187	180	2	1%	-7	-4%
N02A&B	Analgesics	165	176	189	199	209	10	5%	11	5%
N03	Antiepileptics	122	142	149	157	165	8	5%	7	5%
N05A	Antipsychotics	166	177	175	171	167	-4	-2%	-4	-2%
N06A	Antidepressants	191	187	135	127	127	-8	-6%	0	0%
N	Other therapeutic areas	440	481	522	567	619	44	9%	52	9%
P	Antiparasitic products	17	16	15	15	15	0	-1%	0	-3%
R	Respiratory system	477	504	539	565	596	26	5%	30	5%
S	Sensory organs	123	138	148	154	160	6	4%	6	4%
V	Various	116	125	130	140	148	10	8%	8	6%
A-V	ALL DRUGS	6 304	6 702	6 921	7 056	7 336	135	2%	280	4%

Expenditures are presented in million Swedish Crowns (MSEK) (1 Euro = 10.5 SEK).

thermore, the emergence of viruses resistant to current drugs is driving the need for new antiretroviral agents [40]. Examples of new drugs include darunavir, maraviroc, enfuvirtide and tifuvirtide. Increasing use of combinations of inhibitors that target different steps of the viral life cycle will also contribute to increasing expenditure.

Increased expenditure is also expected for the treatment of hepatitis. Around 500 new cases of hepatitis C (HCV) are identified in Stockholm each year. This number may increase further with the introduction of retrospective screening for transfusion-transmitted HCV infections [41]. The current treatment of chronic HCV infection consists of a combination of pegylated interferon and ribavirin. New drugs in development include HCV-specific protease inhibitors, polymerase inhibitors, immune modulators and ribavirin analogues [42]. Two of these, thymalfasin and taribavarin, have recently been launched. The management of chronic hepatitis B (HBV) has improved over the last decade with the development of new drugs such as lamivudine, adefovir and dipivoxil, in addition to interferon (IFN)-alpha therapy [43]. Many other new drugs are under development which may contribute to increasing expenditure. These have been factored into the forecast.

The expenditure for antibiotics is predicted to remain stable in 2010-2011. In June 2009, Strama (the Swedish

Strategic Programme against Antibiotic Resistance) and the Swedish Institute for Infectious Disease Control (SMI) launched the seventh report on the use of antibiotics and resistance in human medicine in Sweden, Swedres 2008 [44]. The use of antibiotics in Sweden is highest among the elderly and children with prescription rates varying considerably between different regions. The proportion of children aged 0-6 years treated with at least one course of antibiotics in 2008 ranged from 38 per cent in Stockholm county to 25 percent in Västerbotten county, with a national average of 33 percent.

The use of antibiotics both in primary and secondary care seems to be changing in a desirable way, with broad spectrum antibiotics being replaced by narrow spectrum substances. Various types of penicillins have increased and the use of cephalosporins and fluoroquinolones is decreasing. This is in accordance with the guidelines on the reduction of prescription of fluoroquinolones against lower urinary tract infections in women, actively promoted by Strama and the DTCs for many years [45]. There is a certain risk that the decreasing utilization will be counteracted by a recent reform increasing patient access to primary healthcare physicians in Stockholm, so continuous activities are needed. Despite these efforts we expect that expenditure in secondary care will increase in the long run due to a continuous increase in the use of more expensive antibiotics as antimicrobial resistance develops. This will be factored into future predictions.

We expect the expenditure for vaccines to increase by 7% annually. A number of new vaccines with major potential for controlling infectious diseases have just been licensed or are at advanced stages of development. The predicted increases are mainly attributable to the introduction of a new seven- and later 13-valent conjugate pneumococcal vaccine and the use of subsidized vaccines for the prevention of cervical cancer caused by human papilloma virus (HPV) [46,47]. The decision by the Swedish National Board of Health and Welfare that HPV vaccination should be included in the official vaccination program for all girls aged 11-12 years is likely to increase expenditures by 33 million SEK. Completely new or significantly modified vaccines may appear in the future. For the H1N1 influenza, Sweden decided to promote vaccination for its entire population. The vaccine cost for Sweden has been estimated at 1.2 to 1.3 billion SEK and total costs (including administration costs) at around 2.5 billion SEK [48]. This corresponds to a vaccine cost of approximately 0.25 billion SEK for the Stockholm region, more than the total expenditure for analgesics in the region during a year.

Antineoplastic and immunomodulating agents (ATC L)

Increasing expenditure (5% annually) is expected for antineoplastic and immunomodulating agents. The increase is principally confined to immunomodulating agents as we do not expect any increase in the total costs for antineoplastic drugs during 2010-2012 for the reasons outlined below. The increase is mainly due to the widening indications for TNF alpha inhibitors and other drugs already available on the market (Figure 3). Cancer therapy is characterized by multimodal treatment using surgery, radiotherapy and a rapidly increasing number of antitumour agents. Today, most agents are introduced for patients with late stage (metastatic) disease. In many cases such as for example breast cancer, the efficacy in metastatic disease translates into increased cure rates when the new drug is used in earlier stages of the disease in conjunction with surgery [49,50]. Many drugs are under development, and both academic institutions and the pharmaceutical industry are investing in cancer research at levels previously unseen. All of these factors contribute to the predicted increase in expenditure over time, but as discussed below during the time period 2010-2012, this will be counteracted by the patent expiration of several top selling cancer drugs.

Recent advances in the knowledge of the biology of breast cancer have resulted in targeted treatments, such as the monoclonal antibody trastuzumab (targeting HER2-overexpressing cells) [51]. In 2009, trastuzumab was the top selling oncology drug in our region with total sales of 72 million SEK, corresponding to € 7.2 million. However, we predict that the sales will level off during the coming years since the drug has already reached its target population in breast cancer. This will be counterbalanced by trastuzumab recently approved in advanced HER2-overexpressing gastric cancer. However, there are a more limited number of patients.

Colorectal cancer, the third most common malignancy after cancers of the breast and prostate, was treated with surgery alone until the 1980s when the combination of 5-fluorouracil and leucovorin was introduced. During the past ten years, new agents have been introduced and life expectancy has increased from 5 to 20 months in patients with metastatic disease [52]. These improvements have, however, resulted in a dramatic increase in the costs of medical treatment. In recent years, the addition of biological agents like the monoclonal antibodies bevacizumab as well as cetuximab and panitumumab have further improved response rates [53]. None of these drugs has, however, showed activity in the adjuvant setting. Consequently, no major increase in their use in colorectal cancer is expected in the period 2010-2012. The overall use of bevacizumab is expected to increase though mainly due to other indications including advanced breast, lung and renal cancer.

Advances in molecular medicine have also provided insights into the biology of several haematological diseases such as chronic lymphatic leukemia (CLL), chronic

myeloid leukemia (CML), multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) [54,55]. This has led to new treatments like the monoclonal antibody rituximab, which has improved survival rates in patients with aggressive NHL and become an important therapeutic option in the treatment of indolent lymphoma [56]. As a result, Rituximab had the second highest expenditure of oncology drugs in the region in 2008 helped also by utilisation in rheumatoid arthritis (RA - below). We predict that sales will continue to grow, mainly due to the widening of indications in haematology (CLL), but also in rheumatoid arthritis (see below). Imatinib has become the backbone of treatment of CML for which several other drugs have also been approved or are in development. Dasatinib and nilotinib are presently approved in second line treatment of CML. If these drugs are approved in first line treatment, this will have a major impact on costs as treatment of CML takes place over many years, and can be considered almost chronic treatment. Bortezomib is indicated in MM for which there are now also several new therapeutic options including lenalidomide [54,55]. Increase in the total drug costs for MM is to be expected.

The rapid increase in expenditure due to new drugs is counteracted by savings due to the introduction of generics for many oncology drugs. The patent recently expired for bikalutamide leading to a rapid price decrease. Over the next two years, patent expiries are expected for several of the best selling oncology drugs including aromatase inhibitors, docetaxel and temozolamide, resulting in the expected moderation in growth in 2010 and 2011. This moderation in growth though is dependant on the rapid uptake of generics at low prices building on previous examples [10]. It is also likely that current resource constraints may increase the need for prioritization of the utilisation of new oncology drugs with only limited improvements in survival in most new cancer drugs compared to current treatments and their high prices. This issue is currently a major focus among health technology assessment units, and in the evaluation of the actual benefit of new cancer drugs [57].

Expenditure has increased rapidly for the treatment of rheumatoid arthritis (RA) due to the introduction of anti-tumor necrosis factor (TNF)-alpha and anti-interleukin (IL)-1 agents (infliximab, adalimumab, etanercept and anakinra). Further increases are expected since the indications have widened and they are increasingly used in patients with inflammatory bowel disease and psoriasis. This considerable widening of indications for TNF-alpha blockers has not though resulted in any price reductions in Sweden. New drugs are also being introduced for the treatment of rheumatoid arthritis patients not responding to conventional treatments, which may also contribute to increasing expenditures. Such drugs include the anti-CD20 monoclonal antibody rituximab, which inhibits B-cell activity, the T-cell activation inhibitor abatacept, and other interleukin inhibitors [58].

Nervous system (ATC N)

We predict the expenditure to decrease for antipsychotics and antidepressants, while it will increase for other CNS acting drugs (Figure 4).

The expenditure on analgesics has increased by 5-13% annually the past years due both to increased volumes and increased prescribing of more expensive products such as tramadol and oxycodon. This development is likely to continue despite efforts from the DTC to moderate their use since they are not considered to provide any advantages over other recommended drugs. New formulations of fentanyl may also contribute to increased expenditures as well as the new fixed combination of naloxone and oxycodon. Some savings will be achieved through patent expiry and the introduction of generics to sumatriptan. This may, however, partly be counteracted by increased utilization of triptans. Other drugs for the treatment of migraine are under development, and it is likely that the first agonist acting on vascular calcitonin-gene related peptide (CGRP) receptors, telcagepant, will be introduced on the market in 2011 [59].

We predict expenditure for antiepileptic drugs to increase by 5% annually, mainly due to increased utilization of lamotrigine and pregabalin for nonepileptic conditions. These include various psychiatric disorders and pain syndromes [60]. Price competition is weak for these drugs since it has been decided nationally that they can not be substituted in pharmacies unlike other generic drugs [10]. Evidence for their benefit in these conditions varies though and further studies are needed to be able to fully determine their place in management. In the USA, the FDA approved pregabalin for treatment of fibromyalgia in June 2007 and the manufacturer filed for the same indication in Europe. However, EMA didn't approve an extension of indication for pregabalin to include the treatment of fibromyalgia [61].

We predict that increase in the expenditure for antipsychotic drugs will moderate over the next two years (Figure 4). This is mainly due to patent expiry and generic competition for risperidone. In 2011, we also expect generics to be introduced for the top-selling drug in the group, olanzapine. Further savings are unlikely though due to the commercial pressures to prescribe the single sourced antipsychotics quetiapine and aripiprazole.

The substantial decrease in expenditure for antidepressants in 2009 is explained by the patent expiry for, and subsequent introduction of generics to venlafaxine (Figure 4). With total sales of 58 million SEK in 2008, venlafaxine accounted for the largest proportion of antidepressant expenditure in the region. The sales are expected to remain stable over the coming years.

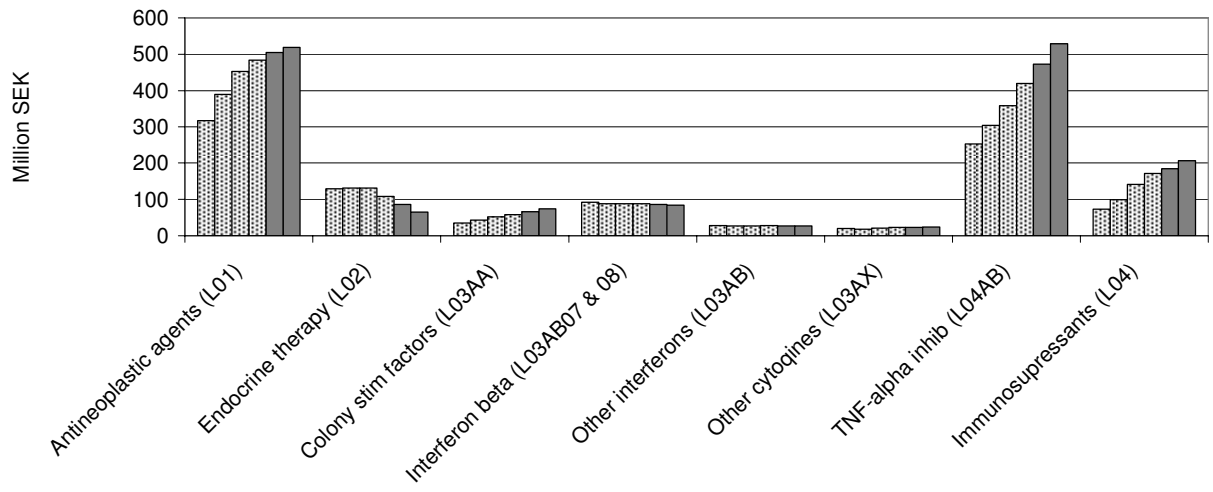

Figure 3 Historical and predicted drug expenditures 2010 and 2011 for antineoplastic and immunomodulating agents (ATC L) in the Stockholm County Council.

The expenditure for ADHD-medications is expected to increase by 33% annually. The increases are expected both for children and adults. Sweden had earlier a low utilization of these drugs compared to other western European countries, mainly due to strict governmental regulations against the prescription of ADHD medications [62]. Changes in the legislation may partly explain the increasing utilization and also that the disease and the drugs have been heavily discussed in media.

Sensory organs (ATC S)

The increasing expenditure for ophthalmic preparations has mainly been attributed to the introduction of the vascular endothelial growth factor A (VEGF-A) antagonist ranibizumab to treat neovascular age-related macular degeneration [63]. Studies are ongoing with ranibizumab and other agents for the management of diabetic retinopathy and a widening of the indication is likely to occur in 2011.

Discussion

Forecasting pharmaceutical utilization and expenditure patterns is a complex undertaking. Factors that drive increases in pharmaceutical expenditures can be divided into increases in price or in volume (i.e. more users and/or longer durations of therapy), and changes in utilization patterns that favour newer, more expensive agents over older, less expensive yet perhaps equally effective alternatives [64]. Part of the increase may also be attributable to the introduction of drugs for diseases that were previously untreatable with existing medications [64].

There are well established methods to predict changes related to these factors, but the traditional models may have difficulties in forecasting the uptake of and expenditures for biological drugs [65,66]. Traditional models may also face problems with reforms and market measures to obtain lower prices for generics and for interchangeable brands in a class if these initiatives are new to the health service. We believe we have addressed both of these issues in our forecasting model for drug utilization and expenditure. Furthermore, the process of including local experts offers the potential to assess early on how regional diffusion rates of new medicines or adoption of guidelines are influenced by local therapeutic traditions and plan for this. Consequently, it is likely that our model may be more accurate to predict future expenditures than macro-forecasting performed at the national level. We would also like to emphasize the importance that the DTC members are involved and balance and question the opinions of the members of the expert groups. A DTC where members have shared evaluation principles and priorities of value of drugs is important as well as transparent declaration of potential conflict of interests for all involved experts according to a guideline [10].

The predicted growth in expenditures for 2010 and 2011 is similar to that found by others. Tuffer et al projected an annual increase of 5,6% in 2010 for prescription drug expenditures in the US [66]. Slightly lower figures were predicted for the US market by Hoffman et al who projected a 0-2% increase in drug expenditures in outpatient settings, a 1-3% increase in expenditures for clinic-administered drugs, and a 1-3% increase in hospital drug expenditures for 2009 [65]. The predicted growth in expenditure is considerable lower than the a 5-7% increase in drug expenditures in outpatient settings, 12-14% increase in clinics, and 4-6% increase in hospitals

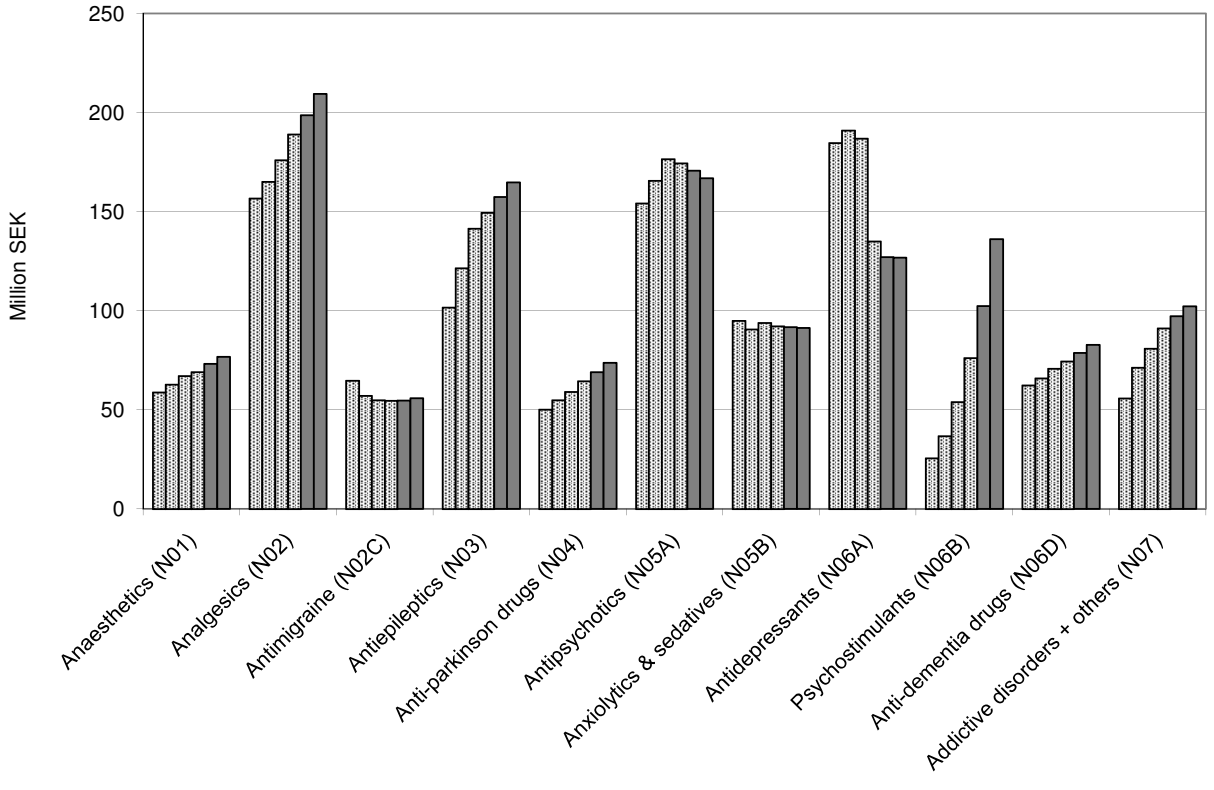

Figure 4 Historical and predicted drug expenditures 2010 and 2011 for nervous system drugs (ATC N) in the Stockholm County Council.

forecasted by Hoffman and colleagues for 2008 [64]. The moderation is mainly explained by the worldwide economic downturn and growing economic uncertainty [65,66].

The slowdown in growth of ambulatory care drug expenditure in recent years has largely been attributable to the increased use of generics through guidance and financial incentive schemes coupled with market measures to obtain low prices for generics, and there is certain evidence that the era of frequent new "blockbuster" drugs is ending [67-69]. Consequently, the current trend in drug development seems to be switching to personalized and specialized drugs, which emphasizes the need to develop new models to introduce drugs in healthcare.

The development may also be influenced by the financing systems applied in the healthcare system. Financial incentives have been used for many years in primary care in the region [15] and no further substantial changes are expected over the coming years. However, the decision to introduce strict budgets for all hospitals may influence both the overall expenditure and the rate of uptake of new medicines in the future. Financial incentives may moderate the annual increase in drug expenditure and in some cases reduce it. Ethical concerns may be raised as the long term impact of cost containment incentives on the quality of care has not been thoroughly evaluated [70-72].

We acknowledge that there are weaknesses in our model for predicting future drug expenditure. The relative lack of information on launch dates for new products and the selective and delayed publication of results from trials [73] are important problems when trying to estimate the potential value of a new drug and the marketing strategies to come. The pricing of a new drug is also difficult to project unless it is merely another competitor in an established or similar therapeutic class. Early horizon scanning and long term forecasts (more than a couple of years) will thus entail considerable uncertainty. Robust methodologies for horizon scanning [16,74] coupled with the involvement of local experts who keep abreast of developments may, however, provide a reasonable basis for prediction. Other changes in the pharmaceutical market are also difficult to predict, both with regard to timing and effect. For example, estimating patent expiration dates has become a challenge since these dates may change due to litigation, additional patents, exclusivities, and other factors which are difficult to anticipate [75,76]. Another potential limitation is the estimated time for diffusion of new drugs in our model. Diffusion patterns may change due to increased safety concerns with newly

approved medications and heightened prescriber sensitivity to the high costs of many new medicines [64]. However, marketing strategies are also changing, and the emergence of personalized medicine with very expensive drugs that are handled by few specialists is creating a new situation that is difficult to evaluate precisely. We believe the utilisation of expert groups in our model helps to address this. Further research is still needed though to determine the current "life cycles" of various therapies as well as factors influencing it.

We are convinced that the model presented here can be developed into more refined models of 'value' based forecasting of drug use in a healthcare region. Value based forecasting can be used to influence treatment patterns through systematic improvements in the selection of patients and drugs for specific pharmacotherapeutic approaches in defined patient populations. Such forecasting may in the future be critical for society to decide priorities and target groups for new expensive treatments or diagnostic procedures compared to the existing ones [77]. Concerns about unethical priorities regarding treatment with expensive drugs could in part be resolved by the use of critical evaluation procedures to elucidate when new drug treatments may be justified. In addition ahead of their launch, determine with key groups which patient populations are likely to most benefit from new drugs and where costs can be controlled by more rational use of generics at low prices and/or established patented alternatives. Solid forecasts are essential in the process of prioritization. A better "prepared" healthcare system will have greater chances of releasing or reallocating resources to help fund valuable new drugs [7,77].

We also believe that it is important to set up registries for monitoring the use of some of the new drugs in specific populations (oncology, rheumatology, MS etc). Such a registry has, for example, been very useful in rheumatology in Sweden [78]. By monitoring the introduction and use of new very costly drugs in special therapeutic areas, a better understanding of their patterns of use and their therapeutic value in practice will be achieved.

Finally, a limitation with our approach is that it only predicts direct expenditure for drugs. New innovative therapies may result in savings in other parts of the healthcare system, such as reduced needs for hospital care or rehabilitation, or reduce societal costs outside of the healthcare system [79,80]. In future models also marginal costs should be considered if other health care costs such as reduced length of stay, and the need for other interventions can be included with some degree of certainty in the estimates. Incorporation of the wider societal perspective also depends on the ability to transfer responsibility and funds between budgets including both health and social care.

Conclusions

We predicted the annual increase in total expenditure for prescription and hospital drugs to be 2.0% in 2010 and 4.0% in 2011. The utilisation of and expenditure for drugs is difficult to forecast due to uncertainty about the rate of adoption of new medicines and various healthcare reforms and activities to improve the quality and efficiency of prescribing. Nevertheless we believe our model will be valuable as an early warning system to start developing guidance for new drugs including systems to monitor their effectiveness, safety and cost-effectiveness in clinical practice.

Competing interests

The authors are all involved in the regional Drug and Therapeutics Committee in Stockholm County. No other conflicts of interest.

Authors' contributions

The model was originally developed by BW, MEP, NW, SK, MK and LLG, and the forecasting for 2010-2011 was performed with all the authors in close collaboration with a large number of experts from the Regional Drug Expert Consortium in Stockholm. In particular, MEP carried out the horizon scanning, BW was responsible for the drug utilization data modelling, MP participated in the statistical analyses, NW, PH and MK participated as pharmacotherapeutic experts in oncology, cardiovascular medicine and infectious diseases, respectively. BG participated as an external advisor coordinating a network with international colleagues. BW was the main responsible coordinating for the manuscript production with active participation from all co-authors. All authors read and approved the final manuscript.

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Author Details

[1]Department of Drug Management and Informatics, Stockholm County Council, Stockholm Sweden, [2]Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm Sweden, [3]Department of Oncology and Pathology, Karolinska Insitutet, Stockholm, Sweden, [4]Department of Infectious diseases, Karolinska University Hospital Solna, Stockholm, Sweden, [5]Division of Clinical Pharmacology, Department of Medicine Solna, Karolinska Institutet at Karolinska University Hospital Solna, Stockholm, Sweden, [6]Mario Negri Institute, Milan, Italy and [7]Nordic School of Public Health, Gothenburg, Sweden

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Research Article

Usage, Risk, and Benefit of Weight-Loss Drugs in Primary Care

Tomas Forslund,[1] Pauline Raaschou,[2] Paul Hjemdahl,[2] Ingvar Krakau,[3] and Björn Wettermark[4]

[1] *Gröndal Primary Care Centre, P. O. Box 470 43, 100 74 Stockholm, Sweden*
[2] *Department of Clinical Pharmacology, Karolinska University Hospital, Solna, 141 86 Stockholm, Sweden*
[3] *Centre for Family and Community Medicine, Karolinska Institutet and Stockholm County Council, Huddinge, Sweden*
[4] *Drug Management and Informatics, 118 27 Stockholm, Sweden*

Correspondence should be addressed to Tomas Forslund, tomas.forslund@sll.se

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Purpose. To investigate the use of the weight-loss drugs rimonabant, sibutramine, and orlistat in primary care and to characterize the patients receiving the drugs. *Methods*. In this retrospective, descriptive study, 300 randomly selected patients having started weight-loss drug treatment at 15 primary care centres were investigated using the patient's medical records and their complete drug purchase data. *Results*. Even though 48% of the patients specifically demanded drug treatment, 77% continued treatment less than one year. 28% of rimonabant patients and 32% of sibutramine patients had a history of depression or antidepressant treatment. 41% of sibutramine patients had a history of hypertension and/or cardiovascular disease. 36% had no documented weight after treatment initiation. *Conclusions*. These results suggest that weight-loss drug treatment was often initiated upon patient request but was of limited clinical benefit as it was managed in a large portion of Swedish primary carecenters.

1. Introduction

Obesity is a prevalent chronic condition which is associated with significant morbidity and mortality [1]. The prevalence is increasing rapidly in all countries, with WHO estimating 1.6 billion overweight adults and 400 million obese adults in 2005 [2]. Although not being one of the worst inflicted countries, the prevalence of obesity in Sweden has also increased substantially over the last decades, and it has been estimated that 10% of both men and women are obese, and a further 40% are overweight [3]. Consequently, there is an urgent need for effective life-style interventions and often also pharmacological treatment.

The development of antiobesity medicines has been problematic and characterized by heavy marketing followed by withdrawals from the market after reports of safety problems, including pulmonary hypertension (aminorex), valvular lesions (dexfenfluramine-phentermine), and addiction (amphetamine) [4]. This pattern has continued in recent years with the withdrawal of rimonabant (Acomplia) in October 2008 and sibutramine (Reductil, Reduxade, Zelium) in January 2010 due to safety concerns [5, 6]. Currently, orlistat is the only registered weight-loss drug on the European market, but new drugs are in the pipeline [7, 8].

In the metropolitan health region of Stockholm, Sweden, a model has been developed which includes horizon scanning (to prepare for drugs to come), forecasting of drug utilization and expenditures, critical drug evaluation, and structured programs for the introduction and followup of new drugs [9]. When rimonabant was given the marketing approval in 2006, the subsequent marketing activities led to concerns about improper use and inappropriate increase in expenditure. Rimonabant was, therefore, one of the drugs selected for a structured introduction and followup program. In 2006, the total expenditure for weight-loss drugs was 154 million SEK in Sweden [10].

This study is a characterization of the use of weight-loss drugs in the primary health care setting of Stockholm County. The aim was to analyse the utilization and effectiveness of the three weight-loss drugs rimonabant, sibutramine,

Table 1: The three weight-loss drugs on the Swedish market in 2008.

Rimonabant
Rimonabant (Acomplia) is a cannabinoid CB1-receptor earlierly registered in Europe for the treatment of overweight with risk factors (BMI over 27 with dyslipidemia or diabetes) or obesity (BMI over 30) in combination with lifestyle interventions. In Sweden, the drug was reimbursed only if BMI was over 28 with dyslipidemia or diabetes, or if BMI was over 35 [11]. A meta-analysis has shown a placebo-adjusted weight loss of 4.3 kg after one year of treatment [12]. Contraindications included ongoing depression or treatment with antidepressant drugs [11]. Rimonabant was withdrawn from the market in October 2008 due to the risk of psychiatric side effects [5].
Orlistat
Orlistat (Xenical) is a gastrointestinal lipase inhibitor registered in Europe and the US for the treatment of overweight with risk factors (BMI over 27 with dyslipidemia or diabetes) or obesity (BMI over 30) in combination with diet interventions. In Sweden, the drug is reimbursed only if BMI is over 28 with dyslipidemia or diabetes, or if BMI is over 35 [13]. A meta-analysis has shown a placebo-adjusted weight loss of 2.7 kg after one year of treatment [12]. Malabsorption is a contraindication [13].
Sibutramine
Sibutramine (Reductil) is a serotonin, norepinephrine, and dopamine reuptake inhibitor earlierly registered in Europe for the treatment of overweight with risk factors (BMI over 27 with dyslipidemia or diabetes) or obesity (BMI over 30) in combination with lifestyle interventions. In Sweden, the drug was reimbursed only if BMI was over 28 with dyslipidemia or diabetes, or if BMI was over 35 [14]. A meta-analysis has shown a placebo-adjusted weight loss of 4.3 kg after one year of treatment [12]. Contraindications were among others cardiovascular disease, psychiatric disease, ongoing treatment with antidepressant or antipsychotic drugs, and uncontrolled hypertension [14]. Sibutramine was withdrawn from the market in January 2010 due to an increased risk of cardiovascular incidents [6].

and orlistat (see Table 1) which were on the Swedish market in 2008. Rimonabant was withdrawn from the market toward the end of the study period, which limits the possibility of conducting a 1-year evaluation for this drug. Sibutramine was withdrawn after the study period, while orlistat still remains on the market.

2. Methods

2.1. Medical Record Data. We conducted a retrospective, descriptive study based on data extracted from electronic medical records in primary healthcare. All data were extracted using Rave3 software (Medrave Software AB, Stockholm) [15, 16]. The Rave3 software extracts data from the medical record database in a systematic way making it possible to link most of the recorded data such as diagnosis, laboratory findings, and text registered in the medical record. A validation was done confirming that the extracted data was in agreement with the medical records. Rave3 performed well regarding the extraction of data documented in association with a specified term, but an additional manual analysis had to be performed to include the missing medical data.

A total of 36 primary healthcare centres (PHCs) comprising the Southwest district of the Stockholm County Council were invited to participate in the study. 24 of them used electronic medical records adapted to the Rave3 software and were thus able to participate. Among them, 15 practices agreed to participate and were included in the study.

Specific parameters as well as unformatted medical record information from November 1, 2005 to February 28, 2009 were centrally extracted with Rave3, anonymised, and entered into a database for further analysis. Thus all patients could be evaluated during at least 15 months after the start of treatment. Data regarding diagnosis of depression, antidepressant treatment, or earlier treatment with orlistat or sibutramine were also extracted back to the year 2000 in order to obtain some important characteristics of the patients before November 1, 2005.

2.2. Prescription Data. To assess to what extent the patients redeemed their prescriptions, data from the medical records were linked to data on dispensed drugs in the Swedish Prescribed Drug register [17]. The National Board of Health and Welfare is responsible for keeping this register which contains data on all prescription drugs dispensed in Sweden from 2005 and onwards, their amounts and dosages, expenditures and reimbursement, as well as the age, the gender and the unique identifier (personal identification number) of the patient. Using anonymised record linkage, we analysed the dispensing histories for all of patients' prescriptions between November 1, 2005 and February 28, 2009 to assess all the drugs that the patients actually had purchased from the pharmacy, regardless of the origins of the prescriptions. It also permitted an analysis of the persistence of weight-loss treatment.

The terminology and methodology used for measuring persistence varies across studies [18]. We defined persistence as the total number of days on treatment measured by the amount of drugs purchased from the pharmacy divided by the usual number of dosages for the drug. The reason for our choice is that weight-loss drugs have not been indicated for long-term risk reduction but for a limited period of weight-loss treatment. The duration of treatment is, thus, more important in this case than for chronic treatment where adherence is more interesting. Defined daily doses (DDD) were not used due to the availability of sibutramine in both 10-mg and 15-mg compositions, which would have overestimated the treatment duration of this drug.

2.3. Statistics. Standard descriptive statistics (numbers, proportions, median, interquartile range, and range) were used to describe the study cohort and the utilization patterns. Data are presented with 95% exact binomial confidence intervals (CI) for proportions, where appropriate.

2.4. Ethics. The study was approved by the regional ethics committee.

3. Results

3.1. Population. The 15 PHCs included were responsible for a total of 205, 440 patients in 2008. Rave3 identified a total of 876 patients who had commenced treatment with weight-loss drugs at these primary care centres between November 1, 2006 and November 30, 2007, that is, a period of 13 months. 370 patients (42%) had received rimonabant, 230 patients (26%) had received orlistat, and 276 patients had received sibutramine (32%). The number of unique patients was 829 due to the fact that an individual patient could have started treatment with different weight-loss drugs during this time period. The present analysis was limited to 100 randomly chosen patients for each weight-loss drug, that is, 300 patients in total. The number of unique patients analysed was 294.

3.2. Selection Bias. In order to detect possible selection bias, we characterized the participating PHCs and compared them to the nonincluded centres. The participating centres were more often publicly managed and had more patients than the nonparticipating centres. The proportion of older patients, the number of visits per patient, the average drug expenditure per patient, and the proportion of prescriptions for weight-loss drugs compared to the total amount of prescriptions were similar. The population-base living next to the centres was also similar, as evaluated by age spans, unemployment, beneficiaries of social aid, immigrants, as well as levels of education and proportions of low- and high-income households. Thus, the comparison revealed no potentially important differences between PHCs who participated in the study and those who did not (data not shown).

3.3. Diabetes and/or Dyslipidemia. Of the patients who initiated weight-loss drug treatment, 65% had a diagnosis of diabetes and/or dyslipidemia, treatment for such a diagnosis, or laboratory tests indicating such a condition (see Table 2). The incidence was evenly distributed among the three weight-loss drugs. 32% had treatment for diabetes and/or dyslipidemia.

3.4. Cardiovascular Disease. Cardiovascular disease or uncontrolled hypertension was contraindications for treatment with sibutramine. 41% of the patients who started treatment with sibutramine had at least one diagnosis or treatment consistent with hypertension and/or other cardiovascular disease (see Table 2). The first or last blood pressure during the study period was above 140/90 mm Hg in another 7% of the patients.

3.5. Psychiatric Disease. Contraindications for rimonabant and sibutramine included ongoing depression or treatment with antidepressants. 28% of the patients who started treatment with rimonabant and 32% of the patients with sibutramine had a diagnosis of depression and/or antidepressant treatment during the study period (see Table 2). Whether the depression and/or antidepressant treatment was present before the initiation of weight-loss drug treatment, occurred during the treatment, or occurred after the treatment, has not been analysed. 58% of rimonabant patients and 56% of sibutramine patients had signs of psychiatric problems in their medical history (anxiety, sleeping disorder, stress disorders, professional burnout, eating disorder, or treatment for such conditions). Psychiatric disease was a contraindication for sibutramine. Patients treated with orlistat had a slightly higher frequency of both depression or treatment of depression and other psychiatric problems, but such patients can be treated with the drug without additional risk.

3.6. Initiative to Treat. In 48% of the cases, it was clearly stated in the medical file that the patient asked for treatment with weight-loss drugs, often with the wish for a specific drug. It was unclear whether the patient or the prescribing physician had taken the initiative to drug treatment in 50% of the cases. In only 2% of the cases, it was clearly stated that the physician had proposed treatment with the weight-loss drug.

3.7. Prescription of Other Weight-loss Drugs. In total, 40% of the patients had tried one or both of the other weight-loss drugs during the study period −48% of those receiving rimonabant, 46% of those receiving sibutramine, and 27% of those receiving orlistat.

3.8. Weight Change. In 51% of all 300 patients, Rave3 found no documentation of the patient's weight under the right heading in the electronic medical record. We therefore also conducted a manual evaluation of the case records. We limited this analysis to patients having been prescribed the weight-loss drug for at least one year since a meaningful effect on weight requires a long period of treatment. Among the 300 manually analysed patient records, 100 patients had been prescribed the drug for one year or longer −48 had had rimonabant, 31 sibutramine, and 21 orlistat. These patients were further analysed regarding the last documented weight after at least 9 months of treatment. In 62 patients the data were insufficient to evaluate changes in weight. 28 patients had lost weight, and 10 patients had an unchanged weight.

Only 18 out of the 300 patients, that is, 6% had the drug prescribed for at least one year and a confirmed clinically relevant weight-loss of at least 5% after at least 9 months of treatment (see Figure 1). Whether the weight loss achieved depended on the drug treatment or other factors cannot be concluded in this study, and possible long-term changes in weight among other patients could not be deduced from the medical records.

3.9. Documentation of Weight. 26% of the patients who had been prescribed the weight-loss drug for at least one year lacked documentation of his/her initial weight or weight within 3 months prior to the prescription. 36% lacked a followup weight on any occasion after the initiation of treatment. For these reasons, it was impossible to draw any conclusions regarding treatment efficacy in 45% of the patients. This indicates that the management and followup of patients treated with weight-loss drugs was inadequate.

Table 2: Patient characteristics (Values within parentheses are 95% Confidence Intervals (CI). CIs around medians calculated by binomial method, and around relative frequencies by exact binomial method.).

	All patients ($N = 300$)	Rimonabant patients ($N = 100$)	Sibutramine patients ($N = 100$)	Orlistat patients ($N = 100$)
Median age	47	55 (50–57)	42 (40–45)	49 (45–53)
P_{25}	39	44	35	39
P_{75}	59	63	54	59
Age span	17–96	23–78	17–76	21–96
Men	23%	23% (15–32)	18% (11–27)	28% (19–38)
Women	77%	77% (68–85)	82% (73–89)	72% (62–81)
Body Mass Index				
No BMI	29%	25% (17–35)	31% (22–41)	31% (22–41)
BMI <28 kg/m^2	5%	5% (2–11)	3% (0.6–9)	7% (3–14)
BMI 28–35 kg/m^2	32%	36% (27–46)	27% (19–37)	32% (23–47)
BMI >35 kg/m^2	34%	34% (25–44)	39% (29–49)	30% (21–40)
Concomitant diseases and treatments				
Diabetes	24%	31% (22–41)	13% (7–21)	28% (19–38)
Dyslipidemia	63%	72% (62–81)	60% (50–70)	57% (47–67)
Diabetes, and/or dyslipidemia	65%	75% (65–83)	60% (50–70)	61% (51–71)
Treatment for diabetes	19%	26% (18–36)	9% (4–16)	22% (14–31)
Treatment for dyslipidemia	24%	36% (27–46)	15% (9–24)	21% (13–30)
Treatment for diabetes and/or dyslipidemia	32%	43% (33–53)	21% (13–30)	33% (24–43)
Cardiovascular disease and/or hypertension	51%	66% (56–75)	41% (31–51)	47% (37–57)
Depression and/or antidepressant treatment	34%	28% (19–38)	32% (23–42)	42% (32–52)
Psychiatric problems	60%	58% (48–68)	56% (46–66)	66% (56–75)
Pain and other musculoskeletal problems	66%	67% (57–76)	65% (55–74)	66% (56–75)

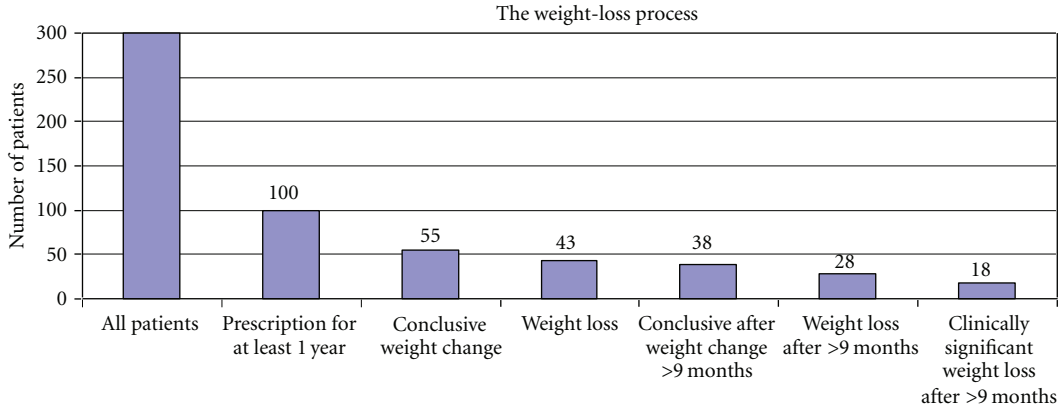

Figure 1: The weight loss process.

3.10. Treatment Persistence. Although 33% of the 300 patients in the present study had been prescribed drug treatment for at least one year, it appears that 23% of them actually purchased the drugs for at least one year of treatment −32% on rimonabant, 25% on sibutramine, and 13% on orlistat (see Figure 2). Among the 300 patients, 6% never filled the first prescription at the pharmacy.

