ePrescribing

Studies in Pharmacoinformatics

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Abstract

The thesis aimed to study the developments, in the area of pharmacoinformatics, of the electronic prescribing and dispensing processes of drugs - in medical praxis, follow-up, and research.

For hundreds of years, the written prescription has been the method of choice for physicians to communicate decisions on drug therapy and for pharmacists to dispense medication. Successively the prescription has also become a source of information for the patient about how to use the medication to maximize its benefit. Currently, the medical prescription is at a transitional stage between paper and web, and to adapt a traditional process to the new electronic era offers both opportunities and challenges.

The studies in the thesis have shown that the exposure of prescribed drugs in the general population has increased considerably over three decades. The risk of receiving potentially interacting drugs was also strongly correlated to the concomitant use of multiple drugs, polypharmacy. The pronounced increase in polypharmacy over time constitutes a growing reason for prescribers and pharmacists to be aware of drug interactions. Still, there were relatively few severe potential drug interactions.

Recently established national prescription registers should be evaluated for drug interaction vigilance, both clinically and epidemiologically. The Swedish National Pharmacy Register provides prescription dispensing information for the majority of the population. The medication history in the register may be accessed online to improve drug utilization, by registered individuals, prescribers, and pharmacists in a safe and secure way. Lack of widespread secure digital signatures in healthcare may delay general availability. With a relatively high prevalence of dispensed drugs in the population, the National Pharmacy Register seems justified in evaluating individual medication history.

With a majority of prescriptions transferred as ePrescriptions, the detected increased risk for prescription errors warrants quality improvement, if the full potential of ePrescriptions is to be fulfilled.

The main conclusion of the studies was that ePrescribing with communication of prescribed drug information, storing and retrieving dispensed drug information, offers new opportunities for clinical and scientific improvements.

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To my beloved family

Seek, and you will find [a]

[a] Luke 11:9. Scripture taken from the New King James Version. Copyright © 1982 by Thomas Nelson, Inc. Used by permission. All rights reserved.

Where is the Life we have lost in living?
Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information? [b]

[b] Opening stanza of T.S. Eliot's The Rock, 1934.

List of publications

The thesis is based on the following original papers
(subsequently referred to by their Roman numerals)

I **Detection of potential drug interactions – a model for a national pharmacy register**

Åstrand B, Åstrand E, Antonov K, Petersson G
Eur J Clin Pharmacol (2006) 62: 749-756

II **The Swedish National Pharmacy Register**

Åstrand B, Hovstadius B, Antonov K, Petersson G
Stud Health Technol Inform (2007) 129: 345-49

III **Potential drug interactions during a three-decade study period: a cross-sectional study of a prescription register**

Åstrand E, Åstrand B, Antonov K, Petersson G
Eur J Clin Pharmacol (2007) 63: 851-9

IV **Improving the quality of outpatient ePrescriptions: an observational study at three mail-order pharmacies**

Åstrand B, Åstrand E, Petersson G, Ekedahl A
Submitted

[PubMed publications]

Populärvetenskaplig sammanfattning

Det övergripande syftet med den här avhandlingen har varit att, inom området läkemedelsinformatik, studera utvecklingen av elektroniska stöd inom läkemedelsförskrivning; för klinisk praxis, uppföljning och forskning.

Under århundraden har det handskrivna receptet varit det sätt, med vilket läkare förmedlat sina läkemedelsordinationer till apotekare, vilket också för patienten blivit en informationskälla för hur läkemedel ska användas för att göra bästa nytta. Nu genomgår receptet en förändring från pappersbaserat till elektroniskt meddelande och att anpassa en traditionell process till en ny elektronisk era innebär både möjligheter och utmaningar.

