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High adherence to the "Wise List" treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines

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Key words:
Adherence, drug and therapeutics committee. essential medicines, prescribing, guidelines, health systems, rational use of medicines

Abstract

Objectives: To present the "Wise List" (a formulary of essential medicines for primary and specialised care in Stockholm Healthcare Region) and assess adherence to the recommendations over a 15-year period.

Design: Retrospective analysis of all prescription data in the Stockholm Healthcare Region between 2000 and 2015 in relation to the Wise List recommendations in the same time period.

Setting: All outpatient care in the Stockholm Healthcare Region.

Participants: All prescribers in the Stockholm Healthcare Region

Main outcome measures: The number of substances included in the Wise List, the adherence to recommendations by Anatomic Therapeutic Chemical (ATC) 1st level using Defined Daily Doses (DDDs) adjusted to the DDD for 2015, adherence to recommendations over time measured by dispensed prescriptions yearly between 2001 and 2015.

Results: The number of recommended core substances was stable (175 to 212). Overall adherence to the recommendations for core medicines for all prescribers increased from 77% to 84% (2001 to 2015). The adherence to recommendations in primary care for core medicines increased from 80% to 90% (2005 to 2015) with decreasing range in practice variation (32% to 13%). Hospital prescriber adherence to core medicine recommendations was stable but increased for the combination core and complementary medicines from 77% to 88% (2007 to 2015). Adherence varied between the four therapeutic areas studied.

Conclusions: High and increasing adherence to the Wise List recommendations was seen for all prescriber categories. The transparent process for developing recommendations involving key opinion leaders and prescribers using strict criteria for handling potential conflicts of interests, feedback to prescribers, continuous medical education and financial incentives are possible contributing factors. High quality evidence based recommendations to prescribers, such as the Wise List, disseminated through a multifaceted approach, will become increasingly important and should be developed further to include recommendations and introduction protocols for new expensive medicines.

Strengths of the study:

- The study data covers all prescriptions for the Stockholm Healthcare Region (population 2.2 million)
- The study includes all care providers in the Stockholm Healthcare Region

Limitations of the study:

- The study does not include a control group
- A causal relationship between the guidelines and the seemingly high adherence cannot be determined

Background

Inappropriate use of medicines increases the risk of therapeutic failure, adverse events, antimicrobial resistance, and is a waste of resources.[1-6] This recognition was a driving force behind the establishment of Drug and Therapeutics Committees (DTC)[7-9] and the Essential Medicines concept[10] introduced by the World Health Organization (WHO) in the 1970s. DTCs select medicines based on scientific evidence and influence physician prescribing to achieve rational use of medicines (RUM).[8 10 11] As part of their strategies, DTCs develop treatment guidelines and formularies but changing behaviour takes time and adherence to recommendations varies among prescribers and is surprisingly poor in most cases.[12 13] Consequently, new models need to be developed and evaluated to provide trust and adherence to recommendations of essential medicines throughout the healthcare system.

In 1996 a new Swedish law stipulated that each healthcare region should have at least one DTC to issue guidelines/recommendations and promote RUM.[8] This law has been essential as a platform and base for gaining trust in and assuring resources for DTCs in Stockholm. Six years after introduction of the law medicines budgets were devolved from the national to the regional level.[14] These changes prompted new ways to communicate independent prescribing recommendations such as the "Wise List" concept of essential medicines for common diseases introduced in Stockholm (Box 1).[15] The concept was designed based on the understanding that prescribing recommendations should be issued in one version for the whole region irrespective of whether patients were treated in primary or in specialised care in public or private facilities. Furthermore, a key consideration was that the recommendations have to be based on evidence and should be issued jointly by respected experts and clinicians with an aim to enhance quality of care.[8 11 15-18] The Wise List concept was developed knowing that multifaceted contextualized methods are needed to implement recommendations. Such strategies may include professional ownership, continuous medical education, active dissemination, "point-of-care" access to independent information about medicines as well as feedback of prescribing patterns to physicians using modern Information Communication Technology (ICT).[17 19] These concepts were all applied in what was introduced as the "Stockholm Model for Wise Use of Medicines" (Box 2). The Stockholm Healthcare Region had five local DTCs with their own formularies from 1980s to 1999, but a joint formulary for the entire Stockholm Healthcare Region was first issued by the regional coordinating DTC in 2000.[15] The Wise List concept has since then continuously improved to reach a mature design and work process.[15] In 2008 a minor financial incentive was introduced for primary health care centres (PHCs) achieving high adherence. Since its launch the Wise List concept has been further refined to address the increasing challenge to manage the introduction of new expensive medicines as well as to reduce the negative environmental impact of medicines.

Due to increasing costs for developing medicines, generic competition and the strained global healthcare budgets, pharmaceutical companies have changed their focus from blockbuster medicines to niched orphan drugs that have a potential to generate more revenue.[20] At the same time, there is growing evidence that the pharmaceutical industry influences prescriber practices,[21 22] but healthcare funders and medical professionals are increasingly implementing

measures to minimise negative consequences of this.[23] In the context of the changing medicines market the need for independent, evidence-based information for prescribers becomes increasingly important. To our knowledge there have been no scientific evaluations of health system wide interventions aiming to tackle this challenge. It is therefore important to evaluate the effects of such work done to further refine strategies for optimising use of medicines. The objective of this paper is to describe the content of the "Wise List" since its launch and to assess prescribers´ adherence to the recommendations over a 15-year period.

Box 1: The Wise List concept (www.janusinfo.se/In-English/The-Wise-List-2015-in-English/)[24]

- The Wise List ("Kloka Listan" in Swedish) was developed for the whole Stockholm Healthcare Region in 2000 (the name "Wise List" was launched in 2001)
- Includes around 200 recommended core medicines for the treatment of common diseases in primary and hospital care
- Includes 100 complementary medicines for common diseases in specialised care (since 2007)
- Covers 24 therapeutic areas
- Is a pocket-sized booklet and also available in a web-version
- Trusted medical colleagues and pharmacotherapeutic experts together with clinical pharmacologists, pharmacists and nurses agree on recommendations based on review of scientific evidence using clear transparent criteria, including cost-effectiveness evaluation
- Includes non-pharmacological advice for several therapeutic areas. For some therapeutic areas there are step-wise recommendations linked to disease severity and concomitant diseases
- This joint effort across disciplines and institutions including a policy for conflict of interest with annually renewed declarations has been a prerequisite in achieving trust in and adherence to recommendations
- The Wise List also includes around 10 "Wise piece of advice" (short, focussed messages) selected yearly to improve certain pharmacotherapeutic practices for which there are potential for improvement in quality of medicine use, e.g. "*Do not treat uncomplicated acute bronchitis with antibiotics*"
- The Wise List is communicated through a comprehensive communication, branding and marketing strategy with experts in a key role and integrated with a program for continuous medical education[15 18] (Box 2)

Definitions used in this paper

Core medicines = Essential medicines for common illnesses, recommended both for primary and specialised care.

Complementary medicines = Additional essential medicines to be recommended primarily for specialised care.

These definitions are based on the WHO model list of essential medicines.[25]

Box 2: The Stockholm model for wise use of medicines
The core part of the model is The Wise List (central part of figure). The outer circle represents the Key Strategies and the Organisational Unit, which are a pre-requisite for the collaborative work for a wise use of medicines. Since 1996 a new Swedish law stipulated that each healthcare region should have at least one Drug and Therapeutics Committee (DTC). This has provided mandate and organisational stability to issued recommendations by DTCs.[8] The jigsaw puzzle shows key elements necessary for producing the Wise List and implementing its guidelines in medical practice in the Stockholm Healthcare region.

Material and methods

Study area

This study was conducted in Stockholm Healthcare Region with approximately 2.2 million inhabitants served by more than 200 PHCs, seven emergency hospitals as well as geriatric clinics, psychiatric services, private specialists, nursing homes and other healthcare providers (e.g. occupational health, school health, rehabilitation). Swedish healthcare is financed through public taxation with limited patient co-payment for prescribed medicines and health care visits.[26]

Data sources

The number of different substances recommended as core or complementary medicines was collected from a database of the contents of the "Wise List" from 2000 to 2015. Data are presented by therapeutic area ATC 1st level and year.[27] The year 2000 was chosen as the initial year of observation as the first joint list of recommendations for the whole region was launched that year.

We also compiled all "Wise pieces of advice" (short messages aimed at improving pharmacotherapy (Box 1)), from each edition of the "Wise List".

Data on dispensed prescriptions were collected from the Swedish Prescribed Drug Register. In addition to the prescriptions, the register contains patient demographic data as well as information about the unit where the prescription was issued.[28]

Data analysis

Number of substances and the Wise pieces of advice
The number of substances included in the Wise List each year was calculated and presented according to their classification as core or complementary medicines.

The Wise pieces of advice were grouped within four areas, i.e.: (i) choice of medicine – i.e.

preferred choice of substance within a group of medicines used for a specific disease, (ii) overtreatment – i.e. avoid using medicines unnecessarily, (iii) under treatment – i.e. reminders to test for and treat conditions that are under diagnosed and/or under treated in the Stockholm region, or (iv) any other type of general advice related to RUM.

Adherence to recommendations

Data were analysed by ATC using Defined Daily Doses (DDDs) adjusted to correspond to the DDD for the year 2015.[27 29] The year 2002 was chosen as baseline since a national regulation for mandatory generic substitution resulting in substantial price reductions for generics was introduced in October that year, thus changing the pharmaceutical market substantially.[14 30] Separate analyses on the overall adherence were also made for each individual PHC in 2005, 2010 and 2015 to assess to what extent variation between practices had changed over time.

Data on prescriptions were analysed with respect to the overall adherence to the Wise List recommendations – both for all caregivers together and by category of caregiver. Caregiver categories were primary care, outpatient hospital care and others. The latter included psychiatry, geriatrics, rehabilitation, school health, occupational health and private practitioners of various specialities. Data on category of caregiver was available from 2003.

Change over time in adherence to recommendations

Adherence to recommendations was measured based on all dispensed prescriptions in Stockholm Healthcare Region each year between 2002 (when prescriber work place ID was added to the Swedish Prescribed Drug Register) and 2015. We also studied adherence to the guidelines in four different pharmacotherapeutic areas: (1) proton pump inhibitors (PPIs), (2) COX-inhibitors, (3) statins and (4) selective serotonin receptor uptake inhibitors (SSRI) or serotonin-noradrenaline reuptake inhibitors (SNRI). These medicines were selected as there were specific "Wise pieces of advice" relating to these groups of medicines during the study period. The Wise pieces of advice concerning these pharmacotherapeutic areas were warranted either because of safety concerns or because there was a need to counteract commercial pressure on physicians to prescribe new, less cost-effective treatments.[31 32]

Statistical analyses

Descriptive statistics were used including numbers and proportions expressed in percentages for different groups. The adherence to the Wise List was measured using the Drug Utilization 90% (DU 90%) method.[33] This method is recommended by the 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.[33] This method is routinely used in the Stockholm region to monitor the adherence to the Wise List recommendations as well as to provide feedback to prescribers forming the basis for local quality assessment and continuous medical education.[19 34]

Variation between practices was calculated using the extremal quotient (ratio of maximum to minimum value).

All data were analysed using the statistical package SAS version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel 2010.

Ethical considerations

This work was based on routinely available aggregate prescribing information from databases used for monitoring healthcare with no possibility to identify individual patients or prescribers. The analyses were part of ongoing quality improvement work at Stockholm Healthcare Region. All data analyses complied with Swedish Personal Data Act and no application for approval by the Regional Institutional Review Board was therefore needed.

Results

Number of substances included as recommendations in the Wise List over time

The number of recommended core medicines in the Wise List was relatively stable over the years, fluctuating between 175 and 212 substances. Complementary medicines were included in the Wise List from 2007 and have remained at around 100 substances since then (fig. 1).

Categories of Wise pieces of advice

The concept of Wise pieces of advice was introduced in 2003. There have been around 10 individual pieces of advice every year, comprising in total 55 unique messages. Some advice were only included in the list for one year, whereas 20 of the advice have been included for 3 years or more. Most advice (n=19) addressed choice of medicine within a class, the remaining concerned general advice (n=14), over treatment (n=12) or under treatment (n=10). The pharmacotherapeutic areas with the highest number of Wise pieces of advice were cardiovascular diseases (n=9), infectious diseases (n=8), general/geriatric (n=7), psychiatry and pain treatment (both n=7). Examples of advice are listed in table 1.

Overall adherence to the Wise List

The overall adherence to the Wise List recommendations for core medicines for all prescribers (primary and specialised care) in the region increased steadily from 77% in 2001 to 84% in 2015. The adherence rates differed between prescriber categories, but increased for all of them.

The adherence to recommendations in primary care for core medicines increased from 80% in 2005 to 90% in 2015 (fig 2) and showed a decreasing range in variation between practices over time from 32% (57% to 89%) in 2005, 26% (69% to 95%) in 2010 to 13% (84% to 97%) in 2015. The extremal quotient showed a significant reduction from 1.6 in 2005, 1.4 in 2010 to 1.3 in 2015.

For prescribers at hospitals the adherence to core medicine recommendations was stable from 2003 to 2015 (71% to 73%) but increased for the combination core plus complementary medicines between 2007 and 2015 from 77% to 88%. For all other prescriber categories the

adherence increased over the time periods both for core (65% to 72%) and for the combination core plus complementary medicines (71% to 83%) (fig 2).

Adherence to specific pharmacotherapeutic areas in the Wise List

Statins: Wise pieces of advice for statins have been included in the Wise List most years since its launch. The recommendation has been both to increase the use of statins in high-risk patients, as well as to choose simvastatin. Simvastatin had good documentation and low price due to patent expiry already in 2003 and was, before patent expiry of atorvastatin, considered more cost-effective than the other statins.[35] The volumes of statins increased throughout the period and simvastatin was the dominating substance. Prescribing of other statins remained at a low level but when the patent for atorvastatin expired and less expensive generics became available, the Wise List included this substance among the recommended ones (from 2013), which is also reflected in higher volumes of atorvastatin prescriptions dispensed (fig 3).

PPIs: There have been several Wise pieces of advice related to the use of PPIs in the Wise List over the study period. These have aimed to decrease unnecessary use of PPIs, as well as recommending omeprazole (and pantoprazole and lansoprazole in 2002-2003) instead of other less cost-effective PPIs. Despite this, volumes of PPIs more than doubled between 2002 and 2015 to the equivalent of 4.5% of the population constantly treated with PPIs with the vast majority of prescriptions for omeprazole (fig 4).

SSRI/SNRI: Due to strong marketing pressure from the industry to prescribe the S-enantiomer of citalopram (escitalopram),[36] a Wise piece of advice was introduced in 2011 recommending the prescriber to use either citalopram or sertraline for patients in need of pharmacological treatment of depression. Citalopram and sertraline dominated the treatment throughout the period, but prescriptions for all other antidepressants have also increased (fig 5).

COX-inhibitors: In 2012 the Wise List changed its recommendation from diclofenac to naproxen based on accumulated evidence indicating an increased risk for cardiovascular events in patients using diclofenac.[37] A rapid change in prescribing patterns was observed with a marked decrease in diclofenac prescribing with a corresponding increase for naproxen (figure 6).