3.11. Treatment Discontinuation. Most commonly, no reason for discontinuation was documented (65% of the patients). The most common cause for discontinuation of rimonabant was prescription until, or past, the date of market withdrawal which is reported under "Other" (see Table 3). Other common reasons included side effects reported by 15% and dissatisfaction with the effect reported by 11%. The

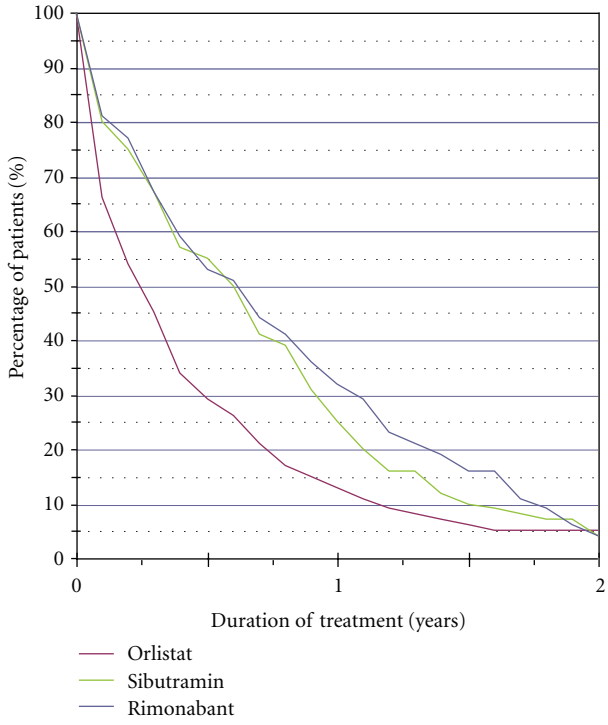

Figure 2: Percentage of patients left on treatment.

most commonly documented causes for discontinuation for patients having received sibutramine were dissatisfaction with the effectiveness of the drug and side effects reported by 11% each. 7% of the patients having received orlistat stopped treatment due to dissatisfaction with the effectiveness, and 4% quitted due to side effects.

4. Discussion

In this retrospective, descriptive study, prescription routines for 300 randomly selected patients having started weight-loss drug treatment at 15 primary care centres were investigated using patients' electronic medical records and their complete drug purchase data from the Swedish National Board of Welfare. Generally, patients who received weight-loss drugs had a poor health status with cardiovascular disease, diabetes, dyslipidemia, depression, and other psychiatric problems. Many had attempted treatment with other weight-loss drugs, and a significant proportion had listed contra-indications to the prescribed drug. Even though the patients often specifically demanded weight-loss drug treatment from the doctor, 77% continued treatment for less than one year. A large proportion of the patients were not weighed prior to treatment initiation and not followed within the context of a structured lifestyle intervention.

Prescription of weight-loss drugs was the most common in the Stockholm County Council than elsewhere in the country [10]. Our results are thus not generally applicable throughout Sweden but suggest problems that probably exist to varying degrees at many primary care centres. However, our earlier analysis of national prescription data for weight-loss drugs in Sweden showed similar results with a frequent history of use of other weight-loss drugs and antidepressant drugs, and with many patients who were not on drug treatment for diabetes and/or dyslipidemia [10]. Needless to say, the management of overweight patients might vary between different units and prescribers.

The present results suggest that many patients were prescribed weight-loss drugs despite possible or definite contraindications. It is remarkable that information about the key variable of interest, that is, body weight, was so often lacking in the medical records. All three weight loss drugs were only licensed for weight-loss treatment in combination with a structured weight loss program including exercise and diet. Regular followup including weight measurements both before and during such a program is essential and should be a mainstay in the treatment of overweight. The moderate weight loss seen in clinical trials of these drugs [12] is not generally applicable to short-term treatments without followup. Frequent prescriptions for patients with contraindications or other conditions prompting for caution are an important safety aspect. Both rimonabant and sibutramine have been withdrawn from the market. The present data support the wisdom of these withdrawals.

Even though advertising for prescription drugs is illegal in the European Union, it was often stated in the medical records that the reason for consulting the doctor was to obtain weight-loss drug treatment, often with the wish for a specific drug. Safety and efficacy concerns normally appear to have a major influence on the use of new drugs in primary care [19]. However, denying treatment to a patient who through media, friends, the Internet, or other sources has got the impression that there are effective drugs for losing weight is a delicate task and requires knowledge on the behalf of the prescriber in order to motivate his/her decision to treat or not to treat with a drug. Additional possibilities to advertise directly to patients would probably further increase the problems described in this article [20, 21].

In our earlier analysis of the national prescription data, we found that only 1/3 of the patients who started treatment with rimonabant during its first six weeks on the market continued the treatment after 6 months [10]. A Canadian evaluation of the treatment persistence with sibutramine and orlistat showed that less than 10% of the patients remained on treatment after one year, and less than 2% continued treatment after 2 years [22]. Maintaining the patients on treatment has been a problem also in the clinical trials [12, 23]. For example, the drop-out rate in the clinical trials of rimonabant was 35–50% during the first year [24–27]. Lack of persistence with treatment was a major problem in this study as well. Lack of efficacy or adverse events are the likely major causes of premature discontinuation of treatment. However, the reasons are seldom clearly stated in the medical record.

4.1. The Future. It is likely that the trend of informed patients actively seeking medical treatment for lifestyle-related conditions will increase. It might be problematic to achieve a rational use of drugs which are seldom prescribed

Table 3: Reasons for discontinuation.

	Unclear	Not terminated	Other	Lack of effect	Neurological side effects	Psychiatric side effects	Gastrointestinal side effects	Cardiovascular side effects	Other side effects
Rimonabant ($N = 100$)	53%	0%	21%	11%	3%	5%	4%	0%	3%
Sibutramine ($N = 100$)	65%	9%	4%	11%	1%	4%	1%	4%	1%
Orlistat ($N = 100$)	78%	6%	5%	7%	0%	0%	2%	0%	2%

by the average general practitioner, especially if the treatment is new on the market. Unbiased continued medical education about new drugs appears to be important, and electronic tools for prospective data collection could possibly improve the quality regarding both initiation of therapy and followup of particularly sensitive and/or expensive drug treatments. These results show the importance of prioritizing the development of such assistance.

5. Conclusions

In conclusion, this observational study suggests that the treatment with weight-loss drugs was of limited clinical benefit the way they were used in a large proportion of Swedish primary care. Also, our results indicate that effective models are needed to evaluate the risks and benefits of treatment with life-style drugs in the everyday clinical setting.

Conflict of Interests

The authors declare that they have no conflict of interest.

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Research paper

Financial incentives linked to self-assessment of prescribing patterns: a new approach for quality improvement of drug prescribing in primary care

Björn Wettermark MSc Pharm PhD
Senior Researcher, Department of Drug Management and Informatics, Stockholm County Council and Karolinska Institutet, Centre for Pharmacoepidemiology and Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska University Hospital – Huddinge

Åke Pehrsson BA
Administrator

Maria Juhasz-Haverinen, MSc Pharm
Pharmacist, Division of Finance and Healthcare Planning, Stockholm County Council, Sweden

Aniko Veg PhD
Senior Researcher, Department of Public Health and Caring Sciences, Uppsala University, Sweden

Maria Edlert BA
Administrator, Department of Drug Management and Informatics, Stockholm County Council

Gunilla Törnwall-Bergendahl BA
Chief Economist

Henrik Almkvist MD
Head of Department

Division of Finance and Healthcare Planning, Stockholm County Council, Sweden

Brian Godman BSc
Researcher, Institute for Pharmacological Research 'Mario Negri', Milan, Italy

Fredrik Granath PhD
Statistician, Centre for Pharmacoepidemiology and Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Ulf Bergman MD PhD
Senior Medical Officer, Department of Drug Management and Informatics, Stockholm County Council and Karolinska Institutet, Centre for Pharmacoepidemiology and Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska University Hospital – Huddinge

ABSTRACT

Background Financial incentives have been suggested to be effective in increasing the quality and efficiency of drug prescribing. Concern has been raised in relation to potential negative consequences on the quality of care.

Aims To describe and analyse the impact of an incentives model linking payment with adherence to drug and therapeutics committee (DTC) guidelines and self-reflection of prescribing pattern in a 'prescribing quality report'.

Methods The study was performed in the county of Stockholm, Sweden, with 139 (out of 154) primary healthcare centres (PHCs) participating in the project and 15 PHCs not participating. The study consisted of two parts: a quantitative observational study of prescribing patterns and a qualitative analysis of the submitted prescribing quality reports. All prescriptions issued from PHCs and dispensed at pharmacies during October to December 2005 and October to December 2006 were analysed, using adherence to

the regional DTC guidelines as the main outcome measure. Adherence was assessed using the drug utilisation 90% methodology, i.e. focusing on drugs constituting 90% of the prescribed volume and the proportion of drugs included in the guidelines. The qualitative analysis focused on reports on the quality of drug prescribing submitted by each PHC in early 2007.

Results The 139 PHCs participating in the programme accounted for 85% of all prescriptions issued in primary care during October to December 2006. Mean adherence to guidelines increased among participating practices by 3.3 percentage units (95% confidence interval (CI) 2.9–3.7%) to 83% (82.6–83.7%) during the year. The adherence among practices not participating increased by 3.1 percentage units (95% CI 1.7–4.4%) to 78.8% (95% CI 76.7–80.9%). The higher adherence achieved during the year corresponded to savings estimated at five times greater than the cost of running the programme including the financial incentives. In addition, many areas for improving prescribing were identified, such as limiting the prescribing of drugs with uncertain safety profiles and documentation as well as reporting adverse drug reactions.

Conclusion Although no causal effect can be attributed without a control group, we have shown the feasibility of a model linking payment to DTC adherence. This approach with its own quality assessment and goal setting offers an example to other regions and countries of how to increase the quality and efficiency of drug prescribing within limited resources.

Keywords: general practice, incentives, prescribing, primary health care, quality indicators

How this fits in with quality in primary care

What do we know?

There is room for improvement in adherence to guidelines for rational prescribing as current strategies have only limited effects in enhancing implementation. Financial incentives can be used to improve the quality and efficiency of prescribing. However, many incentive schemes are short lived and costly to administer and lead to uncertain effects on the quality of care. Few studies have reported whether the benefits/savings achieved using financial incentives outweigh the costs of performing the intervention.

What does this paper add?

A model linking financial incentives to drug and therapeutics committee (DTC) adherence and local assessment of prescribing performance in a 'prescribing quality report' demonstrated the feasibility of using financial incentives to stimulate activity to increase the quality of prescribing in primary health care. The increased adherence to DTC guidelines achieved during the first year of the programme corresponded to decreased annual expenditure for prescription drugs by approximately €21 000 per practice (with an average of six general practitioners). Self-assessment of quality and goal setting based on self-reflection of prescribing patterns differed from prescribing incentive schemes used in other countries, and offers a way to increase the quality, safety and efficiency of drug prescribing within relatively limited resources.

Introduction

Most countries are facing the challenge of growing healthcare demand with limited available resources. The cost of pharmaceuticals is particularly in focus since the growth in expenditure has been greater than for other healthcare components,[1–6] and will accelerate with increased prevalence of chronic diseases combined with the continued launch of new expensive medicines.[7] Consequently, various strategies have been applied in pharmaceutical policymaking to influence the quality and efficiency of prescribing, including positive and negative financial incentives, educational interventions, prescribing targets and regulatory changes.[6,8–15]

Financial incentives can be used to reduce the use of healthcare resources, improve compliance with practice guidelines or achieve general health targets. Allocating drug budgets to doctors has been suggested as an effective method to influence physicians and increase the cost-effectiveness of prescribing.[6,14,6–19] Consequently, incentive schemes and drug budgets are applied today in many countries in Europe and also in the United States.[3,6,12,18,20,21]

In Sweden, initiatives to improve the quality of drug prescribing have been organised by drug and therapeutics committees (DTCs).[6,22,23] These activities include decision-support systems for prescribing, educational programmes, feedback on prescribing patterns, and evidence-based guidelines for drug treatment.

In recent years, financial incentives have also been introduced. A range of models have been used, from financial incentives linked to certain targets to capitation-based drug budgets.[6,24] Some regions apply population-based models, while others allocate a specific budget to each practice based on historic prescribing patterns. The former model is more common in rural areas and the latter more common in major cities.

The provision and financing of health services in Sweden is a public sector responsibility, primarily resting with 21 county councils. Primary health care is the basis of the Swedish healthcare system but it has no gatekeeper function and therefore many healthcare providers are involved in patient management and drug prescribing. In the county of Stockholm, the local primary healthcare centres (PHCs) only account for one-third of consultations and dispensed prescriptions to the population in the surrounding area.[25,26] Consequently, it is not feasible to link drug budgets to specific patient populations, and a model with incentives linked to prescribing behaviour and adherence to guidelines was introduced in Stockholm in 2006.

The new model included extra payments linked to the level of adherence to the DTC guidelines (measured as the proportion of the drugs prescribed included in the guidelines) and the submission of a 'prescribing quality report'. Templates were issued including questions about the doctors' opinion of their adherence to DTC guidelines, goals for improvement including their prescribing of new medicines, documentation and reporting of adverse drug reactions (ADRs), contacts with the pharmaceutical industry, participation in clinical trials and continuing professional development. The intention of the model was to use financial incentives to increase doctors' cost-consciousness, while at the same time stimulating them to assess the quality of their drug prescribing and finding potential ways to improve it. The aim of this study is to describe the model and PHCs' experiences with it.

Methods

The study was performed in the county of Stockholm, Sweden, which has 1.9 million inhabitants and 169 PHCs; 154 PHCs were invited to participate, with one municipality excluded due to a separate healthcare organisation. This was an observational study without a formal control group and was based on quantitative data on prescribing patterns from 2005 to 2006 and qualitative data summarised in the 'prescribing quality reports' for 2006. The quantitative analyses provided a description of the adherence to the guidelines before and after the incentives were introduced, and the qualitative analysis contributed to a deeper understanding of which factors the PHCs considered important to improving the quality of drug prescribing.

Quantitative analysis of prescribing patterns

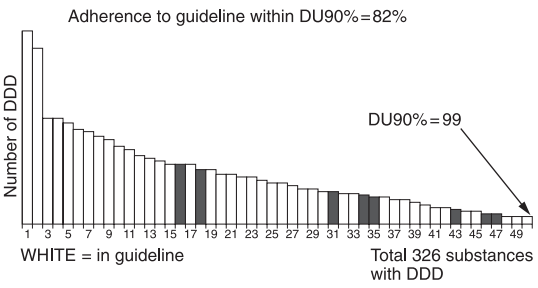
The quantitative analysis was performed with routinely collected data on dispensed prescriptions in ambulatory care patients from all PHCs participating in the programme. Data were collected from the Swedish National Prescription Register administered by the National Corporation of Swedish Pharmacies.

The time periods for analyses were October to December 2005 and October to December 2006. These periods were chosen to reflect prescribing before and after the schemes were introduced. Using dispensing data from the last quarter of each year would minimise the problem with older repeat prescriptions issued before the project started (a prescription is valid for one year in Sweden).

Data were classified according to the ATC (Anatomic Therapeutic Chemical) classification.[27] Drug utilisation was expressed as defined daily doses (DDDs), prescription items and expenditures in Euros. Adherence to DTC guidelines was assessed using the DU90% (drug utilisation 90%) method which assesses the number of drugs constituting 90% of the prescribed volume expressed in DDDs and adherence to guidelines within this segment (see Figure 1).[28–30]

The guidelines for comparison were the list of drugs recommended by the DTC in Stockholm in 2006, the so-called 'Wise Drug List'.[6,22,23,31] These guidelines are produced by over 20 expert groups, which include general practitioners (GPs), hospital specialists, pharmacists and clinical pharmacologists. They consist of diagnosis-specific evidence-based recommendations with some 200 to 240 pharmaceutical products suggested as first-line choices for outpatient treatment of common diseases.[6,22,23] In this study, adherence was calculated by substance regardless of which pharmaceutical product (brand or generic) was prescribed and dispensed to the patient.

Descriptive statistical values (mean, median, 95% confidence interval (CI) and range) were calculated. Crude comparisons of adherence to the DTC in 2005 with respect to activities reported in the prescribing quality reports were performed by *t* tests. The same comparisons were also performed using a multiple linear regression model. Crude and mutually adjusted differences are presented together with 95% CIs. The association between reported activities and change in adherence between 2005 and 2006 was assessed using analysis of covariance, where the 2005 value was included as a covariate in order to allow for ceiling effects. A corresponding analysis of covariance was performed to assess the change in adherence between



	SUBSTANCE	(DDD)	DDD	%TOT	Rx	COST	COST/DDD
1	**Acetylsalicylic acid**	1tablet	24 977	5.4%	291	14 755	0.59
2	**Enalapril**	10 mg	22 641	4.9%	236	14 379	0.64
3	**Simvastatin**	15 mg	13 263	2.9%	205	15 783	1.19
4	**Metoprolol**	0.15 mg	13 185	2.8%	289	60 001	4.55
5	**Metformin**	2 g	12 862	2.8%	184	22 515	1.75
6	**Paracetamol**	3 g	11 559	2.5%	385	31 773	2.75
7	**Cyanocobalamin**	1 mg	11 456	2.5%	137	9 549	0.83
8	**Hydroc.thiazide + amiloride**	1 tablet	11 106	2.4%	124	6 618	0.60
9	**Furosemide**	40 mg	10 861	2.3%	124	11 371	1.05
10	**Zopiclone**	7.5 mg	10 336	2.2%	212	10 056	0.97
11	**Omeprazole**	20 mg	10 094	2.2%	185	40 369	4.00
12	**Citalopram**	20 mg	9 400	2.0%	129	7 086	0.75
13	**Bendroflumethiazide**	2.5 mg	9 094	2.0%	70	8 188	0.90
14	**Budesonide**	*	8 792	1.9%	122	65 052	7.40
15	**Ramipril**	2.5 mg	8 412	1.8%	29	5 511	0.66
16	**Atenolol**	75 mg	8 401	1.8%	104	7 267	0.87
17	**Levothyroxine sodium**	0.15 mg	8 306	1.8%	143	11 303	1.36
18	**Felodipine**	5 mg	7 606	1.6%	79	8 264	1.09
19	**Terbutaline**	*	7 525	1.6%	147	28 560	3.80
20	**Propiomazine**	25 mg	6 458	1.4%	93	7 575	1.17
…							
99							
DU 90%	**1-99**		417 592	90.0%	6 935	1422 776	3.41
	100-326		46 152	10.0%	1 330	397 887	8.62
TOTAL	**1-326**		**463 744**	**100%**	**8 265**	**1820 664**	**3.93**

***Bold* = in guideline**
**** = different DDDs for various routes of administration***
Medicines without DDD excluded (64, corresponding to 108 009 SEK)

Figure 1 Example of a drug utilisation 90% (DU90%) prescribing profile for a PHC centre based on drugs dispensed at all pharmacies in the country October to December 2006. DU90% = drug utilisation 90% – the number of drugs constituting 90% of the volume expressed in DDDs. Adherence is calculated as the percentage of DDDs for drugs in the regional DTC guideline compared with the total number of DDDs within the 90% segment. Rx = number of prescription items, cost is presented in Swedish Crowns (SEK), 100 SEK = 10.5 Euro (March 2009)

units with and without incentives. Differences were considered statistically significant for $P < 0.05$.

Correlation between adherence and cost/DDD (see Figure 3) was calculated using Pearson's correlation coefficient (r). A value for $P < 0.05$ was considered significant. Potential savings relating to increased adherence to the guidelines were calculated by multiplying the proportional decrease in cost/DDD for each percentage increase in adherence with the total number of DDDs prescribed.

Qualitative analyse of submitted prescribing quality reports

Each PHC received a questionnaire by email. The questionnaire was developed through a consensus procedure by the regional division of finance and healthcare planning at the beginning of 2007 (see Box 1). Most questions were closed (yes/no), to facilitate analyses. The reports were submitted by the head physician in each PHC to enhance the robustness of the answers, and embodied reflections on one year's prescribing patterns at the local PHC. Two open-ended questions (Q2 and Q8, Box 1) were analysed qualitatively, since they were strongly related to the aim of the reports and the answers were sufficiently long to build a short text.

A thematic analysis of the contents of the submitted quality reports was made by two of the authors (AV and ME). The first step of the analysis was a thorough reading of each short text. The second step involved formulating the initial categories in order to start collating the replies. Additional categories were derived with ongoing analysis of the text. The derived

Box 1 Template for quality reports submitted in early 2007, *italic* = open-ended questions

Q1 Has the PHC participated in any former project to improve the rational use of drugs and/or to increase the cost-consciousness of drug prescribing?
Q2 Describe three observations acquired when analysing your prescribing patterns.
Q3 *Which prescribing feedback reports available through the internet (www.janusinfo.se) did you use to assess your quality of prescribing (DU90%, DC90%*, prescribing targets, others)?*
Q4 *Suggest three areas for improvement.*
Q5 *Which new drugs have you introduced recently and how do you assess the value of them for patient care?*
Q6 Does your PHC have routines for reporting adverse drug reactions (ADRs)? Do you discuss ADR case reports as a part of your continuing professional education?
Q7 How many and which ADR reports have you submitted during 2006?
Q8 Describe which other factors may have influenced your prescribing patterns.
Q9 *Describe your participation in educational activities arranged by the DTC, other professional organisations and the pharmaceutical industry.*
Q10 Have you received support from an information doctor/pharmacist when analysing your prescribing patterns?
Q11 Are the recommended drugs marked separately in your electronic medical record?
Q12 Did you participate in any clinical trial during 2006? For which drug?
Q13 Has any doctor at your PHC been a member of the DTC or any expert group during 2006?

*DC90% = drug cost 90%, substances accounting for 90% of the total expenditures

final list of categories constituted both factors promoting and factors explaining difficulties in reaching good adherence to recommendations (see Table 3). These categories were subsequently discussed with the other members of the research team before embarking on the analysis to enhance the robustness.

Results

A total of 139 out of 154 invited PHCs (90%) agreed to participate in the study. The main reasons for not participating were that PHCs missed the deadline for inclusion, or concerns about additional workload. The 15 non-participating PHCs subsequently served as the 'controls'. The first quality reports were submitted in early 2007 based on 2006 data. In 2006, a total of €2 million was spent on incentives to the 139 participating PHC centres, with payments per practice varying depending on their performance. As an example, a PHC with seven GPs and an adherence to the DTC guidelines of 87% received €18 000; average adherence was 82% in October to December 2006.

Quantitative analysis of prescribing patterns

During October to December 2006, after the incentives were introduced, 4.4 million prescription items were dispensed to the inhabitants of Stockholm County. This represents an average of 2.4 prescription items per inhabitant. Forty-three percent of all prescriptions had been issued in primary health care. The 139 participating PHCs accounted for 85% of all prescriptions issued by all 169 PHC centres in the county. The total expenditure for prescribing in primary health care was €35 million, constituting 26% of the total ambulatory care prescribing in the county. The number of prescriptions increased by 10% and the expenditure by 4% compared to October to December 2005.

Adherence to the DTC recommendations was on average 83.1% (95% CI 82.6–83.7%) in October to December 2006, and varied between 62% and 90% among participating practices. The practices not included were smaller (8000 versus 11 500 dispensed prescription items/practice/quarter). They also had a significantly lower adherence to guidelines than those participating in the scheme (78.8% (95% CI 76.7–80.9%)).

Adherence to DTC guidelines increased by 3.3 percentage units (95% CI 2.9–3.7%) among practices participating compared to 3.1 percentage units (CI 1.7–4.4%) in those not participating. A significantly lower increase among non-participating centres was observed after adjustment for the ceiling effect, i.e. that the participating practices had a significantly higher adherence prior to introduction of the schemes (see Figure 2).

After the incentives were introduced, a clear correlation was observed between high adherence and low

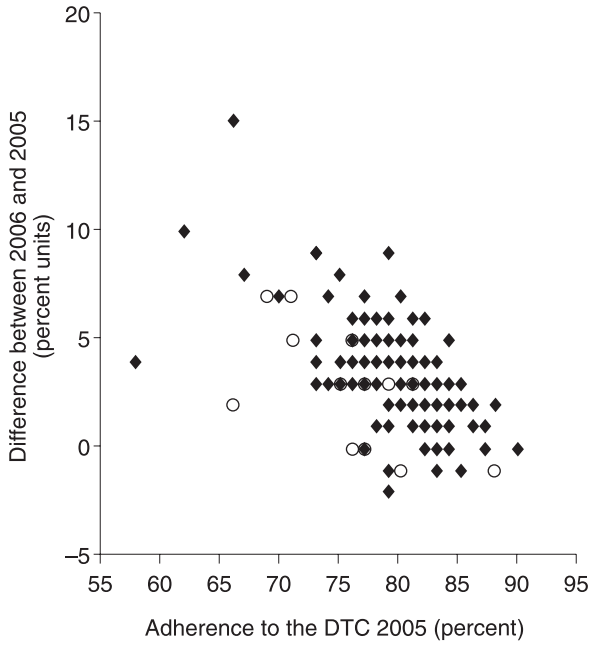


Figure 2 Baseline adherence to the DTC recommendations using DU90% in October to December 2005 and change between October to December 2005 and October to December 2006. Primary healthcare centres in the county of Stockholm were invited to participate in the schemes (n = 154). Dark diamonds represent the 139 practices participating in the schemes, white circles show the 15 non-participating PHCs serving as 'controls'

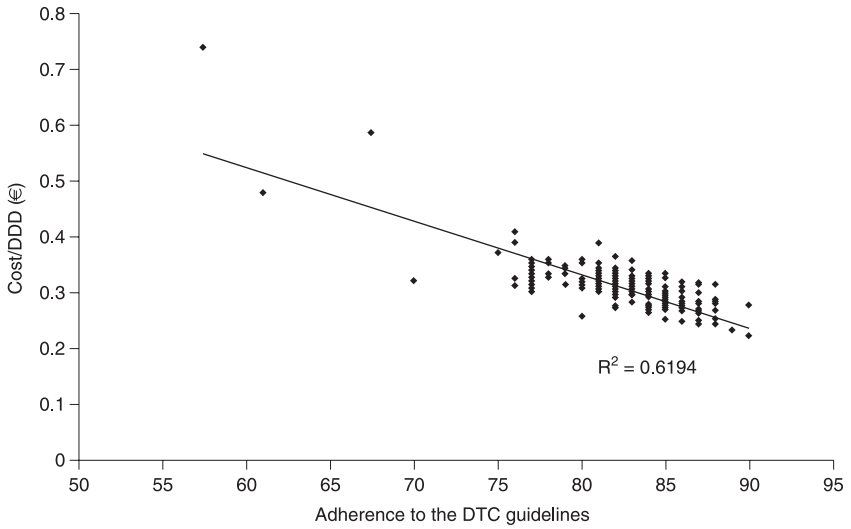


Figure 3 Correlation between adherence to DTC guidelines (within DU90%) and average cost/DDD, October to December 2006 in all PHC centres in the county (n = 169). R^2 = coefficient of determination

cost/DDD (see Figure 3). An increased adherence of 1% corresponded to €0.47 lower cost/prescription item. For a PHC of average size (six GPs), this corresponded to an approximately €21 000 lower annual drug expenditure. Consequently, with a total of 6.4 million prescription items dispensed in 2006 at participating PHC centres, increasing adherence by 3 percentage units resulted in estimated annual savings of more than €10 million.

Prescribing quality reports

More than half of all PHCs (58%) claimed that they had participated in previous projects with the aim of improving prescribing quality and/or increasing the cost-effectiveness of prescribing. A majority of participating and non-participating practices, 84% and 83% respectively, received support from information doctors and/or pharmacists (medical doctors or pharmacists with special training employed or financed by the Drug and Therapeutics Committee to disseminate guidelines and educate healthcare professionals in rational pharmacotherapy) or had guideline drugs highlighted in the electronic prescribing support system to enhance the quality and efficiency of prescribing. One-quarter of the PHCs (26%) had participated in clinical trials and 22% had doctors who were members of the DTC or one of the expert groups.

The analysis of the prescribing quality reports emphasised the need for improving documentation and reporting of ADRs. Fifty-two percent of the PHCs had local processes for documenting ADRs, and 85% claimed that they regularly discussed cases of ADRs at their internal meetings. However, many PHCs also suspected a substantial under-reporting of ADRs. In the prescribing quality reports, these PHCs stated that they had submitted a total of 300 ADRs to the regional ADR monitoring unit in 2006. This corresponded to half of all submitted ADR reports (n = 585) from all PHCs in the region.

There were certain differences in adherence to the DTC recommendations between participating PHCs in October to December 2005, before the programme started, with a significantly higher adherence at baseline for PHCs previously participating in projects or with doctors that were members of the DTC or one of the expert groups (see Table 1).

However, the change in adherence during the year showed the opposite pattern, with greater increases in adherence observed among PHCs having the lowest baseline adherence rates initially (see Table 2). These differences disappeared when adjusted for the ceiling effect.

Qualitative analysis of submitted quality reports

A total of 137 prescribing quality reports were submitted. The result of the analysis of question Q2, 'Describe three observations acquired when analysing your prescribing patterns', showed most PHCs were satisfied with their own improvements in drug prescribing, and they considered themselves to have good adherence to the DTC guidelines. A common conclusion was that the most frequently prescribed drugs were recommended in the guidelines. However, there were also observations of high prescribing of certain drugs that were not recommended, which is now being addressed, such as 'reducing unnecessary prescribing of antibiotics'. Some explanatory factors behind high or low adherence to the guidelines are presented in Table 3.

Table 1 Association between activities reported in prescribing quality reports (see Box 1) and guidelines adherence in October to December 2005

Question in prescribing quality report	Mean		Difference – crude			Difference – adjusted		
	Yes	No	Yes – no	95% CI	*P* value	Yes – no	95% CI	*P* value
Q1 Participation in former project	80.8	78.8	1.97	(0.46–3.48)	0.01	2.00	(0.41 to 3.59)	0.01
Q6a Routines for reporting ADRs	80.1	79.9	0.25	(–1.31 to 1.80)	0.75	–0.63	(–2.19 to 0.93)	0.43
Q10 Support from information doctor/ pharmacist	80.2	78.6	1.56	(–0.63 to 3.76)	0.16	0.73	(–1.59 to 3.05)	0.53
Q11 Recommended drugs marked in electronic medical record	80.2	78.8	1.36	(–0.69 to 3.42)	0.19	1.49	(–0.55 to 3.53)	0.15
Q12 Participation in clinical trial	79.1	80.3	–1.21	(–2.94 to 0.52)	0.17	–1.48	(–3.16 to 0.21)	0.08
Q13 Member of DTC	82.0	79.4	2.57	(0.78 to 4.36)	<0.01	2.44	(0.64 to 4.25)	<0.01

Univariate analysis (crude) and multivariate analysis (adjusted)
Data are mean and difference including 95% confidence intervals (n = 121 reports)

The PHCs identified therapeutic areas or single drugs where a substantial improvement in adherence would be possible, for example: 'reducing the prescribing of angiotensin receptor blockers in favour of ACE [angiotensin-converting enzyme]-inhibitors' or 'increasing the prescribing of start-packages when possible'. The suggested strategies were in accordance with the guidelines; these included increasing prescribing of recommended drugs when initiating drug therapy with new patients, or reserving certain drugs as second-line choice for more restricted indications. Furthermore, many PHCs wanted to increase their knowledge of pharmacotherapy through educational activities, perform regular reviews of their prescribing patterns, and in general: 'increase knowledge about drugs and their adverse effects'.

Discussion

This study has demonstrated the feasibility of using financial incentives to stimulate the quality of prescribing through increased adherence to evidence-based drug therapies recommended by the expert groups in the DTCs and through self-assessment of ways to improve future prescribing. In the first year of the programme, adherence to DTC guidelines increased on average by 3 percentage units from 80% to 83%, a substantially higher increase than the 0–2% achieved in previous years.[30] Although 3% does not seem to be a high figure, it is more than generally achieved through educational interventions.[11,13] In addition, the study started from a high average adherence rate of 80%. It is likely that the programme supported this increase, although this cannot be concluded with this observational study since it does not correct for other factors influencing prescribing patterns, such as pharmaceutical company marketing activities for new and existing drugs, new indications for existing drugs and changes in regulatory policies.[32–34] It is interesting that adherence rates increased by a similar extent among PHCs not participating in the programme. However, these PHCs were not completely comparable. As discussed, they were smaller and had a lower adherence to the guidelines initially with, consequently, greater room for improvement. Furthermore, they may have been contaminated by the intervention since they participated in the same professional networks and educational activities.[31]

It is a challenge to change professional behaviour. Simple diffusion or dissemination of printed material

Table 2 Association between activities reported in prescribing quality reports (see Box 1) and change in adherence to guidelines adherence between October to December 2006 and 2005, respectively

Question in prescribing quality report	Change 2005–2006			Adjusted difference (yes/no)		
	Yes	No	Crude difference	Yes – no	95% CI	*P* value
Q1 Participation in former project	3.00	3.97	–0.97	–0.15	–0.89 to 0.58	0.68
Q6a Routines for reporting ADRs	3.20	3.56	–0.36	–0.41	–1.12 to 0.29	0.25
Q10 Support from information doctor/pharmacist	3.29	3.88	–0.59	0.29	–0.75 to 1.35	0.58
Q11 Recommended drugs marked in electronic medical record	3.33	3.60	–0.27	0.35	–0.58 to 1.28	0.46
Q12 Participation in clinical trial	3.78	3.23	0.55	0.10	–0.67 to 0.87	0.80
Q13 Member of DTC	2.96	3.49	–0.53	0.69	–0.15 to 1.53	0.11

Crude change and multivariate analysis adjusted for 2005 value
Data are mean and difference including 95% confidence intervals ($n = 121$ reports)

Table 3 Perceived factors influencing the adherence to DTC guidelines reported by PHCs in prescribing quality reports

Promoting factors	Interfering factors
Internal review of prescribing patterns assisted by an information pharmacist or physician from the drug and therapeutics committee (DTC)	Therapy initiated by a hospital-based specialist or other physician
Continuing professional education organised by the DTC	Frequent changes in the recommendations
Participation in drug-related studies and/or carrying out studies at the PHC locally	The practice staff consist of temporarily employed doctors
	Patient characteristics, e.g. immigrants, elderly people living in nursing homes, demanding and self-sufficient patients
	Difficulties in changing recommendations from the previous year

and mailed feedback on prescribing patterns may influence professionals' awareness and knowledge, but they seldom change behaviour.[11,35–37] More intensive strategies such as 'academic detailing' as well as guideline development coupled with comprehensive dissemination strategies do change behaviour, although few studies have reported if the benefits/savings achieved using these strategies outweigh the costs of performing them.[11,15,35,38,39] Although it cannot be definitely concluded that the increased adherence was solely due to the incentives programme, the calculated savings were five times higher than the cost of running the programme. Alongside this, physicians identified a number of activities to help improve future prescribing

quality. Consequently, our model suggests a potential way to increase the quality and efficiency of drug prescribing with relatively limited resources. The calculated savings were based on the observed correlation between adherence and cost/DDD. This negative correlation between adherence and cost has arisen in recent years and is explained by ongoing reforms in Sweden to achieve low prices for generic medicines coupled with programmes to encourage generic prescribing as first line.[6,23] In most cases generic drugs are equally effective and less expensive than the corresponding patented drugs.[6,40–43] Recently, the National Audit Office in the UK also documented that considerable savings (£227million) could be achieved by increasing prescribing of generic simvastatin, omeprazole and ACE inhibitors compared with branded drugs in the same or related classes.[6,34]

Overall, financial incentives have been shown in previous studies to be effective in improving the quality and efficiency of prescribing.[18,19,21,44,45] However, the effects can be short lived,[16,17] and the long-term effects on the quality of care are less well studied. In a systematic review of studies published between 1993 and 1999, it was suggested that financial incentives for drug prescribing could decrease the quality of care by limiting continuity, reducing the preventive services offered and increasing inappropriate use of emergency services.[46] Concern was also raised about the potential change in the doctor–patient relationship, and the potential negative consequences in the long term of reducing time for teaching and research. Consequently, such initiatives must be carefully planned and monitored. We consider the risk of negative consequences to be low with our approach, since the incentives were not linked to specific medical decisions but used to stimulate overall adherence to guidelines that had been developed with robust technologies. In addition, the DU90% method used to monitor adherence offers advantages since it focuses on those medicines accounting for 90% of the volume, thereby leaving some latitude to deviate from guidance if needed. In addition, we gave physicians the opportunity to reflect on ways to improve their own prescribing. We believe that measuring adherence with routinely collected data is preferable since it is known that self-reported data produce an overestimate of adherence to guidelines.[39,47] Furthermore, too strong a focus on auditing and payment for performance may also pose a threat to the validity of the data recorded if physicians take the opportunity to manipulate the data to increase their incomes.[39,48,49]

As previously stated, the quality reports were an addition to the prescribing incentive scheme, enhancing the opportunity for physicians to increase both the quality and efficiency of their prescribing. They also offered the potential for local ownership and learning, which contrasts with the top-down approaches in most incentive schemes. The importance of local ownership is in line with the recent experience from the UK and the Netherlands.[13,21,45,50] Perhaps not surprisingly, future recommendations included reducing prescribing of drugs that were not recommended, as well as generally increasing knowledge about the effectiveness and safety of the drugs prescribed to improve future decision making. Future analysis will reveal whether PHC recommendations have been implemented. This will also reveal whether PHCs subsequently increase ADR documentation and reporting, compared to the under-reporting that was identified.

Finally, it is important to emphasise that adherence to prescribing guidelines and quality reports were only two aspects of quality of care. Quality assessment should include all aspects of care, including structure, process and outcome.[51] Nevertheless, drug prescribing is important and our findings should stimulate debate in other countries on future methods to enhance the quality and efficiency of prescribing. The model could also easily be adapted to include other aspects of patient management and outcome.

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ADDRESS FOR CORRESPONDENCE

Björn Wettermark, Department of Drug Management and Informatics, Stockholm County Council, Box 17533, SE-118 91 Stockholm, Sweden. Email: bjorn.wettermark@sll.se

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Clinical Pharmacology in Research, Teaching and Health Care

Considerations by IUPHAR, the International Union of Basic and Clinical Pharmacology

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1. Executive Summary

a. Definition. Clinical pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. The term 'clinical pharmacologist' is also used in the professional sense to refer to those physicians who are specialists in clinical pharmacology. They have undertaken several years of postgraduate training in many aspects of the above relationship involving teaching, research and health care. Such clinical pharmacologists have as their primary goal that of improving patient care, directly or indirectly, by developing better medicines and promoting the safer and more effective use of drugs.

Author for correspondence: Michael Orme (Emeritus Professor), University of Liverpool, Lark House, Clapton-on-the-Hill, Cheltenham, Gloucestershire GL54 2LG, UK (e-mail michaelorme@larkhouse.co.uk).

b. Aims. This document aims to set the scene for clinical pharmacology in the early part of the 21st century following the concepts of an earlier report by the World Health Organization in 1970 [1]. This document is aimed primarily at decision-makers in a variety of organizations, particularly in governments and their healthcare ministries, in addition to chief executives and board level directors of primary and secondary care systems and directors in pharmaceutical companies. We hope they will realize the great benefits that expertise in clinical pharmacology can bring to the delivery of better healthcare for all populations.

c. Clinical care. Clinical pharmacology has developed a number of ways in which the clinical care of patients can be improved. The prime aim is to improve the rational use of drugs (RUD) both for individual patients and for patient populations wherever they may reside. The clinical pharmacologist will be expert in the critical evaluation of new and

old therapies, and will use drug utilization studies and pharmacoepidemiological services to help in this task as well as skills such as pharmacogenetics. Clinical pharmacologists have an important role on Drug and Therapeutics Committees where they help the rational introduction and use of new and expensive medicines into the delivery of health care. Clinical pharmacologists will provide, in association with other healthcare staff such as pharmacists, drug information services to a wide variety of prescribers.

Specialist services may include therapeutic drug monitoring (TDM), involvement in clinical drug toxicology and pharmacovigilance. Adverse drug reactions (ADRs) still cause many problems for patients, and healthcare systems could do more to prevent these as most of them are predictable through a knowledge of pharmacology.

The concept of personalized medicine is one where drug therapy can be based on the pharmacogenetic characteristics of a particular patient. While in its infancy as a discipline, there are now good examples whereby adverse effects can be minimized and drug efficacy enhanced by a knowledge of the genetic make-up of patients.

d. Research is a vital part of the training and everyday work of a clinical pharmacologist. The endeavour of a pharmacologist working in the clinical environment is to develop methods and strategies that improve the quality of drug use in individual patients and patient populations. Clinical pharmacological research has always been translational in the sense that the discipline aims to take new scientific data on drugs into rational patient care.

Clinical pharmacologists could be even better equipped to undertake 'translational' research, especially the design and execution of the early phase of drug studies in humans (Phase 1). Too few contemporary clinical pharmacologists are actively engaged in the design, conduct and improvement of clinical trials.

e. Teaching is a vital part of the work of a clinical pharmacologist. Although all doctors and many health care professionals need regular education concerning drugs, perhaps the most important area currently is the training of new prescribers which is primarily new physicians as pharmacists and nurses do comparatively little prescribing when looked at in a worldwide sense. The ability of new young physicians to prescribe safely and effectively has been criticized in recent years and new systems are being developed so that much more attention is paid to these skills in the training of medical students. As assessment drives learning, the assessment systems are being improved, too. Specialist training of clinical pharmacologists is addressed in Addendum II, as there is a worldwide shortage of such specialists. However, the needs, the resources and the regulatory arrangements available in different countries mean that the approach suggested is a general one.

f. Pharmaceutical companies have been at the forefront of helping to train clinical pharmacologists. While many of the skills acquired in such companies are useful for the general training of a clinical pharmacologist (e.g. clinical trials), a long-term career in such a company requires a new set of skills for which training is needed.

g. Governments need clinical pharmacologists to help deliver the goal of ensuring safe and effective drug therapy for their populations, whether the clinical pharmacologists are working in hospitals, regulatory agencies or in health technology assessment (HTA). With a few notable exceptions, the discipline of HTA has emerged in the absence of contributions from clinical pharmacology. This needs to change if HTA is to meet its full potential.

h. Clinical pharmacologists have a crucial role to play in helping to deliver the WHO agenda of 'Guidelines for the Development of National Drug Policies' to which more than 150 countries are now signed up [2]. The policies aim to ensure:

- the quality, safety and efficacy of medicines
- equitable access to medicines for all the population
- the rational/quality use of medicines
- a viable and responsible local pharmaceutical industry.

Clinical pharmacologists could do much more to meet the health needs of those peoples who have in the past been marginalized. They include children, those with rare diseases, and those with conditions that are endemic in the poorest parts of the world. Training of clinical pharmacologists to meet these needs will have to be rather different from that envisaged in 1970 when the first WHO report was published [1].