Studierna som ingår i avhandlingen har visat att exponeringen av förskrivna läkemedel i en allmän befolkning har ökat under de senaste tre decennierna. Risken för potentiella interaktioner mellan läkemedel, varmed avses den risk som finns att olika läkemedel kan påverka varandras effekter och biverkningar, har också visat sig öka starkt desto fler läkemedel som används av en individ. Denna ökade samtidiga användning av flera olika läkemedel, så kallad polyfarmaci, medför att det finns en större anledning för förskrivare och farmacevter att uppmärksamma risken för potentiella interaktioner mellan läkemedel.

De nyinrättade nationella receptregistren över uthämtad receptförskriven medicin bör användas bland annat för att upptäcka potentiella läkemedelsinteraktioner, såväl i vårdens utövning som inom läkemedelsepidemiologisk forskning. Den svenska läkemedelsförteckningen, som omfattar information om uthämtade receptförskrivna läkemedel för huvuddelen av den svenska befolkningen, bedöms ha en stor klinisk potential. Den enskilde individens historiska information om uthämtade läkemedel är tillgänglig för individen på Internet med hjälp av e-legitimation; även förskrivare och farmacevter på apotek kan ta del av informationen med den enskildes samtycke. Brist på tillgång till enhetliga och säkra autenticeringsmetoder inom hälso- och sjukvården kan dock fördröja tillgången på individuell läkemedelsinformation för förskrivare. I och med att de flesta recepten i Sverige nu skrivs och överförs elektroniskt är det viktigt att kvalitetsmässiga aspekter tas tillvara så att en iakttagen ökad risk för receptförskrivningsfel inte överförs i informationskedjan.

Avhandlingens slutsats är att e-förskrivning, med kommunikation och användning av lagrad information om receptexpeditioner, möjliggör att läkemedelsbehandling som process kan följas och studeras på ett helt nytt sätt.

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Abbreviations and glossary

List of abbreviations appearing in the thesis

Acronym	Definition
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification
CDSS	Computerized Decision Support System
CI	Confidence Interval
CPOE	Computerized Physician Order Entry
DDD	Defined Daily Dose
DIKW	Data, Information, Knowledge, Wisdom
DRP	Drug Related Problem
EMR/EHR/EPR	Electronic Medical/Healthcare/Patient Record
ETP	Electronically Transferred Prescription
ICT	Information and Communication Technology
MeSH	Medical Subject Heading; vocabulary for indexing biomedical papers
OTC	Over The Counter; sales of non-prescription drugs
pDUR	Prospective Drug Utilization Review
PIN	Personal Identification Number
RR	Relative Risk
SD	Standard Deviation
W.H.O.	World Health Organization

Glossary

Some essential expressions in the thesis	Page(s)
Adherence, compliance, and concordance	6-8
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Introduction

For hundreds of years, the written prescription has been the method of choice for physicians to communicate decisions on drug therapy and for pharmacists to dispense medication, while at the same time being a source of information for the patient about how to use the medication in order to maximize its benefit. Currently, the medical prescription is at the transitional stage between paper and web, and to adapt a traditional process to the new electronic era offers unique opportunities and challenges. In the present thesis, ePrescribing is studied within the area of pharmacoinformatics.

ePrescribing

The introduction of electronic prescriptions, ePrescriptions, in healthcare has been suggested to have a positive impact on the prescribing and dispensing processes, implicating that ePrescribing can improve safety, quality, efficiency, and cost-effectiveness. A compilation of selected published articles sorted by year with relevance for ePrescribing, reveals an increased interest during recent years (Appendix 1), both in Europe and in the US.

Definitions

A straightforward definition of ePrescribing is "Entering a prescription for a medication into a data entry system and thereby generating a prescription electronically, instead of handwriting the prescription on paper".[119] This definition calls attention to the new technology of producing prescriptions electronically.

Another definition, "ePrescribing is the ability of a physician to submit a "clean" prescription directly to a pharmacy from the point of care.",[8] puts emphasis on the quality aspect of delivering unambiguous and correct prescription information.