Discussion

This study demonstrates high adherence to the Wise List recommendations in the Stockholm Healthcare Region. The overall adherence rate increased steadily over time, but with variations between therapeutic areas. Additionally the number of recommended core substances has been kept stable (around 200 substances) for the 15 years since the introduction of the Wise List despite the number of substances with market authorisation in Sweden increasing from 1235 to 1554 in the same time period. A limited number of recommendations is critical to make it feasible for prescribers to choose the best therapies for

their patients, keeping knowledge up to date among prescribers about the clinical pharmacology and pharmacotherapeutic characteristics of each recommended medicine.[8 9 15]

High adherence to the Wise List recommendations was seen across all therapeutic areas both in primary and hospital care. There could be several reasons for this. We consider that the transparent development process of recommendations involving key opinion leaders and prescribers within different therapeutic areas and strict criteria for handling potential conflicts of interests are essential for the high success rates to recommendations.[15 38] Financial incentives were introduced in Stockholm healthcare region in 2008[14] and have also been shown to contribute to the high adherence.[34] Originally, these incentives were introduced in primary care where PHCs received a small bonus linked to their adherence to the Wise List if the adherence was more than 80% and if they reflected on their prescribing patterns in a "quality report".[34] Since 2008 core Wise List medicines (about 200) are free of charge for all hospitals whereas they have to fund 50% of the cost of all other prescribed medicines. Previously the healthcare region covered all costs for prescriptions across hospitals and healthcare institutions centrally. Sound and trusted evidence based guidelines in combination with a communication strategy consisting of a branding and marketing strategy for both prescribers and the public, integrated with a program for continuous medical education, are major factors for successful adherence to DTC recommendations. Multifaceted interventions, academic detailing and reminders have all been found to be effective.[16 39 40] In Stockholm the communication strategy, including an active continuous medical education programme is an ongoing, continuously evolving important part of the Wise List strategy.[18] Prescriber ownership of the strategy has strengthened the Wise List work in developing and adopting state-of-the-art recommendations.[11-13 15 16]

Our findings from the specific therapeutic areas demonstrate that the prescribers switched substances within a therapeutic area and reduced under treatment in accordance with the Wise List and Wise pieces of advice. However, the list has not been successful in reducing overtreatment. The failure in reducing PPI use is in concordance with other European countries where prescribing of PPI has also increased several-fold.[31] In contrast, there was a marked switch in COX-inhibitor prescriptions from diclofenac to naproxen after a change of recommendations in the 2012 Wise List edition. An important explanation for the difference in adherence between these therapeutic areas may be the fact that using omeprazole has no clear medical disadvantage. The reason for switching from diclofenac to naproxen was accumulated evidence showing increased risk of cardiovascular disease with diclofenac,[37] which was clearly accepted by clinicians. Another factor that might have contributed is the difference in pressure from the pharmaceutical industry. Similar to the findings for COX-inhibitors the prescribers followed the recommendations for statins and SSRI/SNRI to a high degree and the prescribing of non-recommended escitalopram was low despite high marketing pressure similar to that of esomeprazole.[36] The adherence to the recommendation to use simvastatin instead of atorvastatin or rosuvastatin resulted in substantial economical savings for the Stockholm Health Care Region in contrast to other countries where rosuvastatin was the most prescribed statin.[41] To illustrate this, if just 10% of the simvastatin DDD had been replaced by rosuvastatin in 2008 this would have increased costs by 14.4 million SEK (1 SEK

~ 0.1 € in 2008). This is similar to a Canadian study of publically funded outpatient medicines where implementing harmonised prescribing recommendations could save pharmaceutical cost.[42] Regional differences in medicine costs within the Medicare system in the US have been shown to depend on the medicines selected for the formulary.[43]

Although we can relate prescribing data to the content of the Wise List and the Wise pieces of advice, without a control group we cannot know whether the seemingly high adherence is in fact due to a causal relationship between these factors. However, a major strength of the study is that we have data for a whole region, including all prescriptions from all care providers.

New niche medicines, soaring medicine costs and limited budgets pose new challenges to health care systems globally. Furthermore, the large number of new expensive biological medicines in pipeline has highlighted the importance of priority setting and development of methods to monitor the adherence to the recommendations,[44] and high quality evidence based recommendations to prescribers, such as the Wise List, become increasingly important. In our view, it is of critical importance that trusted recommendations and introduction protocols are developed for the use of new expensive medicines. A DTC/Wise List with focus on and with recommendations for specialised healthcare is necessary to ensure cost-effective and egalitarian use of medicines in the future. New multifaceted methods for safe and successful evidence-based introduction of medicines must be developed. This will be a major challenge for the future but could build on components in the Wise List concept that has led to high adherence to recommendations sustained for 15 years.

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Competing Interest Statement
All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work and no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. Jaran Eriksen is member of an expert panel of the Stockholm DTC since 2013. Kristina Ateva, Pia Bastholm-Rahmner, Maria Juhasz-Haverinen, Malena Jirlow, Marie-Louise Ovesjö, Björn Wettermark are employed by Stockholm Healthcare Region that finances the Drug and Therapeutics Committee (DTC) issuing the "Wise List" in Stockholm. Eva Andersén-Karlsson served as chair-woman of Stockholm DTC 2010-2016, Lars L Gustafsson as chairman 2000-2009 and Gerd Lärfars is chair woman since 2016 and Rickard Malmström deputy chairman since 2016.

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Data sharing

We have used routinely available prescribing data for a selected group of therapeutic classes. More analyses can be made for these medicines as well as for other medicines prescribed in Sweden.

Contributorship statement

JE contributed to the conception and design of the study, analysis and interpretation of the data, drafted and revised the manuscript. LLG contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. KA contributed to data acquisition, analysis and interpretation, and revised the manuscript. PBR contributed to data analysis and interpretation, and revised the manuscript. BW contributed to the conception and design of the study, data acquisition, analysis and interpretation of the data, and revised the manuscript. MJ contributed to data analysis and interpretation, and revised the manuscript. MJH contributed to the data acquisition, analysis and interpretation of the data, and revised the manuscript. RM contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. MLHO contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. GL contributed to data analysis and interpretation, and revised the manuscript. EAK contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. All authors critically revised and approved the final manuscript.

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Table 1. Some examples of the 55 individual Wise pieces of advice included in the Wise List since 2005. Categories: (i) choice of medicine – i.e. preferred choice of substance within a group of medicines used for a specific diagnosis, (ii) overtreatment – i.e. avoid using medicines unnecessarily, (iii) under treatment – i.e. reminders to look for and treat conditions that are often inadequately diagnosed and/or treated, or (iv) any other type of general advice related to drug therapy.

Example of advice	Category of advice
Use naproxen as first choice when prescribing cox-inhibitors	Choice of medicine
Choose simvastatin for prevention of cardiovascular disease in high-risk patients with normal to medium increased levels of cholesterol.	Choice of medicine
Do not use quinolones for treatment of uncomplicated Urinary Tract Infection (UTI) in women	Choice of medicine
Always give the patient an updated medication list.	General advice
Estimate and consider renal function in the selection and dosing of medicines.	General advice
Verify the diagnosis before treating according to the "heart failure treatment ladder" and seek to establish good heart rate control (below 70 beats/min in sinus rhythm).	General advice
Do not treat uncomplicated acute bronchitis with antibiotics.	Over treatment
Do not treat asymptomatic bacteriuria in the elderly and only culture from urine if the patient is experiencing urinary tract symptoms.	Over treatment
Treatment with proton pump inhibitors is not advisable in the case of stomach pain of unknown cause.	Over treatment
Improve antihypertensive treatment: determine a target blood pressure together with the patient, combine medicines more often and follow up.	Under treatment
Treat depression to complete remission.	Under treatment
Increase the use of medicines to prevent relapse in alcohol dependence and follow up treatment outcome.	Under treatment

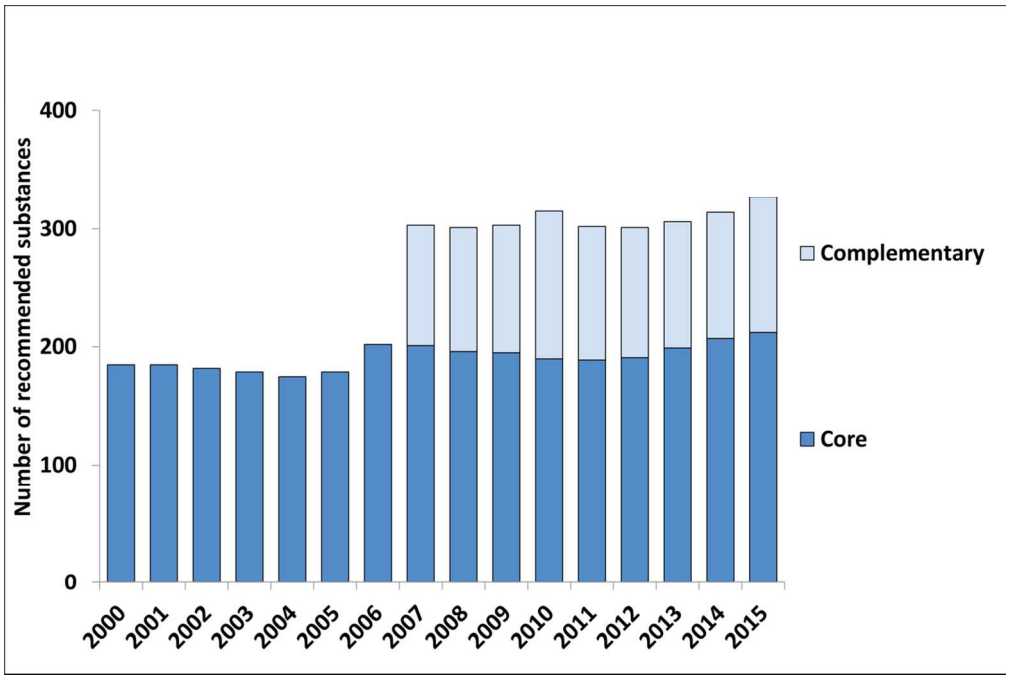


Figure 1. Number of substances included in the Wise List over time. Core medicines = Essential medicines for common illnesses, used both in primary and hospital care. Complementary medicines = Additional essential medicines to be used primarily for specialised care 25.

116x77mm (300 x 300 DPI)

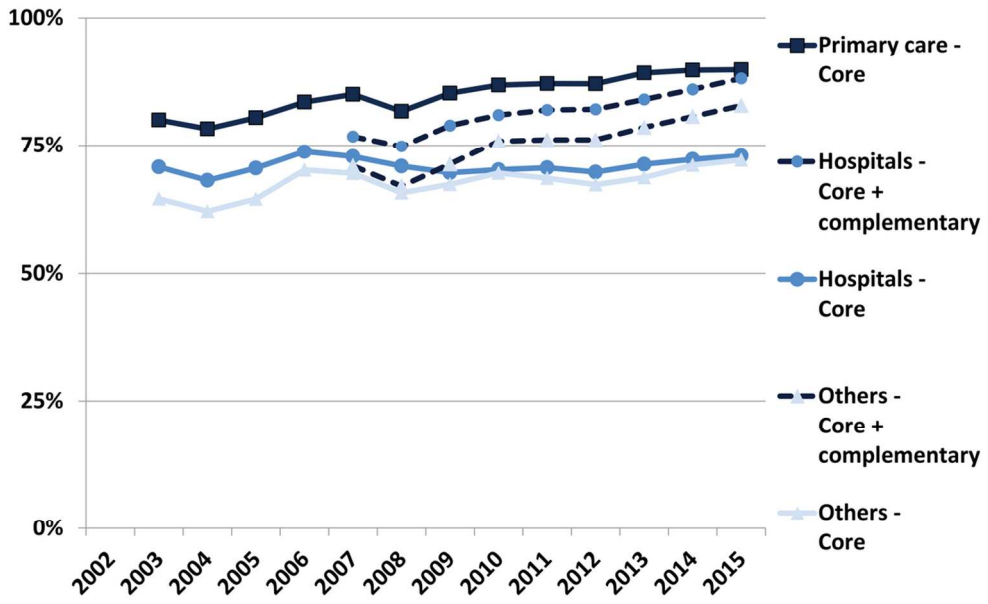


Figure 2. Adherence to recommendations (DU90%) for different prescriber categories between 2001 and 2015 (data on complementary medicines available only from 2007). "Others" includes psychiatry, geriatrics, rehabilitation, school health, occupational health and private practitioners in various specialties.

113x73mm (300 x 300 DPI)

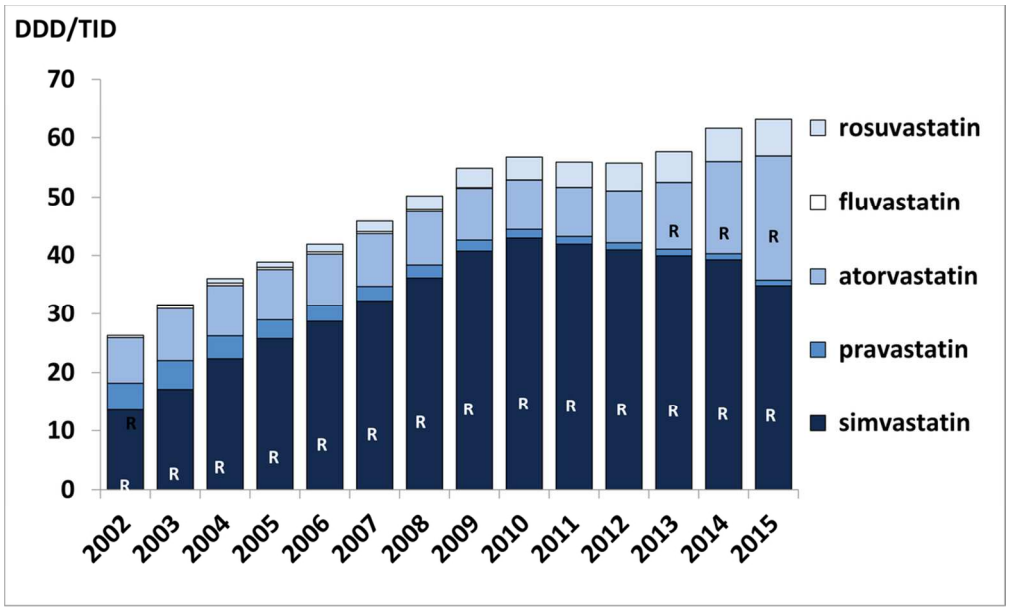


Figure 3. Prescribing patterns for statins in Stockholm Healthcare Region between 2002 and 2015. All prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was recommended in the Wise List that year. DDD/TID = Defined daily dose/1000 inhabitants per day

104x62mm (300 x 300 DPI)

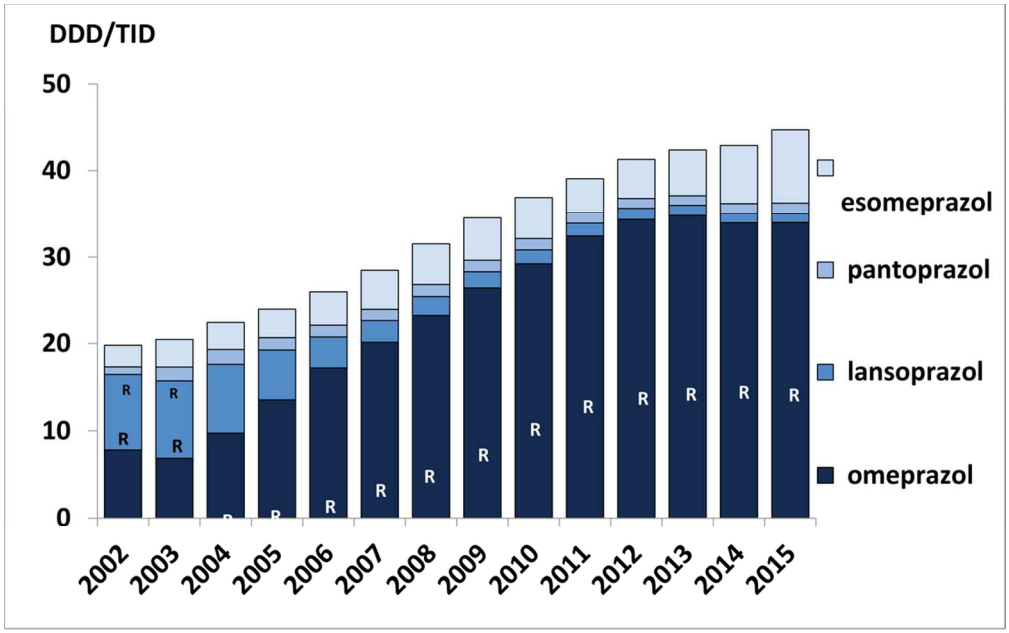


Figure 4. Prescribing pattern for proton pump inhibitors between 2002 and 2015. The letter "R" signifies that the drug was recommended in the Wise List that year. DDD/TID = Defined daily dose/1000 inhabitants per day

108x67mm (300 x 300 DPI)

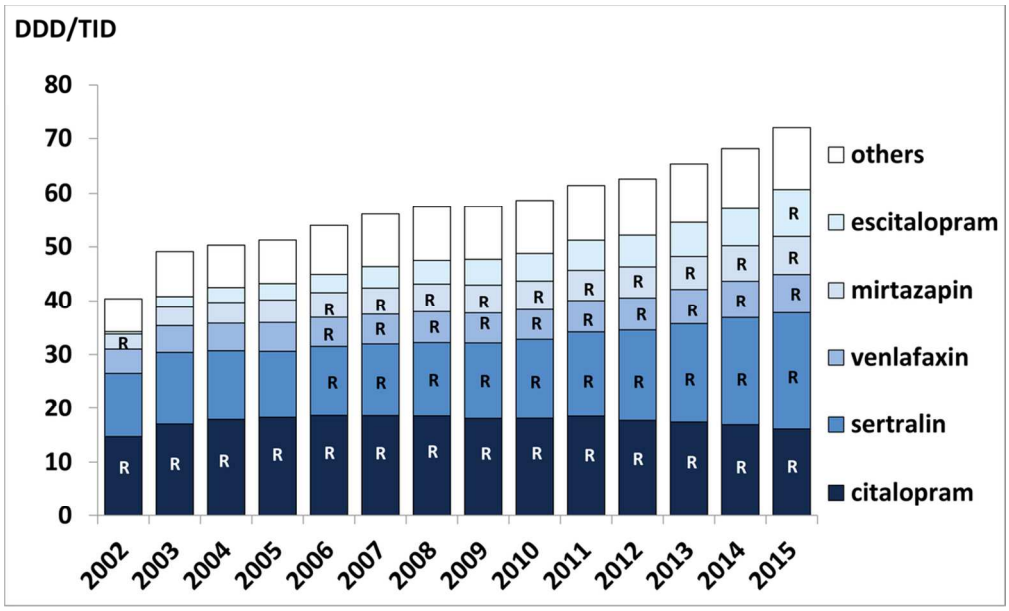


Figure 5. Prescribing pattern for SSRIs and SNRIs between 2002 and 2015. The letter "R" signifies that the drug was recommended in the Wise List that year. ("Others" includes duloxetine, fluoxetine, paroxetine). DDD/TID = Defined daily dose/1000 inhabitants per day.