2. Introduction

Some 40 years ago, the World Health Organization brought together a group of experts in clinical pharmacology and therapeutics (CPT) to define the discipline of clinical pharmacology and to outline how it could help to improve the use of drugs in the delivery of health care [1]. In the last four decades, the importance of drug therapy has changed markedly in terms of the potency of the drugs we use, in the number and diversity of drugs that are available, and in the number of diseases that can be treated. In addition, the discipline of molecular biology has had an increasing impact on the development of drugs but solid knowledge about the pharmacological principles that underpin the RUD is just as relevant now as it was in 1970.

Since the production of the 1970 report, the cost of developing drugs has risen substantially and the cost of taking a new chemical entity to market can easily be in excess of $US 1000 million (£600 million, €700 million). As a result, newly developed drugs are very expensive making it more difficult for resource poor countries to fund drug therapy for their inhabitants although there are welcome exceptions in the provision by Big Pharma of modern drugs at a very low or no cost (e.g. ivermectin for onchocerciasis). Even resource-rich countries have limitations in financing drug therapy and this has led to new concepts such as the cost-effectiveness of drug therapy and to the discipline of pharmacoeconomics.

While clinical pharmacology is learning to face these new problems, we are still dealing with problems in drug therapy that were recognized in the 1970s. We knew then that ADRs were among the more common causes of admission to hospi-

tal [3] and this problem has not decreased in importance over the decades largely because little is done about it. In addition, the problem of ADRs is worsened by the increasing use of combination therapies and the higher proportion of elderly patients in the population. We know that ADRs (the formal study of which has now given rise to the discipline of pharmacovigilance) cause some 7% of admissions to hospital and they are also a not uncommon cause of death, particularly in elderly patients [4,5]. Many of these ADRs are predictable and could be prevented if the process of educating prescribers was taken more seriously. Another problem that has not improved significantly over the years since 1970 is the errors made during the prescribing process in spite of the widespread availability of computers and the Internet providing easy access to appropriate information and knowledge [6]. These problems do not only affect resource-rich countries, although the scale of the problem may be less in resource-poor countries.

It is clear then the time has come to modernize the original WHO report in the hope that lessons will have been learned and the problems addressed. We hope that WHO itself will do this over the next year or so by a modification of this International Union of Basic and Clinical Pharmacology (IUPHAR) report. After a period of expansion in the last 20 years of the 20th century, clinical pharmacology, as a discipline, declined somewhat in many countries. However, during the last few years, there have been signs both of new growth in and new enthusiasm for the discipline [7], although the importance of clinical pharmacology to pharmaceutical companies has never been in doubt. A recent report on the relationship between the pharmaceutical industry and the National Health Service (NHS) in the United Kingdom has stated that re-building clinical pharmacology as a core discipline in the NHS is of vital importance for the future of health care in the UK and this is likely to be true in many other countries [8].

This document aims to set the scene for clinical pharmacology in the early part of the 21st century using the concept of the original WHO report and updating it for IUPHAR. We have gathered a group of distinguished clinical pharmacologists who have written the individual sections which are designed to address the role of clinical pharmacology in health care, research and teaching as well as describing the discipline's link with industry and governments. We hope that the document will prove useful to many people, perhaps particularly young doctors who are looking to establish themselves in a clinical speciality and who have a particular interest in improving drug therapy and making it safer and more effective as exemplified in the WHO Rational Use of Drugs policy. However, this document is primarily aimed at decision-makers in a variety of organizations, particularly in governments and their healthcare ministries as well as chief executives and board level directors of primary and secondary care organizations and directors in the pharmaceutical industry. We hope they will realize the great benefits that expertise in clinical pharmacology can bring to the delivery of better health care for all populations.

3. Definition of Clinical Pharmacology

Clinical pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. Its breadth includes the development of new drugs, the application of drugs as therapeutic agents, the beneficial and adverse effects of drugs in individuals and society, and the deliberate misuse of drugs. Clinical pharmacology is a science that may be of significant interest to a variety of professions including physicians, pharmacists, nurses and scientists in many different disciplines.

The term 'clinical pharmacologist' is also used in the professional sense to refer to those physicians who are specialists in clinical pharmacology. They have usually undertaken several years of postgraduate training (see Addendum II) focusing on important aspects of clinical pharmacology including clinical trials theory, drug evaluations, pharmacoepidemiology, pharmacoeconomics, pharmacogenetics, pharmacovigilance and clinical drug toxicology. Such clinical pharmacologists have as their primary goal that of improving patient care, directly or indirectly, by promoting the safer and more effective use of drugs.

4. History of Clinical Pharmacology

Clinical pharmacology is both old and young. The practice of drug therapy goes back to ancient times and the discovery of drugs such as quinine, reserpine and artemisinin which were first used as herbal medicines. William Withering's publication on the use of foxglove in the treatment of heart failure [9] may very well be considered the first scientific account of the discipline but it took 200 years before the pharmacology of digitalis was explored with accurate, clinical pharmacological methods.

As a scientific discipline and academic subject, clinical pharmacology is young having originated from the middle of the 20th century. It is difficult to find who first coined the name as opinions differ between countries. Several distinguished pharmacologists active in the middle of the century brought pharmacology and clinical know-how about drugs together and helped to transform drug evaluation from the trial and error state to a scientific discipline.

In the Anglo-Saxon literature, Harry Gold at Cornell [9,10] is commonly quoted as the person who first introduced the name clinical pharmacology in the early 1940s. However, in 1914, a textbook was written by Hans Horst Meyer and Rudolf Gottlied in German the title of which was translated as 'Pharmacology, Clinical and Experimental'. In addition, also in the German literature, Paul Martini, professor of medicine in Bonn, published his monograph in 1932 entitled 'Methodology of Therapeutic Investigation' and he is considered by some as the first clinical pharmacologist [11]. According to Shelley and Baur, his contributions escaped the attention of the English-speaking world [11].

In the English literature, there is a long tradition of 'materia medica', particularly in Scotland. In 1884, John Mitchell Bruce wrote his textbook entitled 'Materia Medica and

Therapeutics. An Introduction to the Rational Treatment of Disease' and this, in its 20th edition, became Dilling's 'Clinical Pharmacology'. This book was published in 1960, the same year as Desmond Laurence's textbook entitled 'Clinical Pharmacology'.

There is no doubt that the most vigorous attempts to develop clinical pharmacology as an academic discipline were made in the United States [12,13]. Important landmarks are the first edition of Goodman and Gilman's 'The Pharmacological Basics of Therapeutics' and the successful attempt (1960) by Walter Modell, also at Cornell, to launch the first scientific journal in the subject entitled 'Clinical Pharmacology and Therapeutics'.

In the early 1960s, the United States became the world centre for the training of clinical pharmacologists. The NIH chief James Shannon and his colleagues Bernard B. Brodie and Julius Axelrod introduced biochemical pharmacology as a science and drug measurements in body fluids as tools in clinical pharmacology. Several centres of excellence in clinical pharmacology offered training to potential clinical pharmacologists from all parts of the world. The efforts to improve clinical drug evaluation by Louis Lasagna, a pupil of Harry Beecher at John Hopkins Hospital, should be especially recognized [11,12]. In 1966, Lasagna published a brilliant, still valid, account in *Science* of the present status and future development of clinical pharmacology [12]. The birth of clinical pharmacogenetics can be ascribed to the pioneering contributions of Werner Kalow and A.G. Motulsky [14,15]. Parallel developments occurred in Europe, particularly in the UK, where the strong infrastructure in basic pharmacology and clinical medicine formed an excellent basis for a rapid growth of the discipline. Names that usually are mentioned in this context are Sir John Gaddum, Sir Horace Smirk and Sir Austin Bradford Hill [9]. Chairs in clinical pharmacology were created at the end of the 1960s in Germany, the UK and Sweden, although chairs in Materia Medica had long been established in Scotland. Academic growth of the discipline also took place in France [16].

The IUPHAR took early initiatives to develop clinical pharmacology. A section of clinical pharmacology was formed in the early 1970s and a division in the 1990s. Several IUPHAR executives strongly supported the discipline, particularly the first president Börje Uvnäs in Sweden, but also Sir Arnold Burgen in the UK and Helena Raskowa in Czechoslovakia, who all realized that pharmacology had to reach out to the bedside in order to develop. WHO brought together a Study Group in 1970 [1] to write a report on the scope, organization and training of clinical pharmacology, led by the late Sir Derrick Dunlop (UK), and containing, amongst others, the late professors Louis Lasagna (USA), Franz Gross, (Germany) and Leon Goldberg, (USA). In 1991, WHO Europe put together a booklet and a series of papers in the *European Journal of Clinical Pharmacology* about the roles of clinical pharmacology in teaching, research and health care [17]. For the first time, the potential usefulness of the discipline for the RUD in primary health care was emphasized.

Several Nobel Prize laureates in medicine can be considered as representatives of clinical pharmacological research at its best such as Sir John Vane, Sir James Black, George Hitchings, Gertrude Elion and Arvid Carlsson. They all 'practised' clinical pharmacology during their efforts to introduce new pharmacotherapeutic principles into clinical medicine.

5. The Global Medicine Scene

Modern drug therapy has unquestionably transformed the health of peoples in developed countries over the last 50 years. Conditions such as poliomyelitis, diphtheria and pertussis have largely been eliminated in wealthier nations. Many lethal communicable diseases can be cured by modern antimicrobial agents. And complex surgery, beyond the imagination of our forefathers, can be performed safely and effectively using modern anaesthetic agents. Those with chronic diseases have benefited immeasurably with the emergence of safe and effective treatments for asthma, hypertension and hypercholesterolaemia.

Nevertheless, there remains massive unmet clinical need in developing, emerging and developed countries. There is, for example, a pressing need for effective vaccines against HIV/AIDS, malaria and tuberculosis. We have nothing to prevent the inexorable decline in neurological function in people with neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease or Huntington's disease. And, when effective vaccines and treatments have been developed, they are too often unavailable to those in the poorer parts of the world.

During most of the second half of the 20th century, research-based pharmaceutical companies were, for practical purposes, the sole source of new medicines. They discovered, developed and delivered products – often with considerable ingenuity – for healthcare systems that were able to afford the costs required to maintain the industry's infrastructure. People in poorer countries, unable to meet these costs – as well as lacking an appropriate healthcare infrastructure – only rarely benefited.

The prospect for satisfying unmet medical need has, in some senses, never been brighter. Advances in molecular techniques offer the promise of identifying drug-sensitive targets that might attenuate or cure many miserable and life-threatening conditions. The massive chemical libraries available to most pharmaceutical companies, coupled with high-throughput screening and combinatorial chemistry, offer unimaginable rewards for us all. In addition, the emergence of an array of biotechnological techniques offers unique approaches to the development of innovative medicines.

Yet, despite the promise from the science, the outlook is not favourable. Despite record investment in biomedical research by the public sector and not-for-profit organizations, as well as by pharmaceutical and biopharmaceutical companies, the number of new active molecules registered by drug regulatory authorities has fallen dramatically. The costs of bringing a new product to the market are increasing at a

rate of 10% per annum, due in part to the failures of products during development, but also to the extended requirements for evidence-based documentation from regulatory authorities (e.g. in elderly patients). Added to this, many of the largest pharmaceutical companies are facing, by 2011, a reduction of 30–40% in turnover as their 'blockbusters' come off patent.

There have also been spectacular withdrawals of some marketed medicines over the last few years because of safety concerns. As a consequence, drug regulatory authorities have become increasingly risk averse and place ever greater demands on manufacturers to demonstrate the safety of their products before and after marketing. While this may have some benefits for drug safety, these measures are likely to increase the cost of medicines unless they are implemented with considerable care.

Moreover, healthcare systems across the world are struggling to meet the apparently high prices that pharmaceutical companies seek to charge for new products that do reach the market. Those responsible for meeting the health needs of the populations they seek to serve are under increasing pressure to provide affordable care. The increasing numbers of elderly and very elderly people (many with long-term chronic diseases requiring multiple drug therapy), the greater availability of effective screening measures (especially in the elderly), and the growing expectations of the public, all mean that resources are constrained. One of the reasons for the rapid emergence of HTA facilities, across Europe and North America, is because of the necessity to look ever more closely at the clinical and cost-effectiveness of therapeutic strategies.

The future prospects.

Despite this gloomy outlook, a number of relatively recent initiatives suggest that remedial action is being taken:

1. Drug regulatory authorities themselves recognize the need for change if people are to have access to innovative medicines. Both the Food and Drug Administration in the United States [18] and the European Medicines Agency (EMEA) in the EU [19] have published plans for expediting the regulatory process of innovative medicines that are appropriately safe and effective.
2. The process of drug discovery, confined for most of the 20th century to the laboratories of research-based pharmaceutical companies, has become much more pluralistic. In particular, academic scientists working in universities have become 'drug hunters' and some have been spectacularly successful. And, whereas 25 years ago, major pharmaceutical companies were unwilling to even contemplate developing products that had not been discovered in their own laboratories, they are now prepared to do so with enthusiasm. Indeed, companies are pursuing truly collaborative projects with academic scientists to the extent that they are allowing access to their chemical libraries.
3. An increasing number of not-for-profit organizations such as the Bill and Melinda Gates Foundation (in Seattle) and the Hereditary Disease Foundation (in New York) are supporting drug discovery and development in co-operation with both academia and pharmaceutical companies.
4. Some major pharmaceutical and biopharmaceutical companies are increasingly recognizing that their traditional models of discovery, development and pricing no longer meet the needs of either patients, healthcare systems or their shareholders [20]. Changes include moving away from seeking 'blockbusters'; expanding sales to include the emerging markets in Asia; and discussing, with healthcare systems themselves, what future products would bring most value for money.

Conclusions.

These changes in the global medicines scene require the contributions of appropriately trained clinical pharmacologists if innovative new medicines are to reach those in need:

1. Clinical pharmacologists should be better equipped to undertake 'translational' research especially the design and execution of Phase 1 studies.
2. Too few contemporary clinical pharmacologists are actively engaged in the design and conduct of clinical trials. The founding fathers of the discipline (such as Lou Lasagna) made crucial contributions to health care by undertaking clinical trials – often in relatively small patient populations – that characterized a compound's properties (especially dose–response relationships).
3. With a few notable exceptions, the discipline of HTA has emerged in the absence of contributions from clinical pharmacology. This needs to change if HTA is to meet its full potential.
4. Clinical pharmacologists could do so much more to meet the health needs of those peoples who have in the past been marginalized. They include children, those with rare diseases and those with conditions that are endemic in the poorest parts of the world.

6. Roles of Clinical Pharmacology

6.1 Research.

Introduction. In the first WHO report on clinical pharmacology in 1970 [1], the section on research emphasized the need for studies that explored the mechanisms of action of drugs and identified their pharmacokinetics in humans. Improvement of the early studies of new drugs in humans and conventional therapeutic trials were also prioritized. Research in clinical pharmacology has now taken new paths and this satisfies many principles of translational medicine defined as taking scientific data on drugs into rational patient care. However, we should be aware that not all research into drugs falls within the remit of translational medicine.

The endeavour of a pharmacologist working in a clinical environment is to develop methods and strategies that improve the quality of drug use in individual patients and patient populations. Research in drug evaluation, drug utilization, pharmacovigilance and pharmacoepidemiology –

areas that were only superficially mentioned in the 1970 document – is now the priority. All these research areas have great potential for supporting healthcare personnel in their RUD.

Rational use of drugs implies that drugs should be chosen according to efficacy, ADRs and cost as potentially equally important parameters. Research in clinical pharmacology therefore also includes studies that elicit new data about drugs in use such as new indications and treatment of neglected patient populations (children, elderly). It also includes research into ADRs, pharmacogenetics and drug interactions. Research in clinical pharmacology is usually interdisciplinary and hence often carried out in collaboration with other professions: pharmacists, drug analytical chemists, molecular biologists, statisticians, computer specialists as well as clinical researchers from other medical specialities.

Pharmacokinetic, pharmacodynamic and pharmacogenetic studies in human volunteers. This research should lead to a fundamental understanding of the mechanisms involved in the actions of the drugs on the organism or the actions of the organism on the drugs. The research is particularly focused on intra- and interindividual differences in pharmacokinetics and pharmacodynamics, an area in which clinical pharmacologists have made important contributions in the past. The mechanisms in such variability usually involve inherited individualities in the genes encoding drug targets, drug transporters and drug metabolizing enzymes. The perspective of the research should not only be in understanding the molecular mechanisms but also in designing genotyping or phenotyping tests, which may be applied to forecast drug response and to differentiate between genetic and non-genetic modifiers of the outcome of drug treatment. *In vivo* research is often combined with experimental studies *in vitro* and *in silico* (see glossary). The research aims to identify the routes of metabolism and excretion of drugs.

There are two separate approaches in pharmacokinetic research, one based on several drug measurements over a fixed time schedule in a few subjects and the other being based on sparse measurements in each subject of a large population of individuals (population pharmacokinetics). Such data may help to identify subpopulations with impaired or enhanced elimination capacity. The population approach can also be applied to pharmacokinetic–pharmacodynamic evaluation.

Clinical drug evaluation and clinical trial Phases I–III. Important research areas are to improve the methods used to evaluate drugs in humans. The first examination of the effects of a new drug in humans (Phase I) is done with great care and in great detail, few subjects being tested. These Phase I studies are often done by clinical pharmacologists working in industry or in specialized clinical trial units. When the time comes to examine the effect of the drug in patients with the disease to be treated (e.g. hypertension), again small numbers of patients will be studied in detail (Phase II studies). The training that clinical pharmacologists undergo gives them the skills to do such studies.

The randomized controlled trial (RCT) or its extension to meta-analysis or systematic reviews of several RCTs is considered to be the gold standard for documenting the efficacy of drugs. The RCT has advantages but also disadvantages, and other methods for the evaluation of clinical interventions are needed [21]. Clinical pharmacologists have been the pioneers in introducing the RCT and in particular in introducing the placebo as control. The RCT is now mastered by clinical intervention researchers in practically all medical specialities and is no longer solely the province of clinical pharmacologists. The RCT is a method with which all clinical pharmacologists should be familiar as it still forms the basis of most drug evaluations. One area in which clinical pharmacologists could make a difference is the detection of relatively frequent ADRs that are predictable and understandable on the basis of the mode of action of the drug. Another area is the evaluation of biomarkers as measures of drug action in clinical trials. In the case of new drugs, the studies described above are part of the Phase I clinical trials.

Therapeutic drug monitoring. Therapeutic drug monitoring is a scientific medical technology where clinical pharmacology has made major contributions. The measurement of drug concentrations in blood or plasma will often help to achieve better understanding of the nature of individual drug exposure, how this relates to expected exposure values at the given dose, and recommended target ranges in plasma at which there is an optimal therapeutic effect or an increased risk of ADRs. Therefore, the clinical use of TDM is obvious for drugs that have a narrow therapeutic window and for which individual exposure is difficult to predict from the given dose owing to extensive interindividual differences in pharmacokinetics. It may provide direct guidance for individual dose adjustments in cases of ADRs or therapeutic failure.

TDM is based on the assumption that the plasma concentration of the drug reflects the concentration at the drug target, although this may not always be the case, for instance with some central nervous system (CNS)-active drugs or anti-infective agents used to treat localized tissue infections.

TDM research into clinical routine samples has been important for a safer use of specific drugs in subgroups of patients at risk: the elderly, children and patients with renal or hepatic failure. TDM research has also helped to detect and manage drug–drug interactions and to understand the clinical impact of genetic polymorphisms in drug elimination pathways.

Following the mapping of the human genome and the revolutionary developments in biotechnology and human molecular medicine, research at the beginning of the 21st century mainly aims at understanding the role of genetic variation in the capacity or function of drug metabolizing enzymes, drug transporters and receptors and their relationship to the clinical effects of drug treatment. Many TDM laboratories now offer genotyping services, in addition to TDM, and medical input is crucial for an individualized, clinical interpretation.

Clinical pharmacologists need to understand the principles of the laboratory methods that are used, although they may not necessarily be able to perform them. In experimental studies on TDM or pharmacogenetics, the main responsibility of the clinical pharmacologist is to formulate a clinically relevant problem, design the study that will help to bring further understanding to this problem, be medically responsible for the study volunteers and translate the results into clinical practice.

Pharmacovigilance. When a new drug enters the market, it has been tested in only 3–5000 patients. There ought to be solid documentation that its actions are superior to placebo or comparable to or even better than the existing treatment. Its most common adverse effects should be known and in particular those that are predictable from their basic pharmacological properties or readily explained in the context thereof. However, at marketing, serious or even lethal but very rare ADRs that cannot be explained by the basic pharmacology of the drug and that occur in, say, 1 out of 10,000 patients or even less commonly, may not have occurred or been recognized. Spontaneous ADR reporting is carried out in order to detect unknown potential drug toxicity. The method consists of collecting individual case reports of clinical suspicions of ADRs. Data mining in ADR research is the search for structures and patterns in large ADR databases, manual inspection no longer being possible. Data mining involves the development, testing and implementation of computer methods, routine algorithms and tools for finding such associations and patterns of associations between drug intake and adverse events.

Drug utilization studies. Clinical pharmacologists play a key role in drug utilization research, which can be defined as an eclectic collection of descriptive and analytical methods and theories for the quantification, understanding and evaluation of the processes of prescribing, dispensing and consumption of medicines. The subject is also concerned with the testing of interventions to enhance the quality of these processes. It is common to quantify drug utilization by defined daily doses, which by definition is the typical maintenance dose of the drug in an adult for its main indication.

Pharmacoepidemiology. Sometimes an RCT is either unethical (e.g. in detecting harmful effects on the foetus) or impossible because hypothesis testing or signal generation will require very large numbers of patients. Clinical pharmacologists have been pioneers in establishing pharmacoepidemiology, which may be defined as the science of studying the utilization and actions of drugs in large populations. Pharmacoepidemiology uses methods from both clinical pharmacology and epidemiology. The purpose of the research may be to detect a signal, to estimate the risk of an ADR or to test a hypothesis. The results of the research can be used to give advice to healthcare organizations and individual patients or to formulate a policy regarding the optimal use of the drug.

Cohort studies are carried out by registering a drug effect (cure, death, ADR) in a sample of patients treated with a particular drug. A sample of patients not treated with the drug is used as a control group. Random allocation and blinding are not applied and that presents problems with confounding and bias but methods have been developed to at least partly overcome this. In case–control studies, drug use in patients with a symptom suspected of being an ADR is compared with drug use in a sample of patients without the symptom. Thus, the odds ratio for developing an ADR can be calculated. Linkage studies are carried out by linking data from individual level prescription databases to health outcome databases. Pharmacoepidemiology is an important new development in clinical pharmacology. For the sake of the continued development of the scientific discipline, it is important that part of pharmacoepidemiology be anchored in clinical pharmacology.

Pharmacoeconomics. Pharmacoeconomics is the scientific discipline that evaluates the clinical, economic and humanistic aspects of pharmaceutical products, services and programmes as well as other healthcare interventions. The aim is to provide healthcare decision-makers, providers and patients with valuable information for optimal outcomes and the allocation of healthcare resources. Pharmacoeconomics incorporates health economics, clinical evaluations, risk analysis, technology assessment and health-related quality of life, epidemiology, decision sciences and health services research in the examination of drugs. Clinical pharmacologists are important in the field of pharmacoeconomics as they are best placed to formulate research questions of medical importance and critically to propose medically relevant outcome measures to make the correct medical interpretation of the research.

The main role of a clinical pharmacologist in this discipline is to assess the quality and suitability of clinical trials data for inclusion in the overall analysis, in order to determine whether a new drug has any clinical advantage over the existing treatments. It is necessary to arrive at an objective quantitative evaluation of 'benefit' or 'effectiveness' to put into cost-effectiveness models that health economists have developed. The clinical pharmacologist is uniquely able to do this evaluation which may end up not conforming to the appraisal or claim submitted by manufacturers.

6.2 Teaching.

Increasing demands on prescribers of drugs. For most physicians, drug therapy is the main tool at their disposal to influence the health of their patients. New graduates are typically expected to start prescribing drugs regularly as soon as they begin their first medical post. The prescribing demands placed on this group in healthcare systems have progressively increased because of many important trends:

- The number of drugs available continues to rise so that physicians often have to prescribe drugs with which they are less familiar.

- Patients are taking more drugs, increasing the complexity of their treatment regimen and the potential for drug interactions.
- Medication errors and ADRs, many of which are avoidable, constitute a major challenge to public health.
- Patients who receive drugs are older and sicker, and more vulnerable to adverse events.
- Patient throughput is increasing (matched by a similar increase in prescribing episodes) imposing higher workloads on individual prescribers.
- The expansion of evidence-based medicine and HTA has enabled the beneficial and adverse effects of drugs to be quantified more accurately, and this knowledge has expanded the number of clinical guidelines that define norms of acceptable drug use.
- Patients increasingly expect their physicians to provide information about the drugs they are being given to inform their own choices about treatment.
- Poor access to trained medical staff in developing and emerging countries.
- Increasing problems with poor quality drugs and combination therapies for chronic diseases such as HIV/AIDS and tuberculosis in developing and emerging countries, in particular in Africa.
- There are more sources of opinion and 'disinformation' available to patients and prescribers, largely as a result of increasing access to the Internet.
- The marketing activities of pharmaceutical companies remain a potential threat to cost-effective prescribing decisions and may, in future, be complicated by direct-to-consumer advertising.

Prescribing drugs is a skilled task that always carries a risk of significant harms as well as benefits. Although newly qualified physicians are usually protected from the requirement to undertake high-risk practical procedures, they are often expected to prescribe powerful drugs from their first day of clinical work. Indeed, these inexperienced doctors typically write most hospital prescriptions in many healthcare systems. It is clear that all medical graduates should have a firm grounding in the principles of practical prescribing, as underpinned by the science of clinical pharmacology, at the point of graduation, as the basis for rational prescribing. The primary determinant of the effectiveness of a prescriber in most areas of practice will be the education and ability of a prescriber to respond to changes in pharmacotherapy. The increasing support of other healthcare professionals, such as pharmacists, and the availability of prescribing support systems and electronic prescribing will help the prescribers in their task but they are no substitute for education and training.

Several studies have shown that lack of training and familiarity with drugs among prescribers is an important factor in serious medication incidents [22]. New graduates rate prescribing as the most challenging aspect of their profession and the one for which they are least well prepared. Importantly, educational interventions such as the 'WHO Guide to Good Prescribing' have been shown to improve prescribing performance.

Undergraduate education. A key aim of undergraduate medical education should be to provide the learning opportunities to enable all students to acquire the requisite knowledge, skills and attitudes, and also to put in place appropriate assessment to ensure that these outcomes have been achieved.

As the rate of drug development increased in the 1960s, CPT emerged as a new teaching discipline and many medical schools incorporated it into their curricula as a distinct course. Most medical schools provide teaching in both basic and clinical pharmacology, the former during the first 2–3 years and the latter during the fourth to sixth years of the medical curriculum. When students start clinical training, they have usually passed examinations in basic pharmacology and are expected to understand the principles of drug action [23–26].

The core content of a curriculum in CPT can be conveniently divided into knowledge and understanding, skills and attitudes with emphasis on critical drug evaluation (Addendum I). Most of these outcomes are generic requirements for the safe and effective use of drugs in all areas of clinical practice. These core CPT learning objectives can be linked to a number of specific drugs and therapeutic problems which might be used to provide relevant clinical examples of the principles of CPT in practice. Teaching about specific drugs is organized in different ways in different countries. One model is to focus teaching on a selected list of the most commonly prescribed 50–100 drugs that will be influenced by the pattern of disease in the country concerned. These should be selected in such a way that their pharmacological properties reflect the important pharmacodynamic and pharmacokinetic principles on which rational drug use should be based. The list could be close to a National Drug List, a regional list for 'Wise Drug Prescription' or the WHO Essential Drug List but will normally contain far fewer drugs than such lists. An extensive list of drugs should be avoided as the professional prescription of drugs will be practised several years later when the prescribers have chosen their speciality. Specific lists of drugs that should be familiar to the prescribers will then differ between, for example general practitioners, internists, psychiatrists and oncologists. Postgraduate and continuing education in clinical pharmacology rather than undergraduate education will thus determine the drugs that are commonly prescribed. However, an understanding of the basic principles of CPT should allow physicians to take a logical approach to learning about any of the drugs they will encounter during their practice. The principal recommendations for the delivery of CPT in the undergraduate medical curriculum are summarized below:

- CPT and prescribing (or equivalent) should be identified as an important component of the curriculum, visible to students in all years, either as an identified course itself or a theme that integrates with other modules.

- Core learning objectives in CPT should be clearly identified including knowledge and understanding about drugs, skills related to the prescribing of drugs and attitudes towards pharmacotherapy.
- The factual burden posed by the large number of drugs should be eased by prioritizing learning around a core list of commonly used drugs (a 'student formulary'), similar to the process used by the WHO in developing their 'Essential Drugs' policy.
- There should be an identifiable and robust assessment that indicates whether the main learning objectives have been met. This might form part of an integrated assessment but it should not be possible to compensate for a poor performance in this area by a good performance in other items.

Student formulary. Medical students are often overwhelmed by the large number of drugs that they encounter during their training. This can be demoralizing and lead to a lack of clarity and objectivity in learning. As suggested above, a potential solution is to develop a list of core drugs that could be considered as the 'student formulary' that helps to prioritize study and provide learning objectives that are realistic and attainable. This has already been done in a number of medical schools in Europe and elsewhere. The list should contain 50–100 drugs that are commonly prescribed and used to treat common diseases. For each drug or group of drugs, students might be expected to have an understanding of the mechanism of action, recognize the appropriate indication and contra-indication, know about potential interactions and adverse effects, know how to monitor effects and be able to explain the salient features of all the above to the patient. The students should also learn about the principles for stopping irrational drug therapy. The list of core drugs can be organized by organ system and set alongside the common therapeutic situations in which they are used. This arrangement emphasizes the suitability of a problem-based approach to develop learning about CPT and the ease with which CPT can be integrated within a system-based curriculum.

Delivering the core CPT curriculum. Variability in the structure of medical courses will require local solutions for delivery of the CPT curriculum. Where there are traditional arrangements, there may be a preclinical phase containing scientific disciplines that include pharmacology and later courses in 'CPT' or 'pharmacotherapy' and this model is straightforward. Delivery is more challenging when the traditional barriers have been removed in the production of a truly integrated curriculum, often with an emphasis on problem-based learning. In these circumstances, CPT learning objectives must compete simultaneously with many others, usually dispersed across many different modules and through several years of the course. This poses practical difficulties for CPT teachers coordinating learning opportunities across many modules over which they have limited influence. Nevertheless, the importance of CPT should be emphasized in all clinical modules in which there are continuous opportunities to observe and appraise critically the patient drug charts, see the beneficial and adverse effects of drugs and practice relevant skills (e.g. prescribing, dose calculations, drug preparation and administration, and searching for good quality information to inform prescribing decisions).

CPT leadership. A key factor in the successful implementation of the CPT core curriculum, particularly in an integrated course, will be strong and enthusiastic leadership. All medical schools should be able to identify an individual who will oversee delivery and ensure that the generic principles of safe and effective use of drugs are highlighted throughout the course. This role should ideally be undertaken by a senior individual with a background and training in CPT, helped by colleagues in the discipline some of whom may be trainees in CPT. In medical schools without CPT departments, other specialists with an enthusiasm for ensuring that principles of CPT are prominent throughout the curriculum should be identified.

The coordination of CPT learning opportunities can be devolved to many teachers across the course, often within organ-based specialities. They too should be encouraged to emphasize these principles and remind students about the effects of drugs beyond individual organ systems. Simply providing a link between drugs and clinical conditions is insufficient to develop an appreciation of the complex considerations that surround the decision to initiate a prescription. All schools should ensure that, in each case, students are helped to tackle the practical issues of weighing the harms and benefits of drug therapy, prescribing the drug and monitoring the impact of therapy. Clinical pharmacists who are usually available in greater numbers than CPT specialists also have an important role to play in reinforcing learning during clinical attachments, working with other pharmacotherapeutic experts.

Learning styles. The successful delivery of the core curriculum may involve a variety of learning styles (e.g. lectures, problem-based tutorials) depending on local preference but the content should increasingly be based around inquisitive rather than passive learning. There should be an appropriate balance of teaching in large groups and small groups, practical classes and opportunities for self-directed learning. The core curriculum in CPT is well suited to take advantage of the increasingly popular style of problem-based learning. Most prescribing episodes are a direct attempt to solve a clinical problem and require the appropriate knowledge, skills and attitudes outlined in Addendum I. Several schools have developed a series of 'therapeutic case discussions' that offer students a case vignette and pose direct problems relating to prescribing and therapeutics. These can be undertaken in live time, even within relatively large groups, or researched and discussed at intervals over several weeks. Other approaches to CPT involve writing case reports containing discussion about therapeutic aspects (e.g. portfolio cases), discussing prescribing decisions with patients as part of communicating skills, critiquing clinical trials involving drugs, appraising claims for new drugs and searching for information about drugs.

e-Learning. Many CPT departments have now embraced web-based approaches as an opportunity to deliver learning

opportunities and self-assessment in CPT. Certainly, it is important that students should be exposed to and trained in the principles of electronic retrieval of reliable drug information. Computer-assisted learning packages are constantly accessible. As the change from paper to electronic prescribing spreads worldwide, aided by advances in virtual reality environments, this approach will be able to provide increasingly realistic simulation of real-world therapeutics [27].

An e-learning approach is foreseen to be of high relevance in resource-poor countries with chronic lack of educated staff. Innovative teachers should be able to use the academic high-speed networks for provision of distance learning, interactive teacher–student contact. This may also be applicable in many developing countries.

Assessment. Assessment drives learning and is critical in emphasizing the importance of CPT in the course and ensuring that graduates are fit to practice. All medical schools should have validated and reliable schemes of assessment in place to ensure that students demonstrate that they have achieved the curricular outcomes. It is important too that assessments should not simply be knowledge-based but test the acquisition of practical skills (e.g. writing a prescription, offering information to a patient about a drug and spotting potentially dangerous prescriptions). The objective structured clinical examination (OSCE) is an ideal format for this kind of assessment. Relatively few schools now have a traditional CPT examination as changes to the curriculum bring the assessments of diverse learning objectives together in integrated examinations. Where this is the case, there should be a clear, identifiable and robust component devoted to the knowledge and skills that support rational prescribing. Furthermore, whether assessment is integrated or part of a collection of discipline-based assessments, it is normally not appropriate for students to be able to compensate for a poor performance in prescribing or therapeutics with good performances in other assessments. Students should also be provided with formative assessments and the chance for self-assessment at regular intervals during the medical course.

Quality assurance. All schools should have some form of external quality assurance to ensure that the CPT learning opportunities and assessments they provide are fit for purpose, i.e. deliver graduates with sufficient knowledge and skills. Such reviews might examine whether the goals outlined earlier in this section have been met. The appointment of external examiners with CPT expertise might also help to ensure that appropriate standards are met.

Postgraduate. Education in CPT and prescribing should be a continuing process in postgraduate medicine, not only because of the constant emergence of new medicines but also rapid changes in the knowledge base of those that are already established in clinical practice (see Addendum II). The previous section outlines the importance of developing a firm platform on which to build postgraduate training. There should be a progression from undergraduate training for broad-based, supervised prescribing through to progressively specialized and less supervised work during subsequent years. Curricula for specialist training and related assessments will be critical in promoting the importance of CPT principles and knowledge. In the case of specialists in primary care or hospital-based disciplines, arrangements for continuing medical education (CME) (often known as Continuing Professional Development) will be important in updating knowledge and skills and fostering reflective practice. The emergence of new prescribing groups (e.g. pharmacists, nurses) in some countries offers a further opportunity for CPT education to be used to enhance health care.

There are several important challenges for postgraduate CPT education. Perhaps the greatest is to find the necessary time in already busy clinical schedules. However, this problem is being increasingly circumvented by the development of more flexible web-based learning solutions and recognition within the relicensing/revalidation process that all doctors require protected time for CME. Another important challenge is to provide good quality non-promotional education. Recent years have seen pharmaceutical companies play a well-resourced highly influential role in the delivery of postgraduate education. Clinical pharmacologists should embrace the opportunity to contribute to the planning of non-promotional educational events in collaboration with pharmacists and other pharmacotherapeutic experts.

6.3 Patient care.

Introduction. The ways in which clinical pharmacological services could be integrated in healthcare systems were first outlined 1970 in the WHO Technical Report referred to earlier [1]. In 1977, a working group employed by the WHO Regional Office for Europe elaborated further on services that the discipline ought to undertake in patient care [28] which was followed up by WHO a decade or so later [17]. Compliance with these recommendations has varied between countries but has been generally unsatisfactory.

The quality and outcome of conventional drug therapy in patient care can be greatly improved by using cost-effective and evidence-based treatment with drugs according to the needs of patient populations and individual patients. Advances in drug development provide patients with new drugs, novel drug combinations, expensive biological drugs and targeted drug therapy adapted to the molecular characteristics of the disease [29,30]. Easy access to evidence-based drug information will assist physicians and healthcare staff in monitoring the effectiveness and safety of drug therapy and optimal allocation of limited resources [31,32].

Today, patients and patient organizations are eager to explore what new therapies can offer in terms of health benefits compared to existing treatments, but new drugs and drug combinations may not be affordable for all patients and healthcare institutions. As a result, greater emphasis must be placed on the overall cost-effectiveness of new drug therapies from a societal perspective in order to guide drug selection and reimbursement decisions [29,33,34]. Clinical pharmacology with its emphasis on critical drug evaluation is strategically positioned to bridge the knowledge gap between

stakeholders such as patients, clinicians, pharmacists, administrators, politicians and pharmaceutical companies within and outside healthcare institutions.

The quality of drug therapy can be improved in all healthcare settings irrespective of the wealth of the country. Patients can be provided with effective and safe therapy if well-documented drugs are prescribed and the drugs are used according to medical, social and environmental circumstances. The gap between knowledge about drugs and their use in clinical practice needs to be reduced in order to promote the principles governing the RUD. These principles have to be communicated, learnt and practised by students, doctors, healthcare staff and patients in their daily clinical practice [35]. An optimal strategy for eliminating the knowledge–practice gap in drug therapy is to apply a multifaceted approach including practice-governed quality assurance programmes combined with interactive continuous medical education and prompt electronic access to evidence-based guidelines [34]. The principles of RUD have to be integrated with healthcare planning and with resource allocation given the scarcity of resources that healthcare institutions are facing.

Clinical pharmacologists with their focus on drug evaluation and on the principles of RUD are needed in patient care [29,33,35]. They should train healthcare staff in the principles of drug evaluation and promote the use of guidelines and drug recommendations based on scientific evidence. Unbiased decisions free from improper influence by special interest groups is particularly important in view of the relentless increase in the cost of new drugs.

Key clinical pharmacological services. These services are not listed in any particular order as their importance will vary from country to country.

(a) *Participation in Drug and Therapeutics Committees (DTCs)* should have high priority for a clinical pharmacologist since these bodies provide a basis for implementing the principles of rational drug prescribing [31]. DTCs should issue drug recommendations ('Wise Drug Lists') for common diseases based on the WHO Essential Drug concept [31,35]. Clinical pharmacologists have a responsibility to train DTC members in critical drug evaluation. They should ensure that these drug recommendations are based on scientific evidence and medical needs as assessed by independent drug experts in various pharmacotherapeutic areas.

Clinical pharmacologists should also participate in the development of a National Medicines Policy that aims to improve patient care within the budget available (see also section 6.5 governments on pages 544 et seq.)

(b) *Critical drug evaluation* of new and old therapies is fundamental for patient care. It should be considered as a core service in clinical consultations, in the provision of drug information, in services to DTCs, in consultations with clinical colleagues/clinics in drug selection and in the design of clinical trials. Critical drug evaluation should be a key theme in CME of clinical colleagues and other healthcare professionals. Critical drug evaluation is the cornerstone for RUD and is important in rich as well as in resource-poor settings. The role of critical drug evaluation is particularly important when new and expensive drug therapies and drug combinations are introduced (see also Section 6.2 on Teaching).

(c) *Drug utilization studies and pharmacoepidemiological services* are closely linked to the work of DTCs and to quality assurance of drug therapy in clinics and in hospitals [36,37]. Ideally, a multiprofessional approach is preferred involving experts in clinical specialities, pharmacoepidemiology, pharmacoeconomics and clinical pharmacology. This service is important for a systematic introduction and monitoring of new drug therapies in health care and can then be linked to forecasting of future drug use in healthcare organizations [34]. Knowledge about the use of drugs is a prerequisite for follow-up studies of the adherence of prescribers to drug recommendations.

(d) *Drug information services* are primarily meant to guide clinicians in evaluating and solving drug problems in patients. While the descriptive part of the work of a drug information service is often well provided by pharmacists, the problem-oriented provision of the service is best delivered by a clinical pharmacologist who has the necessary medical training. Drug information services build on systematic literature searches in databases and reference books combined with an evaluation of the literature on patient-related diagnostic problems. This service should assist DTCs in literature searches as the foundation of evidence-based drug recommendations. A drug information service is also helpful for provision of unbiased drug information in academic drug detailing, which is well documented to improve adherence to drug recommendations and guidelines and should be part of the activities of the DTCs [38].

(e) *Services in pharmacovigilance* may include the responsibility to be a coordinating centre for reports of ADRs from clinicians and other prescribers at a regional or national level [39]. The reports should be evaluated systematically and the conclusions fed back to the reporting clinicians. Ideally, selected cases should be examined with available methods for drug analysis. Regional clinical pharmacology centres for pharmacovigilance have been successfully implemented in countries such as France and Sweden [39].

(f) *Continuing medical education*. The focus should be on major pharmacotherapeutic areas, on the principles of RUD and on new drug therapies and drug combinations. Interactive models for learning such as integration of e-learning tools in academic drug detailing may be of interest. CME should preferably be interactive as this will foster the best involvement of clinical colleagues.