A more elaborate definition was presented by the National Council for Prescription Programs in the US: "two way [electronic] communication between physicians and pharmacies involving new prescriptions, refill authorizations, change requests, cancel prescriptions and prescription fill messages to track patient compliance." Electronic prescribing is not faxing or merely printing paper prescriptions. It also has a potential for information sharing with other

healthcare partners including eligibility to formulary information and medication history.[1]

A process perspective

However, with the introduction of electronic support into the prescribing process, a novel view is possible, allowing a *process* perspective on the involved activities.[205] Prescribing may be seen as an essential part of a continuous workflow in healthcare and pharmacy. In the same way, patients need to have updated and correct information on their drug therapy, both current and past. With modern Information and Communication Technology (ICT), the information may be updated, correct, readily available, and shared by different stakeholders, independent of time and space. In this respect, the same information will be transferred and stored to be available for dispensing, both new prescriptions and refills; for prescription renewals, clinical follow-up, statistics, and epidemiologic research of drug utilization (*Figure 1*).

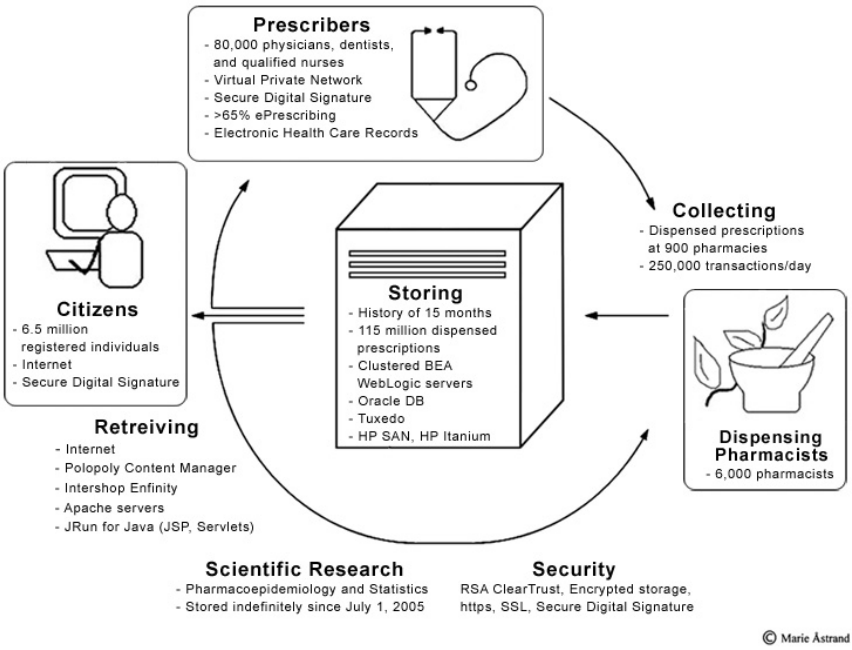


Figure 1. Information model applied to the ePrescribing situation in Sweden 2007, with electronic support in the process of ePrescribing (II). [c]

To make the right choice of medication and dosage regimen for each individual patient, a computerized decision support system (CDSS) is often an essential component. Furthermore, the patients demand for fast and reliable healthcare

[c] Abbreviations: JSP is short for Java Server Pages, BEA is BEA Systems Inc., DB is database, HP is Hewlett-Packard Inc., RSA is RSA Security Inc., and SSL means Secure Sockets Layer.

services and modern patients' claims for empowerment also need to fit into a good definition.

Hence, ePrescribing, for all involved stakeholders, has, on the one hand, safety and quality aspects and, on the other, efficiency and cost-effectiveness aspects. The empowerment claim has a democratic aspect in patients' search for increased involvement in decision-making in healthcare. A more motivated and engaged patient is supposed to be more prone to adhere to the mutually decided therapy, increasing concordance and resulting in better quality and outcome of the therapy.