104x62mm (300 x 300 DPI)

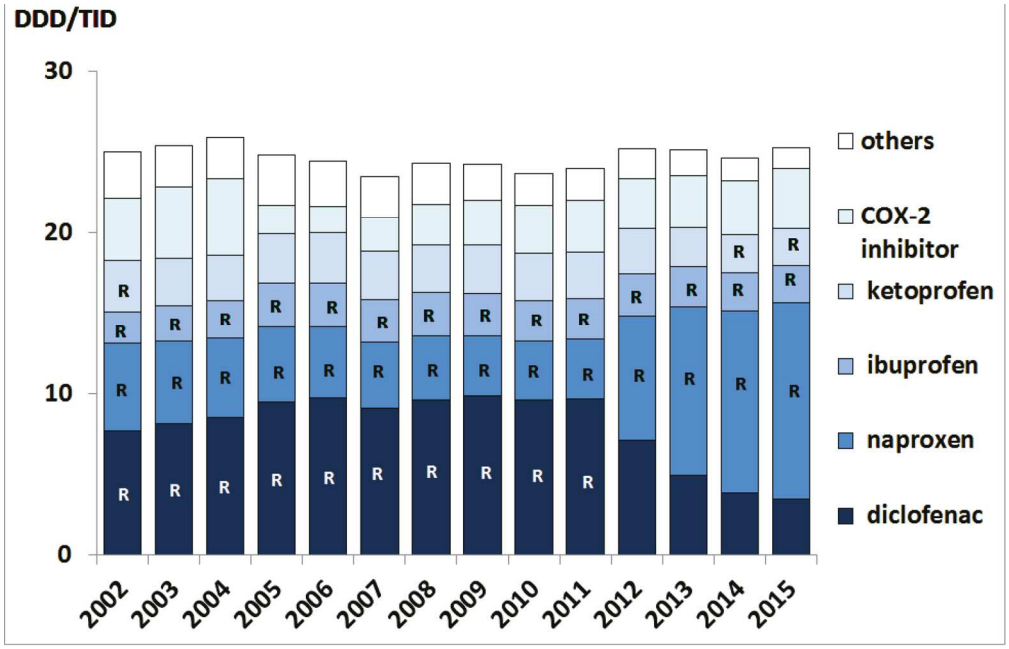
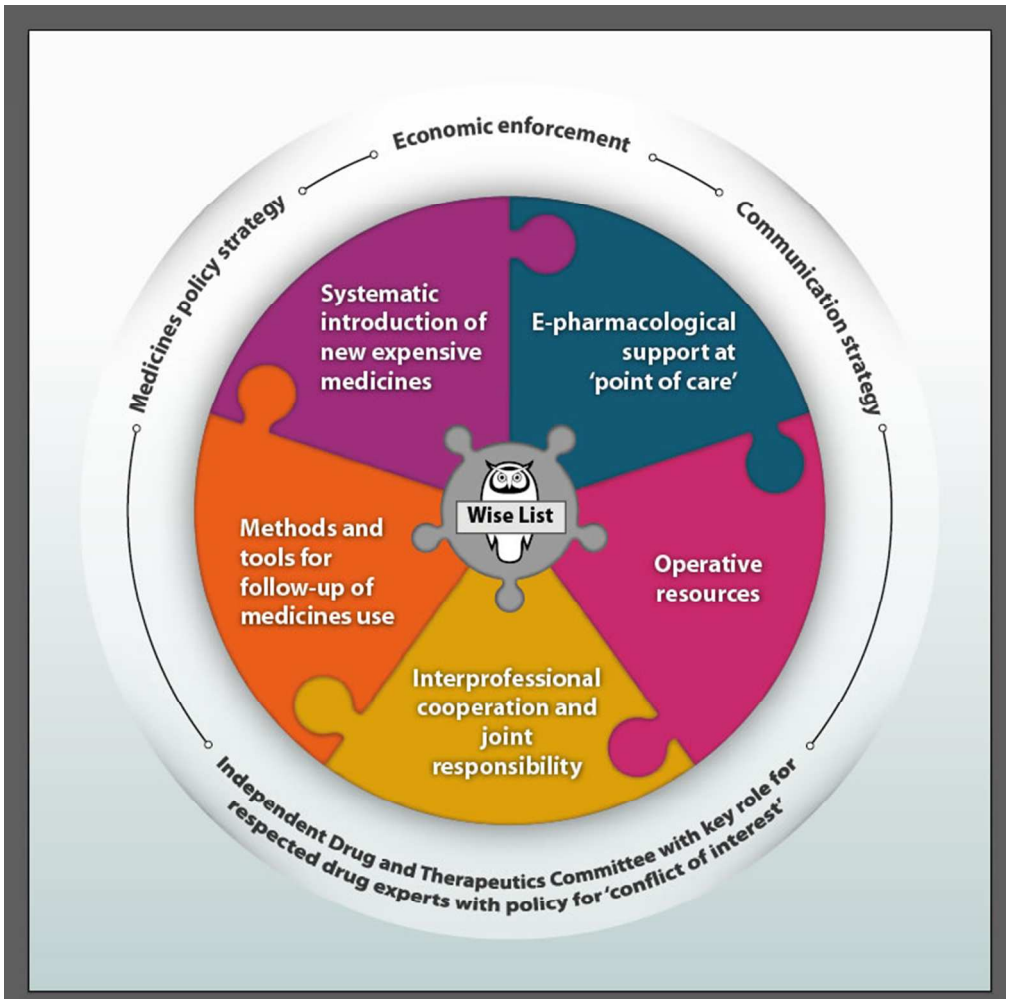


Figure 6. Prescribing pattern for COX-inhibitors between 2002 and 2015. The letter "R" signifies that the drug was recommended in the Wise List that year. ("Others" includes aceclofenac, dexibuprofen, phenylbutazone, indomethacin, ketorolac, lornoxicam, meloxicam, nabumetone, piroxicam, sulindac, tenoxicam). DDD/TID = Defined daily dose/1000 inhabitants per day

159x102mm (300 x 300 DPI)



287x285mm (72 x 72 DPI)

SQUIRE 2.0 Checklist

Title and Abstract		**Comment**
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)	Yes, included: *High adherence to the **"Wise List" treatment recommendations in Stockholm:** a 15-year retrospective review of a **multifaceted approach promoting rational use of medicines***
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	a. included b. Yes, all points included except background and local problem (as the abstract has been formatted according to BMJOpen guidelines).
Introduction	Why did you start?	
3. Problem Description	Nature and significance of the local problem	In the background, second paragraph, the problem and its significance in the Stockholm Healthcare Region is described.
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies	Described in first and second paragraphs in the background section.
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that	Described in the second paragraph of the background

	were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	
6. Specific aims	Purpose of the project and of this report	Stated in the last sentence of the background.
Methods	What did you do?	
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)	Explained under “study area” (first section of “material and methods”)
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work	Explained in “box 1” and “box 2”
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)	a. Explained under “data analysis”: three sections explaining each of the three approaches. b. Described in “statistical analysis”
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability	a. Described under “data sources”

	b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data	b. Described in the three subsections of "data analysis" c. N/A
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable	a. Described under "statistical analysis"
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	"Described in the section "ethical considerations"
Results	What did you find?	
13. Results	a. Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with	a. All results presented as change over time, e.g. all figures b. N/A c. Described where relevant, e.g. under subheading "adherence to specific pharmacotherapeutic areas…" for statins: page 10, line 7.

	the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data	d. Described for each of the therapeutic areas on page 10 e. Described for each of the therapeutic areas on page 10 f. N/A
Discussion	What does it mean?	
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project	a. First paragraph of discussion b. Described on page 12, second paragraph
15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs	Described in second and third paragraphs of the discussion.

16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations	Described in second paragraph page 12
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps	Described in the last paragraph of the discussion
Other information		
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	Described in competing interest statement

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High adherence to the "Wise List" treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines

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High adherence to the "Wise List" treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines

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Key words:
Adherence, drug and therapeutics committee. essential medicines, prescribing, guidelines, health systems, rational use of medicines

Abstract

Objectives: To present the "Wise List" (a formulary of essential medicines for primary and specialised care in Stockholm Healthcare Region) and assess adherence to the recommendations over a 15-year period.

Design: Retrospective analysis of all prescription data in the Stockholm Healthcare Region between 2000 and 2015 in relation to the Wise List recommendations in the same time period.

Setting: All outpatient care in the Stockholm Healthcare Region.

Participants: All prescribers in the Stockholm Healthcare Region

Main outcome measures: The number of core and complementary substances included in the Wise List, the adherence to recommendations by Anatomic Therapeutic Chemical (ATC) 1st level using Defined Daily Doses (DDDs) adjusted to the DDD for 2015, adherence to recommendations over time measured by dispensed prescriptions yearly between 2002 and 2015.

Results: The number of recommended core substances was stable (175 to 212). Overall adherence to the recommendations for core medicines for all prescribers increased from 77% to 84% (2001 to 2015). The adherence to recommendations in primary care for core medicines increased from 80% to 90% (2005 to 2015) with decreasing range in practice variation (32% to 13%). Hospital prescriber adherence to core medicine recommendations was stable but increased for the combination core and complementary medicines from 77% to 88% (2007 to 2015). Adherence varied between the four therapeutic areas studied.

Conclusions: High and increasing adherence to the Wise List recommendations was seen for all prescriber categories. The transparent process for developing recommendations involving respected experts and clinicians using strict criteria for handling potential conflicts of interests, feedback to prescribers, continuous medical education and financial incentives are possible contributing factors. High quality evidence based recommendations to prescribers, such as the Wise List, disseminated through a multifaceted approach, will become increasingly important and should be developed further to include recommendations and introduction protocols for new expensive medicines.

Strengths of the study:

- The study data covers all prescriptions for the Stockholm Healthcare Region (population 2.2 million)
- The study includes all care providers in the Stockholm Healthcare Region

Limitations of the study:

- The study does not include a control group
- A causal relationship between the guidelines and the seemingly high adherence cannot be determined

Background

Inappropriate use of medicines increases the risk of therapeutic failure, adverse events, antimicrobial resistance, and is a waste of resources.[1-6] This recognition was a driving force behind the establishment of Drug and Therapeutics Committees (DTC)[7-9] and the Essential Medicines concept[10] introduced by the World Health Organization (WHO) in the 1970s. DTCs select medicines based on scientific evidence and influence physician prescribing to achieve rational use of medicines (RUM).[8 10 11] As part of their strategies, DTCs develop treatment guidelines and formularies but changing behaviour takes time and adherence to recommendations varies among prescribers and is surprisingly poor in most cases.[12 13] Consequently, new models need to be developed and evaluated to provide trust and adherence to recommendations of essential medicines throughout the healthcare system.

In 1996 a new Swedish law stipulated that each healthcare region should have at least one DTC to issue guidelines/recommendations and promote RUM.[8] This law has been essential as a platform and base for gaining trust in and assuring resources for DTCs in Stockholm. Six years after introduction of the law medicines budgets were devolved from the national to the regional level.[14] These changes prompted new ways to communicate independent prescribing recommendations such as the "Wise List" concept of essential medicines for common diseases introduced in Stockholm (Box 1).[15] The concept was designed based on the understanding that prescribing recommendations should be issued in one version for the whole region irrespective of whether patients were treated in primary or in specialised care in public or private facilities. Furthermore, a key consideration was that the recommendations have to be based on evidence and should be issued jointly by respected experts and clinicians with an aim to enhance quality of care.[8 11 15-18] The Wise List concept was developed knowing that multifaceted contextualized methods are needed to implement recommendations. Such strategies may include professional ownership, continuous medical education, active dissemination, "point-of-care" access to independent information about medicines as well as feedback of prescribing patterns to physicians using modern Information Communication Technology (ICT).[17 19] These concepts were all applied in what was introduced as the "Stockholm Model for Wise Use of Medicines" (Box 2). The Stockholm Healthcare Region had five local DTCs with their own formularies from 1980s to 1999, but a joint formulary for the entire Stockholm Healthcare Region was first issued by the regional coordinating DTC in 2000.[15] The Wise List concept has since then continuously improved to reach a mature design and work process. In 2008 a minor financial incentive was introduced for primary health care centres (PHCs) meeting agreed prescribing targets and writing an annual quality report.[14] Since its launch the Wise List concept has been further refined to address the increasing challenge to manage the introduction of new expensive medicines as well as to reduce the negative environmental impact of medicines.[20]

Due to increasing costs for developing medicines, generic competition and the strained global healthcare budgets, pharmaceutical companies have changed their focus from blockbuster medicines to niched orphan drugs that have a potential to generate more revenue.[21] At the same time, there is growing evidence that the pharmaceutical industry influences prescriber

practices,[22 23] but healthcare funders and medical professionals are increasingly implementing measures to minimise negative consequences of this.[24] In the context of the changing medicines market the need for independent, evidence-based information for prescribers becomes increasingly important. To our knowledge there have been no scientific evaluations of health system wide interventions aiming to tackle this challenge. It is therefore important to evaluate the effects of such work done to further refine strategies for optimising use of medicines. The objective of this paper is to describe the content of the "Wise List" since its launch and to assess prescribers´ adherence to the recommendations over a 15-year period.

Box 1: The Wise List concept[20]

- The Wise List ("Kloka Listan" in Swedish) was developed for the whole Stockholm Healthcare Region in 2000 (the name "Wise List" was launched in 2001)
- Includes around 200 recommended core medicines for the treatment of common diseases in primary and hospital care
- Includes 100 complementary medicines for common diseases in specialised care (since 2007)
- Covers 24 therapeutic areas
- Is a pocket-sized booklet and also available in a web-version
- Respected experts and clinicians together with clinical pharmacologists, pharmacists and nurses agree on recommendations based on review of scientific evidence using transparent criteria, including cost-effectiveness evaluation
- Is a joint effort across disciplines and institutions and includes a policy for conflict of interest with annually renewed declarations. This policy contains rules and regulations for definitions of conflict of interest and how to handle them[25]
- Includes non-pharmacological advice for several therapeutic areas. For some therapeutic areas there are step-wise recommendations linked to disease severity and concomitant diseases.
- The Wise List also includes around 10 "Wise piece of advice" (short, focussed messages) selected yearly to improve certain pharmacotherapeutic practices for which there are potential for improvement in quality of medicine use, e.g. "*Do not treat uncomplicated acute bronchitis with antibiotics*"
- The Wise List is communicated through a comprehensive communication, branding and marketing strategy with experts in a key role and integrated with a program for continuous medical education[15 18] (Box 2)

Definitions used in this paper

Core medicines = Essential medicines for common illnesses, recommended both for primary and specialised care.

Complementary medicines = Additional essential medicines to be recommended primarily for specialised care.