(g) *Therapeutic drug monitoring (TDM) and pharmacogenetic* services are ideally provided by a Division or Department of Clinical Pharmacology. Assay of drugs can be done in many laboratories but true TDM services also involve clinical interpretation of the data taking diagnoses, drug interactions, kidney function and pharmacogenetics into consideration. An important service, particularly for elderly patients, is to ensure that drug dosages are adapted to the reduction in kidney function that occurs with age. An example of successful translation of the scientific development of pharmacogenetics into the clinic is the abacavir hypersensitivity syndrome which now can be prevented [40]. Moreover, the discipline of personalized medicine is rapidly growing, particularly in the field of cancer.

(h) *Measurement of drug concentrations for the diagnosis and prevention of drug abuse and other toxicological services.* In many hospital settings, clinical pharmacologists are involved in toxicological services such as diagnosis and treatment of drug intoxication. Although the availability of causal treatment with antidotes is limited, a correct diagnosis of the drug involved, through drug analysis, is important for follow-up and future prevention. A new function in some countries is to participate in the prevention of the abuse of doping agents such as anabolic steroids among athletes and in society at large [41].

(i) *Direct Patient Services.* Clinical pharmacologists can provide care of patients in a variety of ways. In some countries, clinical pharmacologists take responsibility for the direct care of patients with particular clinical problems (e.g. intensive care), in patients with particular organ disease such as hypertension or areas such as paediatrics and geriatrics. In some countries, clinical pharmacologists are mainly used for their skills in the evaluation of clinical drug problems such as therapeutic failures, ADRs, drug interactions and inappropriate polypharmacy. Clinical pharmacologists can assist in the development, implementation and evaluation of efficacy and safety of combination therapies in the treatment of major infectious diseases such as HIV/AIDS, tuberculosis and malaria.

(j) *Electronic Pharmacological (e-Pharmacological) Services.* Evidence-based databases for rational drug prescribing are now available through websites in many countries [32,39,42]. They can be integrated into electronic medical journals and linked to lists of prescribed drugs. E-pharmacological services include tools, knowledge databases on drug recommendations, drug–drug interactions, drugs to be used in pregnant or lactating women, ADRs and tools for the solution of drug-based problems. E-pharmacological services provide a link between published evidence and clinical practice. These services are predicted to become of particular importance with the accelerating spread of mobile phones and Internet access in poor countries.

6.4 Pharmaceutical industry.

Overview and the industry environment. Pharmaceutical companies have until recently driven the discovery, development and marketing of new and established drugs. They include a range of organizations varying from 'big pharma' global companies such as Pfizer and GlaxoSmithKline, to smaller, usually disease-focused, specialized companies, large (e.g. Genentech) and small biotechnology companies, and companies focused on generic, over-the-counter (OTC) or complementary medicines. The clinical pharmacologist has a broad perspective of all aspects of drug discovery and use, and all of the 'sub-specialities' of clinical pharmacology from pharmacokinetics/pharmacodynamics to pharmacoepidemiology, pharmacovigilance (benefit/harm management) and pharmacoeconomics are critical. More importantly, the clinical pharmacologist can integrate knowledge of the drug target, disease pathophysiology, context and management and preclinical and clinical data to guide drug development in an ethical, informed and efficient manner.

Globally, pharmaceutical companies operate in a complex environment where evolving economic, regulatory, social and political influences constantly force change. Investment in R&D has increased rapidly, but has not been matched by the rate of emergence of new products onto the market. The high expectations of innovation models that involve combinatorial chemistry, high-throughput screening, rational drug design, pharmacogenomics, bioinformatics and disease and pathway modelling have not, at least not yet, been met despite the high level of investment. The risks in a business model that concentrates on a few 'blockbuster' drugs are also becoming apparent as patents expire or are challenged vigorously by generic companies, and new drug pipelines to replace them are meagre. There have also been highly visible failures of potential blockbusters at a late stage in development and a number of high-profile safety-related post-marketing drug withdrawals that have resulted in an increased regulatory focus on risk management during the drug development process. At another level, consumers, health insurers and governments are increasingly focusing on paying for health outcomes rather than drugs, and sales and marketing approaches used in the industry are being questioned with a resulting reduction in trust. What changes are being driven by these factors?

At the discovery level, there is recognition that diseases are complex and that a focus on single targets may not be the optimal approach, resulting in a move back to disease models rather than target-based R&D. The previously separate silos of discovery, preclinical development and clinical development are being vertically integrated into development teams that include functions from early discovery through to pharmacoeconomics and marketing. Companies are emphasizing translational research to facilitate the efficient transition from *in vitro* and preclinical animal research to human applications, and medicines are being developed for more tightly targeted patient groups who are identified as likely to respond using biomarkers and/or pharmacogenomic approaches, thus improving the cost-effectiveness of the

treatment (so-called 'personalized medicine'). Companies will increasingly market medicines coupled with related services and diagnostics to identify responsive patients and there is growing recognition of developing markets and neglected diseases as targets for drug development and marketing. The increasing focus of payers on cost-effectiveness is driving companies towards development of medicines that produce real health benefits, and the biotechnology paradigm is progressively replacing the chemical, with biologicals providing high benefits coupled with high value and cost. 'Big Pharma' is accessing biotechnology medicines through in-house R&D, licensing, sponsored R&D, partnerships and the acquisition of small, vigorous, fast moving and innovative biotechnology companies that have often been started by academics.

Despite the problems facing the industry, the demand, and therefore the market, for medicines is likely to rise during the second decade of the 21st century owing to ageing populations and the emergence and growth of new markets particularly in developing countries. Companies are consolidating through mergers and acquisitions and this trend is set to continue. Paradoxically, they may become less homogeneous, with niche market, biotechnology and generics companies all emerging as significant players.

Overall, this is a dynamic and interesting environment for a clinical pharmacologist to work in. Clinical pharmacologists can work in a wide range of roles across companies, but will need to develop skills and expertise beyond those normally associated with the discipline in the academic or hospital setting. The types of roles available, and the knowledge, skills and attitudes required are discussed below.

Roles and career paths for clinical pharmacologists in industry. Traditional roles: The clinical pharmacologist in industry customarily has been involved at the early stages of clinical drug development – planning, design, conduct, analysis, interpretation and reporting of Phase I and Phase II studies in humans. These activities include:

- First in human trials, involving the first exploration in humans of dose, tolerability and pharmacokinetic and (where appropriate) pharmacodynamic parameters. The clinical pharmacologist works with preclinical, translational medicine/ biomarker, drug metabolism/PK, and toxicology partners to synthesize all the available data, to plan the optimal Phase I strategy for clinical development, and eventual filing for marketing approval.
- Phase II proof of concept clinical trials to establish efficacy in a restricted patient population
- Follow-up on PK/PD studies exploring issues such as drug interactions, effects of disease states, bioavailability and/or bioequivalence of dosage forms used during early and late development, and special patient groups such as the elderly or children.

Specialized roles: Clinical pharmacologists can have diverse areas of special interest within the discipline, and many of these are applicable in the industry setting [43–45]. Given the broad background in medicine and pharmacology/clinical pharmacology, clinical pharmacologists are well placed to integrate their special area of interest across functional and therapeutic area groups. Some examples are

- Preclinical development
- Pharmacogenetics
- Pharmacoepidemiology
- Pharmacovigilance (benefit/harm management)
- Pharmacoeconomics
- Late clinical development – Phase III confirmatory trials.

Other activities: Clinical pharmacologists in industry will become involved to greater or lesser extents in a range of other activities which may include

- Regulatory – preparation of submissions, interactions with regulatory authorities and regulatory strategy planning.
- Outsourcing – managing CRO and academic contracts.
- Advisory – arranging and managing scientific and clinical advisory boards, interactions with key scientific and clinical advisers to ensure appropriate product development.
- Intellectual property management – assisting with the preparation of patents, liaising with patent lawyers and responding to queries from patent offices around the world; involvement in IP protection strategies including decisions to patent, retain as in-house know-how or put in the public domain; scientific and clinical advice for patent defence.
- Due diligence activities – involvement in scientific and clinical analysis of data and the scientific, clinical and market potential of products or companies.
- Management and financial activities – human and physical resources – planning most efficient development paths – quicker development gives higher net present value.

Roles in small pharmaceutical or biotechnology companies: The clinical pharmacologist in this setting will fulfil a much broader role, being involved in overall discovery, development and marketing. The company will often function in a specific therapeutic area with a small number of products in development and/or on the market. The role will usually involve a broader strategic planning, management and financial focus. Clinical pharmacologists will find themselves involved in many aspects of the overall business including raising funding on the financial markets, development strategies in relation to funds available, and making decisions about developing to market stage, or licensing or sale of the product at an earlier development stage.

Career paths. Pharmaceutical companies usually have distinct scientific and management career streams. Clinical pharmacologists will normally start in the scientific stream, but are well placed because of their broad background to advance along either career line. Career paths include managing a project or product development team, leading a therapeutic area such as CNS or cardiovascular system (CVS), or leading a functional area such as clinical pharmacology,

benefit/harm management or pharmacoepidemiology. Promotion to higher management roles will lead to involvement in the company's overall discovery, development and marketing strategies.

Knowledge, skills and attitudes. The clinical pharmacologist in industry will normally have basic training as a physician and specialist training in clinical pharmacology. Companies will provide training in-house, or externally, for necessary industry-specific skills such as project management, but much training is gained through hands-on experience. The areas involved may include

- Intellectual property and knowledge management.
- Strategic planning and project management.
- Regulatory requirements – international, regional and country-specific
- Regulatory compliance – GxPs, electronic and hard record data and information management.
- Leadership and decision-making in complex organizations and cross-functional teams.
- Core business skills – including the structure of the industry, a broad understanding of the business issues and models in the industry, the differences between industry sectors, and how product value is created and measured.
- Ethical and societal perspectives and broad industry issues – attitudes and ethical practices in a company or industry sector, medical *versus* marketing department perspectives, values and activities.

A career in the pharmaceutical industry can be interesting, challenging and satisfying for a clinical pharmacologist. After all, the goal of drug development should be to convert intellectual and scientific creativity into medicines that are valuable in terms of both benefits to patients and a sustainable business model for the company. The clinical pharmacologist has the background (and even responsibility) to influence industry practices along appropriate ethical, societal and medical lines. However, it has to be recognized that this will not always be easy, or even feasible, in the context of a large, financially driven organization. A final caveat is perhaps that a career in industry can be fragile, as constant restructuring and reorganization result in a sometimes tenuous hold on the position. Flexibility and mobility are desirable attributes!

6.5 Governments.

The clinical pharmacologist is a physician who has had systematic training in the evaluation of drug therapy and drug products. This makes the speciality suitable and valuable in a number of public activities that relate, for example, to drug approval, post-marketing surveillance, drug therapy selection, reimbursement decisions and ethical review of research projects. Governments should be involved in the ethical, scientific and developmental aspects of medicines. Activities in all these three dimensions are complementary and underpin the most important role of any government: to protect its citizens through support and promotion of public health.

Governments and their respective institutions have to take all necessary measures to make sure that clinical research involving its citizens is not doing them harm or ignoring their basic human rights. This challenging task involves making sure that the research to decide which medicines (or other healthcare interventions) are authorized for use in human beings provides enough grounds to ensure safety. It also involves the task of assessing whether planned clinical research follows scientific principles that can justify both the harms and the expected benefits from this research. This forms the ethical dimension of the role of governments.

History. Following the two world wars, several initiatives were taken around human rights and these were embodied in the World Medical Association's Declaration of Helsinki in 1964. In particular, the Council for International Organizations of Medical Sciences (CIOMS) was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. In the late 1970s, CIOMS set out, in cooperation with WHO, to prepare guidelines 'to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements'. The most important of the publications of CIOMS is its International Ethical Guidelines for Biomedical Research Involving Human Subjects, first published in 1993. The updated version was published in 2002 [46] and is designed to be of use, particularly to low-resource countries, in defining the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for the ethical review of research involving human subjects. Although mainly targeting ethics committees, sponsors and investigators, the CIOMS guidelines, to which several clinical pharmacologists have contributed, have influenced governments thinking about clinical research, especially in resource-poor settings.

Another important facet of research in human subjects is good clinical practice (GCP) which is a 'standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that rights, integrity and confidentiality of trial subjects are protected'. Many GCP guidelines are based on, or refer to, the Declaration of Helsinki, including WHO GCP Guidelines published in 1995 [47] and the International Conference of Harmonization (ICH) GCP (E6) from 1996 [48].

Ethics committees and regulatory bodies. A fundamental requirement for application of ethical considerations is submission of a research proposal to independent evaluation by an ethics review committee. Nowadays, many governments define procedural aspects of the work of ethics committees in detail. For example, the European Commission has laid down strict timelines for processing research applications

which affect the work of ethics committees in all 27 European Union Member States. Clinical pharmacologists can be particularly valuable as members of ethics review committees because of their knowledge of medicines-related clinical research. In addition, governments have to ensure that only effective, safe, good quality medicines are used to treat their citizens. Nowadays, all medicines are subject to marketing authorization approval before they are prescribed. The approvals are based on assessment of the quality, safety and efficacy of the products. The safety monitoring of medicines during their whole life cycle (from marketing authorization to potential withdrawal from the market) is also a task for governments. Usually, these and other medicines-related regulatory functions are carried out by specialized governmental agencies – national medicines regulatory authorities (NMRA) such as the US Food and Drug Administration (US FDA) and in Europe, the EMEA. In a broad sense, the role of the NMRA is to cover multiple dimensions and is derived from their mission. WHO Policy Perspective on Medicines No. 7 'Effective Medicines Regulation: Ensuring Safety, Efficacy and Quality' [49] states the following [49]:

> A clear mission statement, which includes the national regulatory authority goals, is necessary to guide its work. Goals usually include the protection and promotion of public health by ensuring the safety, efficacy and quality of medicines, and their appropriate use; and ensuring the appropriateness of medicines information provided to the public and health professionals.

The EMEA which coordinates the work of the various national experts and has very far reaching responsibilities has a broader mission statement [50]: ''In the context of a continuing globalization, to protect and promote public and animal health by

- developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription medicines through a single European marketing authorization;
- controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals;
- facilitating innovation and stimulating research, hence contributing to the competitiveness of EU-based pharmaceutical industry; and
- mobilizing and coordinating scientific resources throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development programmes, to perform inspections for ensuring fundamental GXP [GXP means 'good clinical practice' (GCP), 'good manufacturing practice' (GMP) and 'good laboratory practice' (GLP) collectively] provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals''.

These are two examples of mission statements. The one from EMEA addresses the three aspects described above: ethical, scientific and developmental. It is very important that regulators involved in the evaluation of safety and efficacy of medicines have the best possible scientific education and background. They should also be able to make a critical scientific evaluation of the clinical data and to understand what, at the time of the assessment, is known and what remains unknown about each drug under review. Some of the NMRA also have units focusing on clinical pharmacology. For example, the U.S. FDA has in its Centre for Drug Evaluation and Research (CDER), the Office of Clinical Pharmacology. Nowadays, safety surveillance, pharmacovigilance, is also a responsibility of the regulators.

Clinical pharmacologists in government. In most countries, governments, directly or through their specialized agencies, are also involved in taking decisions about the selection of medicines for public procurement, developing national treatment guidelines and proposing inclusion of medicines in reimbursement lists. This work may also involve composing and updating national Essential Medicines Lists as promoted by the WHO. Clinical pharmacologists are usually closely involved at the government level in developing and delivering a National Medicines Policy. It is important that such individuals work in an environment that has political support but also where there is a good prospect of continuity of support when governments change.

The monitoring of the performance of drugs in real life after regulatory approval, including cost-effectiveness assessment in the wider context of HTA, needs highly qualified specialists. However, all these activities are linked to promotion of the rational use of medicines, sometimes also called 'quality use' [51]. An example of governmental institutions involved in such activities is the National Institute for Health and Clinical Excellence in the United Kingdom. The activities of such bodies should be based on the best possible scientific methods and knowledge and are part of the scientific dimension of the government's obligation to its citizens. Clinical pharmacologists have proved themselves to be well prepared to meet the challenges of the complex assessment of medicines.

Working at the government level, clinical pharmacologists are well trained to work in the area of HTA. As mentioned previously, clinical pharmacologists have usually not been closely involved in the past but many of the assessments are very much in the field of new drug assessments, especially the new molecular biology drugs, as well as in the administration of drugs by new technologies.

Recent history gives evidence that not all the research necessary for developing and promoting public health by medicines is possible using only private sector initiative and funding. Thus, governments may also be involved in delivering financial support for clinical research involving medicines. Clinical pharmacologists are well positioned to help in making judgements about the scientific value of proposals for governmental funding of research projects. An important

emerging issue is electronic patient health records which have been implemented or are on their way in many countries. Although these may be perceived as mostly administrative tools, they include a huge scientific potential for monitoring the safety and quality of drug therapy. There is already evidence that electronic health records can offer greatly added value for research in pharmacovigilance [52]. Clinical pharmacologists should be actively involved in designing and using electronic patient health records because of the enormous potential for future clinical research including monitoring of rational drug use and safety.

Future challenges. A government's efforts to create a research-friendly environment in its country could be composed of functional legal and other systems which should make government offices well informed about the necessary scientific background, and thus help their effective functioning. Owing to the relative lack of new therapies and pressure from patient groups and industry, governments have been pushed into granting 'early market approvals' under certain pre-conditions. However, effective methods for pharmacovigilance and safety studies in the context of early market access need to be created and tested and clinical pharmacologists have an important role to play [53,54]. Clinical pharmacologists also contribute to the topic of pharmacoepidemiology. This discipline is being increasingly used and sometimes is the only available approach to assess the benefits and harms of long-term pharmacotherapy. Similarly, pharmacoeconomics attempts to give a financial cost and value to everyday drug use which may become the basis for rational reimbursement systems.

In order to implement these various dimensions, governments have to create laws and regulations, the necessary infrastructure in terms of governmental institutions and necessary resource allocations to support the infrastructure. One of the key resources is properly trained specialists, capable of taking decisions based on the best possible scientific methods and evidence. All these dimensions are inter-related and interdependent. Good ethics cannot do without good science; good science can be ethical, whereas bad science can never be.

Conclusion. The clinical pharmacologist is a specialist who, working at government level, can serve the public best by helping to ensure that only safe and effective medicines are authorized for use, as well as facilitating cost-effective prescribing and improving the RUD. The training of clinical pharmacologists should be better tailored to meet the needs of various government services in order to ensure that the best scientific knowledge is used to make decisions in public health. In particular the governments of emerging economies and developing countries could benefit from the expertise of clinical pharmacologists, although few have given the necessary priority to the development of the discipline and many would have difficulty in creating positions that are seen to compete for funds with 'mainstream' disciplines.

7. Organization

Introduction.
Historically, clinical pharmacology developed either from departments of pharmacology or from departments of internal medicine. Clinical pharmacology is now an independent medical speciality in many countries. In countries where it is not a separate medical specialty, clinical pharmacology should be recognized as a scientific discipline in its own right. Clinical pharmacology is usually organized in separate units headed by a clinical pharmacologist. Depending on local and national circumstances, the unit could either be a division of clinical pharmacology in a clinical or in a pharmacology department. It could also be a separate department or institute of clinical pharmacology. Irrespective of which model is used, the optimal setting is in a university hospital as it supports all three major functions of clinical pharmacology: research, teaching and health care. County (or district) hospitals and primary health care also need experts in clinical pharmacology. Such expertise can be provided from the university hospital if the local availability of clinical pharmacologists is limited. In some cases, the discipline of clinical pharmacology may justify only a small organization and here the terminology of 'Unit' may be more appropriate than 'Division'. There are several models of organization, described below.

Independent department of clinical pharmacology in a university hospital
In some countries, clinical pharmacology has developed to such an extent that a separate department in a university hospital has been created. Such departments have sufficient staff for the manifold interests of clinical pharmacology in research, teaching and clinical service. Such staff will comprise both clinical pharmacologists and other drug experts such as pharmacists and drug analytical staff and often include basic pharmacologists.

The department may have beds, and clinical pharmacologists are then fully responsible for the treatment of patients. The advantage of this arrangement is that the clinical pharmacologist is fully integrated in the clinical work in the hospital making it easier for them to relate to clinical colleagues. The disadvantage is that the involvement of clinical pharmacologists in direct health care will reduce their time availability for other important clinical pharmacology activities (see Section 6.3). Thus, in many countries, clinical pharmacologists are not directly responsible for patient care. There are advantages and disadvantages in both models (see above) and which model is chosen should reflect the national and local traditions, circumstances and needs.

Collaboration between basic and clinical pharmacologists enables achievements to be made that are rare when the disciplines work on their own. Finally, the department will need staff with other skills such as nurses, computer experts, statisticians, laboratory technicians and secretaries to fulfil its role properly.

Division or unit of clinical pharmacology in a clinical department

In many countries, this model for clinical pharmacology is more appropriate. It is likely to be the pattern where it is impractical to have a fully independent department. This may be the case where the range of clinical services required is significantly smaller than as listed in Section 6.3 or where the number of staff employed only permits the provision of a limited range of such services. In either case, the long-term aim should be to grow so that a full range of services, relevant to the needs of the community, can be provided. This may result in the creation of an independent department in due course.

Division or unit of clinical pharmacology in a pharmacology department

In some cases, a clinical pharmacology unit (or division) has been organized in close association with (or has developed from) a department of basic pharmacology. The advantages of such an arrangement have been discussed above. There will be a considerable disadvantage if the basic pharmacology department is sited some distance from the hospital.

Development of clinical pharmacology organizations

Many clinical pharmacology organizations start small, but as they grow over the years in response to the healthcare needs of their communities, they develop new skills and require different staff groups.

Thus, there are examples of clinical pharmacology organizations that have developed from basic pharmacology but now have individual clinical pharmacologists who provide direct health care to patients, e.g. by looking after patients who have taken a drug overdose, running a unit for clinical trials, or evaluating patients with pharmacotherapeutic problems such as therapeutic failure or ADRs.

Equally, there are clinical pharmacology organizations that have developed from providing direct patient care to become more involved in the basic science of pharmacology – for example the use of molecular biology skills to understand pharmacogenetic variability and thereby to provide a more personalized approach to drug therapy. The training available for clinical pharmacologists will need to reflect this changing world (see Addendum II).

8. The Relationship with Other Drug Experts

The rise in clinical pharmacology in the 1960s was in a large part due to the realization of basic pharmacologists that their discipline was too far removed from the practice of medicine but also due to the desire of prominent clinicians specializing in pharmacotherapy to develop their science and improve the quality of drug therapy. Clinical pharmacologists at the time had to have fruitful collaboration with both pharmacology and internal medicine and usually had considerable training in both disciplines.

Clinical pharmacology at its best now requires a much broader view of all aspects of medicine in which drugs are used be it internal medicine, paediatrics, psychiatry, geriatric medicine or oncology. The role of clinical pharmacology in all these areas should be to educate other physicians, to perform collaborative research and to disseminate information about the principles of drug evaluation and RUD. These roles are facilitated by having access to diversified methods for monitoring and improving drug therapy.

Collaboration with drug experts representing other professions is equally important, not least with basic pharmacologists and pharmacists whose training in many ways complements that of a clinical pharmacologist. Fruitful collaboration across the three professions is particularly well documented in Drug and Therapeutics Committees and drug information services. In pharmacoepidemiology and pharmacovigilance, collaboration with epidemiologists is necessary. In TDM, collaboration with drug analytical experts is vitally important to maintain accreditation of the analytical methods used. Such experts are usually trained in chemistry or pharmacy. Collaboration with persons knowledgeable in molecular biology is of increasing importance, particularly in pharmacogenetics. Many clinical pharmacologists depend on their collaboration with trained nurses who fulfil a valuable role in areas such as drug utilization, measurement and evaluation.

9. Emerging Roles of CPT: Biologics and Biosimilars

Background.

In the last three decades, drugs produced or extracted from biological sources (e.g. recombinant products, monoclonal antibodies and recombinant vaccines) such as insulin, somatotropin, interferon, granulocyte-stimulating factor, erythropoiesis-stimulating factors like epoetin and TNF-α inhibitors like infliximab have been developed and approved for therapeutic use. Biopharmaceuticals are a rapidly growing segment of newly developed drugs, with sales amounting to about $40 billion in 2006 in the United States [55]. Today, 20–30% of drugs are produced by biotechnological methods. The patent on human insulin was filed in the early 1980s and expired in 2002. Other patents have also ended or are about to expire. Currently, about 400 biopharmaceuticals are under clinical development. About half are used in treating cancers. As many of them are expensive, it is important that generic products can be provided to produce cost savings. It is thus clear that the remit of the clinical pharmacologist has expanded very significantly since the original WHO document appeared in 1970.

In contrast to classical drugs, which are typically manufactured through chemical synthesis, by combining specific chemical ingredients in an ordered process, biologics (or biopharmaceuticals) are manufactured in a living system such as a micro-organism or plant or animal cells. Owing to their production process and mechanism of action, biologics have a different pattern of potential adverse effects compared with chemically synthesized drugs, which deserve special attention [56].

Most biologics are very large, complex molecules or mixtures of molecules. The production is based on recombinant

DNA technologies and the process is often a secret [55]. Accordingly, changes to the production process such as cell lines, vectors, culture media and conditions can lead to the formation of protein isoforms, alteration of glycosylation patterns and/or changes in the tertiary protein structure. Therefore, unlike classical drugs, a medicine produced by such a process in order to mimic an already licensed biologic (the reference drug) is a product that is similar to but not the same as the innovator drug. Therefore, such a product is not called 'generic' but 'biosimilar' or 'follow-on biologic'. Because of the complex science involved, the EMEA recognized that the generic approach is scientifically not appropriate for these products. In addition, clinical pharmacologists working in this field will need to acquire skills in molecular biology rather different from those needed 40 years ago.

Biosimilars – problems in evaluation.
As biosimilars are different from existing biologics in terms of their raw materials and manufacturing processes, biosimilars have the potential to cause, for example, immunogenicity problems that were not detected in clinical trials and did not occur with the original manufacturer's product. Therefore, EMEA has stipulated that a regulatory framework should be established to minimize the risk to patients by requiring extensive testing before approval in order to ensure that biologics are safe and effective. Moreover, biosimilars have to undergo post-marketing monitoring like that required for new biologics. Accordingly, EMEA has taken a case-by-case approach to similar biological products, typically including clinical trials. This means that a multistage process will be developed. The FDA is given some flexibility in deciding how much data and testing are enough to establish attainment of the key standards of safety and efficacy - similarity and interchangeability - for follow-on biologics [57].

In particular, the manufacturer of a biosimilar has to provide a detailed pharmaceutical dossier, including data on the manufacturing process, manufacturing facilities, implementation of non-clinical bioassays, toxicity studies, local tolerability studies, and Phase I to Phase IV studies compared with the reference product. Thus, for biosimilars of epoetin, EMEA stipulated two double-blind studies in a parallel-group design to investigate the efficacy of the new erythropoiesis-stimulating agent in patients with anaemia following renal damage. Currently, it is permitted to extrapolate results on efficacy in a specific therapeutic area to others, e.g. from renal anaemia to the symptomatic treatment of chemotherapy-associated anaemia. However, this current opinion is subject to further review.

As mentioned above, immunogenicity is a major problem of biologics. As they are proteins, an immune response such as the formation of antibodies is more likely than in conventional pharmaceutical products. Thus, in patients treated with epoetin alpha, an isolated erythroblastopenia (pure red cell aplasia) occurred as a consequence of the generation of neutralizing antibodies against erythropoietin [58]. In general, the immunogenic potential of biopharmaceuticals depends on the production process, and also on the mode of application, dosage, duration of treatment and specific characteristics of the individual patient. Therefore, careful pharmacovigilance is needed, as immunological reactions may be without clinical consequences, may sometimes lead to loss of efficacy, or in rare cases may cause improved efficacy or severe adverse reactions. According to EMEA guidelines, at least 300 patients must be observed over at least 12 months in order to assess possible immunogenicity and the profile of adverse events of a biosimilar compared with the reference substance [59].

As the safety data from pre-authorization studies are never sufficient to get a complete profile of the immunogenic potential of a biosimilar, post-authorization safety studies and the preparation of risk management plans are obligatory for biosimilars.

To illustrate the differences of approval for biosimilars of epoetin, Abseamed® (Medice, Iserlohn, Germany) and Binocrit® (Sandoz, Kundl, Austria) were approved in Europe except for subcutaneous injection in patients with chronic renal failure, as data on immunogenicity were considered to be insufficient for this indication. This exception does not exist for the biosimilar Epoetin alfa Hexal® (Hexal, Holzkirchen, Germany).

Conclusions.
The extensive requirements of regulatory authorities concerning preclinical and clinical studies of biosimilars impose substantially higher developmental costs than those for usual generic drugs. It is therefore expected that biosimilars may save only 15–20% of costs compared with the biopharmaceutical original [60].

In summary, the assessment of the harm benefit ratio of biologics and biosimilars is a challenge for physicians, manufacturers and regulatory authorities and requires translational efforts to consider the needs of drug innovation on the one hand and patient's safety on the other hand [61]. It requires the expertise of molecular biologists, immunologists and clinical pharmacologists in order to take advantage of these challenging new medications. The opportunities for clinical pharmacologists in this field are considerable provided the necessary training in molecular biology is taken on board in addition to the standard training that clinical pharmacologists undergo.

10. The Contribution of Clinical Pharmacology to Global Public Health

Background.
Since the first edition of the WHO Technical Report in 1970 [1], the medical world has changed dramatically. New diseases have arisen (HIV/AIDS), developments in molecular biology have generated new biotherapeutic agents, communications have been revolutionized by the Internet and many of the historically important diseases of the developing world are receding and being replaced by non-communicable disease – with the notable exceptions of malaria and multidrug-resistant tuberculosis.

However, more than 50% of countries that replied to a WHO survey in 2003 had no policies in place to improve the use of medicines despite data showing around 50% of all medicines worldwide are being used inappropriately [62]. A prominent example is the excessive use of antibiotics which is a major factor in the current high prevalence of resistance to previously first-line antibiotics for dysentery, pneumococcal pneumonia and hospital-acquired infections [62].

The World Health Assembly, recognizing these problems, urged 'member states to establish or strengthen multidisciplinary national bodies for monitoring medicine use, and implementing national programmes for the rational use of medicines' (WHA resolution 60.16, May 2007).

With this as background, it can be argued that the most important single development that has expanded the role of clinical pharmacologists in global public health has been the recognition by many developed and developing countries of the value of a National Medicines Policy. The initiative came to a focus in the WHO 'Guidelines for the Development of National Drug Policies' published in 1988 [2]. More than 150 countries now have their own policies in varying stages of implementation.

These policies aim to ensure:

- The quality, safety and efficacy of medicines
- Equitable access to medicines for all the population
- The rational/quality use of medicines
- 'A viable and responsible local pharmaceutical industry' (quotation from the Australian National Medicines Policy, 2000).

Clinical pharmacologists have clear and demanding roles in the implementation of at least the first three of these key ingredients.

Quality, safety and efficacy of medicines.

Quality of medicines is threatened by counterfeiting, poor manufacturing practice or the unscrupulous marketing of time-expired products – each of these is a contemporary problem, especially in the developing world [63]. In many countries, clinical pharmacologists contribute substantially to drug regulation.

The pre-marketing assessment of the quality, safety and efficacy of a new medicine demands critical skills possessed by the trained clinical pharmacologist, including a capacity to evaluate clinical trials performed in many different clinical areas. The ability to assess the relevance and possible problems of a new medicine for a particular population also requires an understanding of local epidemiology (if only to establish whether or not the country 'needs' this particular medicine – based on an assessment of the prevalence and severity of any particular medical condition) and possible racial variations in, for example, the metabolism of medicines.

Increasingly, pharmaceutical companies are conducting clinical trials in developing countries in the expectation that this will be a cost- and time-efficient way of recruiting large numbers of patients. The trial results feed into the regulatory system at the point of pre-marketing assessment. Clearly, this provides an opportunity to obtain country-specific data, but it also raises the question of who takes clinical responsibility for critically assessing trial protocols, who manages the necessary initial research ethics application and clearance, and who takes responsibility for the clinical supervision of patients. These are standard roles for clinical pharmacologists in developed countries and there is a strong case for providing positions in less developed countries for the same purposes.

Safety cannot be fully appraised at the point of marketing and only some form of post-marketing surveillance will permit the timely detection of less common adverse effects not picked up in the limited pre-marketing data.

For many developing countries, limited resources mean that most new medicines approved for marketing have already been used for years elsewhere, and there is a greater probability that their safety has been more fully characterized, allowing for differences in pharmacogenetic variations from country to country. In whichever context, the clinical pharmacologist should have a major role in the setting up of spontaneous reporting systems, in reviewing (and suggesting action on) reported adverse events, and in providing data not only to guide decisions in the home country but also to contribute to the global database [64].

Equitable access.

The individual's right to the 'best possible standard of health' is set out in the Universal Declaration of Human Rights [65]. When challenged in the courts of several countries, the right of access to essential medicines has been upheld as an extension of the right to health [66]. Despite this assertion of principle and intent, WHO estimates that as many as two billion people worldwide do not currently have access to essential medicines.

For the poorest populations, lack of finances may be the major cause. An estimate of annual per capita income adjusted for within-country cost of living, expressed in 'international dollars' (so-called ''Purchasing Power Parities'') for the United States in 2005 was $41,674, $3487 for Sri Lanka and $1892 for Nigeria [67]. With no regular acceptance of the need for medicine prices to be proportional in some measure to national per capita income, the costs of many medicines are beyond the limited resources of the poorer countries as the figures above predict.

Many countries are developing systems for pre-marketing economic evaluation of medicines. While the economic model chosen will influence the outcome, the starting point is always evaluation of the clinical trials data from which the estimate of potential benefit is derived, to set alongside cost in the cost-effectiveness calculation. This requires clinical pharmacological skills. Several governments worldwide now engage clinical pharmacologists as part of the pharmacoeconomic team to address these issues specifically.

In countries where the cost of medicines to the individual is subsidized by government, a list of selected medicines is maintained. This may be the same as the country's 'Essential Medicines List', and this is the case in many low and middle income

countries. However, subsidy of this type – whether funded entirely by government, partly by the patient as a co-payment or through some form of insurance scheme – requires a rigorous examination of not only the quality, safety and efficacy of medicines but also measures of cost-effectiveness and affordability. Clinical pharmacologists are commonly involved in this selection process in developed countries but much less so at present in the developing world – partly because there are so few of them. Buying only medicines that are cost-effective and affordable locally is a potent way of ensuring that limited resources are used to best advantage.

Rational use of medicines.

Having medicines of high quality that are accessible to all does not guarantee that they will be used in the best possible way. More money can be saved and health objectives met by ensuring the highest standard of use. Over the past two decades, methods for measuring and evaluating the quality of use of medicines have been developed and implemented.

- *Drug utilization reviews*
  One of the first steps in improving the way medicines are used in any community is definition of the potential or actual problems.
  Measuring medicine use and relating it to clinical indication in a community, hospital, clinic or at a national level is not the easy task it would be if there were databases that could be linked (with proper attention to confidentiality of the records). Supply is not the same as utilization, although in some circumstances, especially in resource-poor settings, it may be the only surrogate available.
  Commonly, utilization has to be measured prospectively by data collection in a defined area for an adequate time, to ensure representative results. In many countries, this task has fallen to pharmacists who have had special training in the methods. However, when the results are being interpreted, clinical input is required. Clinicians with speciality training may be needed in order to judge whether prescribing has been appropriate. This role can be filled by a clinical pharmacologist with broad clinical training and experience. Standard treatment guidelines (below) that have been endorsed for a country, hospital or community serve as the reference standard and help to define inappropriate practice. The clinical pharmacologist's role is as a member of the evaluating team and also in the design and implementation of interventions to mitigate problems.
- *Standard treatment guidelines*
  The introduction of evidence-based treatment guidelines is one of the interventions that has a large potential to improve the quality of use of medicines [68]. To have the necessary authority, the guidelines should contain the best available evidence, be put together with representative input from all end-users and be sensitive to local conditions (e.g. storage and transport problems for particular formulations of medicines in remote countries with difficult climates such as the isolated island communities of the Pacific region). The guidelines should also be endorsed by local opinion leaders (including government and professional associations) and be revised regularly to maintain currency. Clinical pharmacologists commonly have a central role in developing guidelines and their broad training fits them for this task.
- *Essential medicines lists*
  The essential medicines list should reflect, and derive from, the national standard treatment guidelines. Ideally, guidelines should be prepared first and the essential medicines list produced from their recommendations. Whatever the sequence, the two documents should always be harmonized at each updating and review.
- *Objective information about medicines* (see also Section 6.3)
  In many developing countries, there is a dearth of objective information for health professionals about medicines, the gap being filled by information provided by pharmaceutical companies, with, not unexpectedly, a promotional bias. Many developed and some developing countries produce drug information journals several times each year. These deal with topical issues about the use of medicines, review the profiles of newly introduced medicines and discuss adverse effects. Clinical pharmacologists play a major role in the editorial processes and as authors for such publications. In some developed countries, drug information centres staffed by clinical pharmacologists, pharmacists and other health professionals have been set up to provide patient-focused information.
  Increasingly, medicines information is being produced for consumers, written in non-technical language and in some countries issued with all first prescriptions for medicines.
- *Education of health professionals and of consumers* (see also Section 6.2 and Addenda I and II)
  Clinical pharmacologists working within the health system always have a responsibility to be involved in undergraduate, postgraduate and continuing education. Much evidence suggests that doctors prescribe less well than they might [62]. Undergraduate training, with continuation through into post-graduate and continuing education, has the potential to lift the level of prescribing beyond the mediocre and provide a pattern for life-long learning as new medicines, or new uses for old ones, are introduced.
  Whose business is the education of consumers? Peer education is a powerful technique and several studies have demonstrated its effectiveness in improving understanding and use of medicines. If this is the strategy chosen, the clinical pharmacologist is absolved from being the primary educator but often becomes the adviser who helps to translate the information from medical to everyday language.
  Work in a Drug/Medicines Information Centre and Hospital Medicines and Therapeutics Committees may

be a natural extension of the tasks listed above – especially in larger teaching hospitals.

The clinical pharmacologist's job description for global public health.

There is a wide 'job description' for the clinical pharmacologist working predominantly in the health system. It is good that we can now demonstrate that many of the strategies listed above have strong evidence that they are effective in increasing knowledge, improving prescribing or the consumer's use of medicines [68].

However, while it appears intuitive, there is virtually no evidence to link improved prescribing and use of medicines *uniquely* to improved health outcomes, with the exception of improved compliance/adherence, reflected in better disease control – especially most recently in the treatment of HIV/AIDS – and some instances where antibiotic choice and adherence play the crucial role in patient recovery.

The list of tasks above (and in Section 6.3) reflects the clinical pharmacologist's usual pre-occupation with prescription medicines. A further, emerging role is in the evaluation and investigation of traditional medicines which provide first-line treatment for up to 80% of the world's population. Largely neglected by Western clinical pharmacology, these traditional preparations have the potential to provide surprises. For example, it is arguable that the most important advance in the pharmacotherapy of malaria in the last decade has been the introduction of the *Artemisia* derivatives – which come directly from the Chinese herbal tradition.

Several developed and developing nations have recently set up a regulatory framework for traditional/complementary medicines. The concerns that prompted these initiatives were the need to ensure quality control in the manufacture of these products and to evaluate the potential for unexpected toxicity (as demonstrated, for example, by aristolochic acids in some traditional medicines as a cause of renal impairment and renal cancer). There is also the difficult problem of assessing the efficacy of products that have had little or no scientific study in the past, and which are produced by an industry that has only limited options for patent protection. In addition, there are only limited funds available for the necessary clinical trials work and thus many problems remain to be solved. However, research money is beginning to flow from both pharmaceutical companies and from government sources in some countries.

In several instances, clinical pharmacologists have been members of the national advisory committees making recommendations to government regulators, and in both Australia and the UK these committees have been chaired by a clinical pharmacologist.

Some preparations that have been in use for many centuries warrant investigation and evaluation – a further role for the clinical pharmacologist in relation to global health.

The recognition that medicines are used for treatment or prophylaxis on such a scale in many populations that they assume the same importance as other factors that influence public health has led to the use of epidemiological methods to explore the impact of medicines on populations as a whole. The exploration of ADRs has led to fresh approaches for the linkage of events with medicines use. Case–control studies [69] and health database linkage have raised hypotheses, and sometimes provided hard causality evidence about events stemming from drug exposure. Record linkage is at present only feasible in countries that have the necessary, accessible databases but will undoubtedly spread more widely as the technology comes within the reach of less well-resourced countries.

Conclusions.

The discipline of clinical pharmacology arose from the two imperatives of the need to be able to measure the efficacy of medicines in patients and the even more urgent need to be able to monitor adverse effects.

However, the list of ingredients in a contemporary clinical pharmacologist's work provides a menu too full for a single individual. In reality, and especially in resource-poor countries, clinical pharmacologists will make the biggest contribution, working as part of a team, whether in the hospital, the community or in an administrative position.

Training of clinical pharmacologists to meet these needs will have to be rather different and much broader than envisaged in 1970. It is covered in Section 6.2 and in Addenda I and II.

11. Overview

Section 3. Definition. Clinical pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans and involves research, teaching and delivery of health care, as well as helping to frame policy and giving information and advice about drugs. The term 'clinical pharmacologist' is also used in the professional sense to refer to those physicians who are specialists in clinical pharmacology. They have usually undertaken several years of postgraduate training focusing on important aspects of clinical pharmacology including clinical trials, drug evaluations, pharmacoepidemiology, pharmacoeconomics, pharmacogenetics, pharmacovigilance and clinical drug toxicology. Such clinical pharmacologists have as their primary goal that of improving patient care, directly or indirectly, by promoting the safer and more effective use of drugs.

Section 4. History. Clinical pharmacology is a relatively new medical discipline having been developed extensively in the middle of the 20th century. However, it has its roots in a much older tradition of 'materia medica' going back for centuries. After a period at the end of the 20th century when the discipline was seen to contract in some countries, there are now new signs of optimism (see introduction).

Section 5. The Global Scene. Modern drug therapy has unquestionably improved the health of peoples in developed countries over the last 50 years and yet there is much more that could be done in these countries quite apart from the needs of developing countries.

