

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

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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 dissemination

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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%

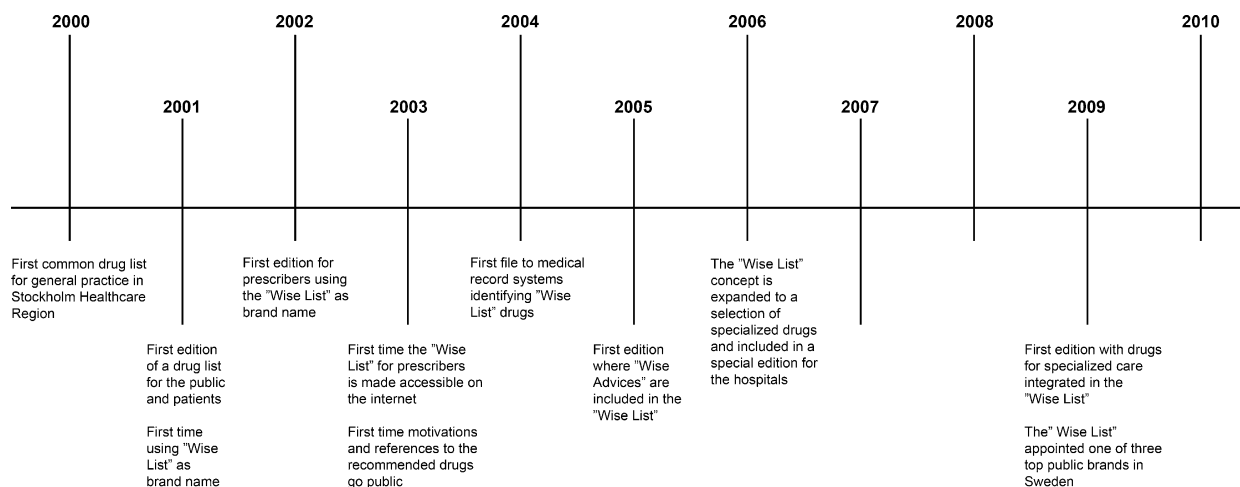


Fig. 1. Overview of the development of the ‘Wise List’ concept in Stockholm Healthcare Region. The first drug formulary in Stockholm was issued for hospital care in 1963. The regional Drug and Therapeutics Committee with expert groups was strengthened in 1996 and onwards by a dedicated annual budget.

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 [ $CV\% = 100 \times (\text{Standard deviation S.D.}/\text{mean})$ ] 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<sup>1</sup> 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 sertraline	Citalopram or sertraline of all SSRIs	(N06AB04 + N06AB06)/N06AB	Citalopram recommended in the 'Wise List' 2003–2009. Sertraline 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.

<sup>1</sup>'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.