The essence of the process of ePrescribing should be to improve drug utilization, which by the World Health Organization (W.H.O.) is defined as the "marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences".[187]

Prescribing of drugs

The desire to alleviate, cure, and prevent diseases with drugs produced from nature has probably been a companion to mankind since the very beginning.

Antitheriaca

In ancient times, *Mithridatium* contained a multitude of ingredients (polypharmacy) and was a panacea for all health related problems. *Antitheriaca* or *mithridatium*, originally created for king Mithridates of Pontus in the second century BC, was the drug of choice for nearly two millennia.[104, 187] The 1746 *London Pharmacopoeia* was the last British pharmacopoeia with its formulation (45 ingredients), but in other countries it still lingered during the nineteenth century.[87, 135, 212]

From polypharmacy to the magic bullet

The polypharmacy approach has been followed by the twentieth century idea of the magic bullet; one single compound to treat a single condition.[67] During the twentieth century, the biochemical era has introduced biological mechanisms of action as models for explaining the effect of old remedies like digitalis and morphine, as well as for novel discoveries of chemical entities.

More and more, drugs are prescribed not only for the treatment of diseases, but also for treating certain risk factors for a disease, like high cholesterol and high blood pressure, striving for a disease protection and prevention effect.[146]

During the last decade, the human genome has been mapped, bringing expectations of more individually tailored drug use, with more specific effects and less adverse drug effects, as well as for hitherto incurable health disorders.[16]

The prescription

For hundreds of years, the written prescription has been the method of choice for physicians to communicate decisions on drug therapy and for pharmacists

to dispense medication. Successively the prescription has also become a source of information for the patient about how to use the medication in order to maximise its benefit. One of the earliest statutes on the control of drugs was passed in the UK in 1540 during the reign of Henry VIII. To ensure that the statutes would be obeyed, official wardens were appointed and given the task to assist physicians in their inspection of apothecaries' shops. Apothecaries who were found guilty of trading defective wares would be punished and excuses would not be tolerated [87, 212]

> ". . . in the Kings Court . . . no wager of law, esoin (excuse) or protection shall be alloweth . . . apothecaries to sell or prescribe any poisonous substance or drug . . . to the body of any man, woman or child save on the written prescription of a physician or upon a note in writing from the purchaser"

Both the "recipe" for drug composition and the dispensing of medications at pharmacies became more and more regulated and were subject to inspection by the authorities to ensure quality for the patient.

Early in modern Western life, the professions of pharmacists and physicians separated, the doctor diagnosing and prescribing the therapy and the pharmacist producing and dispensing the prescribed medication. The prescription, mostly handwritten, but also 'transceived' by phone or fax, has been the instrument to bring the doctor's order from the doctor's office, to be dispensed at the pharmacy by the pharmacist, representing one of the most common transfers of information between different healthcare levels.[139, 144, 194] The patient has traditionally been the natural vehicle for this information transfer.

A prescription should be unambiguous, complete, and correct. Pharmacists are obliged to examine a prescription before dispensing for technical, administrative, and pharmacological accuracy. If a prescription is wrong or vague, and the dispensing pharmacist does not discover this, it may lead to harm for the patient.[51, 121, 130, 144, 164]

Adherence, compliance, and concordance

To attain the intended therapeutic effect, a prescribed drug has to be consumed. The patients' degree of *adherence* to the doctors' prescribed therapy has been described as *compliance*. The term *concordance* has been introduced to indicate a more inclusive and less paternalistic view of the doctor-patient relationship.[22, 36, 55, 71, 93, 111]