Section 6.1. Research. Research is a fundamental part of the training and the work of virtually all clinical pharmacologists. The endeavour of a pharmacologist working in a clinical environment is to develop methods and strategies that improve the quality of drug use in individual patients and patient populations. Research in drug evaluation, drug utilization, pharmacovigilance and pharmacoepidemiology has become more important than at the time of the 1970 WHO report [1]. The RUD implies that drugs should be chosen according to their efficacy, ADRs and cost as potentially equally important parameters. Research in clinical pharmacology therefore includes studies that elicit new data about drugs in use such as new indications and treatment in neglected populations. It also includes research into ADRs, pharmacogenetics and drug interactions. Research in clinical pharmacology is often interdisciplinary.

Section 6.2. Teaching. All clinical pharmacologists will have a considerable role to play in teaching, whether this is at the undergraduate, postgraduate or continuing professional development level. Most attention is currently directed at the undergraduate level because of the increasing demands being placed on new prescribers and because of the evidence that new prescribers are more likely to prescribe less effectively and with more errors than their seniors. A number of different approaches to this problem are described and in a comprehensive Addendum (Addendum I), the Core Knowledge and Understandings, the Core Skills and the Core Attitudes are listed.

Postgraduate teaching of clinical pharmacology is also covered (page 540 and Addendum II) but the approach here is a more general one. This is because there is far greater variability in the availability of staff and resources as well as varying needs around the world in the postgraduate scene than in the undergraduate one.

Section 6.3. Patient care. The prime function of a clinical pharmacologist in patient care is to deliver safe and effective drug therapy in what is often termed the RUD. In some cases, this is done directly where a clinical pharmacologist may have direct charge of patient care but more commonly they will have a range of services to offer colleagues and their patients. Clinical pharmacologists are trained particularly in the critical evaluation of both new and old therapies and so may function on drug and therapeutics committees or by delivering drug information services (often in collaboration with other healthcare professionals such as pharmacists). Special skills are available in drug utilization, pharmacoepidemiology and pharmacovigilance. In addition, many clinical pharmacologists provide a TDM service often linked to pharmacogenetic expertise and this is leading to a personalized medicine approach which in some cases can result in more effective therapy with fewer ADRs.

Section 6.4. Pharmaceutical industries. The clinical pharmacologist has much to offer the pharmaceutical and biotechnology industry at all levels. The clinical pharmacologist's broad knowledge of all aspects of drug use combined with the insights gained from clinical practice provides a unique platform to influence the effective and ethical development and marketing of therapeutic drugs. In turn, a career in pharmaceutical companies can be satisfying and rewarding both professionally and financially. It can involve a career that evolves to a broad high level management position, or a focus on a special area of interest within clinical pharmacology, and also provide the opportunity to develop a range of skills and knowledge not often encountered in academic clinical pharmacology.

Section 6.5. Governments. Governments need to develop systems to serve the public by ensuring that only safe and effective drugs are authorized for use in their populations and the clinical pharmacologist is well suited to this purpose as well as facilitating cost-effective prescribing and improving the RUD. The training of clinical pharmacologists should be better tailored to meet the needs of various government services in order to ensure that the best scientific knowledge is used in making decisions in public health. In particular, the governments of emerging economies and developing countries could benefit from the expertise of clinical pharmacologists, although few have given the necessary priority to the development of the discipline and many would have difficulty in creating positions that are seen to compete for funds with more mainstream medical disciplines.

Section 7. Organization. Clinical pharmacology services can be delivered from a variety of different organizational arrangements. There is little doubt that the most effective system is for the clinical pharmacology services to be delivered from a department or division based within a hospital, whether the hospital is a university hospital or a district general hospital so that all aspects of the discipline can be practised. The needs of primary care have to be considered, although in many countries this is delivered from the hospital setting.

Section 8. The Relationship with Other Drug Experts. Clinical pharmacology is a discipline where the close working relationship with a number of different professional groups is very important.

Section 9. Biologics and Biosimilars. Biologicals play an emerging role in clinical pharmacology. In contrast to common drugs, which are typically manufactured through chemical synthesis, biologicals are made in a living system, hence the generic approach for the common drug is scientifically not appropriate for these products. Biosimilars require a special regulatory framework in order to ensure that biological therapies are safe and effective and require post-marketing monitoring like new innovative biologics. Hence, the assessment of the harm–benefit ratio of biologics and biosimilars is a challenge for physicians, manufacturers and regulatory authorities and requires translational efforts with interdisciplinary expertise.

Section 10. The Contribution of Clinical Pharmacology to Global Public Health. The development of clinical pharmacology has been centred on the 'developed' countries of the world and yet the needs are arguably greater in the developing countries. The skills and resources available in such countries necessitate a different approach to developing the RUD. The discipline of clinical pharmacology arose

from the two imperatives of the need to measure the efficacy of medicine in patients and the even more urgent need to be able to monitor and hopefully prevent adverse drug effects. However, the list of ingredients in a contemporary clinical pharmacologist's work provides a menu that is too full for a single individual. In reality, and especially in resource-poor countries, clinical pharmacologists will make the biggest contribution, working as part of a team, whether in the hospital, the community or in an administrative position.

Training of clinical pharmacologists to meet these needs will have to be rather different, and much broader, than envisaged in 1970 when the initial WHO report was published [1].

Addendum I: Model Core Curriculum for Clinical Pharmacology, Therapeutics and Prescribing for Medical Students

This addendum provides a list of knowledge and understanding, skills and attitudes relevant to the use of drugs that should be core content in the undergraduate medical curriculum. These represent key learning outcomes that will enable all graduates to prescribe safely and effectively at the point of graduation. These core objectives are generic and applicable to most areas of therapeutics. They should be considered in association with a relevant list of core drugs and therapeutic problems to which they apply. Medical schools should be encouraged to identify lists that are appropriate for their local circumstances. For each drug, graduates should be expected to have an understanding of the mechanism of action, recognize the appropriate indications for use, know the appropriate route(s) of administration, and know the important contra-indications and adverse effects. In some cases, a drug class is listed with a commonly used member of the class as an example. The list of drugs chosen might be viewed as a 'student formulary'.

Core knowledge and understanding, skills and attitudes required to support rational prescribing.

Core knowledge and understanding.

Basic pharmacology

- the general mechanisms of action of drugs at a molecular, cellular, tissue and organ level
- the ways in which these actions produce therapeutic and adverse effects
- the receptor as a target of drug action and related concepts such as agonism, antagonism, partial agonism and selectivity
- the development of tolerance to drugs

Clinical pharmacokinetics

- the mechanisms of drug absorption, distribution, metabolism and excretion
- the concepts of volume of distribution, clearance and half-life and their clinical relevance
- how these factors determine the optimal route, dose, frequency and duration of drug administration

Factors that determine inter-individual variation in drug response

- adherence to therapy
- pharmacodynamic variation
- pharmacokinetic variation
- pharmacogenetic variation
- pharmaceutical variation

Monitoring drug therapy

- the importance of monitoring the effect of drug therapy
- the ways in which this can be achieved (e.g. measuring plasma drug concentrations or assessing pharmacodynamic responses)
- the variable relationship between drug dose, plasma concentration and clinical effect

Adverse drug reactions

- the different types of ADRs
- the frequency of adverse reactions in primary and secondary care
- recognition of common susceptibility factors and how risks of harms can be minimized
- the importance of reporting adverse reactions and other approaches to pharmacovigilance

Drug–drug interactions

- the potential for drugs to interact to cause beneficial and harmful effects
- the mechanisms by which drugs interact (pharmaceutical, pharmacokinetic, pharmacodynamic)
- the ways in which interactions can be predicted and avoided

Medication errors

- the different types of medication errors
- the common reasons medication errors occur in practice
- the ways in which individual prescribers can reduce the risk of medication errors

Clinical drug toxicology

- the assessment, recognition and treatment of common intoxications (e.g. paracetamol)
- the principles of removing or counteracting the effects of toxic substances after ingestion
- toxicokinetic and toxicodynamics

Prescribing for special patient groups with altered physiology, pharmacokinetic handling and pharmacodynamic responses

- elderly patients
- children
- women who are pregnant, breast-feeding or of childbearing potential
- patients with renal or liver disease

Legal aspects of prescribing drugs

- categorization of drugs as OTC preparations, prescription-only medicines, controlled drugs
- the prescribing of 'unlicensed' preparations
- the responsibilities associated with prescribing controlled drugs

Developing new drugs

- drug development including clinical trials (Phase I to Phase IV)

- the approval process and major regulatory authorities in the relevant country
- the requirements of good clinical trial design
- consent, ethics, bias, statistics, dissemination of information

Understanding the principles and pitfalls of clinical drug trials
- Aims of the trial
- Relevance of the trial for health care
- Selection of patients, diagnostic criteria and sampling procedure, criteria for inclusion and exclusion
- Controls: cross-over, separate control group, untreated, other therapy, placebo
- Design: double-blind, single-blind, open
- Randomization of treatment
- Pharmacokinetics: dose–effect studies
- Pharmacodynamics: concentration–effect studies, biomarkers
- Drug interaction
- Recording of effects (subjective and/or objective)
- Recording of adverse effects
- Statistical planning
- The author's conclusion: adequate, questionable, irrelevant or impossible?

Managing the prescribing of medicines in the health service
- the role of local formularies
- the role of drug and therapeutics committees
- the influences that affect individual prescribing choices
- the rational assessment of new drugs based on safety, efficacy and cost-effectiveness

Ethics of prescribing
- informed patient consent and adherence to therapy

Commonly used drugs
- the mechanism of action, the indications for use, the appropriate route, frequency and duration of administration, and the important contra-indications and adverse effects of commonly used drugs

Common therapeutic problems
- the management of common acute and chronic therapeutic problems

Alternative therapies
- the motivations that lead patients to seek alternative therapies
- some common indications and appraisal of the evidence for their efficacy
- how such therapies interact with prescription drugs that patients are receiving

Drug information retrieval
- Retrieval of drug information for prescribers and other healthcare staff
- Acquisition of knowledge and practice in how to assess the value and reliability of drug information sources

Core skills.

Taking a drug history
- taking accurate information about current prescription and non-prescription drugs
- making an assessment of adherence to a medication regimen
- recording current and past ADRs and allergies

Prescription writing
- choosing a safe and effective drug and an appropriate dose
- writing accurate, legible and legal prescriptions including controlled drugs
- keeping accurate records of prescriptions and response
- calculation of drug doses based on patient weight or a nomogram
- calculation of the strength of an infusion based on the required rate of drug administration
- prescribing oxygen (flow rate, delivery) and intravenous fluids

Drug administration
- selecting the appropriate route of administration
- administering subcutaneous, intra-muscular and intravenous injections
- preparing drugs for parenteral administration including mixing and dissolving drugs
- preparing and administering drugs by an infusion pump
- preparing and administering nebulized drugs
- advising patients about special modes of drug delivery, e.g. inhaled, topical, insulin

Prescribing drugs in special groups
- elderly, children, pregnancy and breast-feeding, renal and liver failure

Prescribing drugs to relieve pain and distress
- palliation of pain and other distressing symptoms

Adverse drug reactions and interactions
- assessing drugs as a possible cause of symptoms and signs
- recognizing the potential for adverse interactions
- reporting ADRs and interactions

Drug allergy
- recognizing allergic drug reactions and taking a history of allergic reaction
- treating allergic reactions, emergency treatment of acute anaphylaxis

Clinical pharmacokinetics
- using core knowledge of pharmacokinetics to inform safe prescribing

Monitoring drug therapy
- identifying which therapeutic effect to observe
- using measurements of plasma drug concentrations appropriately (which and when)
- acting appropriately with the results

Analysing new evidence
- practising evidence-based prescribing
- assessing the validity of evidence presented on new drugs or therapies
- reading, assessing and criticizing clinical studies
- spotting methodological flaws including sources of bias

- recognizing the difference between clinical and surrogate end-points

Obtaining accurate objective information to support safe and effective prescribing

- using National Formularies
- accessing reliable drug information from medical journals and medical databases
- accessing Poisons Information Services
- assessing the reliability of varying sources of evidence and opinion

Obtaining informed consent to treatment

- providing patients with enough information about drugs to allow them to make informed decisions about their treatment
- discussing benefits and harms of drug therapy with the patients
- exploring patients' own views and wishes in relation to drug treatment

Core attitudes.

A rational approach to prescribing and therapeutics

- identifying the correct clinical diagnosis
- understanding the pathophysiological processes involved
- knowing the drugs that might beneficially influence these processes
- establishing the end-points with which to monitor therapeutic response
- assessing the potential harms and benefits of treatment
- communicating with the patient in making the decision to treat

Assessing the balance of benefit to harm

- recognizing that there are harms and benefits associated with all drug treatments
- recognizing these may differ between patients depending on a variety of factors
- recognizing that doctors should monitor the effects of the drugs they prescribe

Recognizing the responsibilities of a doctor as part of the prescribing community

- avoidance of wasteful prescribing and consumption of limited resources
- recognizing the need to report ADRs for the common good
- controlling the availability of restricted drugs
- adhering to therapeutic guidelines and drug formularies as appropriate
- avoidance of indiscriminate prescribing of antibiotics

Recognizing personal limitations in knowledge

- recognizing the need to seek further information about drugs when faced with unfamiliar prescribing problems

Responding to the future

- recognizing the need to update prescribing practices
- ensuring that patients benefit when possible from advances in medical knowledge
- recognizing the need to assess the benefits and harms of new therapies
- knowing the limitations of applying clinical trial data to individual patients

Recognizing the effect of drugs on the environment.

Addendum II: Model Curriculum for Specialization in Clinical Pharmacology

Introduction.

A clinical pharmacologist is a physician with advanced knowledge of pharmacology and the knowledge and skills needed to achieve safe and effective use of drugs in individual patients and in the population at large. Improving drug use in patients includes consultations on patients referred to the clinical pharmacologist and also having primary responsibility for caring for patients with complex drug therapeutic problems in the clinical pharmacologist's area(s) of special competence. This pattern will vary from country to country. Advancing drug therapeutics more broadly includes, but is not limited to, work on drug discovery and development, drug utilization (both analysis of current practices and research on ways to improve it), teaching about pharmacotherapy, working in drug regulatory activities from local (hospital formulary) through regional, national and multinational organizations, and other problems that arise during the practice of clinical pharmacology (see below).

Aim.

This Model Curriculum is designed to enable the aspiring clinical pharmacologist to obtain the knowledge and skills needed to carry out this professional activity in an efficient and satisfying way. It is deliberately set to be broadly based and thus applicable to as many countries as possible.

Admission requirements.

Physicians are admitted to a clinical pharmacology training programme after they have completed the requirements for registration as a practising physician in their geographical area. In addition, they will usually have completed 2–3 years of work as a practising doctor under supervision in one of the specialities in which drug therapy is the major means of treatment. However, admission requirements will vary depending on national needs and agreements.

We recognize that the above scheme represents the ideal for the training of clinical pharmacologists but in many parts of the developing world it may be necessary, for practical reasons, to reduce the scope of the training in order to see health care delivered by healthcare professionals with a relevant knowledge of clinical pharmacology. Other entry requirements in the form of preparatory/orientation training for general medical officers or general physicians should be determined according to local conditions.

Other interests.

A physician starting the programme after initial medical registration or licensure may wish to acquire additional speciality training. This can be interspersed with clinical pharmacology training by special arrangement with the

directors of both programmes or following the clinical pharmacology training.

Syllabus overview.
The formal clinical pharmacology training programme is normally a 3-year activity but can vary from 2 to 5 years depending on the country concerned. The activities include:

1 Formal instruction for the trainee to acquire the specialist fund of knowledge of a clinical pharmacologist which often involves close working with basic pharmacology.
2 Clinical experience caring for patients with drug problems.
3 Research experience that advances therapeutics more broadly. In many countries, CPT is a research-intensive discipline entailing the production of a thesis.

1. Formal instruction should include:
   a. A review of the broad field of pharmacology including the topics covered in a medical school pharmacology course but at an appropriately high level. It is often of great benefit for the trainee to spend time in a basic pharmacology department and to experience work in such a laboratory including work with animals.
   b. Pharmacological topics of special relevance to the discipline.
      i. Critical evaluation of drug effects, both adverse and desired;
      ii. Principles of research methods in humans, both experimental and observational, e.g. clinical trials methods;
      iii. Informed voluntary consent and ethics of research in humans;
      iv. Data management and biostatistics;
      v. Absorption, distribution, metabolism and excretion (ADME) of drugs in humans;
      vi. Drug intoxications and poisoning, both intentional and accidental;
      vii. Pharmacogenetics;
      viii. Additional sources of variation among people in their dose–response, such as age, sex, pregnancy, liver disease, drug interactions;
      ix. The process of drug discovery, development and regulation;
      x. Drug tolerance, dependence and addiction;
      xi. Drug level measurement and techniques for monitoring drug therapy;
      xii. Pharmacovigilance and pharmacoepidemiology (including drug utilization);
      xiii. Pharmacoeconomics;
      xiv. Adherence to medication regimens;
      xv. Drug information;
      xvi. Other topics of local relevance.

The specific subject matter should be covered at the appropriate time in the complete curriculum.

2. *Clinical experience caring for patients with drug problems.* The trainee should get substantial clinical experience consulting about or caring for patients with serious or complex drug problems with increasing responsibility as the trainee's knowledge and skill levels increase. Ideally, experience with infants and children as well as elderly patients should be included. This experience may be concentrated in one part of the programme or spread throughout it.
3. *Research experience that enhances knowledge of drug therapy more broadly.* The trainee should be able to identify, by the end of their first year of training, an area of drug therapy in which information could be improved, with benefit to future drug therapy. This will usually be done in association with a mentor who can supervise the research to be done.

The trainee will then plan the research to be done, write the protocol and obtain any necessary ethics committee approval for the work to proceed. This work and the study will be done under supervision and the results reported in such a way that they can then be communicated to others, preferably by publication in a learned journal or monograph.

This research experience has been discussed in the broadest terms and should be applicable anywhere. What is important is for the trainee to develop the attitude that gaining new knowledge to improve drug therapy for an identifiable group of patients, no matter how few in number or how small the geographical area in which these patients live, is part of the practice of clinical pharmacology.

Required training resources.
A clinical pharmacology training programme must have resources for the curriculum to be carried out. This requires an adequate number of trained and committed staff, a sufficient number of patients with a variety of illnesses for adequate clinical pharmacology experience for the trainee, supporting clinical services including the ability to measure concentrations of drugs in human plasma and urine, and research facilities for the resident to carry out a research project.

A training programme can be at a single institution with all the resources needed or through a consortium of institutions committed to the training programme, their combined resources being adequate.

Further details of training programmes can be found in the literature (see references [70–75]).

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Editors	**Address**
Prof. Michael Orme	Emeritus Professor, University of Liverpool, Lark House, Clapton-on-the-Hill, Cheltenham GL54 2LG, UK
Prof. Folke Sjöqvist	Professor Emeritus, Department of Clinical Pharmacology, Karolinska University Hospital at Huddinge, S-14186 Huddinge, Sweden
Contributors	
Section 6.4	
Prof. Donald Birkett	Emeritus Professor, Flinders University of South Australia, 9 Raglan Street, Mosman, NSW 2088, Australia
Section 6.1 and Section 7	
Prof. Kim Brøsen	Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, J. B. Winslows Vej 19, DK-5000 Odense C, Denmark
Section 9	
Prof. Ingolf Cascorbi	Institute of Experimental and Clinical Pharmacology, University Hospital Schleswig-Holstein, Bld 30, Arnold-Heller Str 3, D-24105, Kiel, Germany
Section 6.3	
Prof. Lars L Gustafsson	Department of Clinical Pharmacology, Karolinska University Hospital at Huddinge, S-14186, Sweden

Section 6.2 and Addendum I	
Prof. Simon Maxwell	Clinical Pharmacology Unit, Clinical Research Centre, University of Edinburgh, Edinburgh EH4 2XU, United Kingdom
Section 6.5	
Dr. Lembit Rago	World Health Organisation, Avenue Appia, 1211 Geneva 27, Switzerland
Section 5	
Prof. Sir Michael Rawlins	Chairman, National Institute for Health and Clinical Excellence, MidCity Place, 71 High Holborn, London WC1V 6NA, United Kingdom
Addendum II	
Prof. Marcus Reidenberg	Clinical Pharmacology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA
Section 4 and Section 8	
Prof. Folke Sjöqvist	Professor Emeritus, Department of Clinical Pharmacology, Karolinska University Hospital at Huddinge, S-14186 Sweden
Section 10	
Prof. Tony Smith	Emeritus Professor, Clinical Pharmacology, Level 5, Clinical Sciences Building, Calvary Mater Hospital, Waratah, NSW 2298, Australia
Section 9	
Prof. Petra Thuerman	Philipp Klee-Institute of Clinical Pharmacology, Helios Klinikum Wuppertal, University of Witten/Herdecke, Germany
Addendum II	
Prof. Andrew Walubo	Department of Pharmacology, University of the Free State, P.O.Box 339 (G6), Bloemfontein, 9300, South Africa

Abbreviations and Glossary

Abbreviations

ADR	Adverse drug reaction
ADME	Absorption, distribution, metabolism and excretion
AIDS	Acquired immunodeficiency syndrome
CME	Continuing medical education
CNS	Central nervous system
CP	Clinical pharmacology
CRO	Clinical research organization
CPT	Clinical pharmacology and therapeutics
CVS	Cardiovascular system
CYP	Cytochrome P450
EMEA	European Medicines Agency
EU	European Union
FDA	Federal Drug Administration (in the USA)
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GXP	A combination of GCP, GLP and GMP
HIV	Human immunodeficiency virus
HTA	Health technology assessment
IP	Intellectual property
IUPHAR	International Union of Basic and Clinical Pharmacology
NIH	National Institutes of Health (in USA)
NMRA	National Medicines Regulatory Authority
OTC	Over the counter
PK	Pharmacokinetics
PD	Pharmacodynamics
R&D	Research and development
RCT	Randomized control trial
RUD	Rational use of drugs
TDM	Therapeutic drug monitoring
WHO	World Health Organization

Glossary

In silico	The use of computers to simulate biological studies.

Note that the words 'drug' and 'drugs' are used interchangeably with 'medicine' and 'medicines' respectively.

Rationell läkemedelsförskrivning: en kunskaps- och linjefråga

Kvalitativ intervjustudie på tio vårdcentraler i Stockholms läns landsting

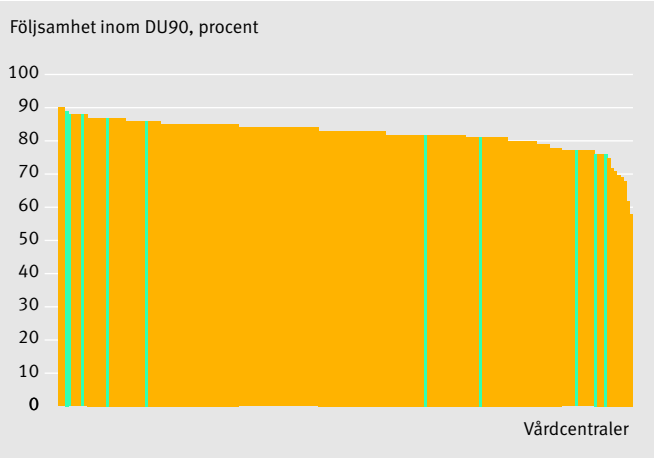
MARIANNE JÄGESTEDT, specialistläkare allmänmedicin, Stureby vårdcentral, Enskede; ledamot i Södra läkemedelskommittén, Stockholms läns landsting marianne.jagestedt@ptj.se
STEN RONGE, apotekare, apoteket vid Södersjukhuset, Stockholm; ledamot i södra läkemedelskommittén, Stockholms läns landsting
BJÖRN WETTERMARK, apotekare, med dr, Läkemedelscentrum, Centrum för vårdutveckling, Stockholms läns landsting; Klinisk farmakologi, Karolinska Universitetssjukhuset Huddinge
EVA ANDERSÉN KARLSSON, docent, överläkare, VO Internmedicin, Södersjukhuset, Stockholm; ordförande i Södra läkemedelskommittén, Stockholms läns landsting

Läkemedelsbehandling är en av de viktigaste delarna i vården av patienter. Det finns dock utrymme för förbättringar i läkemedelsförskrivningen. Det tar tid för evidensbaserade rekommendationer och vårdprogram att etableras i vården, och rapporter har visat på såväl över- som underbehandling av flera folksjukdomar [1-6].

Svårförklarliga variationer

Variationen i förskrivningsmönster mellan till synes jämförbara verksamheter är också påfallande stor och väcker frågor. I vården används i dag ett stort antal olika nyckeltal och kvalitetsindikatorer för bemanning, tillgänglighet och följsamhet till olika vårdprogram och läkemedelsrekommendationer [7, 8]. I Stockholms läns landsting (SLL) används sedan flera år följsamhet till Kloka listan som ett grovt kvalitetsmått för att stimulera läkare till medveten förskrivning. Kloka listan omfattar drygt 200 läkemedel rekommenderade som förstahandsval för behandling av vanliga sjukdomar. Dessa läkemedel rekommenderas utifrån medicinsk och farmaceutisk ändamålsenlighet, miljöaspekter och behandlingskostnader. Som mått på följsamhet används DU90% (drug utilization 90%)-metoden, en analys av de läkemedel som står för 90 procent av den förskrivna volymen i definierade dygnsdoser (DDD) och följsamhet till Kloka listan [9-11]. Varje vårdcentral/klinik kan enkelt följa sin förskrivning i de arbetsplatsrapporter som finns tillgängliga via landstingets webbplats för läkemedelsinformation, ‹http://www.janusinfo.se›. Förskrivningsstatistik inklusive DU90% har i flera år använts för återkoppling och kollegialt lärande [9, 10]. På senare tid har den även legat till grund för frivilliga kvalitetsavtal med vårdbeställarna, där vårdcentraler har erbjudits ekonomisk ersättning för hög följsamhet och strukturerat kvalitetsarbete [11].

Sedan läkemedelsreformen 1998 har den genomsnittliga följsamheten till Kloka listan på vårdcentralerna i Stockholms län stigit med tio procentenheter. Följsamheten till Kloka listan varierar dock mellan olika vårdcentraler (Figur 1). I vissa fall kan variationen förklaras av skillnader i patientkarakteristika, som åldersstruktur eller sjukdomspanorama, men i de flesta fall har skillnaderna varit mera svårförklarliga. Ökad kunskap om orsaken till denna variation vore värdefull för att finna former att öka följsamheten till Kloka listan. Syftet med denna studie var att identifiera faktorer som skulle kunna förklara skillnader i följsamhet till Kloka Listan mellan vårdcentraler. Resultatet är tänkt att utgöra ett underlag för förbättrad fortbildning och att stimulera vårdcentralerna till diskussioner kring kvalitetsarbete.



Figur 1. Följsamhet till Kloka listan inom DU90% (de läkemedel som utgör 90 procent av den förskrivna volymen) för samtliga vårdcentraler i Stockholms läns landsting (n=177). Recept uthämtade oktober–december 2006. Blåa staplar = vårdcentraler i studien.

METOD

Studien genomfördes som en kvalitativ intervjuundersökning under maj–juni 2007. Tio vårdcentraler valdes ut baserat på låg respektive hög följsamhet till Kloka listan (Figur 1). Andra ur-

SAMMANFATTAT

Kritiska framgångsfaktorer för rationell läkemedelsförskrivning undersöktes på tio vårdcentraler i en kvalitativ intervjustudie riktad mot verksamhetschefer och fast anställda distriktsläkare.
God bemanning liksom gott klimat för inbördes diskussion om medicinska sakfrågor inklusive läkemedel förefaller medverka till hög följsamhet till läkemedelskommitténs rekommendationer.
Tydliga mål för läkemedelsförskrivning, fortlöpande utvärdering och fasta rutiner för introduktion av nyanställda i läkemedelspolicyn förefaller vara av värde.
Elektroniskt stöd för val av rekommenderade läkemedel verkar också ha betydelse liksom få personliga kontakter med läkemedelsindustrin.
Aktivt deltagande i läkemedelskommittéarbete och andra kvalitetsutvecklande grupper och nätverk är också förenat med hög följsamhet till läkemedelsrekommendationer och bör eftersträvas.

TABELL I. Fakta om deltagande vårdcentraler. LK = läkemedelskommitté. Källa: Invervjumaterial, vårdbeställarna och förskrivningsstatistik från ‹http//www.janusinfo.se›.

Vård-central	Följsamhet till Kloka listan (procent)	Incitaments-avtal	Journal-system: markering av val i Kloka listan	Ledamot i LK, Läksak, Spesam etc på VC	Driftsform	Verksamhetschef/ personal-kategori	Antal ansvars-patienter[1]	Antal recept-rader[2]	Recept, total-belopp, miljoner kr[2]	Total-belopp, kr/ ansvars-patient[2]
1	Hög (88)	Ja	Ja	Nej	Landsting	Läkare	18 902	17 143	2,7	143
2	Hög (88)	Ja	Ja	Ja	Landsting	Läkare	8 918	8 629	1,5	168
3	Hög (87)	Ja	Ja	Ja	Landsting	Läkare	13 095	11 862	2,3	176
4	Hög (86)	Ja	Ja	Ja	Privat	Sjuksköterska	12 921	13 756	2,0	155
5	Hög (89)	Ja	Ja	Ja	Landsting	Läkare	18 117	16 407	2,8	155
6	Låg (80)	Ja	Ja	Ja	Privat	Läkare	18 196	20 291	3,4	187
7	Låg (80)	Ja	Oklart	Nej	Privat	Sjuksköterska	10 670	8 073	1,6	150
8	Låg (77)	Ja	Oklart	Nej	Landsting	Läkare	15 340	15 598	3,8	248
9	Låg (78)	Ja	Nej	Nej	Privat	Läkare	7 458	4 239	0,7	94
10	Låg (76)	Nej	Nej	Nej	Privat	Sjuksköterska	7 800	7 693	1,8	231

[1] Antal listade och olistade patienter i området.
[2] Gäller fjärde kvartalet 2006.

valskriterier var att deltagande vårdcentraler skulle ha fem till tio distriktsläkartjänster och att vårdcentraler med låg följsamhet till Kloka listan skulle vara belägna inom Södra läkemedelskommitténs verksamhetsområde för att efter studien eventuellt kunna åberopa stöd och samarbeta med Södra läkemedelskommittén kring kvalitetshöjande aktiviteter. De deltagande vårdcentralernas följsamhet till Kloka Listan varierade mellan 86–89 procent och 76–80 procent (Figur 1).

Några för läkemedelsförskrivning relevanta data för deltagande vårdcentraler redovisas i Tabell I. I gruppen vårdcentraler med hög följsamhet var fyra av fem enheter landstingsdrivna, medan fyra av fem med låg följsamhet hade privata driftsformer.

Intervjuer

Kvalitativa intervjuer, baserade på totalt ca 60 öppna frågor utan givna svarsalternativ, gjordes med verksamhetschefen för respektive enhet och med en fast anställd distriktsläkare. I de fall som verksamhetschefen inte var läkare intervjuades den medicinskt ansvarige läkaren på enheten. Således planerades för totalt 20 intervjuer. Av dessa kunde endast 19 genomföras, då en läkare på en vårdcentral med lägre följsamhet avböjde att delta. Intervjuerna utfördes som telefonintervjuer (ca 45 minuter) av ett professionellt marknadsundersökningsföretag, SIFO Research International Navigare. Intervjuformuläret omfattade följande frågeställningar:

- vårdcentralens läkarbemanning och kontinuitet
- ledarskap och samarbete
- uppfattningar om ställda verksamhetsmål samt uppföljningen av målen, i synnerhet uppföljningen av de mål som avser läkemedelsförskrivning
- verksamhetens läkemedelspolicy och hur den förmedlas till nyanställda och vikarier
- journalsystem och hur dess förskrivningsmodul upplevs stödja förskrivare att följa Kloka listan
- remissinstanser och i vilken mån dessa vid initiering av långtidsbehandling påverkar enhetens följsamhet till läkemedelsrekommendationerna
- attityder till den regionala läkemedelskommittén Läksak och den lokala läkemedelskommittén
- relationer till läkemedelsindustrin.

Uppgifter om följsamheten till rekommendationer hämtades från Stockholms läns landstings databas med läkemedelstatistik ‹http://www.janusinfo.se›. Statistiken baserades på analys av recept uthämtade på apotek under fjärde kvartalet 2006 förskrivna från respektive vårdcentral.

Analys- och valideringsmetod

Resultatet av intervjuerna analyserades av intervjuföretaget och presenterades utifrån i förväg utvalda parametrar. Målsättningen var att hitta faktorer som utmärker vårdcentraler med hög respektive låg följsamhet, dvs faktorer som kan vara potentiellt avgörande för förskrivningsmönster och följsamhet. I den inledande analysen bedömdes varje individuellt svar av två initierade projektledare oberoende av varandra enligt en tregradig skala. När det gällde exempelvis frågan om beskrivningen av stämningen på arbetsplatsen klassificerades varje individuellt svar efter om det indikerade en god, mittemellan eller dålig stämning. Samma procedur genomfördes för samtliga studerade parametrar. Därefter jämfördes resultaten av de båda projektledarnas bedömningar, och när oenighet förelåg i något fall inkallades en tredje person för avgörande bedömning. I analysens andra steg jämfördes helhetsbilden av resultatet från den inledande analysen för de båda vårdcentralskategorierna i samtliga studerade parametrar. Även här användes en valideringsmetod med två oberoende bedömningar och eventuellt en tredje för att nå konsensus. I respektive parameter värderades i vilken utsträckning helhetsbilden för vårdcentralerna med hög följsamhet avvek från helhetsbilden för vårdcentralerna med låg följsamhet enligt en 5-gradig betygsskala: klart bättre, tendens till bättre, ingen skillnad, tendens till sämre, klart sämre (Tabell II).

RESULTAT

Det var lättare att ur intervjusvaren tydligt urskilja faktorer som medverkar till högre följsamhet till läkemedelsrekommendationer än faktorer som medverkar till lägre följsamhet (Tabell II). Utifrån intervjusvaren kunde man utläsa att högre följsamhet till Kloka listan var relaterad till bättre bemanning och kontinuitet på läkartjänsterna. På vårdcentraler med låg följsamhet tjänstgjorde under det senaste året alltifrån 1 till 20 vikarier jämfört med 0–3 på vårdcentraler med hög följsamhet.

TABELL II. **Sammanfattande värdering av invervjusvaren.**

Intervjufrågor	Skillnad mellan vårdcentraler med Högre följsamhet		Lägre följsamhet
Vårdcentralens bemanning, läkarkontinuitet	Tendens till bättre		
Ledarskap och samarbete			
Stämning på arbetsplatsen		Ingen skillnad	
Öppenhet		Ingen skillnad	
Samarbete	Tendens till bättre		
Lagarbete	Klart bättre		
Beskrivning av ledarskapet		Ingen skillnad	
Acceptans för verksamhetschefens ord	Tendens till bättre		
Verksamhetsmål			
Tydligt definierade mål		Ingen skillnad	
Gemensam definition finns	Tendens till bättre		
Uppföljning sker[1]			Tendens till bättre
Användning och nytta av verksamhetsmålen		Ingen skillnad	
Mål och utvärdering av följsamhet			
Tydliga mål för följsamhet till Kloka listan	Klart bättre		
Gemensamt definierade mål	Klart bättre		
System för uppföljning av mål	Klart bättre		
Kontroll av individuell förskrivningsprofil	Klart bättre		
Kännedom om befintliga incitament[2]	Tendens till bättre		
Målens bidrag till ökad följsamhet		Ingen skillnad	
Adekvat uppfattning om egen följsamhet	Tendens till bättre		
Läkemedelspolicy till nyanställda	Tendens till bättre		
Elektroniskt stöd för val av rekommenderat läkemedel	Klart bättre		
Övriga parametrar			
Remissinstansernas påverkan på följsamheten		Ingen skillnad	
Privata specialistläkares påverkan på följsamheten		Ingen skillnad	
Attityd till läkemedelskommitténs verksamhet		Ingen skilland	
Attityd till Läksaks verksamhet	Tendens till bättre		
Konsensus om Kloka listans rekommendationer[3]		Ingen skilland	
Representation i läkemedelskommitté, Läksak eller Spesam-grupper	Klart bättre		
Besök på Janusinfo	Tendens till bättre		
Värdet av informationsläkare/apotekare	Tendens till bättre		
Informationsläkare/apotekare, behov av tätare besök		Ingen skillnad	
Frekvens besök och värde av läkemedelsrepresentanter[4]			Klart sämre

[1] Avser frekvens på uppföljning men framgår inte av vad.

[2] På vårdcentraler med lägre följsamhet föreföll man inte ha kommunicerat ut träffade ekonomiska överenskommelser med vårdbeställaren.

[3] De svårigheter att följa läkemedelsrekommendationerna som oftast nämndes gällde hjärt–kärlläkemedel och analgetika.
I övrigt föreföll acceptansen vara god för Kloka listan, vilket avspeglar en generellt högre följsamhet på vårdcentraler jämfört med åtskilliga andra förskrivarkategorier.

[4] Vårdcentraler med lägre följsamhet hade kontakter med läkemedelsindustrin ungefär 3–4 gånger så ofta som de med högre följsamhet.

Såväl samarbete som lagarbete var bättre på vårdcentraler med högre följsamhet. Med samarbete avses framför allt vardagens kommunikation, såsom frågor kring schema och fortbildning. Lagarbete innebär i denna undersökning ett lite vidare begrepp som innefattar gemensamma mål, drift med mera:

»Ett lagarbete. Vi har olika förmågor som kompletterar varandra, vi respekterar våra olikheter och låter varandra visa vad vi är duktiga på.« (Distriktsläkare på vårdcentral med hög följsamhet.)

Beträffande ledarskapet framkom inget stöd för att det i den ena eller den andra gruppen skulle vara starkare/svagare. Däremot fanns en större acceptans för chefens ord på vårdcentraler med högre följsamhet. I definitionen starkt ledarskap finner man i intervjusvaren sådana nyckelord som kollegialitet, tydlighet och respekt och lyhördhet:

»Generellt sett väger hennes ord tungt, uppdrag uppifrån diskuteras alltid gemensamt och därigenom vinner hon vårt stöd, fungerar mer som support.« (Distriktsläkare på vårdcentral med hög följsamhet.)

»Kollegialt ledarskap, fungerar bra i stort, ingen verksamhet som drivs av stora visioner, vi gör vårt jobb, det förekommer inte något större utvecklingsarbete och inte någon större entusiasm för förändringsarbete.« (Distriktsläkare på vårdcentral med låg följsamhet.)

Alla deltagande vårdcentraler hade tydligt definierade verksamhetsmål, men det fanns tendens till mer utförliga målbeskrivningar på vårdcentraler med högre följsamhet. Det föreföll också finnas mer utrymme för kommunikation kring medicinska kvalitetsmål på dessa vårdcentraler. På vårdcentraler med lägre följsamhet hade man dock tätare uppföljning av and-

ra verksamhetsmål. Det förelåg ingen säker skillnad mellan vårdcentralerna avseende upplevd nytta med att ha verksamhetsmål.

»Används i hög utsträckning och gör oss mer delaktiga. Vid avvikelse i någon parameter analyserar vi tänkbara orsaker och kommer med förbättringsförslag.« (Distriktsläkare på vårdcentral med hög följsamhet.)

»Bidrar inte särskilt mycket. Det sätts nästan bara upp kvantitativa mål. De är viktiga, men det finns andra mål som är minst lika viktiga, till exempel hur man behandlar patienter med ischemisk hjärtsjukdom, hur diabetesvården ser ut etc.« (Distriktsläkare på vårdcentral med låg följsamhet.)

Målen för följsamhet till Kloka listan belystes i flera intervjusvar. Vid vårdcentraler med hög följsamhet var dessa mål tydligare definierade och hade i större utsträckning tillkommit under gemensam diskussion mellan kollegorna. Där fanns också en trend till mer strukturerad och organiserad resultatuppföljning. Läkarna på vårdcentraler med högre följsamhet var mer aktiva i dessa frågor och hade i större utsträckning rekvirerat utdrag över sin personliga förskrivning. Man hade också generellt större medvetenhet om landstingets modell för ökat kostnadsansvar för läkemedelsförskrivningen.

»Vi har inte brytt oss så mycket om det, ej bra följsamhet just nu. Ligger långt ned på prioriteringslistan trots att det varit stor kvalitetspeng på det.« (Verksamhetschef på vårdcentral med låg följsamhet.)

»En chef som åtnjuter stort förtroende och som tar till vara och vidareutvecklar läkarnas kompetens når sannolikt störst framgång.«

Vid sidan om Kloka listan fanns inte någon skriftlig policy för läkemedelsförskrivning på någon intervjuad vårdcentral. Rutinerna för information till nyanställda och vikarier tycktes dock vara mer etablerade på vårdcentraler med hög följsamhet.

Samtliga vårdcentraler hade antingen journalsystemet Profdoc eller Medidoc. I båda fallen finns möjlighet att se vilka läkemedel som rekommenderades. På vårdcentraler med lägre följsamhet rådde viss oenighet om huruvida markering finns eller inte, medan man på vårdcentraler med högre följsamhet angav att det var tydligt och enkelt att se vilka läkemedel som rekommenderas.

Bland övriga faktorer som förefaller påverka följsamheten noteras att enheter med högre följsamhet i mycket större ut-

sträckning har distriktsläkare som medverkar i kvalitetsutvecklande verksamheter och nätverk, som lokala läkemedelskommittéer och olika samverkansgrupper. Kontakter med läkemedelsindustrin verkar däremot vara en faktor med motsatt påverkan. Bland de vårdcentraler som hade lägre följsamhet hade man klart fler gruppbesök av läkemedelsrepresentanter. Man var också mer liberal med enskilda besök av konsulenter.

Det fortbildningsstöd som lämnas av Läksak och läkemedelskommittéer uppfattades mycket positivt av alla deltagande vårdcentraler. Hos vårdcentraler med lägre följsamhet kunde man dock utläsa en något mer kritisk hållning till värdet av besökande fortbildningsläkare och informationsapotekare än hos dem med hög följsamhet.