These definitions are based on the WHO model list of essential medicines.[26]

Material and methods

Study area

This study was conducted in Stockholm Healthcare Region with approximately 2.2 million inhabitants served by more than 200 PHCs, seven emergency hospitals as well as geriatric clinics, psychiatric services, private specialists, nursing homes and other healthcare providers (e.g. occupational health, school health, rehabilitation). Swedish healthcare is financed through public taxation with limited patient co-payment for prescribed medicines and health care visits.[27]

Data sources

The number of different substances recommended as core or complementary medicines was collected from a database of the contents of the "Wise List" from 2000 to 2015. Data are presented by therapeutic area ATC 1st level and year.[28] The year 2000 was chosen as the initial year of observation as the first joint list of recommendations for the whole region was launched that year.

We also compiled all "Wise pieces of advice" (short messages aimed at improving pharmacotherapy (Box 1)), from each edition of the "Wise List".

Data on dispensed prescriptions were collected from the Swedish Prescribed Drug Register. In addition to the prescriptions, the register contains patient demographics (age, sex and area of residence of the patient) as well as information about the unit where the prescription was issued.[29]

Data analysis

Number of substances and the Wise pieces of advice

The number of substances included in the Wise List each year was calculated and presented according to their classification as core or complementary medicines.

The Wise pieces of advice were grouped within four areas, i.e.: (i) choice of medicine – i.e. preferred choice of substance within a group of medicines used for a specific disease, (ii) overtreatment – i.e. avoid using medicines unnecessarily, (iii) under treatment – i.e. reminders to test for and treat conditions that are under diagnosed and/or under treated in the Stockholm region, or (iv) any other type of general advice related to RUM.

Adherence to recommendations

Data were analysed by ATC using Defined Daily Doses (DDDs) adjusted to correspond to the DDD for the year 2015.[28 30] The year 2002 was chosen as baseline since a national regulation for mandatory generic substitution resulting in substantial price reductions for generics was introduced in October that year, thus changing the pharmaceutical market substantially.[14 31]

Separate analyses on the overall adherence were also made for each individual PHC in 2005, 2010 and 2015 to assess to what extent variation between practices had changed over time.

Data on prescriptions were analysed with respect to the overall adherence to the Wise List recommendations – both for all prescribers and by category (primary care, outpatient hospital care and others). The category others included psychiatry, geriatrics, rehabilitation, school health, occupational health and private practitioners of various specialities. Data on prescriber category of were available from 2003.

Change over time in adherence to recommendations

Adherence to recommendations was measured based on all dispensed prescriptions in Stockholm Healthcare Region each year between 2002 (when prescriber work place ID was added to the Swedish Prescribed Drug Register) and 2015. We also studied adherence to the guidelines in four different pharmacotherapeutic areas: (1) proton pump inhibitors (PPIs), (2) COX-inhibitors, (3) statins and (4) selective serotonin receptor uptake inhibitors (SSRI) or serotonin-noradrenaline reuptake inhibitors (SNRI). These medicines were selected as there were specific "Wise pieces of advice" relating to these groups of medicines during the study period. The Wise pieces of advice concerning these pharmacotherapeutic areas were warranted either because of safety concerns or because there was a need to counteract commercial pressure on physicians to prescribe new, less cost-effective treatments.[32 33]

Statistical analyses

Descriptive statistics were used including numbers and proportions expressed in percentages for different groups. The adherence to the Wise List was measured using the Drug Utilization 90% (DU 90%) method.[34] This method is recommended by the 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.[34] Note that the calculated adherence rate is not linked to data on diagnosis of the patient, but shows the amount of the substances prescribed for each specific ATC group of substances on the Wise List. E.g. for ATC A02BC (PPI), if a substance recommended on the Wise List is prescribed it is considered adherent to the Wise List recommendation. This method is routinely used in the Stockholm region to monitor the adherence to the Wise List recommendations as well as to provide feedback to prescribers forming the basis for local quality assessment and continuous medical education.[19 35]

Variation in adherence rates between practices was calculated using the extremal quotient (ratio of maximum to minimum value).

All data were analysed using the statistical package SAS version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel 2010.

Ethical considerations

This work was based on routinely available aggregate prescribing information from databases used for monitoring healthcare with no possibility to identify individual patients or prescribers. The analyses were part of ongoing quality improvement work at Stockholm Healthcare Region. All data analyses complied with Swedish Personal Data Act and no application for approval by the Regional Institutional Review Board was therefore needed.

Results

Number of substances included as recommendations in the Wise List over time

The number of recommended core medicines in the Wise List was relatively stable over the years, fluctuating between 175 and 212 substances. Complementary medicines were included in the Wise List from 2007 and have remained at around 100 substances since then (fig. 1).

Categories of Wise pieces of advice

The concept of Wise pieces of advice was introduced in 2003. There have been around 10 individual pieces of advice every year, comprising in total 55 unique messages. Some advice were only included in the list for one year, whereas 20 of the advice have been included for 3 years or more. Most advice (n=19) addressed choice of medicine within a class, the remaining concerned general advice (n=14), over treatment (n=12) or under treatment (n=10). The pharmacotherapeutic areas with the highest number of Wise pieces of advice were cardiovascular diseases (n=9), infectious diseases (n=8), general/geriatric (n=7), psychiatry and pain treatment (both n=7). Examples of advice are listed in table 1.

Overall adherence to the Wise List

The overall adherence to the Wise List recommendations for core medicines for all prescribers (primary and specialised care) in the region increased steadily from 77% in 2001 to 84% in 2015. The adherence rates differed between prescriber categories, but increased for all of them.

The adherence to recommendations in primary care for core medicines increased from 80% in 2005 to 90% in 2015 (fig 2) and showed a decreasing range in variation between practices over time from 32% (57% to 89%) in 2005, 26% (69% to 95%) in 2010 to 13% (84% to 97%) in 2015. The extremal quotient showed a significant reduction from 1.6 in 2005, 1.4 in 2010 to 1.3 in 2015.

For prescribers at hospitals the adherence to core medicine recommendations was stable from 2003 to 2015 (71% to 73%) but increased for the combination core plus complementary medicines between 2007 and 2015 from 77% to 88%. For all other prescriber categories the adherence increased over the time periods both for core (65% to 72%) and for the combination core plus complementary medicines (71% to 83%) (fig 2).

Adherence to specific pharmacotherapeutic areas in the Wise List

Statins: Wise pieces of advice for statins have been included in the Wise List most years since its launch. The recommendation has been both to increase the use of statins in high-risk

patients, as well as to choose simvastatin. Simvastatin had good documentation and low price due to patent expiry already in 2003 and was, before patent expiry of atorvastatin, considered more cost-effective than the other statins.[36] The volumes of statins increased throughout the period and simvastatin was the dominating substance. Prescribing of other statins remained at a low level but when the patent for atorvastatin expired and less expensive generics became available, the Wise List included this substance among the recommended ones (from 2013), which is also reflected in higher volumes of atorvastatin prescriptions dispensed (fig 3).

PPIs: There have been several Wise pieces of advice related to the use of PPIs in the Wise List over the study period. These have aimed to decrease unnecessary use of PPIs, as well as recommending omeprazole (and pantoprazole and lansoprazole in 2002-2003) instead of other less cost-effective PPIs. Despite this, volumes of PPIs more than doubled between 2002 and 2015 to the equivalent of 4.5% of the population constantly treated with PPIs with the vast majority of prescriptions for omeprazole (fig 4).

SSRI/SNRI: Due to strong marketing pressure from the industry to prescribe the S-enantiomer of citalopram (escitalopram),[37] a Wise piece of advice was introduced in 2011 recommending the prescriber to use either citalopram or sertraline for patients in need of pharmacological treatment of depression. Citalopram and sertraline dominated the treatment throughout the period, but prescriptions for all other antidepressants have also increased (fig 5).

COX-inhibitors: In 2012 the Wise List changed its recommendation from diclofenac to naproxen based on accumulated evidence indicating an increased risk for cardiovascular events in patients using diclofenac.[38] A rapid change in prescribing patterns was observed with a marked decrease in diclofenac prescribing with a corresponding increase for naproxen (figure 6).

Discussion

This study demonstrates high adherence to the Wise List recommendations in the Stockholm Healthcare Region. The overall adherence rate increased steadily over time, but with variations between therapeutic areas. Additionally the number of recommended core substances has been kept stable (around 200 substances) for the 15 years since the introduction of the Wise List despite the number of substances with market authorisation in Sweden increasing from 1235 to 1554 in the same time period.[39] A limited number of recommendations is critical to make it feasible for prescribers to choose the best therapies for their patients, keeping knowledge up to date among prescribers about the clinical pharmacology and pharmacotherapeutic characteristics of each recommended medicine.[8 9 15]

High adherence to the Wise List recommendations was seen across all therapeutic areas both in primary and hospital care. There could be several reasons for this. We consider that the transparent development process of recommendations involving respected experts and clinicians within different therapeutic areas and strict criteria for handling potential conflicts

of interests are essential for the high success rates to recommendations.[15 40] Financial incentives were introduced in Stockholm healthcare region in 2008[14] and have also been shown to contribute to the high adherence.[35] Originally, these incentives were introduced in primary care where PHCs received a small bonus linked to their adherence to the Wise List if the adherence was more than 80% and if they reflected on their prescribing patterns in a "quality report".[35] A higher target has not been set, as complete adherence is not considered suitable. This is because the Wise List does not include all possible treatment strategies for e.g. complicated cases, patients with allergies to medicines, or cases with potential drug-drug interactions. Physicians should have the possibility of using their clinical judgment and prescribe a substance not included on the Wise List if this is better for the patients. Therefore, complete adherence is neither wanted nor aimed for. Since 2008 core Wise List medicines (about 200) are free of charge for all hospitals, whereas they have to fund 50% of the cost of all other prescribed medicines. Previously the healthcare region covered all costs for prescriptions across hospitals and healthcare institutions centrally. Sound and trusted evidence based guidelines in combination with a communication strategy consisting of a branding and marketing strategy for both prescribers and the public, integrated with a program for continuous medical education, are major factors for successful adherence to DTC recommendations. In Stockholm this communication strategy and the continuous medical education programme is an ongoing, continuously evolving important part of the Wise List strategy.[18] The branding and marketing strategy is based on principles of social marketing. Core values of the brand Wise List have been defined as a shortlist of the best medicines, set up by respected experts and clinicians, for the best treatment of the most common diseases. This is in contrast to the marketing material provided by pharmaceutical industry. The Wise List has been promoted to prescribers and patients by traditional marketing methods such as ads in print, direct mail marketing like postcards, brochures, letters, and fliers and at oral presentations among stakeholders. The core value of the product has been consistent over the years and so also the key message in the marketing campaigns [14,15,18.] Prescriber ownership of the strategy has strengthened the Wise List work in developing and adopting state-of-the-art recommendations.[11-13 15 16] Multifaceted interventions, academic detailing and reminders have all been found to be effective.[16 41 42]

Our findings from the specific therapeutic areas demonstrate that the prescribers switched substances within a therapeutic area and reduced under treatment in accordance with the Wise List and Wise pieces of advice. However, the list has not been successful in reducing overtreatment. The failure in reducing PPI use is in concordance with other European countries where prescribing of PPI has also increased several-fold.[32] In contrast, there was a marked switch in COX-inhibitor prescriptions from diclofenac to naproxen after a change of recommendations in the 2012 Wise List edition. An important explanation for the difference in adherence between these therapeutic areas may be the fact that using omeprazole has no clear medical disadvantage. The reason for switching from diclofenac to naproxen was accumulated evidence showing increased risk of cardiovascular disease with diclofenac,[38] which was clearly accepted by clinicians. Similar to the findings for COX-inhibitors the prescribers followed the recommendations for statins and SSRI/SNRI to a high degree and the prescribing of non-recommended escitalopram was low despite high marketing pressure

similar to that of esomeprazole.[37] This marketing pressure from the pharmaceutical industry could have contributed to the failure in reducing PPI prescriptions, but despite increasing numbers of prescriptions, the vast majority remained omeprazole, as recommended by the Wise List. The adherence to the recommendation to use simvastatin instead of atorvastatin or rosuvastatin resulted in substantial economical savings for the Stockholm Health Care Region in contrast to other countries where rosuvastatin was the most prescribed statin.[43] To illustrate this, if just 10% of the simvastatin DDD had been replaced by rosuvastatin in 2008 this would have increased costs by 14.4 million SEK (1 SEK ~ 0.1 € in 2008). This is similar to a Canadian study of publically funded outpatient medicines where implementing harmonised prescribing recommendations could save pharmaceutical cost.[44] Regional differences in medicine costs within the Medicare system in the US have been shown to depend on the medicines selected for the formulary.[45]

Although we can relate prescribing data to the content of the Wise List and the Wise pieces of advice, without a control group we cannot know whether the seemingly high adherence is in fact due to a causal relationship between these factors. However, a major strength of the study is that we have data for a whole region, including all prescriptions from all care providers.

New niche medicines, soaring medicine costs and limited budgets pose new challenges to health care systems globally. Furthermore, the large number of new expensive biological medicines in pipeline has highlighted the importance of priority setting and development of methods to monitor the adherence to the recommendations,[46] and high quality evidence based recommendations to prescribers, such as the Wise List, become increasingly important. This is in line with the Lancet's Commission on Essential Medicines Policies' recommendations for achieving Sustainable Development Goal 3.8 for universal access to safe, effective, quality and affordable essential medicines and vaccines.[47] The Wise List already contains recommendations for some new expensive biological medicines, e.g. TNF inhibitors for use in inflammatory bowel disease and rheumatologic diseases. In our opinion, it is of critical importance that trusted recommendations and introduction protocols are developed for the use of new expensive medicines. A DTC/Wise List with focus on and with recommendations for specialised healthcare is necessary to ensure cost-effective and egalitarian use of medicines in the future. In fact, a recent study of ours demonstrated that the most important factor influencing use of anticoagulants, warfarin or a New Oral Anticoagulants, in Stockholm during the last five years was whether the substance was included as a Wise List recommendation.[48] New multifaceted methods for safe and successful evidence-based introduction of medicines must be developed. This will be a major challenge for the future but could build on components in the Wise List concept that has led to high adherence to recommendations sustained for 15 years.

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Competing Interest Statement

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work and no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. Jaran Eriksen is member of an expert panel of the Stockholm DTC since 2013. Kristina Ateva, Pia Bastholm-Rahmner, Maria Juhasz-Haverinen, Malena Jirlow, Marie-Louise Ovesjö, Björn Wettermark are employed by Stockholm Healthcare Region that finances the Drug and Therapeutics Committee (DTC) issuing the "Wise List" in Stockholm. Eva Andersén-Karlsson served as chair-woman of Stockholm DTC 2010-2016, Lars L Gustafsson as chairman 2000-2009 and Gerd Lärfars is chair woman since 2016 and Rickard Malmström deputy chairman since 2016.

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Data sharing

We have used routinely available prescribing data for a selected group of therapeutic classes. More analyses can be made for these medicines as well as for other medicines prescribed in Sweden.

Contributorship statement

JE contributed to the conception and design of the study, analysis and interpretation of the data, drafted and revised the manuscript. LLG contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. KA contributed to data acquisition, analysis and interpretation, and revised the manuscript. PBR contributed to data analysis and interpretation, and revised the manuscript. BW contributed to the conception and design of the study, data acquisition, analysis and interpretation of the data, and revised the manuscript. MJ contributed to data analysis and interpretation, and revised the manuscript. MJH contributed to the data acquisition, analysis and interpretation of the data, and revised the manuscript. RM contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. MLHO contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. GL contributed to data analysis and interpretation, and revised the manuscript. EAK

contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. All authors critically revised and approved the final manuscript.

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Table 1. Some examples of the 55 individual Wise pieces of advice included in the Wise List. Categories: (i) choice of medicine – i.e. preferred choice of substance within a group of medicines used for a specific diagnosis, (ii) overtreatment – i.e. avoid using medicines unnecessarily, (iii) under treatment – i.e. reminders to look for and treat conditions that are often inadequately diagnosed and/or treated, or (iv) any other type of general advice related to drug therapy.