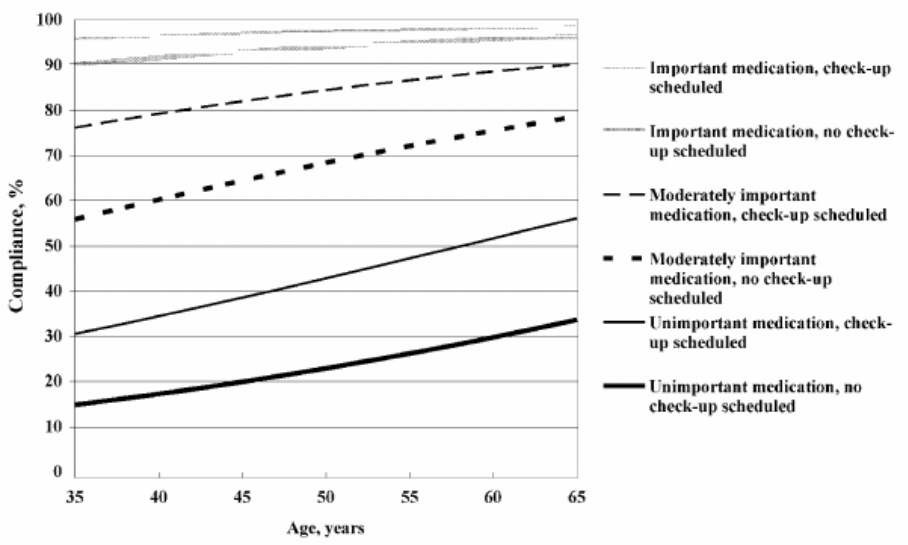


Figure 2. Compliance (%) according to age, importance of medication and scheduled check-up. From "Factors associated with adherence to drug therapy: a population-based study", Annika Bardel et al., European Journal of Clinical Pharmacology, 2007. Reprinted with permission of Springer Verlag. [26]

Adherence seems to depend on the age of the patient, the perceived importance of the medication (*Figure 2*) and the interaction between prescriber and patient.[19, 26, 111, 189] Obviously, prescribing is not always equivalent to the amount of drugs dispensed or the drugs actually consumed by the patient.[145] If the patient does not fill the prescription at a pharmacy, a so-called *primary non-compliance* occurs.[33, 68] As a result of experienced or imagined side effects or otherwise not fulfilled patient expectations, the patient may choose, or just forget, not to continue a medication, although the prescriptions have been presented to a pharmacy and subsequently filled. This is referred to as *secondary non-compliance* and may result in early cessation of a therapy, prescriptions not refilled or simply a reduced intake of the amount of the medication (*Figure 3*).[69, 79, 124]

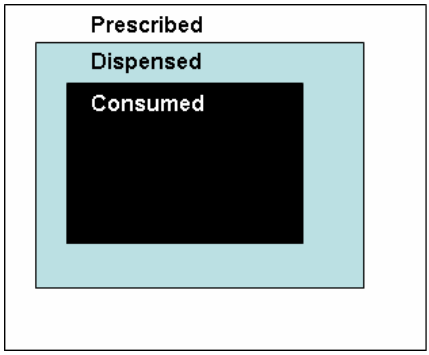


Figure 3. Principal relation between prescribed, dispensed, and consumed drugs.

The adherence A to the prescribed regimen can be expressed as

$$A = f_1 * f_2$$

Where $f_1 = D/P$ and $f_2 = C/D$

P, D and C denotes prescribed, dispensed and consumed drugs, respectively.

Thus, adherence is

$$A = D/P * C/D = C/P$$

To know how the medications are used in reality, drug consumption needs to be measured at the point of care, to receive a true estimate of drug exposure. Measurement of the plasma concentration of certain drugs and other laboratory tests, have been used as a practical means to evaluate drug intake and also to adjust the dose to the individual. As most medications are consumed by otherwise healthy people living at home, a structured, four-item, self-reported adherence measure to assess adherence has been developed and evaluated; also demonstrating a predictive validity to medication adherence.[143] To estimate drug consumption in large populations, measurement of pharmacy dispensing can serve as a rough measure of drug exposure, given that secondary non-compliance is taken into account.[79, 80]