»Fyra gånger per år. Bra. Är verklighetsanpassat och patientbaserat. En diskussion förs. Är en interaktiv utbildning.« (Distriktsläkare på vårdcentral med hög följsamhet.)

»En gång per år. Inget större värde. Kommer inte med någon ny information. Kan redan det de pratar om.« (Distriktsläkare på vårdcentral med låg följsamhet.)

Uppfattningarna om i vilken grad privata specialister och sjukhusspecialister påverkade enhetens läkemedelsförskrivning varierade hos såväl enheter med låg som enheter med hög följsamhet.

DISKUSSION

Denna studie har ringat in ett antal faktorer som kan förklara skillnaderna i följsamhet till läkemedelskommitténs rekommendationer. För att förklara betydelsen av enskilda faktorer krävs kompletterande kvantitativa studier med ett större urval. Deltagande vårdcentraler uppvisade spridning i storlek och verksamhetsform. Urvalet av enheter med låg följsamhet begränsades av att de var belägna inom Södra läkemedelskommitténs verksamhetsområde. Det resulterade i en högre andel privat drivna vårdcentraler med låg följsamhet till läkemedelsrekommendationerna i studien jämfört med länet som helhet. Detta bör dock inte ha påverkat resultatet i någon större omfattning, då det totalt sett inte finns några väsentliga skillnader i följsamhet till Kloka listan vare sig mellan privata och landstingsdrivna vårdcentraler eller mellan norra och södra delarna av länet [11].

Viss bias kan dock ha skett i urvalet av läkare till intervjuerna. Ett kriterium för deltagande i intervju var att vederbörande skulle ha varit verksam på vårdcentralen i flera år. I avsaknad av kompletta personalregister beslöts att låta verksamhetscheferna välja ut läkare att intervjua. Detta kan ha medfört att förskrivare mer positiva till t ex ledarskap och kommittéarbete valts ut vid enheter med hög följsamhet. Urvalet skiljde något mellan enheterna, men det är tveksamt om detta har påverkat resultaten.

Följsamhet – bara en aspekt på kvalitet i förskrivningen

Följsamhet till läkemedelsrekommendationer är enbart en av flera aspekter på kvalitet i förskrivningen. Rationell förskrivning har föreslagits omfatta beslut om läkemedel ska ordineras eller inte, val av lämpligt läkemedel med anpassad dosering för den enskilde patienten, bedömning av risken för interaktioner, ett tydligt skrivet recept samt behandlingsinstruktioner till patienten om hur läkemedlet ska användas och effekten följas upp [12]. Följsamhet till läkemedelsrekommendationer enligt DU90%-metoden har använts i flera vetenskapliga studier och rekommenderas av Medicinska kvalitetsrådet för övergripande kvalitetsarbete kring läkemedelsförskrivningen [9, 13]. Detta kvalitetsmått har styrkan att det ger en helhetsöverblick av förskrivningen som leder till kollegiala diskussioner kring val av evidensbaserad läkemedelsterapi.

Svagheten är att följsamheten helt bygger på aggregerade data utan uppgifter om diagnos/förskrivningsorsak och dosering. En analys av förskrivningen vid samtliga vårdcentraler i Stockholms läns landsting har visat att hög följsamhet är associerad med låg kostnad per förskriven volym [11]. Sambandet mellan följsamhet och andra kvalitetsmått är inte studerat. Hög följsamhet kan sannolikt kostnadseffektivisera valet av läkemedel, med bibehållen medicinsk kvalitet och patientnytta.

Studiens resultat stämmer överens med vad tidigare forskning visat [14-16]. Förskrivningen är komplex och påverkas av en mängd faktorer, alltifrån enskilda förskrivares kunskaper och attityder till ledarskap, organisation och resursfördelning [14-16]. Följsamheten påverkas även av närheten till sjukhus och balansen mellan producentobunden information och kontakter med läkemedelsindustrin [17-19].

Med full bemanning av ordinarie distriktsläkare, som stannar på sina tjänster under flera år, synes det vara lättare att införa en gemensam förskrivningspolicy för läkemedel. Sannolikt är detta en förutsättning för att skapa en arbetskultur med vardaglig kommunikation rörande t ex val av behandling och medicinsk utveckling, vilket också påverkar följsamheten.

Intern diskussion

Tidigare forskning har visat att läkare väljer läkemedel utifrån sin egen personliga »baslista« [15]. Denna baslista etableras redan under grundutbildningen men förändras med tiden och påverkas av kolleger, patienter, fortbildning, regelverk och egen erfarenhet [15]. Ett gemensamt arbete kring läkemedelsfrågor har visats vara ett framgångsrikt sätt att öka följsamheten till rekommendationer [20].

En tydlig intern diskussion om egen läkemedelspolicy och egna mål tycks också medverka till ökad följsamhet. Detta belyser vikten av tillräckligt utrymme för kommunikation kring medicinska mål. Ett journalsystem där förskrivarmodulen tydligt indikerar vilka läkemedel som står på Kloka listan är sannolikt ett effektivt verktyg för att uppnå hög följsamhet till läkemedelsrekommendationer.

Medverkan i läkemedelskommittéarbete och liknande kvalitetsutvecklande nätverk tycks kunna leda till större engagemang i läkemedelsfrågor även bland kolleger. Regelbundna möten med inbjuden fortbildningsläkare eller informationsapotekare kan vara en framgångsrik metod för att stimulera till interna diskussioner.

KONKLUSION

Den genomsnittliga följsamheten till Kloka listan har som mest ökat med någon procentenhet per år i länet [9, 11]. För ökad följsamhet krävs ett systematiskt arbete med motiverade förskrivare [10]. Undersökningen besvarar inte hur vårdcentraler med låg följsamhet snabbast kan öka följsamheten. Dessa enheter tog i studien oftare emot läkemedelskonsulenter. Det är oklart vilken effekt det har att enbart minimera kontakterna med läkemedelsindustrin. Väl utarbetade rutiner i läkemedelsförskrivning för nyanställda och vikarier förefaller kunna vara prioriterat för att öka följsamheten på vårdcentraler med bristande bemanning och läkarkontinuitet.

Evidensbaserad, klok läkemedelsförskrivning för största patientnytta är såväl en kunskapsprocess som en linjefråga. En chef som åtnjuter stort förtroende och som tar till vara och vidareutvecklar läkarnas kompetens når sannolikt störst framgång.

Potentiella bindningar eller jävsförhållanden: Ekonomiskt bidrag till studien erhölls av Läksaks fortbildningsutskott.

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CURRENT OPINION

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Soft Regulations in Pharmaceutical Policy Making

An Overview of Current Approaches and their Consequences

Björn Wettermark,[1,2] *Brian Godman*,[3,4] *Bengt Jacobsson*[5] and *Flora M. Haaijer-Ruskamp*[6]

1 Department of Clinical Pharmacology and Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden
2 Department of Drug Management and Informatics, Stockholm County Council, Stockholm, Sweden
3 Institute of Pharmacological Research 'Mario Negri', Milan, Italy
4 Department of Management Studies, University of Liverpool, Liverpool, UK
5 Södertörn University College, Stockholm, Sweden
6 Department of Clinical Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands

Abstract

It is a challenge to improve public health within limited resources. Pharmaceutical policy making is a greater challenge due to conflicting interests between key stakeholder groups. This paper reviews current and future strategies to help improve the quality and efficiency of care, with special emphasis on demand-side controls for pharmaceutical prescribing.

A large number of different educational, organizational, financial and regulatory strategies have been applied in pharmaceutical policy making. However, the effectiveness of most strategies has not been thoroughly evaluated and there is evidence that the behaviour of healthcare professionals is difficult to influence with traditional methods. During the last decades, new modes of governing and new governing constellations have also appeared in healthcare. However, relationships between those who regulate and those regulated are often unclear. New approaches have recently been introduced, including extensive dissemination strategies for guidelines and extensive quality assessment programmes where physicians' performances are measured against agreed standards or against each other. The main components of these 'soft regulations' are standardization, monitoring and agenda setting. However, the impact of these new modes on health provision and overall costs is often unknown, and the increased focus on monitoring may result in a higher conformity and uniformity that may not always benefit all key stakeholders. Alongside this, a substantial growth of auditing associations controlling a diminishing minority of people actually performing the tasks may be costly and counter-productive.

As a result, new effective strategies are urgently needed to help maintain comprehensive healthcare without prohibitively raising taxes or insurance premiums. This is especially important where countries are faced with extreme financial problems. Healthcare researchers may benefit from researching other areas of society. However, any potential strategies initiated must be

adequately researched, debated and evaluated to enhance implementation. We hope this opinion paper is the first step in the process to develop and implement new demand-side initiatives building on existing 'soft regulations'.

It is a challenge to improve public health and satisfy the needs of a population within limited resources. National healthcare policies seek to balance many conflicting demands such as the need to limit growth in expenditure whilst still allowing the population to have rapid access to new innovative and expensive technologies. Policy making in healthcare is highly politicized and involves many players, including healthcare professionals, the pharmaceutical industry, patients and a variety of stakeholders at the local, regional and national level. We believe that this calls for new forms of governance and approaches in addition to those traditionally applied. Increasing pressures on resources also enhance the need to learn from other areas of society. The pressures on pharmaceutical expenditure are well known and include increased volumes with an aging population and growing prevalence of chronic diseases, stricter management targets, and the continued launch of new expensive drugs costing $US50 000–100 000 per patient per year or more.[1-5] This situation becomes even more challenging and imperative to progress given the current severe economic difficulties.

This article describes the characteristics of the traditional educational, organizational, financial and regulatory methods to influence healthcare professionals. It also presents the theoretical framework behind new modes of governance, i.e. the 'soft regulations', as the first step in developing new demand-side reforms. The paper focuses on pharmaceuticals, since drug prescribing is one of the most important processes in healthcare with costs increasing faster than other aspects of care.[1,6-8] Furthermore, pharmaceutical policy making is driven by both professional and market forces, sometimes strengthening each other, at other times clashing.

We hope this opinion article initiates the debate to develop new methods to enhance the quality and efficiency of healthcare, given growing pressures. These are urgently needed without resorting to other measures such as additional supply-side controls, including very strict clinical and economic criteria for granting premium prices for new drugs, reference pricing across all therapeutic classes as well as stringent price-volume agreements and price cuts, which may not be in the best interest of key stakeholder groups.

To initiate this debate, the paper lists a number of demand-side approaches and concerns. This opinion piece focuses principally on Europe, as this reflects the authors' considerable research experience. The examples are, however, increasingly relevant to the US with its growing public expenditure on health and ongoing demand-side initiatives to ensure the significant proportion of GDP spent on healthcare[9] produces value for all key stakeholder groups. The examples of initiatives in this article are based mainly on a MEDLINE literature search of studies published between 2000 and 2008, using the following search terms: 'pharmaceuticals', 'drugs', 'reforms', 'regulations', 'expenditure', 'guidelines' and 'rational prescribing'. This search was supplemented by additional papers known to the authors, who are active in different research teams representing various disciplines including clinical pharmacology, pharmacoepidemiology, business economics, health policy and social sciences. It is, however, important to stress that this paper is not a systematic review or critical appraisal documenting methodologies, findings and conclusions. Consequently, the paper should be seen as an opinion paper, which we hope will stimulate debate to guide future research and activities.

1. Traditional Models for Influencing Behaviour of Healthcare Professionals

Stakeholders across Europe and the US use a variety of methods to influence physicians' and patients' behaviour. The main strategies can be abbreviated to the 'four Es': **E**ducation, **E**ngineering, **E**conomics and **E**nforcement (table I).[10,11]

Table I. The 'four E' approach adapted from Rice et al.[10,11]

Measure	Explanation and initiatives
Education[11-28]	Range from simple distribution of printed material to more intensive strategies such as educational outreach visits by trained facilitators, monitoring of prescribing against agreed guidance with further interventions if required or various consensus processes Examples of educational activities directed to physicians include quality circles in Germany or the Wise Drug List concept in Sweden combined with monitoring physician prescribing against expert guidance Examples of initiatives targeted to patients include dissemination of prescribing guidance to patients to enhance patient-doctor communications and increase prescribing of recommended drugs; they also include public campaigns involving physicians and patients to enhance rational prescribing, such as rational prescribing of antibacterials in Australia, France and the US
Engineering[11,29-44]	Refers to organizational or managerial interventions Disease management programmes in Germany and the US to address, for instance, under-use or over-use of technologies, and interventions to optimize medication use in nursing homes Prescribing targets, e.g. percentage of proton pump inhibitor prescriptions as generic omeprazole and percentage of statin prescriptions as generic simvastatin Structured programmes for the introduction of new drugs Task delegation such as nurse and pharmacist supplementary prescribing in the UK Initiatives to limit pharmaceutical company contacts and activities with prescribing doctors generally as well as for specific drug classes such as statins and proton pump inhibitors, especially with pharmaceutical companies still an important source of information to physicians for existing and new drugs
Economics[2,6,11,21,26,28,34,45-49]	Include changes in insurance and reimbursement systems, patient co-payment including tier levels, positive and negative financial incentives for physicians and rebate schemes for over-prescribing of agreed drugs Also include devolving drug budgets to physicians with penalties and incentives
Enforcement[8,11,21,22,45,50]	Include regulations by law such as mandatory generic substitution at pharmacies, which has been applied for many years in some European countries and by most US health insurers May also include prescribing restrictions involving, for instance, contacting the insurance company's chief medical officer for authorization to prescribe a new expensive drug in Austria, prior authorization schemes in the US, as well as compulsory prescribing restrictions in Italy and Sweden

All these strategies have their strengths and limitations (table II).

In addition, there has been a general lack of scientific studies analysing the impact of demand-side reforms on physician behaviour. This may be explained by lack of incentives for policy makers to perform such evaluations, their tendency to introduce a plethora of reforms in quick succession,[11,21,22,63] and the practical and methodological difficulties in performing evaluations in the continuously changing healthcare systems.[64,65]

2. Soft Regulations in Healthcare

New types of regulations have appeared during the past decades in healthcare as well as in other areas of society.[66] More rules, guidelines, standards and templates than ever are being developed. However, the relationships between those who regulate and those regulated are often unclear, and often characterized by voluntary behaviour rather than coercion and the threat of sanctions. The regulations tend to be legitimized in terms of the expertise of those involved rather than democracy, and structured on professional rather than organizational grounds. The new modes of governance appear in all areas of society, from publicly funded healthcare systems to business corporations and executive management programmes.[67,68] In addition, trans-national regulations in the European Union and the United Nations display similar patterns. These 'soft regulations' are often voluntary and not connected to punishment. They tend to be motivated by the need for coordination and comparability and are in this sense often seen as administrative issues rather than issues of control and command.[69,70]

The soft regulations include three different modes of governance, which is different from the

Table II. Strengths and limitations of the 'four E' demand-side initiatives

Measure	Strengths and limitations
Education[11-18,21,51-53]	Have, in general, only a modest effect unless combined with other strategies Simple diffusion or dissemination of printed materials and didactic educational meetings may influence professionals' awareness and knowledge but they seldom change behaviour More intensive strategies involving more than one approach may be more effective, especially given the idiosyncratic nature of prescribing; however, until recently, few studies have reported whether the benefits including savings achieved outweigh the costs of implementing the strategies
Engineering[11,34,54-56]	May be effective in removing barriers to change, since it is known that the effectiveness of quality improvement initiatives is to a great extent influenced by the organizational context However, they may be ineffective if there is poor leadership and poor processes In addition, pharmaceutical companies may well seek other ways to influence prescribing to achieve their revenue goals unless adequately addressed
Economics[11,14,21,34,57-60]	Have been shown to be effective in moderating the annual increase in drug expenditure and in some cases reducing this However, the long-term impact on expenditure as well as the impact on the quality of care subsequently provided have been less studied
Enforcement[11,21,22,50,61,62]	May seem a suitable method in policy making since it is easier to implement and may be less expensive to operate than other measures However, whilst effective in regulating the availability of medicines or their prescribing with, for instance, positive lists or sub-population restrictions, enforcement may not be equally effective in regulating human behaviour; like all people, physicians and patients may find ways to bypass the regulations, diminishing the effects of these interventions in reality, unless addressed with strict controls

traditional situation of hierarchical control where one authoritative rule maker issues rules that others have to obey. The three modes are standardization, monitoring and agenda setting[66] (table III). The way in which a mode of governance develops is dependent on how each specific process evolves. The modes are interrelated but the stakeholders and organizations involved in the process are seldom hierarchically connected with each other.

Standardization in healthcare is clearly illustrated by the considerable number of guidelines and guidance produced to support doctors and patients in their decision making.[11,21,22,73-75] These guidelines are in general produced by consensus among experts, backed up by scientific evidence. The credibility of the standards is dependent on the credibility of the experts and evidence. However, it is also possible to gain credibility through active collaboration with key opinion leaders.[44] A useful strategy in guideline implementation is also to involve the target group in the guideline development combined with proactive dissemination.[11,21,22]

A successful example of guideline implementation is the Austrian approach where one guideline is produced per year involving all key stakeholders combined with active dissemination.[22] Feedback suggests that physicians believe the guidelines will improve both the quality and efficiency of prescribing, leading to a significant number of physicians re-evaluating their management practices.[22] Similar experiences exist from the development and implementation of SIGN (Scottish Intercollegiate Guidelines Network) guidelines in Scotland,[75,76] as well as the uptake of treatment guidance contained in the Wise Drug List of the Stockholm County Council in Sweden.[11,21]

Monitoring activities are often intrinsic to rule-setting procedures. They presume the existence of certain standards or a recognized set of criteria for assessment and evaluation. In many healthcare organizations in Europe and North America, process or outcomes data are used continuously in quality improvement programmes, such as the Healthcare Effectiveness Data and Information Set (HEDIS) in the US as well as quality and prescribing targets in Sweden and the Quality and Outcomes Framework (QoF) in the UK.[11,21,34,77-79] In Sweden, monitoring initiatives also include the establishment of 64 national

healthcare quality registers administered by the National Board of Health and Welfare.[11,80,81] These include registers for cancer, coronary heart disease, and CNS and musculoskeletal diseases. Whilst they are voluntary, some have almost 100% coverage, helped by the fact that the professionals entering the data were often involved in registry development.[11]

In recent years, there has been a trend linking quality indicators to financial incentives and paying physicians for reaching identified targets, possibly because policy makers have become impatient about the slow uptake and impact of guidelines. This has been the case in Stockholm, Sweden, where financial incentives are linked to guideline adherence.[11,21] Furthermore, primary care contracts in the UK included 30% of the payment linked to quality indicators in the QoF framework.[77,78] The indicators in the QoF included structure-, process- and outcomes-oriented indicators covering different aspects of care. These range from practice management, record keeping and continuous education to patient satisfaction, clinical outcomes and adherence to guidelines for the treatment of ten common chronic diseases.[78,79] However, few studies have been published on the effectiveness of these initiatives, although there is certain evidence that financial incentive schemes have the potential to make a substantial contribution to the reduction of inequalities in the delivery of clinical care related to area deprivation,[82] as well as contributing to equity in care generally.[11]

Table III. Three modes of 'soft regulations'[66]

Soft regulation	Associated activities
Standardization[71]	Involves the development of potential activities or advice for others regarding what they should undertake Formally, at least, these regulations are voluntary and include large elements of self-regulation and co-regulation
Monitoring[11,21,22,34,63,72]	Comprises various forms of scrutiny Audits, evaluations, reporting and accounting systems as well as more general assessments, comparisons and rankings have expanded and become widespread in healthcare; this will grow
Agenda setting[11,19-21,34]	Expert groups exert their influence by organizing arenas, networks and conferences around certain issues Important topics of these meetings are to discuss the standards and the results of any audits undertaken Such activities are widespread in, for instance, Germany, Sweden and the UK

A similar development using a 'pay for performance' approach has been instigated in the US. The Institute of Medicine (IOM) report *Crossing the Quality Chasm* suggested aligning financial incentives to the implementation of care processes based on best practices and the achievement of better patient outcomes.[83] This is now in operation in a number of health maintenance organizations.[84,85] The IOM also suggested making these performance data publicly available for patients and purchasers to recognize quality differences in healthcare, and subsequently direct decisions and activities accordingly.[83] This is now being undertaken. Although few studies have been conducted to date, it seems that public disclosure of quality information is a strong determinant for choosing health plans.[86]

The third component in soft regulations is *agenda setting*. Many networks are originally established with the aim of coordinating or sharing knowledge. Over time they develop ideas of sharing not only for increased knowledge or experience, but also 'best practices'. They seek to formulate and even assess local practices in order to find and disseminate such practices in the future. This was the concept behind the Quality Circle initiative in Germany,[19] an example of which aimed to improve asthma care in regional localities in the country.[20]

3. Potential Benefits and Adverse Effects of Soft Regulations

Overall, there is substantial room for improvement in healthcare provision and drug prescribing. Various manifestations of irrational use of drugs – such as increased morbidity and mortality, medicalization of diseases, polypharmacy, increased adverse drug reactions and increased bacterial resistance – are discussed more and more in medical journals and in public debate.

There is also a continuing debate worldwide about the rapid increase in pharmaceutical expenditure.[2,3,7,11,21,22,48,63] The fact that both the prices of pharmaceuticals and the overall level of spending differ greatly between different European countries adds further fuel to the debate.[76,87-89]

There is evidence that strategies to promote rational prescribing have not been sufficiently effective.[12,13,15,16] The adoption of guidelines can be slow in clinical practice and policy makers have difficulties in controlling pharmaceutical expenditure. Consequently, further soft regulations may be a way forward for policy makers to increase quality whilst reducing or moderating growth in expenditure. These objectives may be further helped by incorporating financial incentives into future initiatives.[11,21,34,59,60]

However, there can be concerns about the possible negative consequences of too strong a focus on audit and performance measurement. Partly, the adverse effects may be similar to those described as potential effects of financial incentives. In a systematic review of studies published between 1993 and 2000, it was suggested that financial incentives for drug prescribing could decrease the quality of care by limiting continuity, reducing the (preventive) services offered and increasing improper use of emergency services.[90] In a more recent review, there was also concern that incentive schemes could negatively impact on clinical priorities, unfairly reward previously overspending ambulatory care practices, as well as negatively impact on the utilization of new valued technologies.[91] Concern was also raised about potential adverse changes in the relationship between the doctor and patient as well as potential long-term negative consequences of reduced time for teaching and research.[90,92] These issues must be borne in mind when considering future strategies.

Alongside this, however, the prescribing of premium-priced drugs without considering the opportunity costs can seriously affect the general care of other patients when budgets are fixed. This includes, for instance, the prescribing of high-cost drugs such as trastuzumab for early-stage breast cancer. If prescribed without a significant increase in drug budgets, this could well lead to a significant number of other cancer patients in the locality with early-stage disease being denied access to proven technologies.[93]

It must also be borne in mind when developing new initiatives that monitoring activities do not just picture the world in certain ways; they also have a regulating impact on practice. This is captured by Michael Power in his book entitled *The Audit Society*.[72] This is not only a society where auditing is commonplace, but also a society where activities are formed in such a way that they can be audited and auditable.[72] Also in healthcare, many monitoring activities are carried out with the express intention of affecting and regulating the assessed activities. Classification schemes for reporting are introduced not only to highlight certain features of monitored operations, but also as a way of improving these operations. The audit society will also result in a substantial growth of auditing associations controlling a diminishing minority of people actually doing the job. It will also lead to a higher conformity and uniformity since it is targeted at the average and not at the individual, as described in the book *The MacDonaldization of Society*.[94] This may be beneficial in certain situations; however, there must still be room for individuality where pertinent.[91,94]

An important issue is also *the risk of strategic behaviour*, such as concentrating on the activities that are being monitored and neglecting the non-monitored domains or risk-selecting patients, such as excluding high-risk patients. This is clearly described by Goodhart's law of government policy indicators: ''when policy performance is being evaluated, individuals and institutions will dedicate a disproportionate amount of time and effort to meet the targets, thus neglecting any other aspects that are not under investigation.''[95] This may to some extent be counteracted by adding more indicators to the continuous assessment. However, by monitoring too many variables, the increased complexity and contradictory outcomes may confound the observable outcomes and further add to the audit explosion and confusion. These issues can be addressed, however, through the development of well thought-out initiatives in

the future, which will become increasingly essential to address resource pressures.

In addition, the value of monitoring depends on the validity and reliability of the data. Sometimes performance measures are based on self-reporting, for example by writing an annual quality report on prescribing.[11,21,92] This may be a less controversial method to engage professionals in quality assessment. However, care must be taken, as self-reported data can for instance produce overestimations, e.g. adherence to guidelines.[96] Furthermore, self-reporting may result in a phenomenon called decoupling, i.e. professionals (or others) show a facade, whilst in practice doing something completely different.[97] Nevertheless, such approaches can be effective when linked with other activities to increase the quality and efficiency of prescribing. As part of the recently introduced incentive scheme in Stockholm County, Sweden, primary care physicians had to produce an annual report on ways to improve the quality of their prescribing.[11,21,92] Analyses of the reports show physicians readily identified areas for improvement; however, there has been no evaluation to date on whether prescribing subsequently changed.

Auditing and paying for performance may also pose a threat to the validity of the data recorded if physicians take the opportunity to manipulate the data to increase their incomes.[98] A report from the UK has shown that small numbers of practices appear to have achieved high scores in their QoF targets by excluding large numbers of patients by exception-reporting, confirming that manipulation does take place.[79] However, a recent study showed that the rates of exception reporting have generally been low, with little evidence of widespread gaming.[99]

4. The Future Agenda

The rapid changes in healthcare governance and the increasing pressure on resources call for new strategies. Unfortunately, there are few peer-reviewed studies analysing the effects of health policy reforms targeted to doctors and patients. Furthermore, there is limited knowledge about the potential for cross-cultural learning and transferring models between different healthcare systems. As an example, in a Cochrane review, Sturm and colleagues[59] concluded that there are hardly any rigorously designed studies on the effect of financial measures from countries other than the UK and the US, although this is changing.[11,21,60] This reflects the fact that it may be difficult in reality to transfer initiatives from one country to another. The ease of transferability will depend on similarities in, for instance, physician remuneration and incentive schemes, ambulatory care infrastructure, and the extent of national versus regional responsibility, including budget responsibility.[11,21,22,49,50,57,63]

The lack of scientific studies may be partly explained by the methodological difficulties in evaluating outcomes. In theory, evaluation of human behaviour may focus on different levels of change from reaction to learning, behaviour and result.[100] Prescribers' and patients' attitudes may be evaluated using simple questionnaires. Learning and behaviour may, for example, be assessed using simulated patient cases. Outcomes are more difficult to assess due to the length of time needed for the evaluation, the lack of a sufficient number of reliable objective measures of outcomes including surrogate markers,[101] and the large number of potentially confounding factors.

There are many useful guidelines for designing studies to evaluate the effectiveness of healthcare interventions and pharmaceutical policy making.[102-104] A variety of quantitative study designs may be used. These studies include quasi-experimental designs (uncontrolled or controlled before-and-after studies and interrupted time series) and randomized controlled trials (RCTs). RCTs have the highest degree of evidence, as non-randomized designs might introduce selection bias by including in the intervention group doctors or clinics that favour the particular intervention. However, due to ethical, practical and methodological reasons, they are seldom possible to apply when evaluating the impact of demand-side initiatives. Therefore, well designed quasi-experimental studies may be the method of choice. These studies should be designed both to evaluate first-order effects, i.e. substitution between drugs and other therapies, and second-

order effects on other health services, e.g. emergency admissions and physician time, even though it is sometimes difficult to demonstrate a causal link to the latter.[104] It must also be borne in mind that healthcare processes are complex and it is likely that compensatory mechanisms to a certain extent may diminish the effects of individual interventions; for example, an intervention targeted at reducing inappropriate prescribing may be counterbalanced by increased patient demand and marketing from the pharmaceutical industry keen to preserve current revenues.

Alternative research strategies could include the instigation of qualitative research methods to provide a deeper understanding of the subjective aspects of the interaction between healthcare providers and patients – the objective being to seek additional methods to enhance the quality and efficiency of prescribing in the future. The common feature of qualitative studies is that they do not primarily seek to provide quantified answers to research questions. The goal of qualitative research is the development of concepts that can help improve understanding of the social phenomena in natural (rather than experimental) settings, giving due emphasis to the meanings, experiences and views of all the participants.[105] Examples of qualitative methods include in-depth interviews, focus group discussions, observations and various consensus methods. They have been used, for instance, to examine factors influencing general practitioners' prescribing decisions and their attitudes to new drugs.[42,43,52,106] However, any new initiative must be robustly tested for its impact and overall costs before being introduced to enhance implementation.

5. Conclusions

It is of crucial importance that both the benefits and any negative outcomes of pharmaceutical policy making are thoroughly evaluated in isolation before implementation of any new 'soft regulations', given the current paucity of published data and the current tendency of policy makers to introduce multiple reforms within short time periods. We believe the future research agenda must involve a combination of qualitative and quantitative methods as well as a multiprofessional approach to optimally evaluate the impact of future soft regulations and initiatives as well as their overall costs. The goal of future qualitative research is to seek additional methods to enhance the quality and efficiency of future prescribing. Healthcare researchers may also benefit from sharing experiences from other areas of society as well as from other countries, building on some of the examples listed in this paper. Without this serious approach, there is the potential for a significant waste of human and monetary resources without any obvious quality improvement. This must be avoided given increased resource concerns and the need to instigate additional measures to ensure continued comprehensive healthcare without prohibitively raising taxes or insurance premiums. These concerns have recently been exacerbated by the current financial crisis.

These are debates and challenges for the future. We hope this opinion paper discussing soft regulations stimulates such debates and results in new initiatives to help governments achieve their goals.

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Correspondence: Dr *Björn Wettermark*, Centre for Pharmacoepidemiology, Karolinska Institutet, Unit of Clinical Epidemiology, T2, Karolinska University Hospital, SE-171 76 Stockholm, Sweden.
E-mail: bjorn.wettermark@ki.se

Stockholmsmodellen för klok läkemedelsanvändning (Stockholm Model for Wise Use of Drugs): vetenskapliga publikationer och presentationer 1995-2010 (maj) om Läksak, läkemedelskommittéer, klinisk farmakologi och Läkemedelscentrum

De 62 publikationerna beskriver, belyser och utvärderar läkemedelsarbetet inom Stockholms läns landsting. (De med *-angivna berör direkt Läksak.)

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Avhandlingar inom området

1. Johanna Ulfvarson Drug treatment of elderly : The need for changing behaviour among providers and patients. 1 oktober 2004
Kommentar: Avhandlingen i medicin/klinisk farmakologi vid Södersjukhuset med professor Christer von Bahr som huvudhandledare. Arbetet underlättats av Läksaks och läkemedelskommittéernas arbete med läkemedelsgenomgångar. Med. Dr. Johannas Ulfvarson varit mycket aktiv inom kommitésystemet.

2. Pia Bastholm-Rahmner. Doctors and drugs: how Swedish emergency and family physicians understand drug prescribing. 20 mars 2009.
Kommentar: Avhandlingen utgår från Medical Management Centre och Läkemedelscentrum. Första doktoranden vid Läkemedelscentrum som disputerar. Studier kring förskrivningsprocessen och attittyder hos förskrivare till datoriserade beslutsstöd och elektroniska läkemedelstjänster. Avhandlingens resultat legat till grund för LOK (nätverket för läkemedelskommittéordföranden) riktlinjer för hantering av ansvar för gemensam läkemedelslista.

3. Buster Mannheimer. Drug related problems with special emphasis on drug:drug interactions. 25 september 2009.
Kommentar: Avhandlingen i medicin/klinisk farmakologi vid Södersjukhuset med professor Christer von Bahr som huvudhandledare. I arbetet har Läkemedelscentrum medverkat genom expertstöd- med. Dr. Björn Wettermark- och genom att erbjuda tillgång till läkemedelsstatistik och uppföljningssystem.

Ett urval presentationer om Läksaks, expertgruppernas och kommittéernas arbete vid kongresser (vetenskapligt utvärderade bidrag alternativt inbjudningar) eller vid centrala strategiska möten för att presentera ”Stockholmsmodellen för Klok Läkemedelsanvändning”.

1. Gustafsson LL. Inbjuden föreläsare. “Klok läkemedelsanvändning”. Nationellt möte 24 augusti 2007 i Stockholm för folkpartiets sjukvårdspolitiker.

2. Gustafsson LL, Korkmaz S. Inbjudna föreläsare till ledningen för Rikshospitalet Oslo inkluderande gemensamt läkarmöte. Presentation av ”Stockholmsmodellen för Klok Läkemedelsanvändning” 4 juni 2008.

3. Kalin M, Korkmaz S, Persson M, Wettermark B, Almkvist H, Gustafsson LL. Abstract.”Specialläkemedelsprojektet en väg att ytterligare förbättra läkemedelsanvändningen i Stockholms län”. Svenska Läkarsällskapets Riksstämma november 2007.

4. Gustafsson LL, Wettermark B: Invited speakers. Symposium: Monitoring the introduction of new drugs: methods focusing on safety, costs, and appropriate use. Congress International Society of Pharmacoepidemiology, Copenhagen August 2008.

5. Ringertz B. Invited speaker. Riksstämmans symposium i november 2008: “Nya läkemedel-vägen till hälsa och välstånd eller ekonomisk härdsmälta?”

6. Gustafsson LL. Inbjuden föreläsare-”Förbättrad läkemedelsanvändning i Stockholms läns landsting”. Pharmareports fortbildning i Stockholm om ”Framtidens läkemedelsorganisation och nya affärsmodeller -– hur möts vården och industrin?”

7. Wettermark B. Inbjuden föreläsare. Mellansvenska Läkemedelsdagar februari 2009. ”Spaning mot nya läkemedel – har vi bra kikare och vad ser vi?”

8. Malmström R. Inbjuden föreläsare. Vad tillför nya diabesläkemedel? Norrländska läkemedelsdagarna januari 2009.

9. Gustafsson LL. Inbjuden föreläsare vid Pharmaonlines Fortbildningsträff 22 april 2009. Stockholm –“Strukturerad introduktion av nya läkemedel: ett kommittéperspektiv”.

10. Diogene E, Gustafsson LL, Melien O. Invited speakers advanced European course on “Introduction of new expensive drugs in health care” in the section “Local Formulary Development – practical examples and challenges in primary and secondary care”. In collaboration with European Association of Clinical Pharmacology and Therapeutics, Glasgow July 2009.

11. Gustafsson LL. Inbjuden talare. Symposium vid Svenska Läkarsällskapets riksstämma November

EXPERT REVIEWS

Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance

Expert Rev. Pharmacoeconomics Outcomes Res. 9(1), 65–83 (2009)

Brian Godman†, Björn Wettermark, Mikael Hoffmann, Karolina Andersson, Alan Haycox and Lars L Gustafsson

†*Author for correspondence*
Institute for Pharmacological Research 'Mario Negri', Milan, Italy
Tel.: + 39 023 901 41
Fax: + 39 023 546 227
godman@marionegri.it

It is a continual challenge trying to improve the quality of prescribing while concurrently trying to address increasing pharmaceutical development, utilization and expenditure. National and regional reforms and initiatives in Sweden have moderated growth in ambulatory drug expenditure to 2.7% per annum in recent years despite increasing volumes. National reforms include mandatory generic substitution and value-based pricing alongside devolution of drug budgets to the regions. Regional initiatives include strengthening the role of the regional Drug and Therapeutic Committees, further budget devolution as well as strategies incorporating prescribing guidance and monitoring coupled with financial incentives. The extent and nature of the regional initiatives vary depending on their characteristics. In this article, we compare initiatives undertaken in two major counties, Stockholm and Östergötland, and their outcomes. Outcomes include annual drug budget savings while achieving agreed quality as well as increased adherence to prescribing targets and guidance; the latter associated with savings. Appraising these multifaceted reforms can provide guidance to other countries and regions in view of their diversity. Future steps must incorporate measures to improve the utilization of new expensive drugs, which should include horizon scanning and forecasting activities as well as post-launch activities involving monitoring of prescribing and registries. This may well require cooperation with other European countries.

KEYWORDS: Drug and Therapeutic Committee • financial incentive • generic • healthcare reform • pharmaceuticals • pharmacoeconomics • rational prescribing • reference price

Three principles govern decision-making in Swedish healthcare. First, Swedish residents should have equal access to high-quality care irrespective of their status and income; second, patients in greatest need take precedence; and, finally, treatment choices should consider both costs and outcomes [1–3,101]. There are several national bodies involved in enhancing the quality and efficiency of prescribing (**Box 1**).

The overall responsibility for planning, providing and monitoring healthcare for the 9.2 million inhabitants in Sweden is now devolved to 21 county councils and 290 municipalities [1,3,102,103]. The municipalities are responsible for all health services associated with residential care, excluding physician services [3]. County councils and municipalities are politically directed and able to levy taxes as well as decide on copayment for healthcare interventions (except for prescription drugs) to address budget deficits [3]. The county councils vary in size between 60,000 and approximately 2 million inhabitants. Most county councils use some form of purchaser–provider system when negotiating agreements with healthcare units [3,102].

Primary care has traditionally been seen as less important in Sweden compared with other European countries [102,104]. This is despite the long and rigorous training for general practitioners (GPs). Patients in Sweden are either listed at a specific Primary Healthcare Center (PHC) or belong to the PHC in their geographical area [1] with approximately 25% of PHCs being privately run [103]. The number of PHCs that are privately run is increasing following the recent change in government and political majorities in many county councils. Some patients, particularly

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Box 1. National organizations in Sweden regulating, supporting and influencing the quality and efficiency of prescribing, and their responsibilities.

Medical Products Agency

- Regulation and surveillance of the development, manufacturing and sale of drugs and other medicinal products
- Assessing and granting permission to undertake clinical trials
- Inspection and training according to Good Manufacturing Practice
- Monitoring adverse drug reactions and alerting healthcare professionals when necessary
- Dissemination of independent information on drugs and drug utilization through publications, seminars, courses and conferences

Dental and Pharmaceutical Benefits Agency (TLV) – known as The Pharmaceutical Benefits Board (LFN) before September 2008

- Decides, after application by the producer, whether new medicines for ambulatory care should be included in the PBS for the whole population or defined subpopulations
- Regularly reviews the reimbursed prices of generics
- Is currently conducting pricing reviews for 49 drug classes in order to decide which ambulatory care products should continue to be reimbursed at target prices and subpopulations. Classes reviewed to date include drugs for migraine, respiratory diseases, hypertension, antidepressants as well as the diseases caused by acid in the stomach

The Swedish Council on Technology Assessment in Healthcare (SBU)

- Promotes the utilization of cost-effective healthcare technologies with a mandate for reviewing and evaluating healthcare technologies from medical, economic, ethical and societal perspectives
- Two levels of reports are principally produced, 'yellow' and 'alert' reports:
  - Yellow reports are comprehensive reports for identified diseases; for example, moderately elevated blood pressure and dementia. They include executive summaries and conclusions
  - Alert reports are early assessments of single new technologies such as ranibizumab for the treatment of age-related macular degeneration

National Board of Health and Welfare (SoS)

- Collects, compiles, analyzes and disseminates information on healthcare
- Develops standards based on legislation and the information collected
- Supervises county and municipality performance to ensure agreed standards are observed as well as minimizing risk and improving patient safety
- Maintains health data registers and official statistics
- Responsible for the annual national benchmark reports overseen by SALAR including 63 indicators of medical quality (including rational use of drugs), 23 for patient experiences and access to care and a further 15 indicators for cost comparisons between the counties and in some instances individual hospitals
- Involved with developing national quality registers

The National Corporation of Swedish Pharmacies (Apoteket AB – State owned)

- Currently has national responsibility for collecting drug utilization and expenditure data across all healthcare sectors
- Currently has exclusive rights to dispense prescription drugs and to sell OTC medicines in the community. – This is changing with proposed legislation to open up the pharmacy market during 2009
- Has been contracted by all county councils to distribute drugs in hospitals for periods of up to 4 years; this is now changing
- Has provided the public and physicians with factsheets and other information about drugs to improve drug utilization

OTC: Over the counter; PBS: Pharmaceutical benefits scheme; SALAR: Swedish Association of Local Authorities and Regions.
Data from [2,101,109,110,115–119,122,137–140].

those in urban settings, elect to go straight to emergency rooms or specialist clinics in hospitals bypassing GPs as primary care facilities can be limited [1].

Pharmaceutical expenditure

New pharmaceuticals, such as the new biological drugs, are challenging healthcare systems [4,5,105] in view of their high acquisition costs [6,106]. Resource pressures are further challenged by the effectiveness of a number of these products converting fatal conditions into long-term chronic disorders [5,7] as well as their rising costs [105]. Improvements in pharmacogenomics, bioinformatics and proteomics [8,9] will further accelerate the launch of new biotechnology drugs as well as drugs with additional novel mechanisms of action [107], further increasing resource pressures. This is causing growing concern [4], and will increasingly require those in charge to base their decisions on knowledge and evidence without excessive pressure from interest groups including pharmaceutical companies and groups of physicians [10–14]. The prescribing of new expensive drugs [15] combined with increased volumes [15,16,108] resulted in pharmaceutical expenditure growing significantly in Sweden during the 1990s [17,108,109]. This growth rate outstripped the growth rate in other components of healthcare resulting in pharmaceutical expenditure as a percentage of

overall healthcare expenditure growing to approximately 14% in the late 1990s and early 2000s [18]. This led to additional national and regional reforms and initiatives. This article describes these as well as the likely future direction. Those affecting prices are typically instigated nationally (Box 1) and will only briefly be reviewed as they have been covered elsewhere [19]. The county councils (regions) principally instigate initiatives to improve the rationality of prescribing following budget devolution [1,3,102].

The high degree of self-governance following devolution, different political majorities, varying sociodemographic demands and different structures, makes Sweden an interesting example when reviewing various regional initiatives. The multifaceted regional initiatives will be explored through reviewing the different approaches and the underlying rationale among two of the four largest counties, namely Stockholm and Östergötland. Our objective is to provide examples of different initiatives and their impact where known. These initiatives may also be of interest to pharmaceutical companies as they plan their future activities with an increasing role for evidence-based health gain in decision-making [19].