<p><b>1. Independent drug expert organization with network</b></p> <ul style="list-style-type: none"> <li>• 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].</li> <li>• 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'.</li> <li>• 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.</li> </ul>	<p><b>2. One 'Wise List' for ambulatory and hospital care</b></p> <ul style="list-style-type: none"> <li>• <i>For basic care</i>, 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 out-patient hospital care. If necessary, second- or third-line choices.</li> <li>• <i>For specialized secondary care</i>, an additional 97 recommended drugs (2010), if necessary as first-, second- or third-line choices.</li> <li>• <i>Concise texts</i> explaining treatment strategies including preventive measures in important therapeutic areas.</li> <li>• <i>'Wise Advice'</i> 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].</li> </ul>
<p><b>3. Strict criteria for essential drug recommendations with motivations</b></p> <ul style="list-style-type: none"> <li>• <i>Medical suitability</i> based on:             <ol style="list-style-type: none"> <li>a. parameters (solid study end-points) of relevance to evaluate the effects of a drug such as mortality, morbidity and hospital care.</li> <li>b. expected patient value.</li> <li>c. reference to minimum one published pivotal study. Only one drug is recommended first line in a class of drugs.</li> </ol> </li> <li>• <i>Safety</i>: Normally, a drug should have been registered for two years. Safety and adverse effects data should be based on pivotal studies.</li> <li>• <i>Pharmaceutical suitability</i>: The recommended drug should be:             <ol style="list-style-type: none"> <li>a. available in a wide range of strengths and package sizes</li> <li>b. in packages easily handled and readable by patients and hospital staff</li> <li>c. delivered without interruption</li> </ol> </li> <li>• <i>Cost-effectiveness</i>: 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.</li> <li>• <i>Environmental and gender aspects</i> are considered if relevant. The acute risk to the aquatic environment is considered (insignificant, low, moderate or high) [40].</li> </ul>	<p><b>4. A comprehensive communication, branding and marketing strategy with a key role for experts</b></p> <ul style="list-style-type: none"> <li>• 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].</li> <li>• The owl was used as the branding symbol for independent, reliable and trustworthy information and for identification of different editions.</li> <li>• Access for healthcare staff to the official independent website of the DTC organization (<a href="http://www.janusinfo.se">www.janusinfo.se</a>) 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.</li> <li>• Since 2005, an annual 'Wise List' Forum for prescribers with the involved experts as keynote speakers explaining the background to the recommendations.</li> <li>• Launching of each new version of the 'Wise List' with press releases and providing drug information to medical journalists.</li> <li>• Collaboration with respected partners such as pharmacies distributing the 'Wise List' to the public and to patients.</li> <li>• Long-term training of members of the regional DTC system (approximately 400) in mass media contacts and discussion of risk of conflict of interests.</li> </ul>
<p><b>5. Targeted 'Wise List' editions for professional and public needs</b></p> <p><i>Three printed editions of the 'Wise List'. They are also available for healthcare staff at a producer-independent website <a href="http://www.janusinfo.se">www.janusinfo.se</a>, as digital files for EHR systems and accessible as a public version for laymen at <a href="http://www.vardguiden.se">www.vardguiden.se</a>.</i></p> <ol style="list-style-type: none"> <li>a. <i>The 'Wise List' with recommended drugs for prescribers</i> 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.</li> <li>b. <i>A special edition to help ordering procured drugs</i> in hospital wards across Stockholm healthcare institutions since 2003.</li> </ol>	<p><b>6. Feedback to prescribers and chief physicians of prescribing patterns</b></p> <ul style="list-style-type: none"> <li>• <i>Feedback on prescribing patterns</i> and adherence to the 'Wise List' recommendations to all primary healthcare centres and hospital clinics in Stockholm by user-friendly internet tools (<a href="http://www.janusinfo.se">www.janusinfo.se</a>) with standardized tables and graphs. Possibilities for bench-marking using drug utilization 90% profiles for follow-up [24,25].</li> </ul>



Table 2. (Continued)

<p>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.</p> <p>d. The 'Wise List' for prescribers and healthcare staff available electronically (<a href="http://www.janusinfo.se">www.janusinfo.se</a>) as a pdf-file and in html-format since 2001.</p> <p>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].</p>	<ul style="list-style-type: none"> <li>• '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.</li> <li>• Health authorities have linked quality bonuses to adherence rates to the 'Wise List' for general practice [26].</li> </ul>
<p><b>7. Medical leadership and operative resources</b></p> <ul style="list-style-type: none"> <li>• Open long-term leadership with vision, continuous learning, shared values and internal communication with involvement of medical opinion leaders in Stockholm.</li> <li>• Operative resources for managing secretary of the regional DTC, for clinical pharmacologists, pharmacoepidemiologists, administrative staff, IT experts, medical editors and communication specialists.</li> </ul>	

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.