Example of advice	Category of advice
Use naproxen as first choice when prescribing cox-inhibitors	Choice of medicine
Choose simvastatin for prevention of cardiovascular disease in high-risk patients with normal to medium increased levels of cholesterol.	Choice of medicine
Do not use quinolones for treatment of uncomplicated Urinary Tract Infection (UTI) in women	Choice of medicine
Always give the patient an updated medication list.	General advice
Estimate and consider renal function in the selection and dosing of medicines.	General advice
Verify the diagnosis before treating according to the "heart failure treatment ladder" and seek to establish good heart rate control (below 70 beats/min in sinus rhythm).	General advice
Do not treat uncomplicated acute bronchitis with antibiotics.	Over treatment
Do not treat asymptomatic bacteriuria in the elderly and only culture from urine if the patient is experiencing urinary tract symptoms.	Over treatment
Treatment with proton pump inhibitors is not advisable in the case of stomach pain of unknown cause.	Over treatment
Improve antihypertensive treatment: determine a target blood pressure together with the patient, combine medicines more often and follow up.	Under treatment
Treat depression to complete remission.	Under treatment
Increase the use of medicines to prevent relapse in alcohol dependence and follow up treatment outcome.	Under treatment

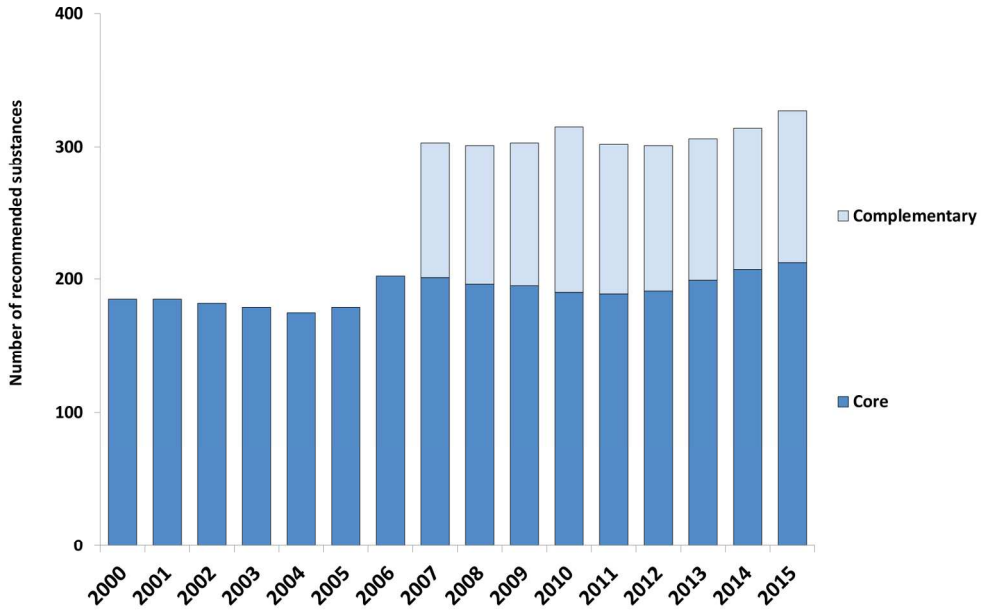


Figure 1. Number of substances included in the Wise List over time. Core medicines = Essential medicines for common illnesses, used both in primary and hospital care. Complementary medicines = Additional essential medicines to be used primarily for specialised care.26

164x108mm (300 x 300 DPI)

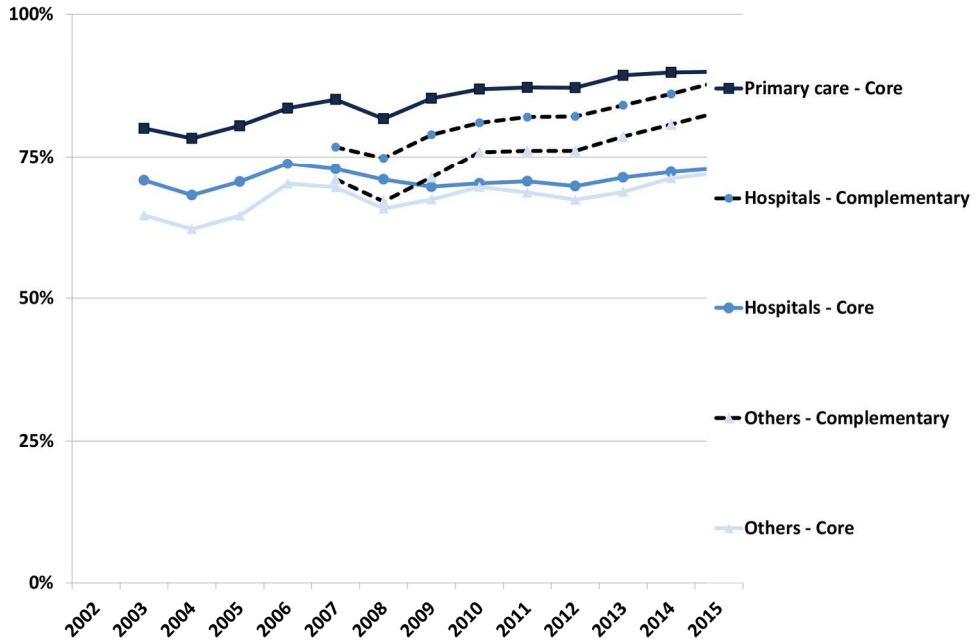


Figure 2. Adherence to recommendations (DU90%) in the Wise List for different prescriber categories in Stockholm Healthcare Region between 2001 and 2015. Data on complementary medicines available only from 2007. "Others" includes psychiatry, geriatrics, rehabilitation, school health, occupational health and private practitioners in various specialties.

166x119mm (300 x 300 DPI)

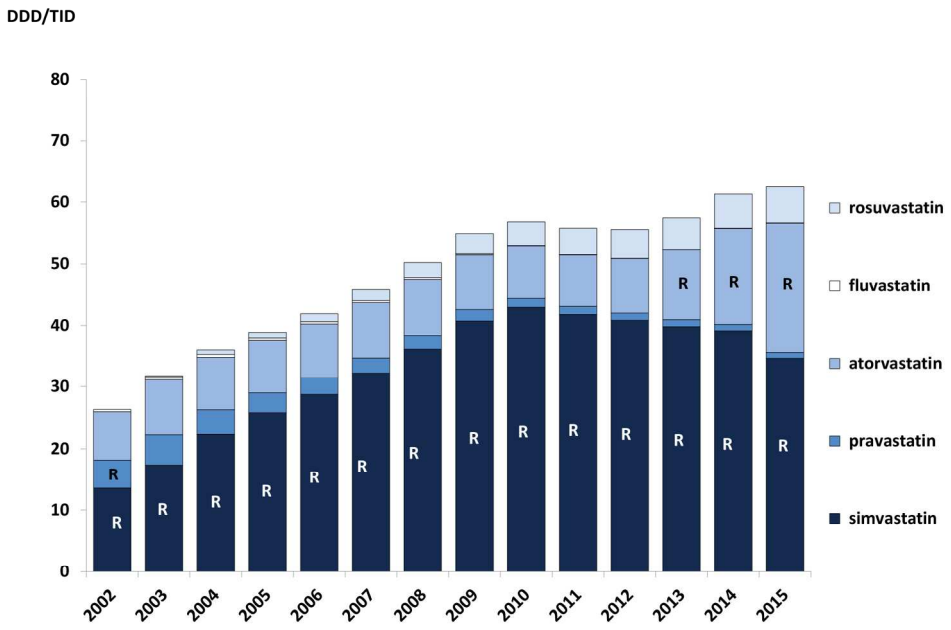


Figure 3. Prescribing patterns for statins in Stockholm Healthcare Region between 2002 and 2015 showing all statin prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. DDD/TID = Defined Daily Dose/1000 inhabitants per day.

172x112mm (300 x 300 DPI)

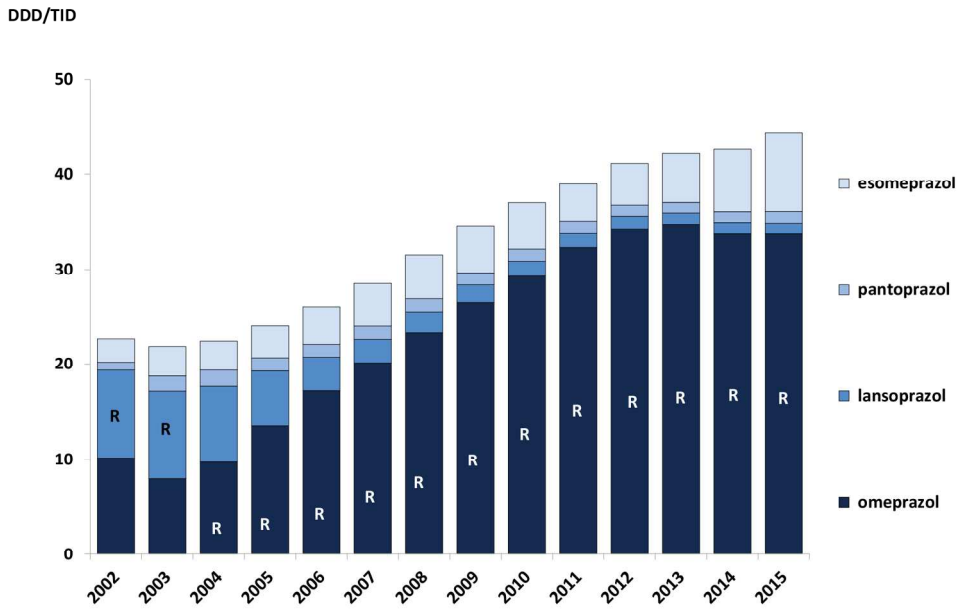


Figure 4. Prescribing pattern for proton pump inhibitors (PPI) in Stockholm Healthcare Region between 2002 and 2015 showing all PPI prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. DDD/TID = Defined Daily Dose/1000 inhabitants per day.

164x106mm (300 x 300 DPI)

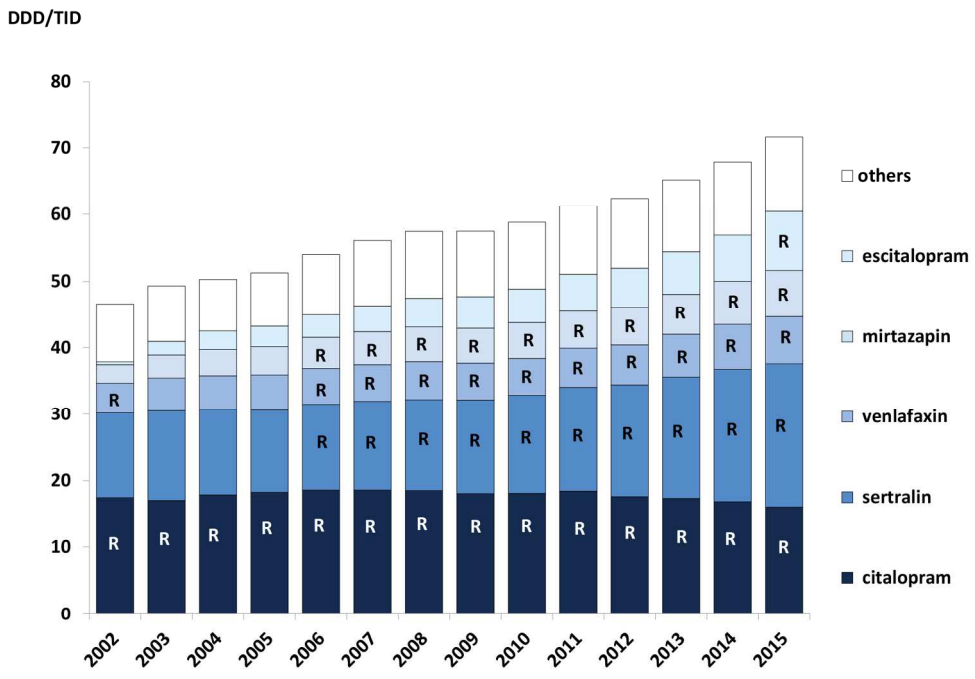


Figure 5. Prescribing pattern for SSRIs and SNRIs in Stockholm Healthcare Region between 2002 and 2015 showing all SSRI and SNRI prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. ("Others" includes duloxetine, fluoxetine, paroxetine). DDD/TID = Defined Daily Dose/1000 inhabitants per day.

167x118mm (300 x 300 DPI)

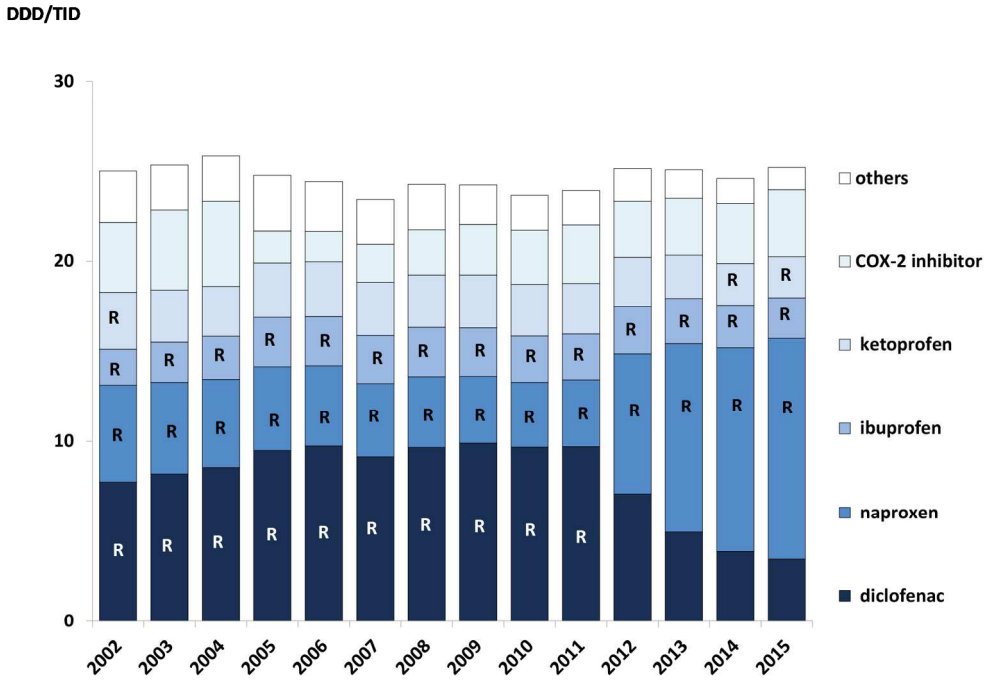
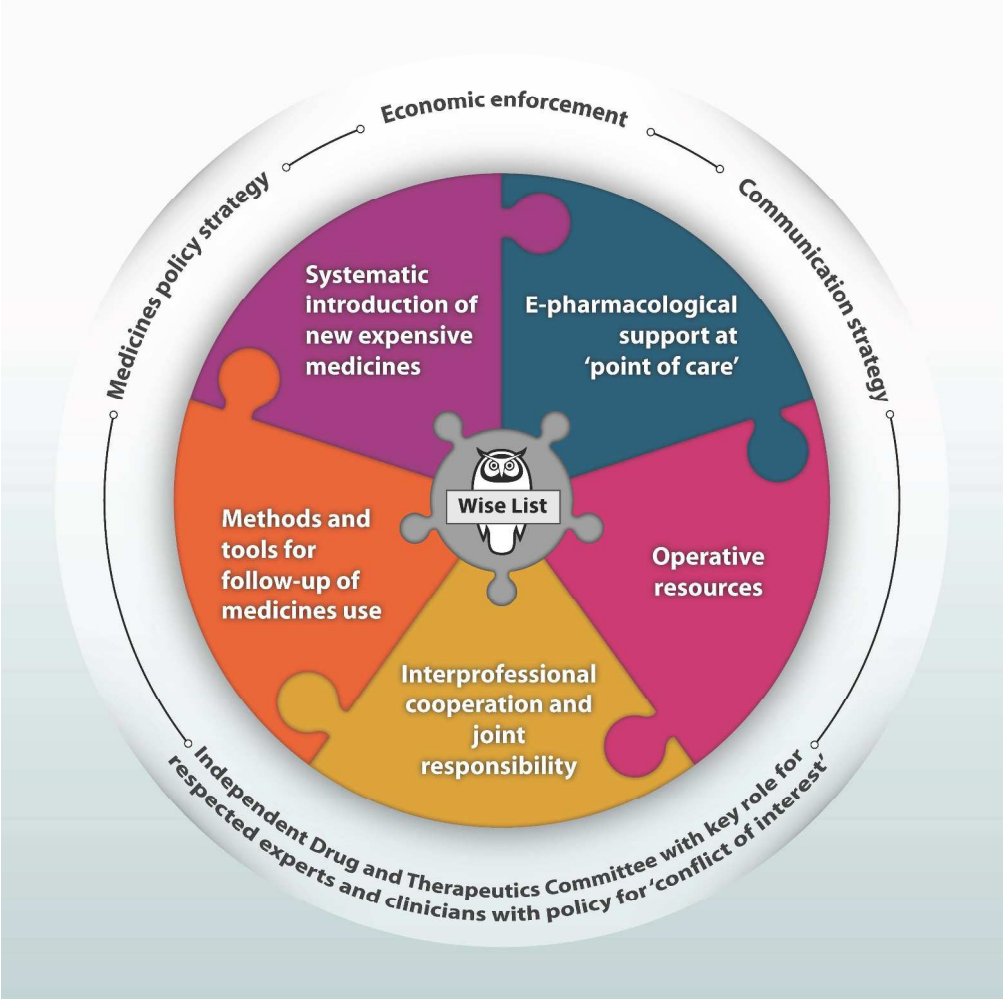


Figure 6. Prescribing pattern for COX-inhibitors in Stockholm Healthcare Region between 2002 and 2015 showing all COX-inhibitor prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. ("Others" includes aceclofenac, dexibuprofen, phenylbutazone, indomethacin, ketorolac, lornoxicam, meloxicam, nabumetone, piroxicam, sulindac, tenoxicam). DDD/TID = Defined Daily Dose/1000 inhabitants per day.