Materials & methods

A thorough review of the literature between 2000 and 2008 was undertaken in MEDLINE using the following terms: 'Sweden', 'pharmaceuticals', 'drugs', 'reimbursement', 'reforms', 'expenditure', 'rational prescribing', 'generics' and 'costs'.

This provided only a limited number of relevant peer-reviewed publications in English. Consequently, the search was supplemented by additional papers known to the authors, especially those written in Swedish; an internet search of websites of relevant authorities and organizations in Sweden (Box 1); internal county documents; insight into ongoing reforms in other countries as part of a PhD thesis [Godman B; Unpublished Data]; and feedback from key stakeholder groups. Costs related to Sweden have been presented in Swedish Kronor (1 Euro = 9.95 SEK; 1 US$ = 7.93 SEK; 1 GB£ = 12.47 SEK, 28 October 2008).

Calculations on the annual increase in ambulatory drug expenditure were derived from data supplied by the National Corporation of Swedish Pharmacies, Apoteket AB [108]. We have not critically appraised the quality of the published papers discussed incorporating for instance criteria used by the Cochrane Collaboration [20]. This is because of the paucity of papers documenting the actual impact of ongoing reforms. We have also not undertaken a systematic review of the reforms including a compilation of the results for similar reasons. We do acknowledge this in addition to discussing areas for future research. We also recognize that a number of the references are from non-peer-reviewed sources. These are included to provide insight from healthcare professionals including payers actually involved with instigating and monitoring the various reforms and initiatives. As such, we believe the findings will be of interest to other European countries as well as innovative pharmaceutical companies as they adapt to the changing environment with its increasingly defined regulations and constraints.

Results

Since pharmaceutical expenditure is derived by multiplying prices and volumes, the various reforms and initiatives can be divided into those that impact on pharmaceutical prices (supply side reforms) and those influencing prescribing quality and volumes (demand side reforms) (Figure 1) [21].

Supply side reforms & initiatives impacting on pharmaceutical prices in Sweden

Recent reforms include rejecting or restricting reimbursement for new ambulatory care drugs, encouraging low prices for generics and value-based pricing.

Rejecting or restricting reimbursement if concerns with the value of new ambulatory care drugs

The Dental and Pharmaceutical Benefits Agency (Swedish acronym: TLV) was established in October 2002 to enhance the rational and cost-effective use of medicines in ambulatory care [110]. Until August 2008, it was known as the Pharmaceutical Benefits Board (Swedish acronym: LFN). Prior to TLV, practically all new medicines were reimbursed apart from a few products and conditions not authorized for reimbursement following decisions from the Parliament or Government [110]. Examples of increased hurdles for reimbursement are given in Table 1.

The basis for TLV's decisions follow the underlying principles of the Swedish healthcare system as discussed earlier [101,110]. However no cost per quality-adjusted life year (QALY) cut-off levels have been established with the TLV willing to accept a higher cost per QALY ratio for patient groups with initial low quality of life and/or low life expectancy [19,22]. This is in line with the principle that patients with the greatest need take precedence [19,109]. There are also concerns that pharmaceutical companies will play the system and any cost per QALY cut-off levels will need to be constantly adjusted to account for inflation [19]. Pharmaceutical manufacturers must provide the TLV with relevant clinical and economic information [111]. However, the documents as well as the application itself are not available to the public. The public is also not informed if and when pharmaceutical companies choose to withdraw an application after discussions with the TLV. Manufacturers are in some cases required to provide the TLV with information that any agreed restrictions are being applied in practice. This includes prospective and retrospective observational studies and market prescribing data. Two internal audits conducted in 2006 demonstrated that there were concerns with the quality of some of the study protocols as well as how specific the questions posed by TLV were [Kieler H *et al.*; Unpublished Data]. As a result, a number of counties have instigated their own studies to monitor prescribing in practice. Counties also typically instigate further guidance to restrict prescribing of new premium-priced products since:

- Many drugs prescribed in hospital for in-patients are not evaluated by TLV with companies generally choosing not to apply for reimbursement for hospital-only drugs. The cost for these drugs is subsequently included within activity-based payments

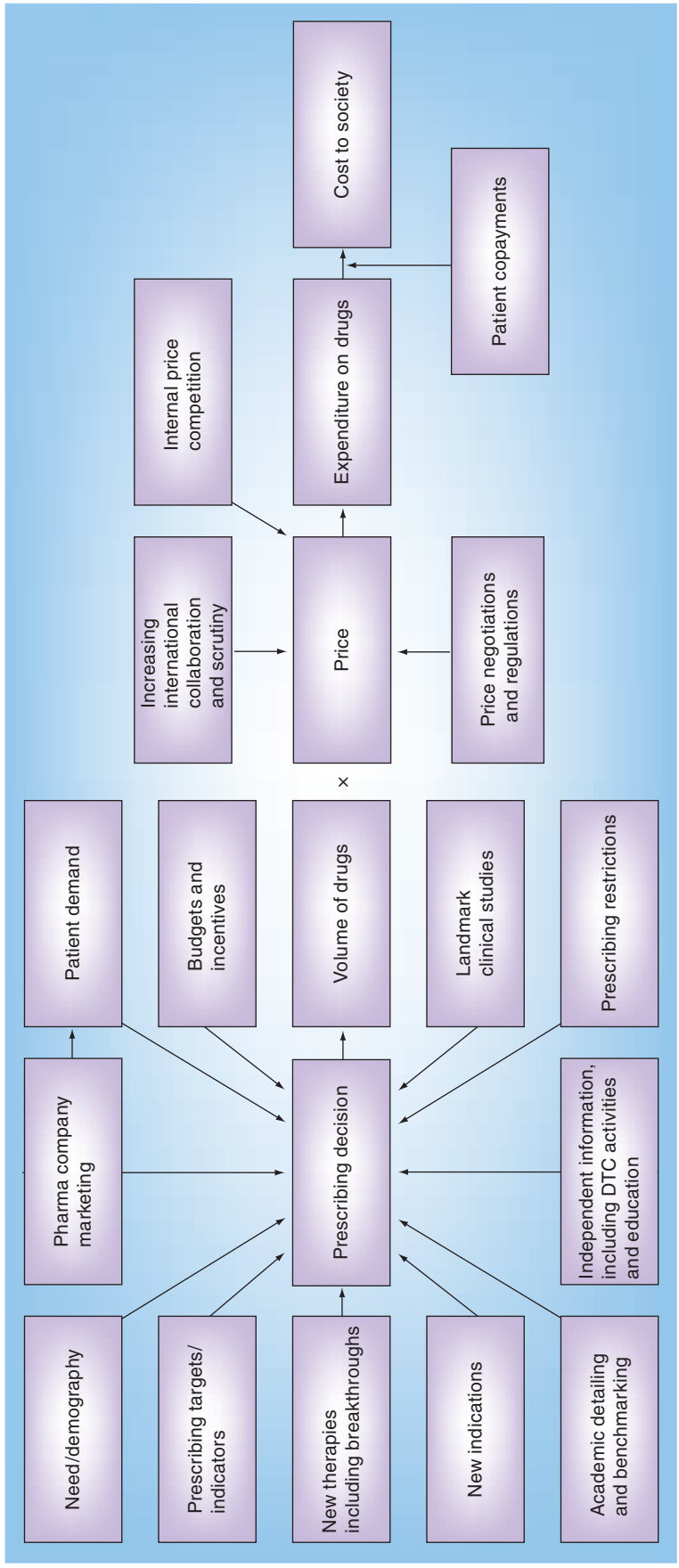

Figure 1. Factors influencing pharmaceutical expenditure.
Data from [21].

from the regional health authorities. These are political bodies responsible for providing inpatient care, who can independently decide whether to increase regional taxes to cover any deficits;

- The TLV does not usually consider possible off-label prescribing in its decisions since there is typically no data available on the effectiveness and cost–effectiveness at submission. However, the TLV has the option to investigate the prescribed indications post launch, and if necessary exclude the drug from reimbursement if off-label prescribing is common;
- The TLV has the option to make new decisions for new indications. This is not always the case and decisions are often not processed fast enough, thereby creating the need for temporary handling of the issue by the counties;
- The TLV uses the societal perspective in its evaluations without considering the healthcare budget impact of new drugs. This issue is supposed to be handled in separate negotiations between the Ministry of Health and Social Affairs and the counties.

Reforms to encourage low prices for generics

Following mandatory generic substitution in October 2002, only the cheapest substitutable product available in the community pharmacy at dispensing is currently reimbursed in Sweden [23,24,112]. The Medical Products Agency reviews and decides which products are substitutable [23,24]. Decision-making has recently accelerated to facilitate price competition. Price competition is also enhanced by technical support systems enabling pharmacists to continually stock the cheapest product, with prices reviewed at least twice a month [19]. Exceptions from mandatory substitution apply only when the prescriber indicates that the drug should not be substituted on medical grounds, when substitution is restricted by pharmacists for reasons such as differences in taste for oral solutions or when the patient decides to pay the price difference for a more expensive brand [23,24,112]. The first two situations are rare in practice [23,24] helped by an increasing focus on drug costs within the counties following budget devolution and physician acceptance of the reforms [25]. According to a previous study, the proportion of patients willing to pay the price difference is associated with its actual size [24]. For instance, analyses have shown that patients may consider a more

Table 1. Examples of stricter reimbursement decisions by the TLV since its formation in 2002.

Year	TLV decisions	Ref.
October 2002–March 2005	The TLV denied reimbursement for 13 drugs out of 107 cases of 'principal importance' (12%) and gave limited or conditional reimbursement to 12 drugs (11%). This was due to concerns over their cost–effectiveness	[17,109]
2006	10% of NCE applications (four out of 40) were not approved for reimbursement; however, two are subject to appeal in the courts Over 20% of NCEs only received restricted reimbursement owing to concerns over their value Examples of limited reimbursement included: rimonabant (removed from the market by the EMEA in October 2008 owing to safety concerns) – only for patients with a BMI higher than 35 kg/m^2; alternatively in patients with Type 2 diabetes and/or dyslipidemia with a BMI higher than 28 kg/m^2; or rosuvastatin – only for patients not achieving target lipid levels with simvastatin	[19,110,141]
2007	Five new applications (10%) were denied reimbursement, with restricted reimbursement assigned to 11 applications Delisting of cough medicines perceived to have limited efficacy and principally prescribed for short-term conditions with relatively minor discomfort	[19,117,142]

NCE: New chemical entity; TLV: [Swedish acronym] The Dental and Pharmaceutical Benefits Agency.

expensive brand if the additional costs are less than 30–50 SEK per prescription, which typically covers 3 months; however, this is not universal. This mixture of market characteristics and reforms has resulted in generic prices falling rapidly in Sweden in recent years [101]. Prices for generics fell by an average of 40% by the end of 2005 compared with 2002 [113], with prices for high-volume drugs falling still further. Overall for high-volume prescription drugs, reimbursed prices have fallen significantly to between 4 and 13% of the originator patent price once multiple sources are available (Figure 2). Possible reasons for any differences in the rate of decline between substances are outside the scope of this paper.

The TLV recently estimated overall savings of €700 million (>6.97 billion SEK) from these various measures from 2002 to the end of 2005 [110]. However, this figure has not been substantiated by other sources. In addition, any acquisition cost savings have to be balanced against patient safety and any extra workload informing patients and healthcare professionals about any substitutions made. Case reports and studies have shown that some patients are unsure of the content of their prescriptions leading, for instance, to duplication [26]. In addition, a recent survey conducted by Apoteket AB in January 2008 among 1548 patients ascertained that 11% of patients believed some generic drugs were less effective than originators [27]. An equal proportion of patients also experienced confusion about which drug or drugs they were taking and 7% of patients claimed they had experienced medication errors, possibly attributable to generic substitution, confirming earlier findings [27]. Recent initiatives to address this include listing all patients' purchases of prescriptions for the past 15 months in a National Pharmacy Register [28] administered by Apoteket AB. This register is available online to patients protected by passwords and can be accessed by healthcare professionals if patients allow this.

Instigation of value-based pricing for existing drugs

Included within the TLV's strong focus on cost–effectiveness is the reassessment of the value of nearly 2000 existing pharmaceuticals [109,110]. Five reviews have been published to date. Each review is concluded with a report suggesting which products should still be reimbursed in all or subpopulations [111] and which should be delisted at current prices. Key stakeholders have 5 weeks to respond, with products now routinely delisted within 3 months unless the appeal court decides to give an 'inhibition'. This will typically only happen if the appeal court decides that the pharmaceutical company has a substantial case. Clinical experts collaborate with the reviews. User groups are also involved, with a user council acting as advisers and critiquing the final drafts [111]. All personnel are required to declare upfront any active involvement with the pharmaceutical industry [111]. In its review of drugs to treat excessive stomach acid, TLV concluded that [114,115] all proton pump inhibitors (PPIs) have similar efficacy with the exception of high-dose esomeprazole in a small subpopulation [115]. TLV considered that a range of PPIs was still needed to account for interpatient variation. Consequently, a price premium of up to 25% was considered acceptable for the remaining patent-protected PPIs to still retain reimbursement [114,115]. TLV believed this premium was sufficient to balance the need for economy with

Box 2. Swedish law concerning DTCs from November 1996: criteria for county DTC.

- Minimum of one DTC in each county
- Each DTC shall have relevant access to medical, clinical pharmacology and pharmaceutical experts
- Each DTC shall work towards the rational use of drugs through recommendations to healthcare personnel. The recommendations should be based on scientific evidence and well-founded experience
- The National Corporation of Swedish Pharmacies (Apoteket AB) are required to provide DTCs with drug utilization data. If the committee realises that there are shortcomings in the prescribing of drugs it should provide education to prescribers to help address this
- Each DTC shall, when required, collaborate with other committees and relevant authorities and universities to help enhance guidance
- Each county shall issue an instruction for its DTCs

DTC: Drug and Therapeutic Committee.
Data from [30].

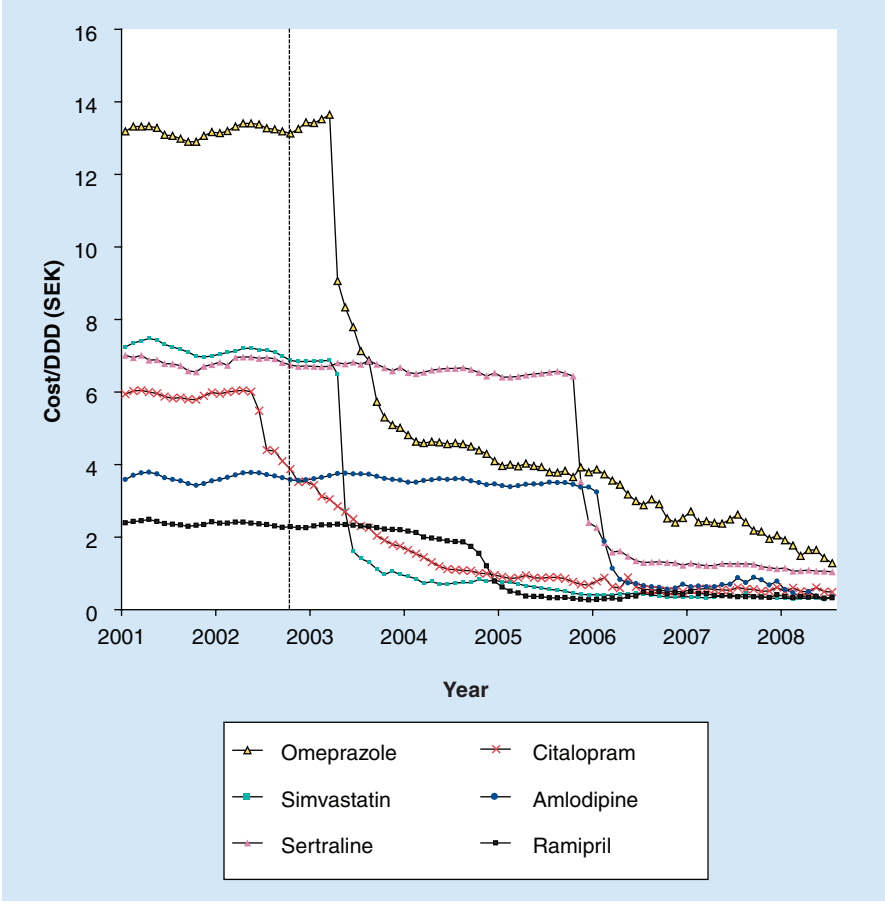

Figure 2. Cost/DDD for six products contained within the top 25 prescribed ambulatory care products in Sweden on a DDD basis where multiple copies became available just before or after 2002.
The dotted line denotes the instigation of mandatory generic substitution.
DDD: Defined daily dose.
Data from [108].

sufficient incentives for pharmaceutical companies [115]. However, this decision was challenged by companies and is still not fully resolved. This situation is less likely to happen in the future with the default position being the rapid instigation of TLV's recommendations. The value-based pricing proposals in the other disease areas have been less prescriptive adjusting for differences in products available [116–119]. The potential savings estimated by TLV are:

- Triptan review: approximately 42 million SEK/year from 2005 onwards [116];
- PPI review: approximately 175 million SEK/year from May 2006 [115];
- Respiratory product review: 40 million SEK/year with full implementation from 2007 [117];
- Anti-hypertensive review: over 400 million SEK/year from September 2008 including restricting angiotensin receptor blockers to patients intolerant to angiotensin-converting enzyme (ACE)-inhibitors [118];
- Antidepressant review: approximately 40 million SEK/year from 2009 largely through pharmaceutical companies reducing their prices with the availability of generics [119].

Estimations of potential savings have been affected by ongoing court cases. This approach will continue across all classes to release valuable resources, especially given the recent changes in the regulations.

Demand-side reforms & initiatives impacting on the quality & efficiency of prescribing

Ongoing initiatives and reforms to enhance the quality and efficiency of prescribing can typically be categorized under education, engineering, economics and enforcement, or the four 'E's [29].These are typically 'softer' regulations than for instance compulsory pricing policies. The nature and extent of regional initiatives depends on the characteristics of each county.

National initiatives

Drug & Therapeutic Committees (education)

County Drug and Therapeutic Committees (DTCs), common since the 1970s, became compulsory in 1997 (**Box 2**) [1,17,30] as part of general reforms to transfer responsibility and costs for drug prescribing to the counties [3,17,30].

The aim of county DTCs is to enhance the rational use of medicines. Most activities are targeted to healthcare professionals with information doctors and pharmacists used by counties to further enhance rational prescribing. Local experts as well as a number of GPs are involved with the development and dissemination of county guidance to enhance uptake in line with published recommendations [31,32]. In most DTCs, all members and affiliated experts have to declare annually any conflict of interest including relationships with pharmaceutical companies. In recent years, the focus has also been on patients and other important stakeholders. DTCs must also provide county administrations with necessary expertise on drug procurement and distribution activities [17,30,120].

National quality registers, quality indicators & prescribing targets in ambulatory care (engineering)

National quality indicators are increasingly used to improve public health and efficiency [121]. The Swedish Association of Local Authorities and Regions (SALAR) and the National Board of Health and Welfare (SoS) have supported the development

of over 60 national healthcare quality registers [33,101,122]. Many of these registries have been initiated and developed within different medical professional groups [7]. As previously stated, they are so far voluntary. However, owing to support from the medical profession and others, national registries for stroke, multiple sclerosis, rheumatoid arthritis [7] and intensive heart care have almost 100% coverage, with the data increasingly made public to improve care. Alongside this, SoS and SALAR have developed 100 indicators to compare the quality and efficiency of care between counties [121]; some of these include prescribed drugs (Box 3).

Box 3. Examples of indicators used nationally to compare the quality and efficiency of drug prescribing between 21 counties in addition to individual county targets.

Medical

- Percentage of people >80 years purchasing ten or more prescribed drugs concomitantly
- Proportion of the population treated with antibiotics
- Proportion of children 0–6 years treated with antibiotics for respiratory tract infections
- Percentage of women prescribed an antibiotic for a urinary tract infection treated with a quinolone
- Percentage of patients with prescribed and dispensed diabetes drugs who are also prescribed lipid-lowering drugs
- Percentage of stroke patients with atrial fibrillation dispensed anticoagulation therapy 12 months after discharge
- Percentage of post acute myocardial infarction patients dispensed lipid-lowering therapy 12–18 months after discharge

Efficiency

- Percentage of patients prescribed generic omeprazole as a percentage of all proton pump inhibitors
- Percentage of patients prescribed either generic simvastatin or generic pravastatin as a percentage of all statins
- Proportion of patients initiated on angiotensin II receptor blocker therapy not prescribed an angiotensin-converting enzyme inhibitor prior to angiotensin II receptor blocker initiation

Data from [121].

Limiting pharmaceutical company activity (engineering)

National agreements have been signed between the Swedish Association of Pharmaceutical Industries (LIF), SALAR and the Swedish Medical Association limiting contact with physicians and other healthcare professionals [109]. The ethical code was revised in 2007 [123]. In the revised code, funding for attending congresses and subsequent report writing have changed with funding for travel and accommodation divided equally between county councils and companies. In addition, physicians need their participation agreed by their head of department with their salary fully covered by the county [123].

Drug budget devolution (economic)

Alongside this, some counties have also allocated indicative prescribing budgets for ambulatory care drugs [1,34] to enhance the cost consciousness of physicians (discussed later). Two models have been used – a population-based model and a prescriber-based model [1] based on historic patterns [1,101]. The former model is more common in rural areas and the latter more common in major cities. In the population model for instance, GPs in PHCs are responsible for the costs of nonspecialist drugs (accounting for 50–80% of overall costs) [1] and hospital departments responsible for the costs of specialist drugs they themselves prescribe. While budget devolution has enhanced the cost consciousness of physicians [101], its impact has been variable. The impact in practice has depended on whether, for instance, health centers had already begun instigating measures to enhance rational prescribing prior to budget devolution [35] and the level of control physicians have over their prescribing costs [1].

Regional initiatives

As discussed earlier, the nature and extent of regional initiatives depends on the characteristics of each county. This includes, for instance, the number of primary care physicians (Table 2).

Two counties, Stockholm and Östergötland, were chosen to appraise recent multifaceted initiatives as they represent two of the four largest counties in Sweden. They also have different characteristics and approaches (Table 2 & 3).

Ongoing initiatives within Stockholm County Council

Multifaceted measures have been introduced in Stockholm County Council within the last few years to enhance the quality and efficiency of prescribing (Table 3), which have been collated into a long-term strategy (Box 4).

Drug & Therapeutic Committee activities (education)

The Stockholm County Council guidelines for rational drug therapy is called the 'Wise Drug List' [30,120,124]. This contains approximately 240 first-line drugs for common diseases incorporating therapeutic ladders or guidelines [36,124]. Recommendations from 23 expert groups and consultations from five local DTCs are used to produce and refine the guidance. Drug selection is based on a range of criteria (Box 5).

As discussed, evidence-based medicine and other considerations are typically used by the DTCs when evaluating clinical papers to revise existing guidance. This is encompassed in a range of questions (Box 6) [120]. Therapeutic ladders in the 2008 Wise Drug List include those for hypertension and affective disorders (Box 7) [124].

Academic detailing (education) & self-monitoring of physician prescribing (engineering & education)

In Stockholm County Council, academic detailing by information doctors and pharmacists is supplemented with a computerized information and feedback system called JANUS. JANUS

Table 2. Characteristics of Stockholm and Östergötland County Councils 2007/2008.

Characteristic	Stockholm county	Östergötland county
Number of inhabitants	1,949,516	420,809
Percentage of the Swedish population (%)	21.2	4.5
Number of physicians employed by the county	6105	1385
Number of physicians employed by the county per 1000 inhabitants	3.13	3.29
Number of primary care physicians	1121	204
Number of primary care physicians per 1000 inhabitants	0.58	0.70
Number of PHCs	175	42
Number of visits to specialized care per 1000 inhabitants	1829	1352
Number of visits to PHCs per 1000 inhabitants	1670	1043
Percentage of PHCs run by the County Council (%)	50	90
Cost for prescription drugs (SEK/inhabitant)	662	623
Percentage of the costs of ambulatory care drugs prescribed by PHC physicians (%)	27*	40.6

*Reflects the high number of private specialists working without contracts with Stockholm County Council.
PHC: Primary Healthcare Center.
Data from [143].

has a dedicated website [125], with part of the facilities integrated into electronic medical record systems [36,37]. JANUS contains, for instance, details of the Wise Drug List, databases on drug–drug interactions, guidance on drug use in pregnancy as well as guidance on new drugs. JANUS also provides alerts for drug–drug interactions. One of the main feedback tools used by Stockholm County Council in its benchmarking activities and educational initiatives is the drug utilization 90% (DU90%) methodology [36,38–40] incorporating two quality indicators. These are the number of different drugs prescribed by an individual ambulatory care physician, or all doctors in a practice, during a defined period, and the overall adherence to the guidance and guidelines recommended by the county (measured as the proportion of recommended drugs among those drugs accounting for 90% of the prescribed volume in DDDs) [36]. Monthly updates are available for each practice on the internet protected by passwords. The DU90% methodology is considered valuable by GPs in Stockholm County helping them assess their adherence to recommended drugs [36,40] and is inexpensive to administer. Average annual savings of more than 40,000 SEK per GP are seen from 2007 for every percentage increase in guideline adherence [19,41].

Patient-orientated educational activities (education)

A separate Wise Drug List has been produced and distributed by Stockholm County Council for its patients [126]. This is seen to enhance patient–doctor communications leading to increased prescribing of recommended drugs.

Prescribing targets in ambulatory care (engineering)

Existing prescribing targets (Table 4) in Stockholm County Council were developed by the DTC after intense consultations and reviews among physicians and medical opinion leaders. Their acceptance is reflected by some targets now being exceeded (Table 4).

A number of new indicators and targets are being developed facilitated by the availability of the National Prescribed Drug Register [42]. These indicators focus on drug combinations, treatment regimes, persistence over time and whether agreed first-line drugs have been prescribed before initiation of second-line drugs. The unique identifiers also enable record linkage with other registers, for example, to study to what extent recommended drugs are prescribed and dispensed to patients discharged from hospitals with certain diagnoses (Box 3) [43].

Structured programs to enhance the rational use of medicines including new, expensive drugs (engineering)

Stockholm County Council has recently introduced a new model to optimize the diffusion of new, expensive drugs with new, specialist drugs accounting for half of total drug expenditure in recent years growing at 4–14% per annum (Box 4) [44]. The model includes both reimbursed drugs initiated by specialists but prescribed in ambulatory care such as the TNF-α inhibitors for the treatment of rheumatoid arthritis, as well as new therapies used in hospital care such as intravenous immunoglobulins and parenteral antimycotics. The model operated through the DTC consists of early detection (horizon scanning), forecasting, critical drug evaluation and structured protocols to assess value in practice [Wettermark B *et al.*, Unpublished data; 45]. Forecasting has recently been enhanced by the development of a new robust validated model. The model has been constructed by dividing existing drugs into their pharmacological group (Anatomical Therapeutic Chemical classification third level) and adjusting for future growth based on [Wettermark B *et al.*, Unpublished data; 45]:

- The estimated position of the various products in the group in the product life cycle [46];
- Envisaged reforms or other expected changes in the market likely to influence utilization, expenditure or both, such as generic availability of treatment standards;

Table 3. Ongoing initiatives within Stockholm and Östergötland County Councils.

Measure	Stockholm	Östergötland
Education Takes many forms including drug formularies and guidance, distribution of educational materials, academic detailing, feedback or a combination of these	• Wise Drug List • Guidelines/guidance. Implementation enhanced by a strict policy of all DTC members declaring any conflicts of interest • Support throughout the county by DTCs of speciality focused continuous medical education • Computerized tools and decision support for rational prescribing including DU90% methodology • Feedback on performance including prescribing targets • Patient-oriented educational activities	• Guidelines and academic detailing • Computerized tools for analysis and bench-marking of drug prescribing • Support for local quality assurance programs • Feedback on performance of drug prescribing focusing particularly on equity • Patient information programs on drugs
Engineering Concerned with introducing organizational changes including monitoring the quality of care	• Structured programs for the introduction of new medicines • Prescribing targets	• Introduction of new drugs through ordinary processes for prioritization and resource allocation
Economic interventions Including devolving drug budgets and copayments	• Financial incentives • Limited projects devolving budgets	• Total budget devolution for drugs to PHCs and specialist clinics at hospitals and in outpatient settings • Monitoring the cost–effectiveness of drug prescribing
Enforcement Includes initiatives that physicians or companies are obliged to follow	• Monitoring prescribing of restricted drugs against agreed guidance with additional interventions if required	• Focusing on equity in access to drugs within different therapeutic classes as part of payment process

DTCs: Drug and Therapeutic Committees; PHC: Primary Healthcare Centers.

- Likely introduction of new drugs, their anticipated price and likely prescribing in practice.

The robustness of the model is enhanced through using local experts. One outcome will be early scrutiny of the role and value of new expensive drugs leading to guidance at launch as these drugs now account for the majority of the projected annual increase in expenditure. Alongside this, likely to see increased instigation of registries to collect data on the effectiveness and safety of new drugs once launched. This builds on the rimonabant registry prior to its withdrawal where prescribing was regularly monitored against agreed guidelines limiting usage in practice. Along with this, the drug's impact on BMI, side effects and persistence was monitored over time [47,48]. The information gained was in line with others prior to its withdrawal.

Prescribing budgets & incentives (economics)

In Stockholm County Council, GPs receive financial incentives according to their adherence to DTC guidelines, meeting agreed prescribing targets and writing an annual quality report [41,101]. The annual report must contain details on self-identified areas for prescribing improvement, systems in place for introducing new medicines and participation in DTC activities. PHCs, accounting for 85% of all prescriptions from primary care, signed contracts in 2006 for the period 2006–2007. Recent content analyses of submitted reports identified many areas for improvement including limiting prescribing of drugs with weak documentation or uncertain safety profile [Wettermark B *et al.*, Unpublished data; 41] enhancing the value of this initiative. Overall in 2006, Stockholm County Council spent 20 million SEK on incentives to the 139 PHCs participating in the scheme [19]. These incentives, combined with other measures such as online benchmarking and academic detailing, has enhanced guideline adherence with an average DU90% of 84% in primary care between October and December 2007. This represents a significant saving from earlier years coupled with sustained quality. Savings are estimated by the authors to be at least five times higher than the cost of the program [Wettermark B *et al.*, Unpublished data; 41].

Ongoing initiatives within Östergötland County Council

Prescribing budgets & incentives (economic)

The demand-side initiatives in Östergötland are different reflecting differences in the characteristics with Stockholm (Table 2). Östergötland is the only county that has fully devolved responsibility for the cost of prescription drugs in ambulatory care to PHCs or specialists clinics (Table 2), with pharmaceutical costs fully integrated into the total remuneration of the PHCs. This initiative has been in place since 1 January 2002. Östergötland County Council has mainly followed the population-based model for drug budget devolution in line with budget allocations of other services [1]. This model also simplifies the integration of budget responsibility for prescription drugs into the total remuneration and regulations for the PHCs, with budget deficits covered by each PHC and clinic if necessary balanced against next year's budget. To facilitate this, total remuneration for the average PHC comprising approximately 10,000 patients doubled in

Box 4. The politically agreed long-term drug strategy for Stockholm County Council to ensure rational, safe and cost-effective treatments – originally introduced in 2003 and recently extended to 2008–2012.

Decision support
- Electronic system providing an overview of patient medicines profile
- Drug interactions and warnings of adverse-events (Janus tool bar)
- E-prescribing
- Janus website
- SIL – a comprehensive database with drug information
- Wise Drug List, Wise Drug Advice
- Other support to help the interaction between the physician and the patient

Continuous professional education and communication
- Education strategy
- Marketing
- Continuous professional education
- Organization, administration
- Dialogue with prescribers and patients
- Relations with the pharmaceutical industry

Economic incentives
- Local quality assessment
- Indicative drug budgets
- Feedback on prescribing with incentives for meeting agreed targets
- Procurement of drugs in hospitals

Drugs and the elderly
- Various strategies to improve prescribing such as regular comprehensive drug utilisation reviews among nursing home patients

Important areas with future implications
- Strategies being developed for the introduction of specialist drugs (new expensive medicines) especially in hospitals
- Environmental issues, research and development, drug policy and lobbying
- Organizational issues and contacts with other important stakeholders

SIL: Svensk Informationsdatabas.

2002 with approximately half of the remuneration, averaging 16 million SEK, covering annual drug costs for the relevant drugs – regardless of prescriber – for patients listed at the PHC. In 2007, most PHCs had surpluses of 0.5–2 million SEK on their annual drug expenditure whilst still meeting quality assurance targets for drugs. The surpluses are typically used by the PHCs to improve or expand other healthcare services, such as offering cognitive behavior therapy for anxiety disorders. Privately run PHCs have the possibility of using all or part of the surplus to provide a dividend to their owners. However, before distribution they have to persuade their patients and the county that the quality of care provided follows local and national guidelines and matches the care provided by the other PHCs in the area. This is done, for instance, through PHC physicians benchmarking their prescribing performance against others for key issues such as equity and quality assurance. Access to prescribing statistics also helps assure patients if necessary of the quality of prescribing. Two representatives from patient organizations are also co-opted members of their local DTC to further help with discussions on the quality of care. Patient organizations are also part of a special working party focusing on over-the-counter drugs and self care [127].

Drug & Therapeutic Committee activities (education)

The main goal of the activities of the DTC in Östergötland County Council is to fully integrate decisions about drugs in the decision-making process at all levels in the county, that is, at the political, professional, administrative and prescriber levels. One important way of doing this is to help physicians with their drug prescribing. This is seen as an integral part of quality assurance programs. As such, the DTC provides guidance on rational drug use as well as monitoring the care provided. The DTC also stimulates quality assurance programs for drug prescribing by developing tools that can help with prescribing. These programs and tools also help politicians in their understanding of key issues surrounding the prescribing of existing and new drugs including cost–effectiveness issues. To facilitate this, the DTC has a health economist as one of its members with the possibility of commissioning other health economists to participate in developing guidelines and giving input into prioritization processes and resource allocation.

Academic detailing (education) & self-monitoring of physician prescribing (engineering & education)

The DTC in Östergötland County Council gives quality-assured and independent information about drugs through academic detailing as a specific service demanded by and financed by the units, primarily the PHCs. On average a PHC receives academic detailing about drugs for 1–2 h four times per year presented by trained staff members. The information is also given through channels and activities arranged by either other county bodies or by the PHCs themselves in the belief that information regarding drugs should be integrated with information about a patient group or a disease. Drug prescribing statistics are mainly handled by the practicing physicians themselves, who are able to benchmark their prescribing behavior against colleagues through an open intranet application. Östergötland has built a system for analyzing reports on the intranet using a standard software package (Cognos Powerplay) [128]. This is used not only for drugs but also for other types of performance analyses within the county. The system uses an easy-to-understand graphic interface reducing the learning threshold for physicians and managers.

Patient-orientated educational activities (educational)

As discussed, patient representatives are members of the local DTC in Östergötland. This has been the case since 2002. Two persons are nominated by the local branch of the Swedish

Box 5 . Five-point criteria used by Stockholm County Council when reviewing drugs for inclusion in its Wise Drug List.

Efficacy and safety

- Based on available evidence preferably including data from randomized, controlled trials as the highest level of evidence [20] to answer a series of prespecified questions (Box 6)

Pharmaceutical suitability

- Formulations, strengths and pharmacokinetic properties

Efficiency

- This is mainly based on comparative reimbursed prices and the overall budget impact of the drug. There is currently limited use of cost–effectiveness data in decision making by the counties [34] since the TLV does not consider the budget impact of drugs in its deliberations [109]. This is crucially important to the counties with their responsibility for the drug budget as they wish to avoid levying additional taxes to address budget deficits unless absolutely necessary

Experience

- Mainly concerned with drug safety. Recommended drugs should generally have been available for at least 2 years; however, more recent drugs can be included if they have shown under evidence-based medicine rules to improve care and that there are no major concerns with the safety of the drug in question

Environmental aspects

- If drugs are considered similar based on available evidence and similarly priced, environmental considerations guide choices. This development is seen as novel among the counties as well as other countries although the issue is of increasing concern [54,55]. This is reflected by the Swedish parliament determining by 2010 that there should be documented information on the environmental characteristics of marketed chemicals including pharmaceuticals [144]. As a result, Stockholm County Council has classified the environmental hazard of drugs routinely prescribed [56,145]

TLV: The Dental and Pharmaceutical Benefits Agency.
Data from [30,120].

Disability Federation. They participate fully in the DTC meetings and can influence both the agenda itself and the proposals put forward to the DTC during a separate meeting with the chairman 1 week before. The contribution of user groups in the decision-making process has made it simpler for physicians and County officials to communicate reasons for, and actual decisions, to different patient organizations [127]. This is also seen as a potential way of influencing physicians' attitudes and actions by proxy. The county information office handles all information about drugs as part of an ongoing dialogue about healthcare. Information campaigns carried include, for instance, the results of class reviews conducted by TLV.

Prescribing targets in ambulatory care (engineering)

In view of its budget devolution philosophy, Östergötland County Council has not established any specific prescribing targets unlike Stockholm County (Table 4) since it is in the healthcare unit's own best interest to prescribe efficiently, following existing guidelines. However the county has recommended PHCs work with specific treatment areas and establish local targets to achieve their goals. In addition, local quality assurance and efficiency programs are supported, though not initiated by the DTC, through providing indicators of cost–effectiveness and quality of prescribing [129]. These are developed in similar way to, and in collaboration with, DTCs in other counties. The different clinics and PHCs subsequently select their own targets from the available list of indicators (Box 8) [130].

As discussed, PHCs, if necessary, have to defend their performance against selected indicators to the county and the public especially if they wish to realize any savings. This is viewed as an integral part of the purchaser–provider interaction directing discussions on the quality of the healthcare provided [130]. Since most of the commonly used prescribing indicators focus on cost-effective drug choices (Box 8) not surprisingly physicians have consistently high compliance versus those in the other counties [131].

Structured programs to enhance the rational use of medicines including new expensive drugs (engineering)

The Dental and Pharmaceutical Benefits Agency (TLV) decides whether a new ambulatory care drug should be reimbursed. If positive, Östergötland County Council can not refuse to reimburse it; however, it can decide the extent of new resources allocated to fund a new drug. In this way help shape decision making with no separate programs in PHCs and clinics for the introduction and funding of new drugs unlike Stockholm County Council (Box 4). As a consequence, the introduction of new drugs is seen as an integral part of resource allocation with PHCs and clinics assessing their role and implications before and during their launch. The reason for this is the assumption that no one knows better what new treatments will shortly become available than practicing specialists. In addition, within the academic hospital in Östergötland there is good knowledge about, and often participation in, ongoing clinical trials. This, together with the provision of trial results and other data, including possible cost and health economic data, helps clinics assess the potential role of these drugs in advance of new budget years. This leads to early discussions about possible increases in resources, with discussions enhanced by the early availability of critical evaluations of the new drugs by the regional DTC supported by health economists employed by Östergötland County Council as data becomes available. These critical drug evaluations, including in some cases crude assessments of cost–effectiveness when data is scarce, are also used to support and defend decision making

Box 6. Questions to be addressed by expert groups in Stockholm Couty Council when considering inclusion of new ambulatory care drugs into the 'Wise Drug List'.

- What was the main scientific question posed?
- How was patient selection conducted and diagnoses made, etc.?
- What patients were included in the control groups and what type of study was conducted (e.g., cross-over, parallel, placebo-controlled, etc.)?
- Was the study double blinded, single blinded, etc.?
- How was the randomization conducted?
- What about the pharmacokinetics?
- What about concomitant medications, are these documented, valid, etc.?
- Are the drug effects well-defined, relevant, reproducible, etc.?
- What about adverse events? Are these well-studied and described, etc.?
- How appropriate was the statistical design and evaluation of the results – were these adequate? What about measures such as absolute risk reduction – can this be calculated?
- What about the conclusions of the studies – were these adequate, doubtful, irrelevant?

Data from [120].

with politicians by the clinical departments and PHCs. These initiatives and activities are seen as essential with no separate ring-fenced funds for new drugs. The decision to allocate resources to a new technology, and as a consequence to certain clinics and PHCs, is made using a formal process including both vertical (by healthcare professionals supported by health economists) and horizontal (by politicians supported by healthcare professionals) prioritization [132,133].

Impact of regional & national initiatives on ambulatory care expenditure

The mosaic of dynamic and interactive reforms in Sweden do appear to moderate ambulatory pharmaceutical expenditure from 2000 to 2007; averaging just over 2.8% per year (Figure 3) [108]. This is against a backdrop of volumes (in DDDs) increasing by an average of 3.2% per year during this period [108].

The expenditure on nonspecialist drugs within Stockholm County Council also only grew by an average of 2% per annum from 2002 onwards [44]. This compares with a much higher rate of increase for specialist drugs, which includes a significant proportion dispensed in hospitals. Additional measures and initiatives should help overcome recent increases in ambulatory care expenditure. These include additional prescribing targets as well as further downward pressure on prices as more therapeutic classes are reviewed by the TLV.

Expert commentary & five-year view

Recent multifaceted reforms and initiatives have moderated the annual increase in ambulatory care drug expenditure in Sweden in recent years despite increased volumes (Figure 3).

Typically, prescribing quality and volumes are less easily controlled than prices with a variety of inter-related measures such as educational activities, interactive educational meetings, reminders and benchmarking (Figure 1) seen as the most effective tools to influence prescribing versus single interventions [32,49–51]. The initiatives reviewed here confirm this and endorse the conceptual thinking that no single method is that useful on its own [32,49]. However, we recognize again that there is a paucity of peer-reviewed publications and other data documenting the actual impact of individual reforms on the quality and efficiency of ambulatory care. This is apart from estimates surrounding generic substitution and market measures to lower generic prices, potential savings from value-based pricing, estimated savings from guidance adherence among ambulatory care physicians in Stockholm County Council, and data on average annual drug budget surpluses among PHCs in Östergötland. As previously stated, a significant amount of sourced data are from websites and internal documents. This must be acknowledged as a weakness of this article from an empirical perspective. However, they are included to add to the paper's interest in view of the richness of the data and the fact that the publications are from professionals including payers actually involved with developing and implementing the various measures.