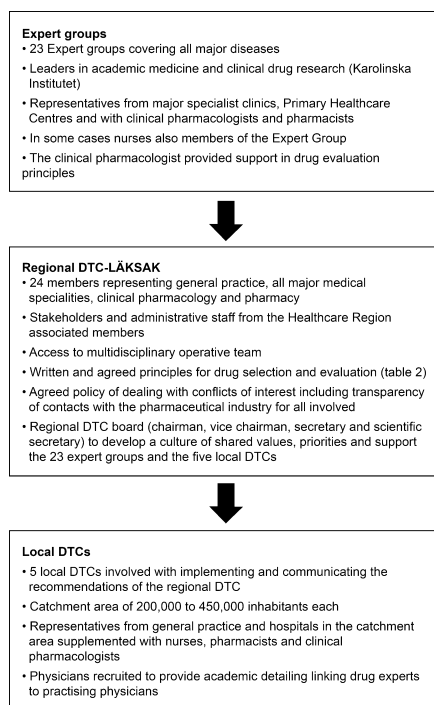


Fig. 2. Organization of the Drug and Therapeutics Committee (DTC) system in Stockholm Healthcare Region 1996–2009.

(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

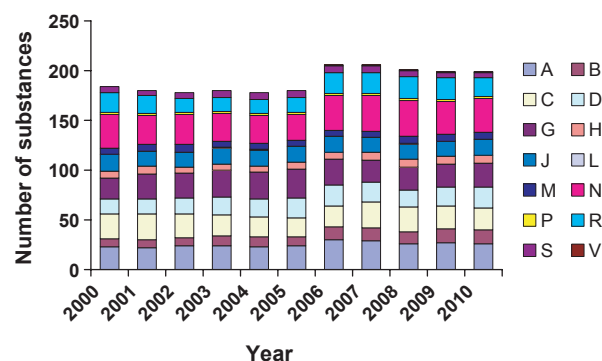


Fig. 3. The number of substances included in the 'Wise List' in Stockholm summarized by ATC groups 2000–2010. From 2009, 100 additional substances were added for specialist care (not shown). ATC group A = alimentary tract and metabolism, B = blood and blood forming organs, C = cardiovascular system, D = dermatology, G = genitourinary system and sex hormones, H = systemic hormonal preparations, J = anti-infectives for systemic use, L = anti-neoplastic 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