Intelligent non-compliance

It may be favourable to use a combination of drugs, if the combination is well documented, to enhance the effect or to reduce adverse effects.[20] However, in the case of patients visiting several different physicians [101, 180], who are prescribing less appropriate combinations of drugs due to being unaware of each other, the outcome of the therapy may be negatively influenced [41, 115, 131, 138, 159]. The

polypharmacy, with accompanied risk for drug interactions,[37, 40, 41, 78, 110, 114, 126, 138] may be so profuse that a low degree of compliance to the prescribed therapy has been named 'intelligent non-compliance', indicating that it may be beneficial for patients not to adhere to the prescribed therapy.[89] Moreover, drug interactions have been shown to significantly contribute to adverse drug reactions, resulting in hospital care.[127, 142]

Withdrawals

There are even examples when manufacturers and regulating authorities, despite disseminated warnings, have not been able to prevent co-prescribing. The consequence has been the withdrawal of the drug in question from the market or restrictions in its use as the continued widespread availability could not be justified any longer due to the associated risk.[109] These withdrawals have led to losses of otherwise valuable pharmaceutical products.[21]

Rational prescribing

With a well thought strategy and an evidence-based attitude, drugs can appropriately be prescribed together to diminish the adverse effects or to enhance the intended effect, with familiar examples including malaria treatment, diabetes regimens or eradication of *Helicobacter pylori*.[20] The concept of rational polypharmacy has been advocated, not at least in neurological and psychiatric disorders.[21, 76] For rational prescribing to also become appropriate, it is crucial that the single patient's prerequisites are taken into account.[108, 154]

Risk and society

Our society has been characterized as a risk society where risks are deliberately introduced in the society as a consequence of our technological progress; the risk term being a 'systematic way of dealing with hazards and insecurities induced and introduced by modernization itself.'[34]

Medical risks

In healthcare, risk has been defined as the possibility of a loss or an injury, or the potential for realization of unwanted, negative consequences of an event.[163] Risk basically introduces a concept of balance between gains and losses. In the end, there is always a chance that the outcome, or net benefit, will be not as good as expected, where the net benefit refers to the difference between benefits and harm.[107]

Medical errors

The basic position in healthcare is not to do any harm to patients. This goes back to the Hippocratic oath (300-400 B.C.);

> "I will follow that system of regimen which, according to my ability and judgement, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous." [4]

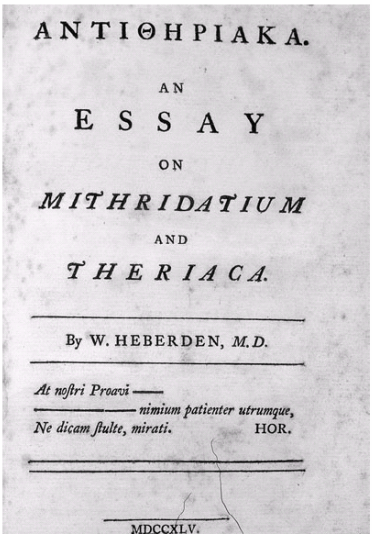
Still, 'iatrogenic illness' or 'medical harm' exists and has been calculated to be one of the major causes of illness in the US.[5, 38, 72] Medical errors are often the result of a complex chain of events with multiple contributing factors, both system errors and human errors. Efforts should be focused on detecting, preventing and minimizing the number of errors in healthcare, both errors of planning and errors of execution, including errors of omission and commission. Although the majority of studies looking at the frequency of patient safety incidents have been conducted in an acute setting, the problems seem to be of the same magnitude in primary care.[59, 166] Many of the errors in the medication process are expected to be reduced by implementing automated technologies in the medication process.[59, 132, 207]

Drug related problems

The term drug related problem (DRP) [196, 197, 199, 200] has been used to describe 'any deviation from an intended beneficial effect of a medication'.[113] An optimal outcome can be seen as an absence of DRPs.[105] If unrecognized or unresolved, DRPs may manifest drug-related morbidity or even mortality, due to the failure of the therapeutic agent to produce the intended outcome.[200]