Despite these concerns, we believe that the Swedish model using a combination of strategies at different levels provides examples to other countries and regions. This is enhanced by contrasting the different approaches in Stockholm to Östergötland (Table 3). Activities in Stockholm County and other counties also encourage consideration of the environmental impact of drugs in decision making, which is a growing concern (Box 5) [52–54]. We acknowledge though, there is an urgent need for further research to asses the impact of ongoing reforms using a variety of quantitative and qualitative study designs [Wettermark B *et al.*, Unpublished data] .

Box 7. Therapeutic ladders for hypertension and affective disorders in Stockholm County Council in 2008.

Hypertension

- First line: thiazide (bendroflumethiazide, hydrochlorothiazide) and/or ACE inhibitors (enalapril, ramipril) or calcium channel blockers (amlodipine)
- Second line: β-blockers (metoprolol) if there are other concomitant indications for prescribing a β-blocker such as heart failure, history of myocardial infarction or migraine
- Intolerance towards ACE inhibitors (e.g., excessive coughing): ARBs (candesartan)

Affective disorders

- First line: SSRIs (citalopram or sertraline)
- Second line: SNRIs (generic mirtazapine or venlafaxine)
- For specialist use: clomipramin or consider additional treatment with lithium

ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker; SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin receptor inhibitor.
Data from [124].

Table 4. Prescribing targets ('Wise Drug Advice') in Stockholm County Council 2007.

Category	Target	2007
Percentage of PPI prescriptions as generic omeprazole	>80% of DDDs	72%
Reducing the prescribing of PPIs for nonspecific dyspepsia	<20 DDDs/thousand inhabitants per day	26 DDD/TID
Percentage of antithrombotic drugs as low dose acetylsalicylic acid	>95% of DDDs	96%
Percentage of statin prescriptions as generic simvastatin	>80% of DDDs	74%
Percentage of renin–angiotensin products as ACE inhibitors	>75% of DDDs	57%
Percentage generic mirtazapine as a percentage of all mirtazapine	>90% of DDDs	51%
Percentage of quinolones prescribed to treat urinary tract infections as opposed to other antibiotics such as trimethoprim, nitrofurantoin, and pivmecillinam	<30% of prescriptions	30%
Percentage of patients prescribed generic nasal budenoside versus other nasal steroids for the treatment of hay fever and other pertinent conditions	>15% of DDDs	25%

ACE: Angiotensin-converting enzyme; DDD: Defined daily dose; PPI: Proton pump inhibitor; TID: Thousand inhabitants per day.
Data from [101,146].

National examples of interest to other countries include measures to obtain low prices for generics (Figure 2). The low prices obtained for generics in Sweden should make it difficult for generic companies to justify significant differences in prices between European countries, which can vary up to 36-fold [55]. The savings potential from lower prices of generics will accelerate with estimated global sales of at least $100 billion/year subject to generic competition in the next 4 years [56]. Countries can also use low prices for generics and originator brands to decrease prices of interchangeable brands in a class or related classes. The proposed transparent pricing for brand PPIs in Sweden [115] provides a benchmark. However, a 50% premium based on DDDs above standard generics for the remaining brands proposed by the Office of Fair Trading in the UK may be more realistic enhancing the availability of alternative products [57,114].

The use of registries to monitor the effectiveness and safety of new expensive drugs in reality is also likely to grow in Sweden building on examples such as the TNF-α inhibitor drugs in rheumatoid arthritis [7] and rimonabant for obesity [47,48]. Similar initiatives are also seen in France [58], Italy [134] and the UK [106]. The findings from the registries can subsequently be used nationally and regionally to reconsider the place of new drugs as well as their price. The Swedish experience also shows that registries can be used to monitor prescribing enhancing physician compliance to guidance and patient compliance to the drugs prescribed [43,59]. They can also be used to develop new robust quality indicators.

Alongside this, France and the USA [60,135] are building on the situation in Sweden to restrict pharmaceutical company activities [109,123]. This should further enhance the quality and efficiency of prescribing when combined with other multifaceted demand-side measures.

The initiatives surrounding the four 'E's in Stockholm County Council (Table 3) do appear to moderate the annual growth in nonspecialist drug expenditure as well as increase rational prescribing (Table 4). One criticism of the DU90% methodology (Table 3) is that it does not link actual drug use to a diagnosis [19]. However, this methodology stimulates discussions on prescribing, as well as helping to identify major problem prescribing areas [19,36,39,40].

Box 8. Examples of indicators in Östergötland County Council to help primary healthcare centers improve the cost–effectiveness and quality of their prescribing.

Quality of prescribing

- Number of patients with diabetes reported to the national quality register for diabetes mellitus
- Percentage of patients with diabetes reaching agreed targets for HbA_{1c} levels
- Percentage of patients with diabetes >40 years prescribed statins
- Percentage of patients with diabetes >40 years prescribed angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists

Equity

- Number of defined daily doses adjusted for the age and sex of different ATC-groups dispensed to patients listed to PHCs regardless of the prescriber
- Costs in SEK adjusted for the age and sex for the different ATC-groups dispensed to patients listed to PHCs

ATC: Anatomical Therapeutic Chemical; PHC: Primary Healthcare Center.
Data from [130].

There have been concerns that following the guidance in the Wise Drug List can compromise the quality of care. The transparent and multifaceted methodology involved in guideline development should help address this [19]. In addition, a preliminary study undertaken in 24 primary healthcare centers found no difference in blood pressure targets attained, or HbA_{1c} levels under control and guideline adherence rates measured using this methodology [Norman C *et al*; Unpublished Data]. Further studies should confirm this as well as confirm considerable savings can be achieved from following the guidance.

Monitoring physician prescribing coupled with education through quality circles has also been successful in various

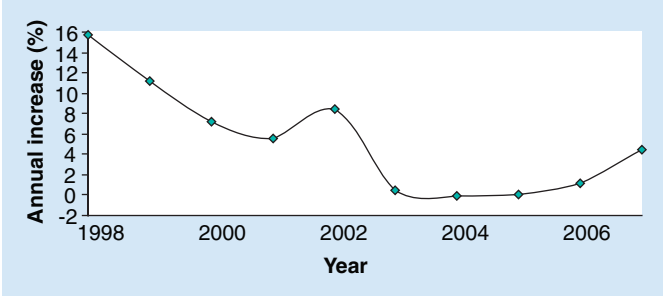

Figure 3. Annual percentage change in ambulatory care pharmaceutical expenditure in Sweden 1998–2007.
Data from [108].

regional states in Germany to enhance the quality and efficiency of care [61,62]. Prescribing targets have also been instigated in other countries. Acceptance is enhanced by local involvement in their development combined with robust methodologies. Savings can be substantial, for example, under the 'Better Care, Better Value' initiative, the National Audit Office in the UK believed modestly increasing prescribing of simvastatin as a percentage of all statin prescriptions, ACE inhibitors as a percentage of all renin–angiotensin prescriptions and decreasing prescribing of clopidogrel would save an estimated £227 million/year alone (2830 million SEK) [136].

Budget devolution has proven successful in Östergötland, with PHCs regularly accruing drug budget surpluses while meeting quality targets and addressing patient concerns. This compares with the GP FundHolding scheme in England where slower rises in prescription costs between fundholding and non-fundholding practices did not persist [63,64]. This may be helped in Östergötland by the large number of high-volume brand drugs losing their patent since 2002 coupled with reforms driving down generic prices (Figure 2). The proactive use of self-selected prescribing and quality targets, routine benchmarking of prescribing habits versus colleagues, as well as the proactive approach to the introduction of new drugs, may well also have contributed.

In Stockholm County with its greater number of private practitioners (Table 2), financial incentives rather than routine budget devolution have enhanced the quality and efficiency of care (Table 4). This complements the findings in other countries [20,65,66]. Overall, it is likely that financial incentives linked with quality incentives and prescribing targets will grow across Europe moderated initially by the lack of studies evaluating their long-term impact.

The role of patients as part of prescribing and quality programs is also likely to grow building on the examples in Austria, France and Sweden. In Austria, patient information booklets of recent guidance are distributed in pharmacies and physician offices to enhance guideline compliance [67]. In France, there have been successive and successful campaigns among patients to enhance the acceptance and dispensing of generics [68,69] and international nonproprietary name prescribing [68].

Additional measures will be needed in the future in Stockholm County to slow down the diffusion of new expensive drugs, with expenditure on specialist drugs in Stockholm growing by over 9% per annum on average since 2002 [44]. This is also a major challenge across Europe [4]. The recent structured program for the introduction of new expensive drugs (Box 4) including forecasting, critical drug evaluation and post-launch activities should help. Budget devolution with proactive approaches to critically evaluate and plan the introduction of new medicines has also helped moderate the utilization of new expensive drugs in Östergötland.

Key issues

- National and regional reforms in Sweden have moderated recent increases in ambulatory drug expenditure despite increased volumes. These include initiatives to significantly lower the price of generics, such as mandatory generic substitution, as well as regional strategies to enhance the prescribing of generics where standard. However, a paucity of data makes it impossible to fully evaluate the impact of these reforms.
- A variety of regional initiatives have been undertaken with regional characteristics dictating approaches. Potential approaches can be classified under the four 'E' approach (education, economics, engineering and enforcement) and vary, for instance, from full budget devolution to financial incentives to enhance the quality and efficiency of prescribing. Sweden has also instigated agreed measures to limit pharmaceutical company activity, which serves as an example to other countries.
- Adherence to guidance can lead to savings while not impacting on outcomes. Prescribing targets are well accepted if they build on robust methodologies, with the potential to develop future prescribing and quality targets with the new Swedish prescribing registers containing unique data on dispensed drugs for individual patients.
- The development of registries in Sweden such as those for the TNF-α inhibitors enables close monitoring of the effectiveness and safety of new drugs in practice. The registries also enable health professionals to monitor physician and patient compliance against agreed guidance post launch.
- National and especially regional initiatives are essential to plan for the introduction of new expensive drugs given growing resource pressures and concerns with patient safety. This includes forecasting, critical drug evaluation and post-launch activities. Evidence- and 'needs'-based introduction also helps balance against commercial pressures and lobbying from interest groups, thereby reducing the potential for prohibitive future increases in local and regional taxes.
- It is likely in the future that there will be greater pan-EU collaboration to share knowledge and guidance about new drugs as well as pan-EU registries to monitor the effectiveness and safety of new drugs in practice. This mirrors pan-EU activities for registration and is a challenge for the future.
- There is an urgent need for further quantitative and qualitative research, especially in ambulatory care, to provide guidance for the future.

In conclusion, we believe our description of national and regional reforms and initiatives in Sweden is worthy of debate and does provide examples to other countries. The findings in Sweden where data exists are consistent with other published studies that a combination of measures is needed to enhance the quality and efficiency of prescribing [32,49]. However, as discussed, we acknowledge that there is an urgent need for more studies analyzing the impact of different interventions. This includes further research among the counties in Sweden as well as across ambulatory care in Europe [Wettermark B *et al*; Unpublished Data]. It is remarkable that there are few consistent models across Europe to enhance the quality and efficiency of prescribing. This is in sharp contrast to the strict models for drug approval in Europe. We believe this will be necessary to fully release valuable resources from generic availability. This process has already started with the instigation of the Piperska group independent of pharmaceutical companies [4]. Future approaches could also include instigating pan-EU databases to routinely collect outcome and safety data for new drugs in practice, as well as coordinated planning for the introduction of new, expensive drugs. There is also an urgent need for independent medical research addressing unanswered questions [70]. These are all challenges for the future.

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Affiliations

- Brian Godman BSc
Institute for Pharmacological Research 'Mario Negri', Milan, Italy
Tel.: + 39 023 901 41
Fax: + 39 023 546 227;
and, Prescribing Research Group, University of Liverpool Management School, Chatham Street, Liverpool, UK L69 7ZH.
Tel.: + 44 151 795 3611
Fax: + 44 151 795 3001
godman@marionegri.it
- Björn Wettermark, MSc Pharm, PhD
Regional Drug and Therapeutic Committee LÄKSAK, Department of Drug Management and Informatics, Stockholm County Council, Sweden;
and, Karolinska Institutet, Department of Laboratory Medicine, Division of Clinical Pharmacology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden
Tel.: + 46 8737 4081
Fax: + 46 8737 4012
bjorn.wettermark@sll.se
- Mikael Hoffmann, MD, PhD
Head of NEPI Foundation, Division of Drug Research, Department of Medical and Health Sciences, Linköping University, SE-581 83 Linköping, Sweden
Tel.: + 46 1322 7385
Fax: + 46 1322 7662
mikael.hoffmann@nepi.net
- Karolina Andersson, MSc Pharm, PhD
Nordic School of Public Health, NHV, Box 12133, SE-402 42, Göteborg, Sweden
Tel.: + 46 3169 3927
Fax: +46 3169 1777
karolina.andersson@nhv.se
- Alan Haycox, BA, MA, PhD
Prescribing Research Group, University of Liverpool Management School, Chatham Street, Liverpool, UK L69 7ZH
Tel.: + 44 151 795 3611
Fax: + 44 151 795 3001
ahay@liv.ac.uk
- Lars L Gustafsson, MD, PhD
Regional Drug and Therapeutic Committee LÄKSAK, Department of Drug, Management and Informatics, Stockholm County Council, Stockholm Sweden;
and, Department of Laboratory Medicine, Division of Clinical Pharmacology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-141 86, Stockholm Sweden
Tel.: + 46 8737 4035
Fax + 46 8737 4012
lars-l.gustafsson@ki.se

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MiniReview

The Nordic Countries as a Cohort for Pharmacoepidemiological Research

Kari Furu[1], Björn Wettermark[2], Morten Andersen[3], Jaana E. Martikainen[4], Anna Birna Almarsdottir[5] and Henrik Toft Sørensen[6]

[1]Norwegian Institute of Public Health, Oslo and Institute of Pharmacy, University of Tromsø, Tromsø, Norway, [2]Karolinska Institutet, Stockholm, Sweden, [3]University of Southern Denmark, Odense, Denmark, [4]Social Insurance Institution, Helsinki, Finland, [5]University of Iceland, Reykjavik, Iceland, and [6]Aarhus University Hospital, Aarhus, Denmark

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Abstract: The Nordic countries have a long tradition of registry-based epidemiological research. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. In recent years, each country has established a national database to track prescription drugs dispensed to individuals in ambulatory care. The objectives were to present an overview of the prescription databases established in the Nordic countries, as well as to elaborate on their unique potential for record linkage and cross-national comparison of drug utilization. Five Nordic countries collect drug exposure data based on drugs dispensed at pharmacies and have the potential to link these data to health outcomes. The databases together cover 25 million inhabitants (Denmark: 5.5 million; Finland: 5.3 million; Iceland: 0.3 million; Norway: 4.8 million; and Sweden: 9.2 million). In 2007, the registries encompassed 17 million prescription drug users (68% of the total population). We provide examples of how these databases have been used for descriptive drug utilization studies and analytical pharmacoepidemiological studies linking drug exposure to other health registries. Comparisons are facilitated by many similarities among the databases, including data source, content, coverage and methods used for drug utilization studies and record linkage. There are, however, some differences in coding systems and validity, as well as in some access and technical issues. To perform cross-national pharmacoepidemiological studies, resources, networks and time are needed, as well as methods for pooling data. Interpretation of results needs to account for inter-country heterogeneity and the possibility of spurious relationships. The Nordic countries have a unique potential for collaborative high-quality cross-national pharmacoepidemiological studies with large populations. This research may assist in resolving safety issues of international interest, thus minimizing the risk of either over-reacting on possible signals or underestimating drug safety issues.

There is an urgent need to assess the effectiveness and safety of drugs used in routine medical practice. Despite recent changes in regulatory demands, new drug development techniques and new models for disseminating medicines in the healthcare system, post-approval observational studies remain necessary to study drug effects, safety and cost-effectiveness [1]. This is particularly important as clinical practice differs substantially from the context of randomized clinical trials in terms of numbers and characteristics of patients, length of drug exposure, dosage and compliance [1,2]. An epidemiological approach to drug use and safety allows assessment of how drugs function in the real world.

Since the 1970s, the Nordic countries have used data on wholesale drug distribution to assess nationwide time trends in drug utilization and to make regional and international comparisons [3,4]. Few other countries have access to such comprehensive longitudinal national data. However, individual-level data are crucial both to accurately measure drug exposure in the population and to permit linkage of records to outcomes.

Europe's first computerized prescription-level tracking system was established in Northern Ireland in 1966 [5]. Since the early 1970s, Sweden has recorded outpatient prescriptions in the county of Jämtland and in a small community called Tierp [6,7]. In Canada, the province of Saskatchewan created one of the first public databases to collect individual-level prescription data for its population of 1 million people already in 1975 [8]. The United States also has several large automated databases with individual-level data on drug use [1]. However, most of these American claims databases were set up by health insurance organizations for administrative purposes and cover only selected populations. In Europe, many databases have been developed primarily for research purposes. The General Practice Research Database in the UK, established in 1987, is one of the most commonly used data resources in pharmacoepidemiological research and collects health information, including drug prescriptions in patient records, from over 460 primary healthcare practices, covering about 5% of the UK population [9]. The

Author for correspondence: Kari Furu, PO Box 4404 Nydalen, No-0403 Oslo, Norway (fax +47 21078146, e-mail kari.furu@fhi.no).

Netherlands [10] and Scotland [11] have established databases containing data on prescriptions dispensed by pharmacies, but neither of them cover the entire population of the countries.

During the late 1980s, pharmacies in the Nordic countries gradually computerized their records of dispensed prescriptions which made it possible to collect data efficiently. National prescription databases, containing data on drugs dispensed at pharmacies (exposure data) to individuals receiving ambulatory care, have been available since 1994 in Finland and Denmark, since 2004 in Norway, since 2005 in Sweden and since 2006 in Iceland [12–18]. Although healthcare systems are not organized identically in the Nordic countries, they have similar parameters. All five countries have a tax-supported public health service with universal coverage. All citizens, independent of socioeconomic status, have unrestricted access to health services, including partial or complete reimbursement of purchased medicines.

This article provides an overview of data collection procedures and content of the Nordic countries' prescription databases. In addition, we discuss their unique potential for cross-national record linkage and for analytical pharmacoepidemiological studies.

Data Collection Procedures and Content of the Nordic Prescription Databases

Each Nordic country has a nationwide prescription database containing electronically submitted information on prescriptions dispensed by pharmacies. In total, the databases cover the countries' 25 million inhabitants (fig. 1). In addition, Denmark has two regional prescription databases established for research purposes. Data from the autonomic region Åland Islands are included in the Finnish data, but the data from the autonomic regions of the Faroe Islands and Greenland are not included in the Danish data. The data collected are determined by country-specific regulations but all include information on the prescriptions together with information from different administrative registries. In most countries, data are transferred electronically monthly from pharmacies to the prescription database. According to the legislation of each country, no informed consent is required for collection of the prescription data, but individuals may see information about themselves if they make an enquiry. The Finnish Prescription Registry originates from an administrative need for reimbursement decisions. Thus, it is used primarily for decision-making. When the registry data, however, are used for research purposes, the possible findings cannot be used for decisions concerning individual patients. In Iceland, they may use the register for individual supervision of both patients and prescribers. The national prescription databases in Denmark, Norway and Sweden cannot be used for supervision of either individual patients or prescribers.

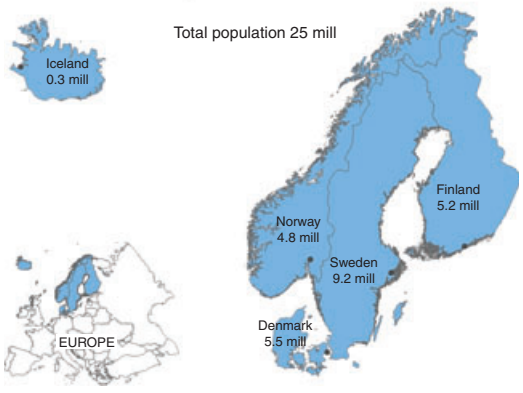

Fig. 1. The five Nordic countries.

Variables.

Data included in the databases fall into four main categories (table 1): (1) *Patient-specific data (*personal identifier, age, gender, place of residence); (2) *Prescriber data* (personal identifier, age, gender, profession, physician speciality, practice/clinic); (3) *Drug* data (e.g. the Nordic article number (which provides the trade name, pharmaceutical form, strength and package size), number of packages, Anatomical Therapeutic Chemical classification (ATC) code, amount in defined daily doses (DDD), prescription category, reimbursement code, prescribing date, dispensing date and price]; and (4) *Pharmacy data* (name, licence number, municipality and county). Some countries include additional variables in their databases. Three of the main categories of data are discussed briefly below:

(1) *Patient-specific data.* All individuals/patients included in the prescription databases have a unique personal identifier based on their person identification number, permitting linkage between various population-based data sources. Some prescription databases routinely include the date of death and migration, while others need to be linked to this information.

(2) *Prescriber data.* Prescribers are also accessible in most of the databases based on either a personal identifier or an identifier of the practice or hospital department of the prescriber. Prescriber information is linked to information on medical speciality (e.g. general practitioner, internal medicine, psychiatry, etc.). Further information on the individual practice/clinic from which the prescriptions are issued is also available to some extent.

(3) *Drug data*. With regard to drug exposure, the Nordic article number is a unique identifier for each drug formulation of a medicinal product used in the Nordic countries. This number constitutes the link to other registries providing detailed information on dispensed drugs. The drugs are classified according to the global ATC system [19]. Numbers of DDD dispensed are recorded, as well as the number of packages and the reimbursement code. There are several challenges in using these data. Firstly, the reimbursement system differs between the countries. Secondly, the indication for the prescription is not yet recorded in the databases. However, the reimbursement code may function as a proxy for diagnosis in some cases [20]. For example, since March 2008, prescribers in Norway have had to use either the 10th edition of

Table 1.

Detailed information on the Nordic prescription databases.

	Denmark			Finland	Norway	Sweden	Iceland
	Odense University Pharmacoepidemiological Database	Pharmacoepidemiological Prescription Database in Northern Denmark	Danish Registry of Medicinal Product Statistics	The Finnish Prescription Registry	The Norwegian Prescription Database	The Swedish Prescribed Drug Registry	The Icelandic Pharmaceutical Database
General	Regional	Regional	Nationwide	Nationwide	Nationwide	Nationwide	Nationwide
Population covered	1.2 million	1.7 million	5.5 million	5.3 million	4.8 million	9.2 million	0.3 million
Year established	1990	1989	1994	1993	2004	1 July 2005	2006
Year data became available	1990	1989[5]	1995	1994	2004	1 July 2005	2003
Frequency of updates	Monthly	Monthly	Monthly	Monthly	Monthly	Monthly	Monthly
Patient							
Unique identifier	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of death[1]	Yes	Yes	Yes	–[6]	Yes	Yes	No
Emigration[1]	Yes	Yes	Yes	–[6]	–[6]	Yes	No
Place of residence	Yes	Yes	Yes	–[6]	Yes	Yes	Yes
Dispensed drug (drug exposure)							
Unique identifier (Nordic article number)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ATC code	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DDD number	Yes	Yes	Yes	–[6]	Yes	Yes	Yes
Number of packages	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Prescribed dose	No	No	No	Free text	Free text	Free text	Free text
Reimbursed drugs	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-reimbursed drugs	No	No	Yes	No	Yes	Yes	Yes
Date of prescription	No	No	No	yes	No	Yes	Yes
Dispensing date	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diagnosis/indication for use	No	No	No	[2]	Free text[3]	No	No
Generic substitution done at pharmacy	No	Yes	Yes	Yes	Yes	Yes	Yes
Prescriber							
Unique identifier	No	Yes	No	Yes	Yes	No	Yes
Age	Yes	Yes	Yes	–[6]	Yes	No	Yes
Gender	Yes	Yes	Yes	–[6]	Yes	No	Yes
Profession (physician, dentist, nurse)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Speciality	Yes	Yes	Yes	–[6]	Yes	Yes	Yes
Practice/clinic/workplace	Yes	Yes	Yes	–[6]	No	Yes[4]	No
Pharmacy							
Unique identifier	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Location	Yes	Yes	Yes	–[6]	Yes	Yes	Yes

[1]Some databases include this information, while others access this information from another database.
[2]Dosage and indication as written by the doctor; for drugs belonging to special refund category: coded indication in case of certain diseases according to Finnish regulations.
[3]Dosage and indication as written by the doctor, ICD-10 codes or ICPC codes for the reimbursed drugs.
[4]Identified through a workplace code on the prescription.
[5]Complete coverage from 1998 onwards.
[6]Can be linked.

the International Classification of Diseases (ICD-10 codes) or the International Classification of Primary Care (ICPC codes) as the reimbursement code for prescriptions. The dispensing date and retail price are included in all the registries, but the prescription date is at present not included in the Norwegian and Danish prescription databases. Most prescribed medicines have received marketing approval in the Nordic countries. However, physicians may apply for a licence to prescribe drugs not yet approved for marketing. Drugs which are prescribed on this basis or by special permission from the National Medicines Agency are also included in the databases.

Information not included.

The majority of sales of non-prescription over-the-counter (OTC) medicines are not in the prescription databases. Only OTC medicines prescribed and dispensed to individual patients, e.g. for obtaining reimbursement in chronic diseases, are included. The indication for use and the prescribed dose are to some extent included, but only in free text not easily used for research purposes. Patient-level data on drug use in hospitals and other institutions are not collected routinely. In Denmark, individual-level information on drug use in nursing homes is included in its three databases. In Sweden, the majority of nursing homes have drugs supplied by prescription or multi-dose dispensing, and these are consequently included in its registry. Iceland started to include drugs supplied by multi-dose dispensing in 2006, but the data are complete only as of 1 January 2007. The Finnish Prescription Registry and the two regional Danish prescription databases do not include non-reimbursed medicines and can be affected by changes in the reimbursement system. None of the registries have complete data on vaccines.

Linkage of the Nordic prescription databases to other registries and data sources.

The Nordic countries introduced the unique civil registration code more than 50 years ago. This identifier is assigned to every person at birth or upon immigration; it is either 10 or 11 digits long and encodes date of birth and gender. The code is included in all national registries, allowing accurate linkage among them. The ubiquitous use of unique personal identifiers, making linkage possible among various population-based registries, has been the driving force behind the long tradition of registry-based epidemiological studies in the Nordic countries. Fig. 2 illustrates research possibilities conferred through linkage among the prescription databases and other available data sources.

Data access and websites.

Researchers may apply to the administrator of the databases in each country for use of data files. In general, the data themselves are free of charge, but costs accrue for administrative handling and file processing. Denmark and Norway have made information about users of a particular drug or drug category, disaggregated by sex, age and geography, accessible online (http://www.medstat.dk and http://www.norpd.no). More detailed information about access to each registry is available at the following websites:

- Denmark: http://www.medstat.dk and http://www.dst.dk/forskning
- Finland: http://www.kela.fi/research
- Iceland: http://www.landlaeknir.is
- Norway: http://www.norpd.no
- Sweden: http://www.socialstyrelsen.se/Statistik/statistik_amne/lakemedel/lakemedelsregistret.htm

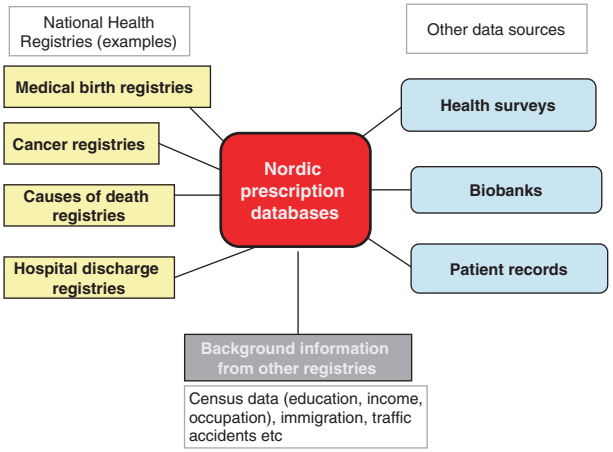

Fig. 2. Potential linkages of the Nordic prescription databases to other registries and data sources.

Key Findings and Publications

In 2007, the registries covered 17 million prescription drug users (68% of the population). The proportion of the population that had been dispensed prescribed medicines was 73.8% in Denmark, 68.8% in Finland, 73.7% in Iceland and 68.3% in Norway and in Sweden. In Denmark, approximately 35% of men and 20% of women did not purchase any prescription drugs during the previous year. Corresponding proportions in Iceland were approximately 30% of men and 20% of women and in Finland, Norway and Sweden about 40% of men and 25% of women. Drug use in different age groups was quite similar in the Nordic countries (fig. 3). In Finland and Norway, however, children used drugs less frequently than in the other countries. We have chosen to present sex-specific figures on statin use in the five countries as one example of utilization of a specific drug group (fig. 4). About 1.9 million people (7.6% of the entire population in the five countries) used statins during 2007. Utilization of statins among individuals aged 40–49 years varied from 2.8% in Sweden to 4.9% in Finland. Among individuals aged 60–69 years, it varied from 21.5% in Sweden to 29.1% in Finland. Differences among the Nordic countries in utilization of statins cannot be explained by variation in morbidity and further analysis is needed to explore the possible influ-

ences of reimbursement policies, guidelines and prescribing behaviour.

A large number of studies have been published, including both drug utilization studies (mainly descriptive studies) and analytical studies linking drug exposure to outcomes in patient registries, registries of road accidents, medical birth registries and cancer registries. Table 2 provides examples of drug utilization studies and table 3 presents a selection of published studies of drug effects conducted in the various Nordic countries.

Until now, there have been very few studies using data from more than one Nordic country. Bramness *et al.* published earlier this year a study of lithium use in three of the Nordic Countries [21]. In addition, there are also in progress Nordic studies of drug use during pregnancy involving all five Nordic countries.

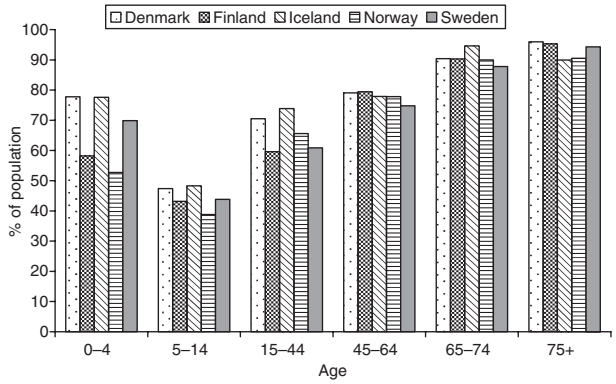

Fig. 3. Overall proportion of individuals (%) receiving at least one prescribed drug during 2007 registered in the Nordic prescription databases, by age and country.

Discussion

Strengths of the databases.

The Nordic prescription databases allow continuous post-marketing surveillance of drug dissemination and drug effects, the two core elements in the definition of pharmacoepidemiology. In pharmacoepidemiological research, complete and valid information on drug exposure is essential [22,23]. Pharmacy records are considered more complete than both medical records and information elicited from interviews and questionnaires [24–26]. Because only information about drugs dispensed and purchased by patients is entered into the databases, primary non-compliance is not an issue [27]. Completeness and accuracy of pharmacy records is high, due to legislation or other incentives motivating pharmacies to collect and send the data electronically to their national databases on all prescription drugs dispensed to and picked up by individuals in ambulatory care. In pharmacy records, drug use can be measured in great detail and the potential for recall and selection bias associated with survey data is eliminated [24,25]. The size of the prescription databases offers the potential for precise estimates of effect and the possibility of studying rare exposures and outcomes.

Weaknesses of the databases.

One potential weakness of the Nordic prescription databases is their lack of information about diagnosis or severity of the conditions treated. Furthermore, drugs dispensed to individuals during a hospital stay are not recorded, creating observation gaps. Some drugs are dispensed only through outpatient clinics (for example, antiretroviral drugs), and some new drug groups including some biological drugs (for example, infliximab) are mainly administered

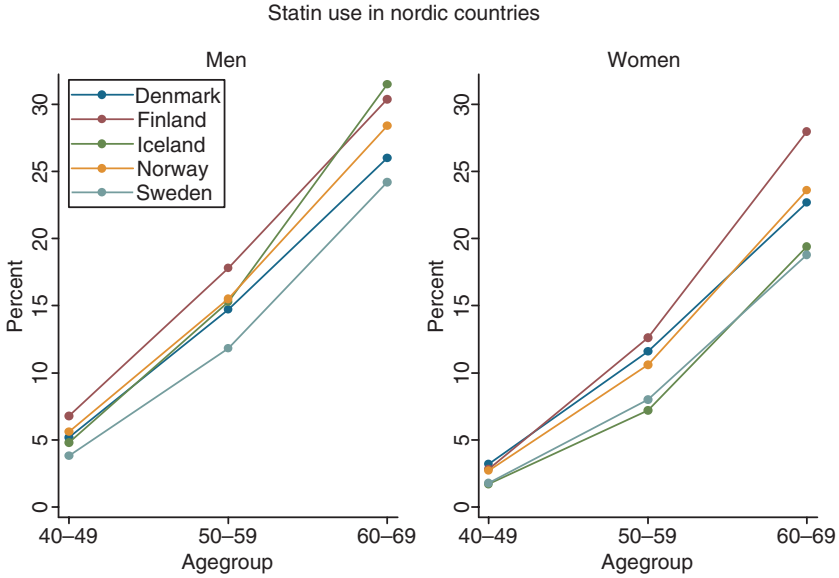

Fig. 4. Proportion of individuals (%) aged 40–69 years receiving statins at least once during 2007, as registered in the Nordic prescription databases, by sex and country.

Table 2.
Examples of drug utilization studies published from 2004 to 2009 using the Nordic prescription databases.

Therapeutic area	Research question	Linkage to other data sources	Setting	Reference
Cardiovascular	Socioeconomic status and drugs dispensed after myocardial infarction	Patient registry, education registry	Sweden	Ringback Weitoft [31]
Cardiovascular	Utilization of lipid-lowering drugs and antihypertensives	Patient registry	Sweden	Silwer *et al.* [32]
Cardiovascular	Secondary prevention after acute coronary syndrome	Hospital discharge registry, cause of death registry	Finland	Salomaa *et al.* [33]
Cardiovascular	Shift of statin use towards elderly	No	Finland	Ruokoniemi *et al.* [34]
Cardiovascular	Drug interactions with lovastatin and simvastatin	Patient registry	Finland	Tirkkonen *et al.* [35]
Cardiovascular	Co-medication with statins and CYP3A4 inhibitors	No	Norway	Devold *et al.* [36]
Cardiovascular	Statin use and education	Education registry and population-based health surveys	Norway	Selmer *et al.* [37]
Stroke	Secondary prevention after stroke	Patient registry	Sweden	Wettermark *et al.* [38]
Cardiovascular	Hospital variation in prescribing	Patient registry	Denmark	Rasmussen *et al.* [39]
Diabetes	Refill adherence of diabetes drugs	No	Sweden	Haupt *et al.* [40]
Diabetes	Utilization of antidiabetic drugs	No	Norway	Strøm *et al.* [41]
Dementia	Education and use of dementia drugs	Education registry	Sweden	Johnell *et al.* [42]
Antibiotics	Quality indicators for antibiotic use	No	Sweden	Ljung *et al.* [43]
Obesity medicines	Quality of prescribing of rimonabant	No	Sweden	Wettermark *et al.* [44]
Analgesics	Introduction of low-dose buprenorphine – influence on use of addictive drugs in non-malignant pain patients	No	Norway	Skurtveit *et al.* [45]
Analgesics	Adoption of celecoxib and rofecoxib	No	Finland	Helin-Salmivaara *et al.* [46]
Antiepileptic drugs	Utilization and co-medication as proxy for indication	No	Funen	Tsiropoulos *et al.* [47]
Asthma	Asthma drug use as proxy for asthma	No	Norway	Furu *et al.* [20]
Asthma	Influence of clinical trial on drug preferences	Industry trial registry	Funen	Andersen *et al.* [48]
Migraine	Pharmacy-based randomized study aimed at improving drug use	No	Funen	Søndergaard *et al.* [49]
Psychotropic drugs	Use of psychotropics is high among very old people	No	Finland	Hartikainen and Klaukka [50]
Psychotropic drugs	Utilization in the elderly	No	Iceland	Samuelson *et al.* [51]
All drugs	Patient educational level and use of newly marketed drugs	Education registry	Sweden	Haider *et al.* [52]
All drugs	Drug use during pregnancy	Medical birth registry	Norway	Engeland *et al.* [53]

in hospitals, and are therefore not usually included in the prescription databases. Drugs used by patients in nursing homes also are not completely recorded, leading to an underestimation of total drug use, especially in the elderly population. A general problem using dispensing data to assess drug use is also the fact that we do not know if and when the dispensed drugs are actually ingested by the patients. Information about lifestyle factors such as smoking habits and alcohol consumption, as well as detailed clinical data, are also lacking in the databases as in many other types of registries. There may also be certain problems of coding and data validity. However, the extent of this problem has been low. The proportion of prescriptions with invalid or missing personal identification codes varies among the Nordic countries, but in all cases is below 2%.

Future challenges.

The population required to detect an association between a particular drug and adverse events depends upon the type of event, the proportion of people using the drug and the magnitude of the risk. As early as 1982, Skegg and Doll pointed out that a population of at least half a million is needed to detect the commonest hazards, and as many as 5 million are required to detect rare events [28]. Nordic prescription databases cover populations ranging from 0.3 to about 9 million inhabitants, in some cases too small a number to detect rare events and thus inter-Nordic collaboration is needed. An on-going initiative aims to establish a Nordic Pharmacoepidemiological Network (NorPEN) to facilitate knowledge exchange, research and training (http://www.nhv.se/norpen). The role of NorPEN is to further the knowledge about the research capabilities

Table 3.
Examples of studies on drug effects (published 2004–2009) using the Nordic prescription databases.

Therapeutic area	Research question	Linkage to other data sources	Setting	Reference
Cardiovascular	Antithrombotic agents and gastrointestinal bleeding	Hospital registry	Funen	Hallas *et al.* [54]
Depression	SSRIs and pregnancy	Medical birth registry	Finland	Malm *et al.* [55]
Depression	Antidepressants and mortality	Cause of death registry	Finland	Haukka *et al.* [56]
Analgesics	NSAIDs and MI	Hospital discharge registry	Finland	Helin-Salmivaara [57]
Gastrointestinal	Acid-suppressive drugs and childhood asthma	Medical birth registry	Sweden	Dehlink *et al.* [58]
Gastrointestinal	PPI and gastric cancer	Cancer registry	North Jutland	Poulsen *et al.* [59]
Antibiotics	Fluconazole use in pregnancy	Medical birth registry	North Jutland	Nørgaard *et al.* [60]
Hypnotics	Benzodiazepine use in alcohol consumers predicts later opiate use	Population-based health surveys	Norway	Skurtveit *et al.* [61]
Hypnotics	Hypnotics and risk of road traffic accidents	Road accident registry and Central Population Registry	Norway	Gustavsen *et al.* [62]
Various drugs	Prescribed drugs and risk of road traffic accidents	Road accident registry and Central Population Registry	Norway	Engeland *et al.* 2007 [63]
Anorectic	Ephedrine/caffeine and cardiovascular events	Patient registry	Denmark	Hallas *et al.* [64]
NSAIDs	Death and reinfarction associated with use of coxibs and other NSAIDs	Patient registry	Denmark	Gislason *et al.* [65]
Cardiovascular	Cardiovascular drugs and suicide	Cause of death registry	Funen	Callreus *et al.* [66]

SSRI, selective-serotonin reuptake inhibitor; NSAID, non-steroidal anti-inflammatory drug; MI, myocardial infarction; PPI, proton pump inhibitor.

of the databases and build a network of Nordic researchers in pharmacoepidemiology. It is important to note that the NorPEN is not a governmental body and is as such unable to function as a common 'gatekeeper' for the Nordic prescription databases. Similarities and differences in methodology, coverage, validity and access to data will require close collaboration between researchers in the Nordic countries. A concern is that *Statistics Denmark* does not make prescription data available for use outside the institution. New rules for access to micro data were introduced in 2001. All data processing is actually done in Statistics Denmark. Data cannot be transferred from Statistics Denmark to the researcher's computer but are analysed using a secure, encrypted Internet connection. Results are e-mailed back to the researcher and checked for revealing too detailed information whereby individual persons may be identified [29]. In the other Nordic countries, the prescription databases are located outside the Bureau of Statistics, and the prescription data may be sent to other Nordic countries. However, there may be some impediments in transferring e.g. socioeconomic data between the countries.

Results obtained from studies in different countries can be combined using meta-analytical techniques, possibly facilitated by coordinating studies in advance to ensure that the design, case and exposure definitions, etc. are compatible. Another solution would be to produce frequency tables with specified covariate patterns for each country and use the combined tables for regression analysis. With these approaches using aggregate data, adjustment for confounding may be incomplete and there is a risk of ecological bias. The best solution for performing a study with data from all the Nordic countries is therefore to retrieve similar data from all countries at the individual patient level. If national data are required, it is at present necessary to transfer all data to Statistics Denmark for analysis as described above. A common framework for analysing Nordic prescription data would, however, be desirable.

In 2003, Professor Stricker pointed out that it is time for Europe to start using epidemiological techniques and methodologies for a more systematic approach to drug safety [30]. The European Medicine Agency (EMEA) intends to further strengthen post-approval monitoring of medicinal products in Europe by facilitating the conduct of independent multi-centre safety studies. To this end, the Agency has established the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), based on expertise and research experience available in the fields of pharmacoepidemiology and pharmacovigilance across the EU (http://www.encepp.eu). The Nordic countries provide a unique resource for collaborative high-quality pharmacoepidemiological studies with large populations. Thus, they may contribute to resolving safety issues of international interest and protect society from either over- or under-reaction to drug safety issues.

Conclusion

The Nordic prescription databases cover the entire population of the five Nordic countries, about 25 million persons. They

provide valid and reliable data to study drug use and to assess beneficial or adverse outcomes of drug use in clinical practice. The databases serve as a resource for conducting longitudinal and record-linkage studies with health surveys and other registries, as well as for other analytical pharmacoepidemiological research. They also offer a sound evidence base for national decision-making in the field of drug utilization.

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