166x121mm (300 x 300 DPI)



Box 2: The Stockholm model for wise use of medicines

The core part of the model is The Wise List (central part of figure). The outer circle represents the Key Strategies and the Organisational Unit, which are a pre-requisite for the collaborative work for a rational use of medicines. Since 1996 a new Swedish law stipulated that each healthcare region should have at least one Drug and Therapeutics Committee (DTC). This has provided mandate and organisational stability to issued recommendations by DTCs.8 The jigsaw puzzle shows key elements necessary for producing the Wise List and implementing its guidelines in medical practice in the Stockholm Healthcare region. Operative resources include an annual budget for staff, continuous medical education of our 200 experts, infrastructure, printing, distribution and marketing of the Wise List.

552x552mm (150 x 150 DPI)

SQUIRE 2.0 Checklist

Title and Abstract		**Comment**
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)	Yes, included: *High adherence to the **"Wise List" treatment recommendations in Stockholm:** a 15-year retrospective review of a **multifaceted approach promoting rational use of medicines***
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	a. included b. Yes, all points included except background and local problem (as the abstract has been formatted according to BMJOpen guidelines).
Introduction	Why did you start?	
3. Problem Description	Nature and significance of the local problem	In the background, second paragraph, the problem and its significance in the Stockholm Healthcare Region is described.
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies	Described in first and second paragraphs in the background section.
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that	Described in the second paragraph of the background

	were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	
6. Specific aims	Purpose of the project and of this report	Stated in the last sentence of the background.
Methods	What did you do?	
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)	Explained under "study area" (first section of "material and methods")
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work	Explained in "box 1" and "box 2"
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)	a. Explained under "data analysis": three sections explaining each of the three approaches. b. Described in "statistical analysis"
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability	a. Described under "data sources"

	b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data	b. Described in the three subsections of "data analysis" c. N/A
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable	a. Described under "statistical analysis"
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	"Described in the section "ethical considerations"
Results	What did you find?	
13. Results	a. Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with	a. All results presented as change over time, e.g. all figures b. N/A c. Described where relevant, e.g. under subheading "adherence to specific pharmacotherapeutic areas…" for statins: page 10, line 7.

	the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data	d. Described for each of the therapeutic areas on page 10 e. Described for each of the therapeutic areas on page 10 f. N/A
Discussion	What does it mean?	
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project	a. First paragraph of discussion b. Described on page 12, second paragraph
15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs	Described in second and third paragraphs of the discussion.

16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations	Described in second paragraph page 12
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps	Described in the last paragraph of the discussion
Other information		
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	Described in competing interest statement

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High adherence to the "Wise List" treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines

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High adherence to the "Wise List" treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines

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Key words:
Adherence, drug and therapeutics committee. essential medicines, prescribing, guidelines, health systems, rational use of medicines

Abstract

Objectives: To present the "Wise List" (a formulary of essential medicines for primary and specialised care in Stockholm Healthcare Region) and assess adherence to the recommendations over a 15-year period.

Design: Retrospective analysis of all prescription data in the Stockholm Healthcare Region between 2000 and 2015 in relation to the Wise List recommendations in the same time period.

Setting: All outpatient care in the Stockholm Healthcare Region.

Participants: All prescribers in the Stockholm Healthcare Region

Main outcome measures: The number of core and complementary substances included in the Wise List, the adherence to recommendations by Anatomic Therapeutic Chemical (ATC) 1st level using Defined Daily Doses (DDDs) adjusted to the DDD for 2015, adherence to recommendations over time measured by dispensed prescriptions yearly between 2002 and 2015.

Results: The number of recommended core substances was stable (175 to 212). Overall adherence to the recommendations for core medicines for all prescribers increased from 75% to 84% (2000 to 2015). The adherence to recommendations in primary care for core medicines increased from 80% to 90% (2005 to 2015) with decreasing range in practice variation (32% to 13%). Hospital prescriber adherence to core medicine recommendations was stable but increased for the combination core and complementary medicines from 77% to 88% (2007 to 2015). Adherence varied between the four therapeutic areas studied.

Conclusions: High and increasing adherence to the Wise List recommendations was seen for all prescriber categories. The transparent process for developing recommendations involving respected experts and clinicians using strict criteria for handling potential conflicts of interests, feedback to prescribers, continuous medical education and financial incentives are possible contributing factors. High quality evidence based recommendations to prescribers, such as the Wise List, disseminated through a multifaceted approach, will become increasingly important and should be developed further to include recommendations and introduction protocols for new expensive medicines.

Strengths of the study:

- The study data covers all prescriptions for the Stockholm Healthcare Region (population 2.2 million)
- The study includes all care providers in the Stockholm Healthcare Region

Limitations of the study:

- The study does not include a control group
- A causal relationship between the guidelines and the seemingly high adherence cannot be determined

Background

Inappropriate use of medicines increases the risk of therapeutic failure, adverse events, antimicrobial resistance, and is a waste of resources.[1-6] This recognition was a driving force behind the establishment of Drug and Therapeutics Committees (DTC)[7-9] and the Essential Medicines concept[10] introduced by the World Health Organization (WHO) in the 1970s. DTCs select medicines based on scientific evidence and influence physician prescribing to achieve rational use of medicines (RUM).[8 10 11] As part of their strategies, DTCs develop treatment guidelines and formularies but changing behaviour takes time and adherence to recommendations varies among prescribers and is surprisingly poor in most cases.[12 13] Consequently, new models need to be developed and evaluated to provide trust and adherence to recommendations of essential medicines throughout the healthcare system.

In 1996 a new Swedish law stipulated that each healthcare region should have at least one DTC to issue guidelines/recommendations and promote RUM.[8] This law has been essential as a platform and base for gaining trust in and assuring resources for DTCs in Stockholm. Six years after introduction of the law medicines budgets were devolved from the national to the regional level.[14] These changes prompted new ways to communicate independent prescribing recommendations such as the "Wise List" concept of essential medicines for common diseases introduced in Stockholm (Box 1).[15] The concept was designed based on the understanding that prescribing recommendations should be issued in one version for the whole region irrespective of whether patients were treated in primary or in specialised care in public or private facilities. Furthermore, a key consideration was that the recommendations have to be based on evidence and should be issued jointly by respected experts and clinicians with an aim to enhance quality of care.[8 11 15-18] The Wise List concept was developed knowing that multifaceted contextualized methods are needed to implement recommendations. Such strategies may include professional ownership, continuous medical education, active dissemination, "point-of-care" access to independent information about medicines as well as feedback of prescribing patterns to physicians using modern Information Communication Technology (ICT).[17 19] These concepts were all applied in what was introduced as the "Stockholm Model for Wise Use of Medicines" (Box 2). The Stockholm Healthcare Region had five local DTCs with their own formularies from 1980s to 1999, but a joint formulary for the entire Stockholm Healthcare Region was first issued by the regional coordinating DTC in 2000.[15] The Wise List concept has since then continuously improved to reach a mature design and work process. In 2008 a minor financial incentive was introduced for primary health care centres (PHCs) meeting agreed prescribing targets and writing an annual quality report.[14] Since its launch the Wise List concept has been further refined to address the increasing challenge to manage the introduction of new expensive medicines as well as to reduce the negative environmental impact of medicines.[20]

Due to increasing costs for developing medicines, generic competition and the strained global healthcare budgets, pharmaceutical companies have changed their focus from blockbuster medicines to niched orphan drugs that have a potential to generate more revenue.[21] At the same time, there is growing evidence that the pharmaceutical industry influences prescriber

practices,[22 23] but healthcare funders and medical professionals are increasingly implementing measures to minimise negative consequences of this.[24] In the context of the changing medicines market the need for independent, evidence-based information for prescribers becomes increasingly important. To our knowledge there have been no scientific evaluations of health system wide interventions aiming to tackle this challenge. It is therefore important to evaluate the effects of such work done to further refine strategies for optimising use of medicines. The objective of this paper is to describe the content of the "Wise List" since its launch and to assess prescribers´ adherence to the recommendations over a 15-year period.

Box 1: The Wise List concept[20]

- The Wise List ("Kloka Listan" in Swedish) was developed for the whole Stockholm Healthcare Region in 2000 (the name "Wise List" was launched in 2001)
- Includes around 200 recommended core medicines for the treatment of common diseases in primary and hospital care
- Includes 100 complementary medicines for common diseases in specialised care (since 2007)
- Covers 24 therapeutic areas
- Is a pocket-sized booklet and also available in a web-version
- Respected experts and clinicians together with clinical pharmacologists, pharmacists and nurses agree on recommendations based on review of scientific evidence using transparent criteria, including cost-effectiveness evaluation
- Is a joint effort across disciplines and institutions and includes a policy for conflict of interest with annually renewed declarations. This policy contains rules and regulations for definitions of conflict of interest and how to handle them[25]
- Includes non-pharmacological advice for several therapeutic areas. For some therapeutic areas there are step-wise recommendations linked to disease severity and concomitant diseases.
- The Wise List also includes around 10 "Wise piece of advice" (short, focussed messages) selected yearly to improve certain pharmacotherapeutic practices for which there are potential for improvement in quality of medicine use, e.g. "*Do not treat uncomplicated acute bronchitis with antibiotics*"
- The Wise List is communicated through a comprehensive communication, branding and marketing strategy with experts in a key role and integrated with a program for continuous medical education[15 18] (Box 2)

Definitions used in this paper

Core medicines = Essential medicines for common illnesses, recommended both for primary and specialised care.

Complementary medicines = Additional essential medicines to be recommended primarily for specialised care.

These definitions are based on the WHO model list of essential medicines.[26]

Material and methods

Study area

This study was conducted in Stockholm Healthcare Region with approximately 2.2 million inhabitants served by more than 200 PHCs, seven emergency hospitals as well as geriatric clinics, psychiatric services, private specialists, nursing homes and other healthcare providers (e.g. occupational health, school health, rehabilitation). Swedish healthcare is financed through public taxation with limited patient co-payment for prescribed medicines and health care visits.[27]

Data sources

The number of different substances recommended as core or complementary medicines was collected from a database of the contents of the "Wise List" from 2000 to 2015. Data are presented by therapeutic area ATC 1st level and year.[28] The year 2000 was chosen as the initial year of observation as the first joint list of recommendations for the whole region was launched that year.

We also compiled all "Wise pieces of advice" (short messages aimed at improving pharmacotherapy (Box 1, Table 1)), from each edition of the "Wise List".

Data on dispensed prescriptions were collected from the Swedish Prescribed Drug Register. In addition to the prescriptions, the register contains patient demographics (age, sex and area of residence of the patient) as well as information about the unit where the prescription was issued.[29]

Data analysis

Number of substances and the Wise pieces of advice

The number of substances included in the Wise List each year was calculated and presented according to their classification as core or complementary medicines.

The Wise pieces of advice were grouped within four areas, i.e.: (i) choice of medicine – i.e. preferred choice of substance within a group of medicines used for a specific disease, (ii) overtreatment – i.e. avoid using medicines unnecessarily, (iii) under treatment – i.e. reminders to test for and treat conditions that are under diagnosed and/or under treated in the Stockholm region, or (iv) any other type of general advice related to RUM.

Adherence to recommendations

Data were analysed by ATC using Defined Daily Doses (DDDs) adjusted to correspond to the DDD for the year 2015.[28 30] The year 2002 was chosen as baseline since a national regulation for mandatory generic substitution resulting in substantial price reductions for generics was introduced in October that year, thus changing the pharmaceutical market substantially.[14 31]

Separate analyses on the overall adherence were also made for each individual PHC in 2005, 2010 and 2015 to assess to what extent variation between practices had changed over time.

Data on prescriptions were analysed with respect to the overall adherence to the Wise List recommendations – both for all prescribers and by category (primary care, outpatient hospital care and others). The category others included psychiatry, geriatrics, rehabilitation, school health, occupational health and private practitioners of various specialities. Data on prescriber category of were available from 2003.

Change over time in adherence to recommendations

Adherence to recommendations was measured based on all dispensed prescriptions in Stockholm Healthcare Region each year between 2000 (the year the first joint list of treatment recommendations in Stockholm was launched) and 2015. Adherence to guidelines in different pharmacotherapeutic areas were studied from 2002 (when prescriber work place ID was added to the Swedish Prescribed Drug Register, and a national regulation for mandatory generic substitution was introduced in Sweden) to 2015. We studied adherence to the guidelines in the following four different pharmacotherapeutic areas: (1) proton pump inhibitors (PPIs), (2) COX-inhibitors, (3) statins and (4) selective serotonin receptor uptake inhibitors (SSRI) or serotonin-noradrenaline reuptake inhibitors (SNRI). These medicines were selected as there were specific "Wise pieces of advice" relating to these groups of medicines during the study period. The Wise pieces of advice concerning these pharmacotherapeutic areas were warranted either because of safety concerns or because there was a need to counteract commercial pressure on physicians to prescribe new, less cost-effective treatments.[32 33]

Statistical analyses

Descriptive statistics were used including numbers and proportions expressed in percentages for different groups. The adherence to the Wise List was measured using the Drug Utilization 90% (DU 90%) method.[34] This method is recommended by the 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.[34] Note that the calculated adherence rate is not linked to data on diagnosis of the patient, but shows the amount of the substances prescribed for each specific ATC group of substances on the Wise List. E.g. for ATC A02BC (PPI), if a substance recommended on the Wise List is prescribed it is considered adherent to the Wise List recommendation. This method is routinely used in the Stockholm region to monitor the adherence to the Wise List recommendations as well as to provide feedback to prescribers forming the basis for local quality assessment and continuous medical education.[19 35]

Variation in adherence rates between practices was calculated using the extremal quotient (ratio of maximum to minimum value).

All data were analysed using the statistical package SAS version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel 2010.

Ethical considerations

This work was based on routinely available aggregate prescribing information from databases used for monitoring healthcare with no possibility to identify individual patients or prescribers. The analyses were part of ongoing quality improvement work at Stockholm Healthcare Region. All data analyses complied with Swedish Personal Data Act and no application for approval by the Regional Institutional Review Board was therefore needed.

Results

Number of substances included as recommendations in the Wise List over time

The number of recommended core medicines in the Wise List was relatively stable over the years, fluctuating between 175 and 212 substances. Complementary medicines were included in the Wise List from 2007 and have remained at around 100 substances since then (fig. 1).

Categories of Wise pieces of advice

The concept of Wise pieces of advice was introduced in 2003. There have been around 10 individual pieces of advice every year, comprising in total 55 unique messages. Some advice were only included in the list for one year, whereas 20 of the advice have been included for 3 years or more. Most advice (n=19) addressed choice of medicine within a class, the remaining concerned general advice (n=14), over treatment (n=12) or under treatment (n=10). The pharmacotherapeutic areas with the highest number of Wise pieces of advice were cardiovascular diseases (n=9), infectious diseases (n=8), general/geriatric (n=7), psychiatry and pain treatment (both n=7). Examples of advice are listed in table 1.

Overall adherence to the Wise List

The overall adherence to the Wise List recommendations for core medicines for all prescribers (primary and specialised care) in the region increased steadily from 75% in 2000 to 84% in 2015. The adherence rates differed between prescriber categories, but increased for all of them.

The adherence to recommendations in primary care for core medicines increased from 80% in 2005 to 90% in 2015 (fig 2) and showed a decreasing range in variation between practices over time from 32% (57% to 89%) in 2005, 26% (69% to 95%) in 2010 to 13% (84% to 97%) in 2015. The extremal quotient showed a significant reduction from 1.6 in 2005, 1.4 in 2010 to 1.3 in 2015.