Most drug therapies are associated with side-effects or adverse effects, which represents a potential and calculated risk in most therapy strategies. If a medical error results in any kind of unwanted event for a patient, it is referred to as an adverse event, related to the use of drugs; the terms adverse drug event (ADE)[208] or adverse drug reaction (ADR) have been used.[23, 133]

Already in 1745, William Heberden attacked the use of Mithridatium: "made up of a dissonant crowd collected from many countries, mighty in appearance, but in reality, an ineffective multitude that only hinder one another"[104]. The risk for drug interactions with the concomitant use of several drugs were here attacked (*Figure 4*).


ANTIΘHPIAKA.

AN

ESSAY

ON

MITHRIDATIUM

AND

THERIACA.

By W. HEBERDEN, M.D.

At noſtri Proavi ——
—— nimium patienter utrumque,
Ne dicam ſtulte, mirati. HOR.

MDCCXLV.

Figure 4. Cover page of the pamphlet by William Heberden (1745), on the risk for drug interactions with the concomitant use of many substances (polypharmacy).[104]

Since the 18th century, the publication, with online retrieval,[64] of medical papers has exploded; during the last decades the growth in publication on drug interactions has been linear (*Figure 5*) (III).

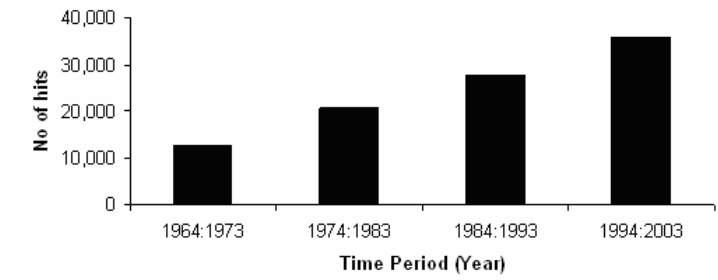


Figure 5. Published articles indexed with the keyword 'drug interactions' (MeSH) at PubMed *per* decade, including drug synergism and drug antagonism (III).

Risk and patients

A single individual may rate a risk differently than a healthcare professional valuing the risk at a population level. Being at risk can be seen as a state somewhere between health and illness.[82] This view supports that patients should participate in healthcare decisions. Risks can be understood and communicated, and patients also want to be informed on alternatives and involved in decisions when there is more than one treatment.[90]

In patient-centred care – understanding the patient as a unique human being – a style of consulting is employed where the physician uses the patient's knowledge and experience to guide the interaction; the physician tries to enter the patient's world, to see the illness through the patient's eyes.[25]

To avoid drug interactions and ADRs, physicians should regularly check the patient's list of medications, computerized or not. The patient's age and number of medications are significant predictors of medication discrepancy. The toxicity of drug combinations may sometimes be synergistic, greater than the sum of the risks of toxicity of either agent used alone. Screening for drug interactions should include all medication, both for inpatients and outpatients, nursing homes included. To ensure effective partnership between different healthcare professionals and the patient, good communication is essential both technically and, not least, personally.[162]

Risk and ICT

ePrescribing holds a potential for more efficient and cost-effective processes in healthcare, pharmacy included. Healthcare organizations have started to offer the renewal of prescriptions on their web sites and patients may benefit from better services in healthcare and pharmacy. ICT, with Electronic Medical/Healthcare Records (EMR/EHR), may be used to improve the situation, but may also introduce new risks with the extended use of the prescription information in large-scale databases[54, 59, 88, 123]; a mistake in data entry by a prescriber may result in the wrong medication being dispensed at the pharmacy but also in the wrong conditions being recorded for future consultations and any research databases; a mistake by a system programmer in a script, if not properly validated, may, in the worst case, also result in the wrong medication being dispensed, not just for a single patient, but for a large group of patients.