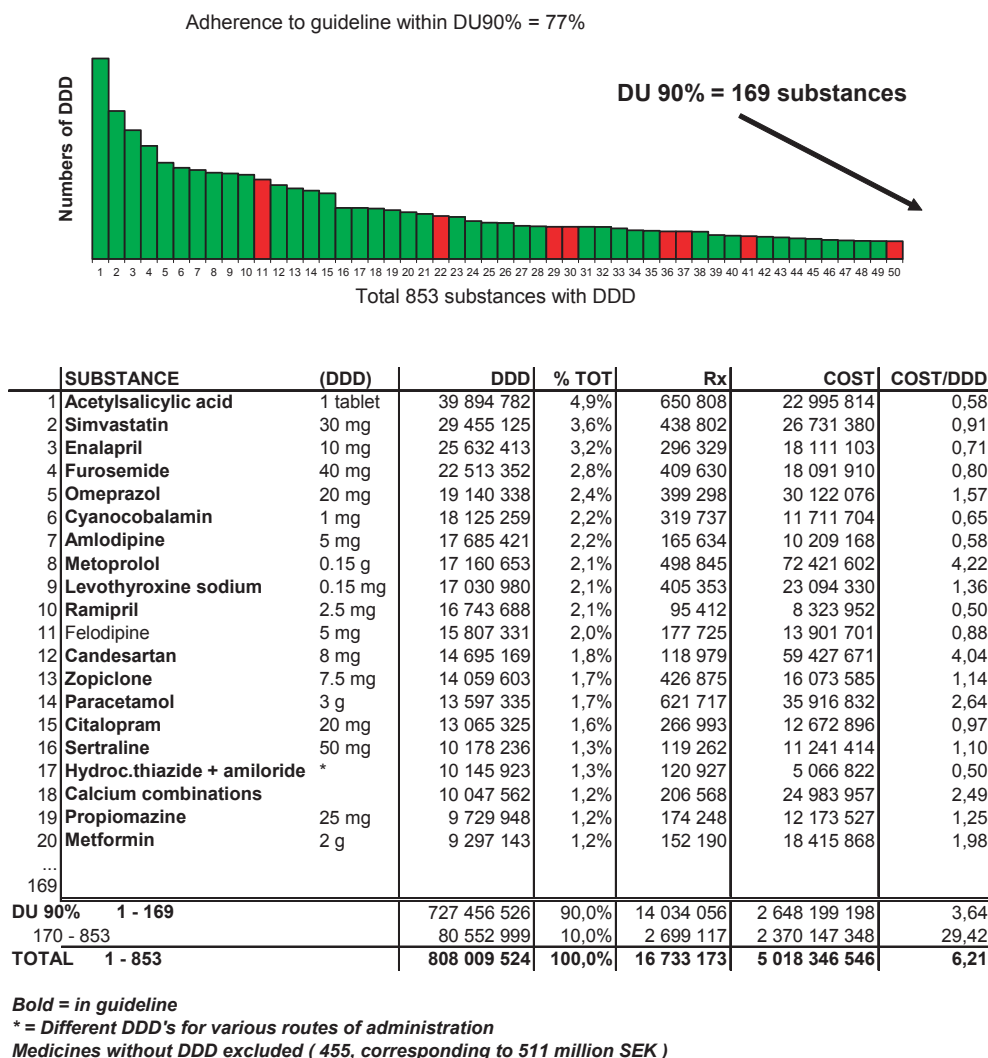


Fig. 4. DU 90% (number of substances accounting for 90% of the volume in DDDs) in Stockholm Healthcare Region in 2009. Red = non-recommended drugs; DDD = defined daily dose; DU = drug utilization.

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

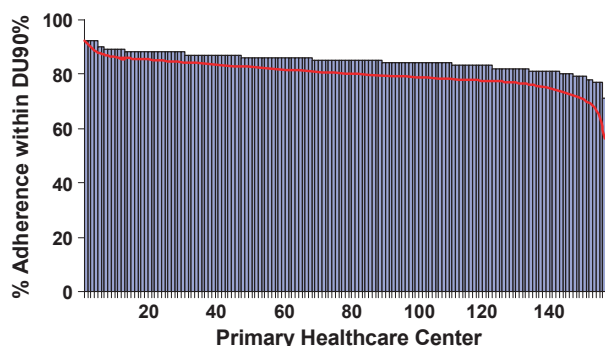


Fig. 5. Adherence to 'Wise List' recommendations for 156 primary healthcare centres for prescriptions dispensed in 2009. Red line equals the adherence range for the same practices in 2003. Observe that the order of the practices may differ between the 2 years.

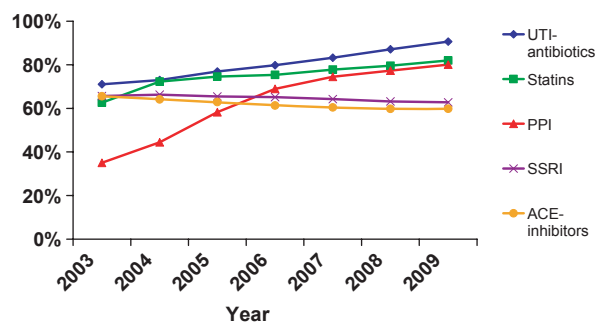


Fig. 6. Adherence to 'Wise Advice' recommendations in primary healthcare centres in Stockholm 2003–2009. Ratios of recommended drugs. Urinary tract infection (UTI) antibiotics = ratio of trimetoprim, nitrofurantoin and pivmecillinam of all UTI antibiotics in number of prescriptions, statins = ratio of 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 sertraline 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](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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