For prescribers at hospitals the adherence to core medicine recommendations was stable from 2003 to 2015 (71% to 73%) but increased for the combination core plus complementary medicines between 2007 and 2015 from 77% to 88%. For all other prescriber categories the adherence increased over the time periods both for core (65% to 72%) and for the combination core plus complementary medicines (71% to 83%) (fig 2).

Adherence to specific pharmacotherapeutic areas in the Wise List

Statins: Wise pieces of advice for statins have been included in the Wise List most years since its launch. The recommendation has been both to increase the use of statins in high-risk patients, as well as to choose simvastatin. Simvastatin had good documentation and low price due to patent expiry already in 2003 and was, before patent expiry of atorvastatin, considered more cost-effective than the other statins.[36] The volumes of statins increased throughout the period and simvastatin was the dominating substance. Prescribing of other statins remained at a low level but when the patent for atorvastatin expired and less expensive generics became available, the Wise List included this substance among the recommended ones (from 2013), which is also reflected in higher volumes of atorvastatin prescriptions dispensed (fig 3).

PPIs: There have been several Wise pieces of advice related to the use of PPIs in the Wise List over the study period. These have aimed to decrease unnecessary use of PPIs, as well as recommending omeprazole (and pantoprazole and lansoprazole in 2002-2003) instead of other less cost-effective PPIs. Despite this, volumes of PPIs more than doubled between 2002 and 2015 to the equivalent of 4.5% of the population constantly treated with PPIs with the vast majority of prescriptions for omeprazole (fig 4).

SSRI/SNRI: Due to strong marketing pressure from the industry to prescribe the S-enantiomer of citalopram (escitalopram),[37] a Wise piece of advice was introduced in 2011 recommending the prescriber to use either citalopram or sertraline for patients in need of pharmacological treatment of depression. Citalopram and sertraline dominated the treatment throughout the period, but prescriptions for all other antidepressants have also increased (fig 5).

COX-inhibitors: In 2012 the Wise List changed its recommendation from diclofenac to naproxen based on accumulated evidence indicating an increased risk for cardiovascular events in patients using diclofenac.[38] A rapid change in prescribing patterns was observed with a marked decrease in diclofenac prescribing with a corresponding increase for naproxen (figure 6).

Discussion

This study demonstrates high adherence to the Wise List recommendations in the Stockholm Healthcare Region. The overall adherence rate increased steadily over time, but with variations between therapeutic areas. Additionally the number of recommended core substances has been kept stable (around 200 substances) for the 15 years since the introduction of the Wise List despite the number of substances with market authorisation in Sweden increasing from 1235 to 1554 in the same time period.[39] A limited number of recommendations is critical to make it feasible for prescribers to choose the best therapies for their patients, keeping knowledge up to date among prescribers about the clinical pharmacology and pharmacotherapeutic characteristics of each recommended medicine.[8 9 15]

High adherence to the Wise List recommendations was seen across all therapeutic areas both in primary and hospital care. There could be several reasons for this. We consider that the transparent development process of recommendations involving respected experts and clinicians within different therapeutic areas and strict criteria for handling potential conflicts of interests are essential for the high success rates to recommendations.[15 40] Financial incentives were introduced in Stockholm healthcare region in 2008[14] and have also been shown to contribute to the high adherence.[35] Originally, these incentives were introduced in primary care where PHCs received a small bonus linked to their adherence to the Wise List if the adherence was more than 80% and if they reflected on their prescribing patterns in a "quality report".[35] A higher target has not been set, as complete adherence is not considered suitable. This is because the Wise List does not include all possible treatment strategies for e.g. complicated cases, patients with allergies to medicines, or cases with potential drug-drug interactions. Physicians should have the possibility of using their clinical judgment and prescribe a substance not included on the Wise List if this is better for the patients. Therefore, complete adherence is neither wanted nor aimed for. Since 2008 core Wise List medicines (about 200) are free of charge for all hospitals, whereas they have to fund 50% of the cost of all other prescribed medicines. Previously the healthcare region covered all costs for prescriptions across hospitals and healthcare institutions centrally. Sound and trusted evidence based guidelines in combination with a communication strategy consisting of a branding and marketing strategy for both prescribers and the public, integrated with a program for continuous medical education, are major factors for successful adherence to DTC recommendations. In Stockholm this communication strategy and the continuous medical education programme is an ongoing, continuously evolving important part of the Wise List strategy.[18] The branding and marketing strategy is based on principles of social marketing. Core values of the brand Wise List have been defined as a shortlist of the best medicines, set up by respected experts and clinicians, for the best treatment of the most common diseases. This is in contrast to the marketing material provided by pharmaceutical industry. The Wise List has been promoted to prescribers and patients by traditional marketing methods such as ads in print, direct mail marketing like postcards, brochures, letters, and fliers and at oral presentations among stakeholders. The core value of the product has been consistent over the years and so also the key message in the marketing campaigns [14,15,18.] Prescriber ownership of the strategy has strengthened the Wise List work in developing and adopting state-of-the-art recommendations.[11-13 15 16] Multifaceted interventions, academic detailing and reminders have all been found to be effective.[16 41 42]

Our findings from the specific therapeutic areas demonstrate that the prescribers switched substances within a therapeutic area and reduced under treatment in accordance with the Wise List and Wise pieces of advice. However, the list has not been successful in reducing overtreatment. The failure in reducing PPI use is in concordance with other European countries where prescribing of PPI has also increased several-fold.[32] In contrast, there was a marked switch in COX-inhibitor prescriptions from diclofenac to naproxen after a change of recommendations in the 2012 Wise List edition. An important explanation for the difference in adherence between these therapeutic areas may be the fact that using omeprazole has no clear medical disadvantage. The reason for switching from diclofenac to naproxen was

accumulated evidence showing increased risk of cardiovascular disease with diclofenac,[38] which was clearly accepted by clinicians. Similar to the findings for COX-inhibitors the prescribers followed the recommendations for statins and SSRI/SNRI to a high degree and the prescribing of non-recommended escitalopram was low despite high marketing pressure similar to that of esomeprazole.[37] This marketing pressure from the pharmaceutical industry could have contributed to the failure in reducing PPI prescriptions, but despite increasing numbers of prescriptions, the vast majority remained omeprazole, as recommended by the Wise List. The adherence to the recommendation to use simvastatin instead of atorvastatin or rosuvastatin resulted in substantial economical savings for the Stockholm Health Care Region in contrast to other countries where rosuvastatin was the most prescribed statin.[43] To illustrate this, if just 10% of the simvastatin DDD had been replaced by rosuvastatin in 2008 this would have increased costs by 14.4 million SEK (1 SEK ~ 0.1 € in 2008). This is similar to a Canadian study of publically funded outpatient medicines where implementing harmonised prescribing recommendations could save pharmaceutical cost.[44] Regional differences in medicine costs within the Medicare system in the US have been shown to depend on the medicines selected for the formulary.[45]

Although we can relate prescribing data to the content of the Wise List and the Wise pieces of advice, without a control group we cannot know whether the seemingly high adherence is in fact due to a causal relationship between these factors. However, a major strength of the study is that we have data for a whole region, including all prescriptions from all care providers.

New niche medicines, soaring medicine costs and limited budgets pose new challenges to health care systems globally. Furthermore, the large number of new expensive biological medicines in pipeline has highlighted the importance of priority setting and development of methods to monitor the adherence to the recommendations,[46] and high quality evidence based recommendations to prescribers, such as the Wise List, become increasingly important. This is in line with the Lancet's Commission on Essential Medicines Policies' recommendations for achieving Sustainable Development Goal 3.8 for universal access to safe, effective, quality and affordable essential medicines and vaccines.[47] The Wise List already contains recommendations for some new expensive biological medicines, e.g. TNF inhibitors for use in inflammatory bowel disease and rheumatologic diseases. In our opinion, it is of critical importance that trusted recommendations and introduction protocols are developed for the use of new expensive medicines. A DTC/Wise List with focus on and with recommendations for specialised healthcare is necessary to ensure cost-effective and egalitarian use of medicines in the future. In fact, a recent study of ours demonstrated that the most important factor influencing use of anticoagulants, warfarin or a New Oral Anticoagulants, in Stockholm during the last five years was whether the substance was included as a Wise List recommendation.[48] New multifaceted methods for safe and successful evidence-based introduction of medicines must be developed. This will be a major challenge for the future but could build on components in the Wise List concept that has led to high adherence to recommendations sustained for 15 years.

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Competing Interest Statement
All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work and no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. Jaran Eriksen is member of an expert panel of the Stockholm DTC since 2013. Kristina Ateva, Pia Bastholm-Rahmner, Maria Juhasz-Haverinen, Malena Jirlow, Marie-Louise Ovesjö, Björn Wettermark are employed by Stockholm Healthcare Region that finances the Drug and Therapeutics Committee (DTC) issuing the "Wise List" in Stockholm. Eva Andersén-Karlsson served as chair-woman of Stockholm DTC 2010-2016, Lars L Gustafsson as chairman 2000-2009 and Gerd Lärfars is chair woman since 2016 and Rickard Malmström deputy chairman since 2016.

The co-authors and collaborators: Tareq Alsaody, Peter Aspelin**,** Peter Bárány, Harry Beitner, Johan Bratt, Torkel B Brismar, Marja-Liisa Dahl, Ulrika Dahnell, Paulina Dalemo, Christine Fransson, Stina Fransson Sellgren, Jan Hasselström, Roger Henriksson, Rose Marie Hallin, Paul Hjemdahl, Margareta Holmström, Charlotte Höybye, Thomas Kahan, Inga Klarin, Angelica Lindén Hirschberg, Synnöve Lindemalm, Mikael Lördal, Mussie Msghina, Ricard Nergårdh, Christer Norman, Åke Örtqvist, Peter Persson, Magnus Röjvall, Michael Runold, Carl-Olav Stiller, Marie Almvik (Sundström), Leif Tallstedt, Inga Tjäder, Mia von Euler, Rumiana Zlatewa are either present member of Stockholm DTC or chairing one of the 21 expert panels of Stockholm DTC. None of the authors or collaborators listed here have received any salary or economic support for the research presented in this work.

Data sharing
We have used routinely available prescribing data for a selected group of therapeutic classes. More analyses can be made for these medicines as well as for other medicines prescribed in Sweden.

Contributorship statement
JE contributed to the conception and design of the study, analysis and interpretation of the data, drafted and revised the manuscript. LLG contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. KA contributed to data acquisition, analysis and interpretation, and revised the manuscript. PBR contributed to data analysis and interpretation, and revised the manuscript. BW contributed to the conception and design of the study, data acquisition, analysis and interpretation of the data, and revised the manuscript. MJ contributed to data analysis and interpretation, and revised the manuscript. MJH contributed to the data acquisition, analysis and interpretation of the data, and revised

the manuscript. RM contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. MLHO contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. GL contributed to data analysis and interpretation, and revised the manuscript. EAK contributed to the conception and design of the study, analysis and interpretation of the data, and revised the manuscript. All authors critically revised and approved the final manuscript.

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Table 1. Some examples of the 55 individual Wise pieces of advice included in the Wise List. Categories: (i) choice of medicine – i.e. preferred choice of substance within a group of medicines used for a specific diagnosis, (ii) overtreatment – i.e. avoid using medicines unnecessarily, (iii) under treatment – i.e. reminders to look for and treat conditions that are often inadequately diagnosed and/or treated, or (iv) any other type of general advice related to drug therapy.

Example of advice	Category of advice
Use naproxen as first choice when prescribing cox-inhibitors	Choice of medicine
Choose simvastatin for prevention of cardiovascular disease in high-risk patients with normal to medium increased levels of cholesterol.	Choice of medicine
Do not use quinolones for treatment of uncomplicated Urinary Tract Infection (UTI) in women	Choice of medicine
Always give the patient an updated medication list.	General advice
Estimate and consider renal function in the selection and dosing of medicines.	General advice
Verify the diagnosis before treating according to the "heart failure treatment ladder" and seek to establish good heart rate control (below 70 beats/min in sinus rhythm).	General advice
Do not treat uncomplicated acute bronchitis with antibiotics.	Over treatment
Do not treat asymptomatic bacteriuria in the elderly and only culture from urine if the patient is experiencing urinary tract symptoms.	Over treatment
Treatment with proton pump inhibitors is not advisable in the case of stomach pain of unknown cause.	Over treatment
Improve antihypertensive treatment: determine a target blood pressure together with the patient, combine medicines more often and follow up.	Under treatment
Treat depression to complete remission.	Under treatment
Increase the use of medicines to prevent relapse in alcohol dependence and follow up treatment outcome.	Under treatment

Figure 1. Number of substances included in the Stockholm Healthcare Region's Wise List over time. *Core medicines* = Essential medicines for common illnesses, used both in primary and hospital care. *Complementary medicines* = Additional essential medicines to be used primarily for specialised care.[26]

Figure 2. Adherence to recommendations (DU90%) in the Wise List for different prescriber categories in Stockholm Healthcare Region between 2003 and 2015. Data on complementary medicines available only from 2007. "Others" includes psychiatry, geriatrics, rehabilitation, school health, occupational health and private practitioners in various specialties.

Figure 3. Prescribing patterns for statins in Stockholm Healthcare Region between 2002 and 2015 showing all statin prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. DDD/TID = Defined Daily Dose/1000 inhabitants per day.

Figure 4. Prescribing pattern for proton pump inhibitors (PPI) in Stockholm Healthcare Region between 2002 and 2015 showing all PPI prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. DDD/TID = Defined Daily Dose/1000 inhabitants per day.

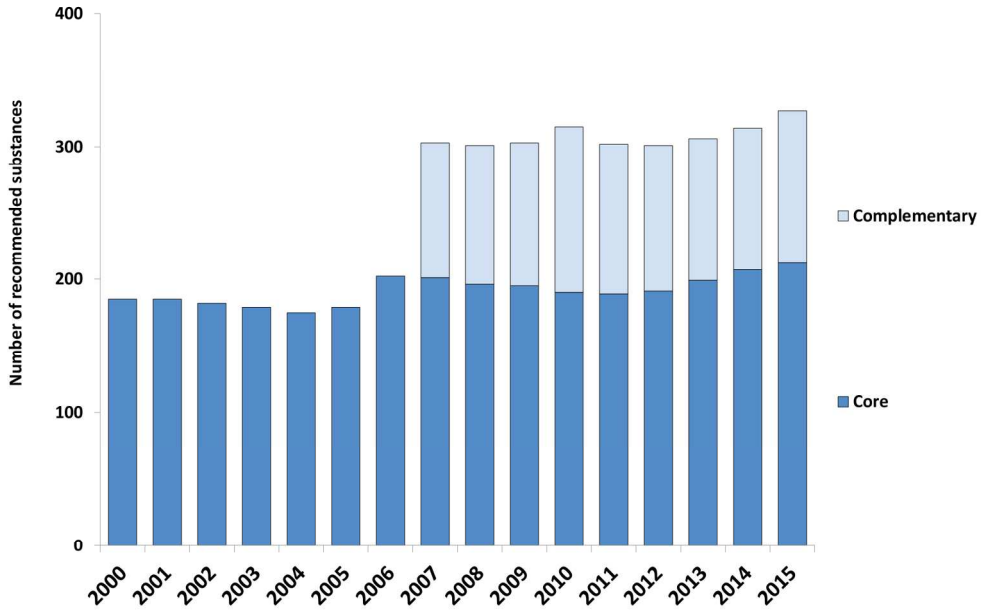
Figure 5. Prescribing pattern for SSRIs and SNRIs in Stockholm Healthcare Region between 2002 and 2015 showing all SSRI and SNRI prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. ("Others" includes duloxetine, fluoxetine, paroxetine). DDD/TID = Defined Daily Dose/1000 inhabitants per day.

Figure 6. Prescribing pattern for COX-inhibitors in Stockholm Healthcare Region between 2002 and 2015 showing all COX-inhibitor prescriptions dispensed to the inhabitants in the region each year. The letter "R" signifies that the drug was a core recommendation in the Wise List that year. ("Others" includes aceclofenac, dexibuprofen, phenylbutazone, indomethacin, ketorolac, lornoxicam, meloxicam, nabumetone, piroxicam, sulindac, tenoxicam). DDD/TID = Defined Daily Dose/1000 inhabitants per day.

Box 2: The Stockholm model for wise use of medicines

The core part of the model is The Wise List (central part of figure). The outer circle represents the Key Strategies and the Organisational Unit, which are a pre-requisite for the collaborative

work for a rational use of medicines. Since 1996 a new Swedish law stipulated that each healthcare region should have at least one Drug and Therapeutics Committee (DTC). This has provided mandate and organisational stability to issued recommendations by DTCs.[8] The jigsaw puzzle shows key elements necessary for producing the Wise List and implementing its guidelines in medical practice in the Stockholm Healthcare region. Operative resources include an annual budget for staff, continuous medical education of our 200 experts, infrastructure, printing, distribution and marketing of the Wise List.



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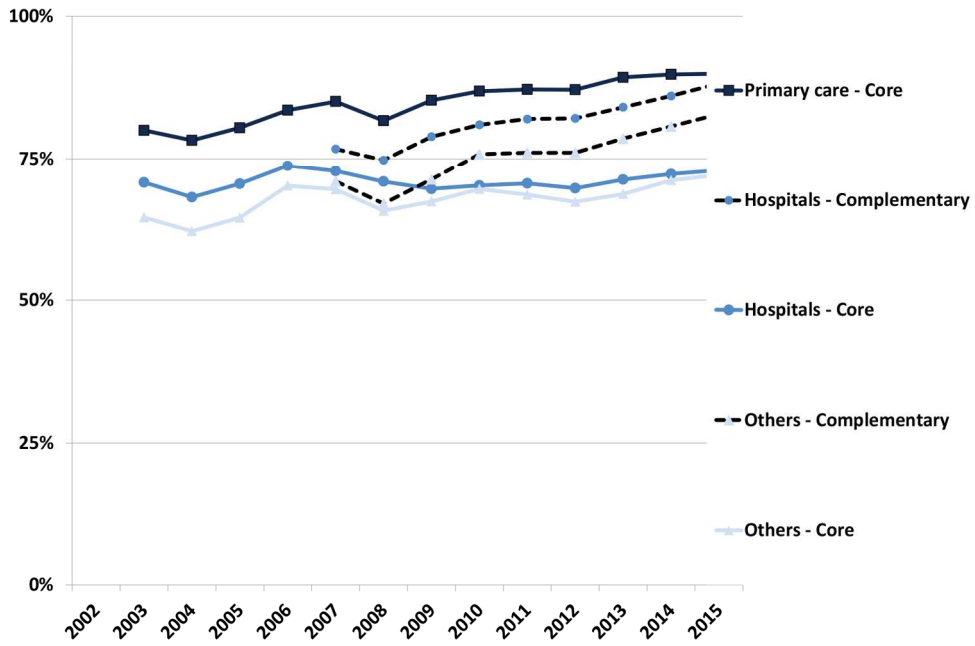

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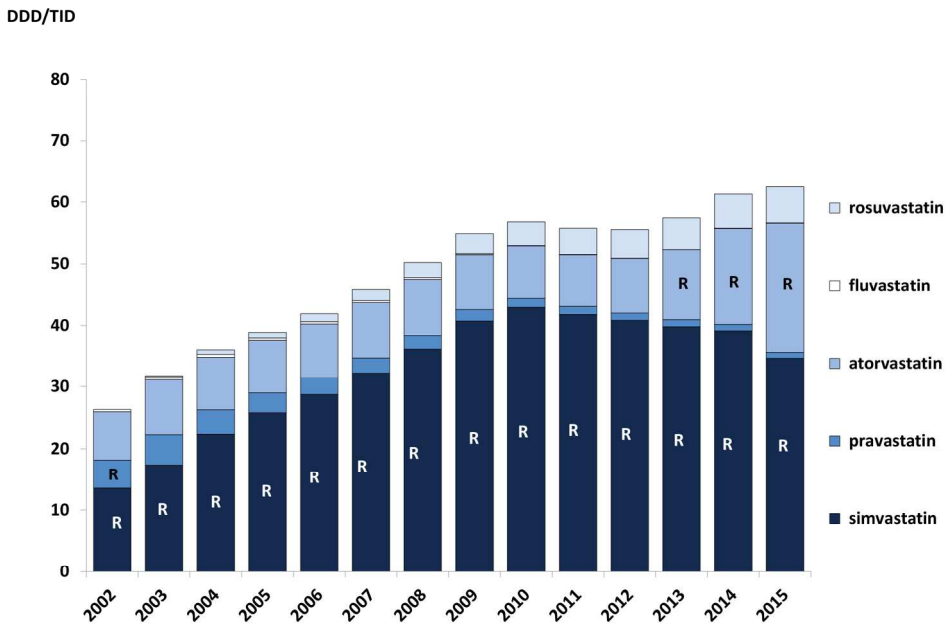

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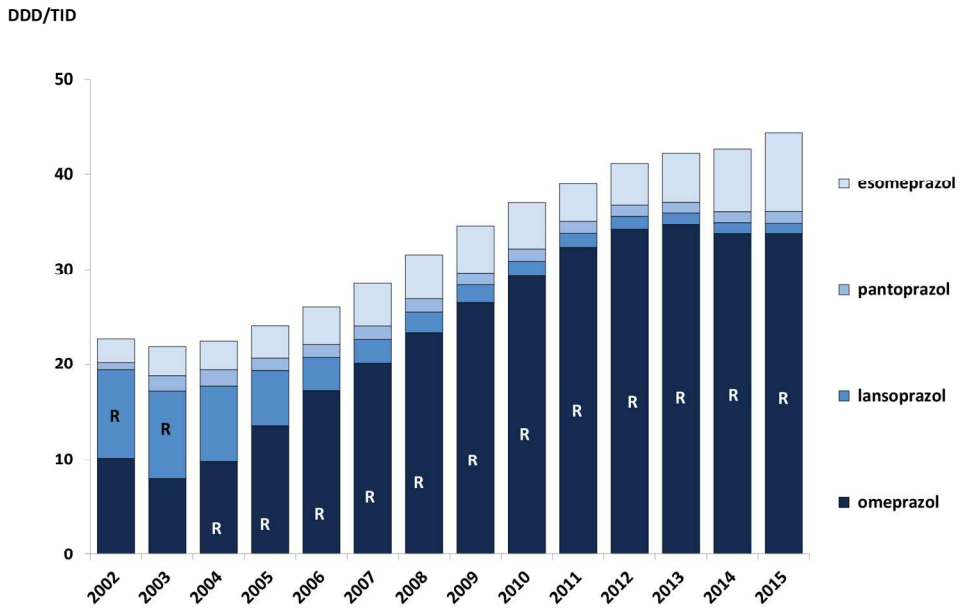

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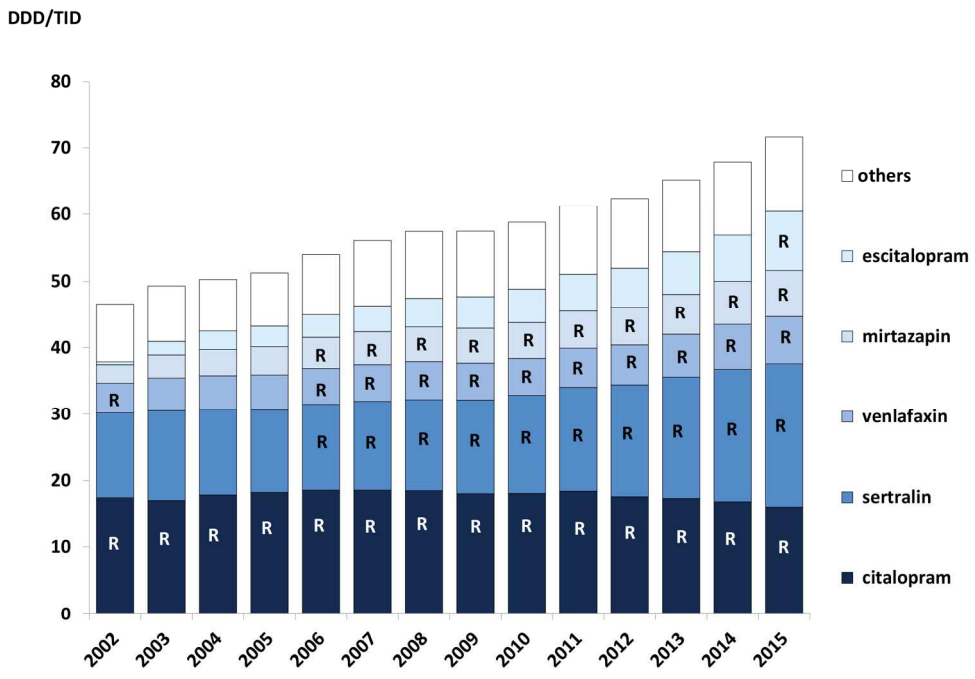

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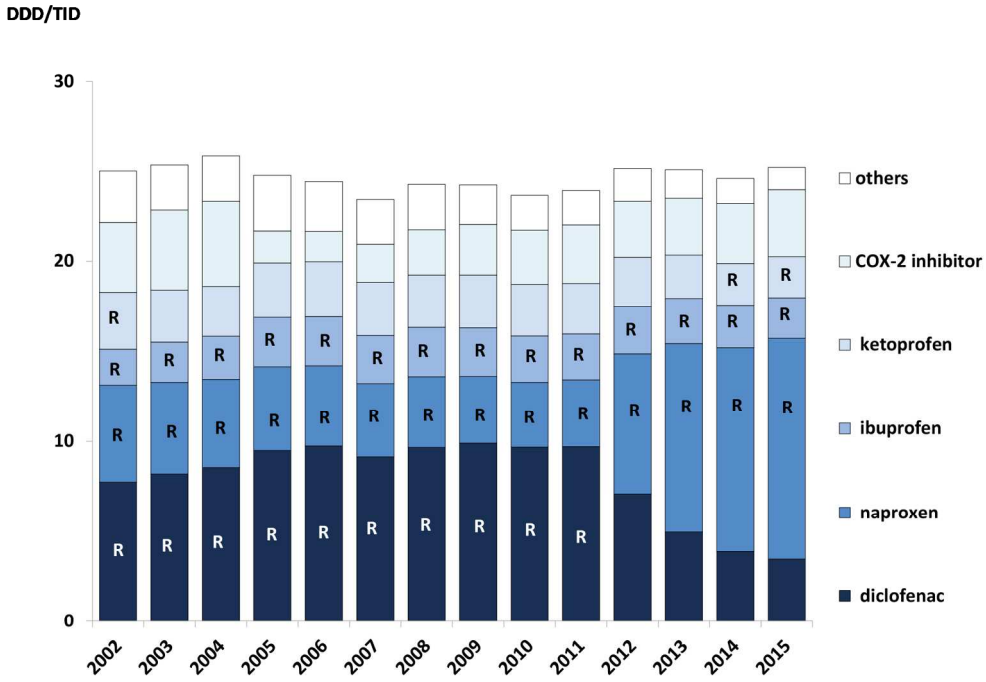
167x118mm (300 x 300 DPI)



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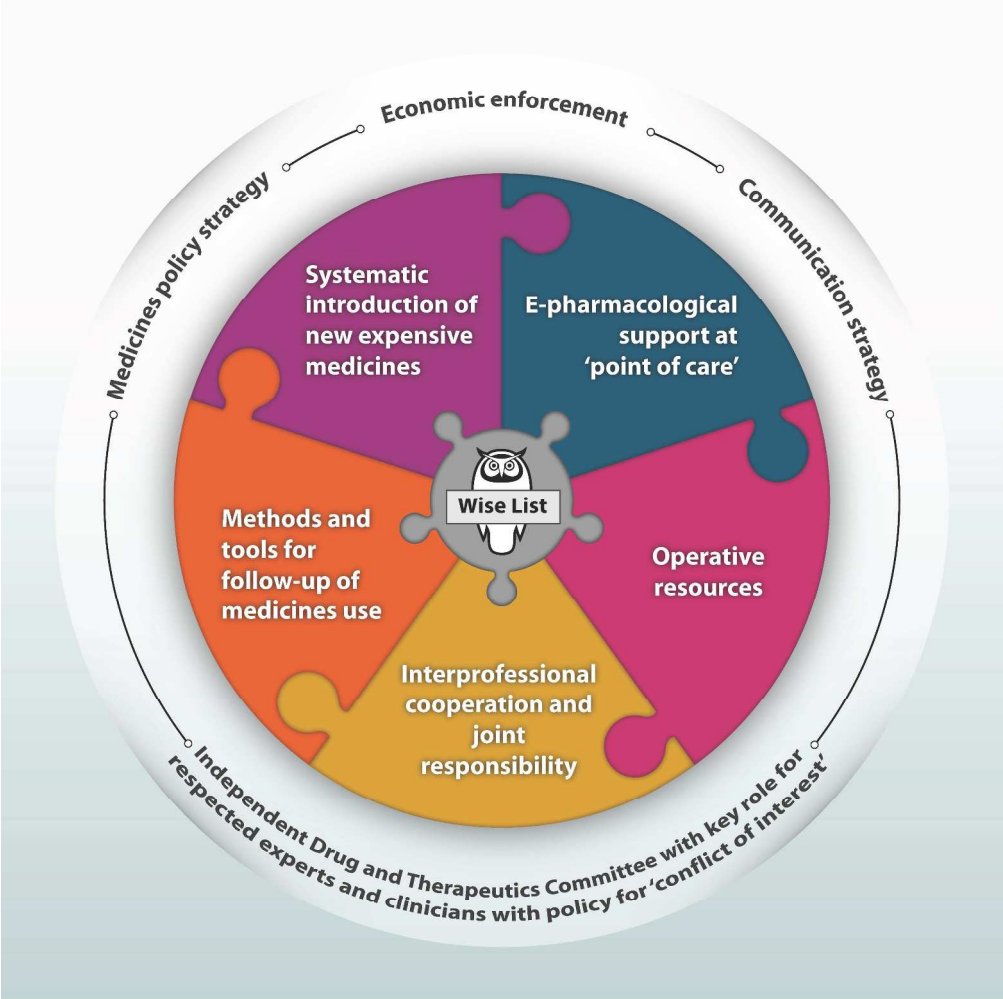

Box 2: The Stockholm model for wise use of medicines

The core part of the model is The Wise List (central part of figure). The outer circle represents the Key Strategies and the Organisational Unit, which are a pre-requisite for the collaborative work for a rational use of medicines. Since 1996 a new Swedish law stipulated that each healthcare region should have at least one Drug and Therapeutics Committee (DTC). This has provided mandate and organisational stability to issued recommendations by DTCs.8 The jigsaw puzzle shows key elements necessary for producing the Wise List and implementing its guidelines in medical practice in the Stockholm Healthcare region. Operative resources include an annual budget for staff, continuous medical education of our 200 experts, infrastructure, printing, distribution and marketing of the Wise List.

552x552mm (150 x 150 DPI)

SQUIRE 2.0 Checklist

Title and Abstract		**Comment**
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)	Yes, included: *High adherence to the **"Wise List" treatment recommendations in Stockholm:** a 15-year retrospective review of a **multifaceted approach promoting rational use of medicines***
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	a. included b. Yes, all points included except background and local problem (as the abstract has been formatted according to BMJOpen guidelines).
Introduction	Why did you start?	
3. Problem Description	Nature and significance of the local problem	In the background, second paragraph, the problem and its significance in the Stockholm Healthcare Region is described.
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies	Described in first and second paragraphs in the background section.
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that	Described in the second paragraph of the background

	were used to develop the intervention(s), and reasons why the intervention(s) was expected to work	
6. Specific aims	Purpose of the project and of this report	Stated in the last sentence of the background.
Methods	What did you do?	
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)	Explained under "study area" (first section of "material and methods")
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work	Explained in "box 1" and "box 2"
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)	a. Explained under "data analysis": three sections explaining each of the three approaches. b. Described in "statistical analysis"
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability	a. Described under "data sources"

	b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data	b. Described in the three subsections of "data analysis" c. N/A
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable	a. Described under "statistical analysis"
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest	"Described in the section "ethical considerations"
Results	What did you find?	
13. Results	a. Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with	a. All results presented as change over time, e.g. all figures b. N/A c. Described where relevant, e.g. under subheading "adherence to specific pharmacotherapeutic areas…" for statins: page 10, line 7.

	the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data	d. Described for each of the therapeutic areas on page 10 e. Described for each of the therapeutic areas on page 10 f. N/A
Discussion	What does it mean?	
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project	a. First paragraph of discussion b. Described on page 12, second paragraph
15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs	Described in second and third paragraphs of the discussion.

16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations	Described in second paragraph page 12
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps	Described in the last paragraph of the discussion
Other information		
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting	Described in competing interest statement