Future decisions, clinically as well as scientifically, may be based on wrong facts and assumptions, due to poor quality in data provided. Thus, quality issues are even more attenuated in the electronic world.[112]

Information society

Our period in history, the post-industrial society, has also been named the knowledge society or the information society, in which the creation, distribution, diffusion, use, and manipulation of information is a significant economic, political, and cultural activity.[202] The United Nations, at the World Summit on the Information Society in 2003 and 2005, recognized that "ICT have an immense impact on virtually all aspects of our lives. The rapid progress of these technologies opens completely new opportunities to attain higher levels of development. The capacity of these technologies to reduce many traditional obstacles, especially those of time and distance, for the first time in his-

tory makes it possible to use the potential of these technologies for the benefit of millions of people in all corners of the world." [7]

Pharmacoinformatics

The term *informatics* was established in different languages during the 1950's and 1960's; informatik (in German 1957)[178], informatics (in English 1962)[32], informatique (in French 1962)[65] and informatika (in Russian 1966)[141], denoting the interdisciplinary study of the design, application, use and impact of ICT.[9] The design of this technology is not solely a technical matter, but also takes into account the social, cultural and organizational settings in which computing and information technology is used.

Medical informatics[85] or more recently *health informatics*, a somewhat broader concept, are used interchangeably, for the professional and scientific application of informatics within the medical area.[d] The electronic revolution was early on anticipated to have an impact on healthcare.[3] Health informatics can be regarded as an umbrella for medical informatics, bioinformatics, and pharmacoinformatics, reflecting that informatics plays a significant role in all parts of health care.

Pharmacoinformatics is the discipline where, equivalent to medical informatics, ICT intersects with any aspect of drug delivery, from the basic sciences to the clinical use of medications in individuals and populations.[2]

Data and information

Studies in informatics are associated with the concept of information. At a glance, the concept may seem rather straightforward and familiar. The word *information* can be derived from the Latin noun *informatio* (concept or idea) and the verb *informare* (give form to, to form an idea of). In Greek, the ancient word for *form* was *eidos*; used by Plato and Aristotele to denote the ideal identity or essence of something. Today, some scientists in physics claim that the universe is built on information and that the essence of quantum mechanics, the irreducible kernel from which everything else flows, the atom of information, is the bit - the quantity contained in the answer to a yes or no question.[206]

Symbols have been used by mankind for story telling since ancient times. Famous examples are cave paintings (prehistoric 30,000-40,000 years ago) and rune stones (Early Middle Ages). In the present, these symbols can convey a story of human life over space and time, unintentional or with a certain purpose. But not until it was meaningful for man to gather data in a way that it could be presented for other humans on a larger scale, independent of time and space, did the concept of information become commonly used. The concept of information may appear both vague and disguised by human inconsistency, but is still widely used, with 2,690,000,000 hits when 'googled' (May 17, 2007). A

[d] The first global MEDINFO conference on medical informatics took place in Stockholm, Sweden in 1974.

survey of scientists understanding of the concepts of data, information and knowledge revealed that they bore a diversity of meanings.[210]

The content of the human mind has been suggested to be classified into five categories. The first four categories relate to the past; they deal with what has been or what is known. Only the fifth category, wisdom, deals with the future because it incorporates vision and design (Table 1).[13]

Table 1. *Classification of the human mind, after Russell Ackoff.*[13]

Category	**Description**
Data	Symbols
Information	Data that are processed to be useful; provides answers to "who", "what", "where", and "when" questions
Knowledge	Application of data and information; answers "how" questions
Understanding	Appreciation of "why"
Wisdom	Evaluated understanding

Information has been presented as part of a cascade Data, Information, Knowledge, and Wisdom (the DIKW hierarchy) (*Figure 6*),[35] and also as a DIKW pyramid with data in the base and wisdom at the top. First to mention the hierarchy between information, knowledge, and wisdom was the poet T.S. Eliot in 1934[70]

> "Where is the wisdom we have lost in knowledge?
> Where is the knowledge we have lost in information?"

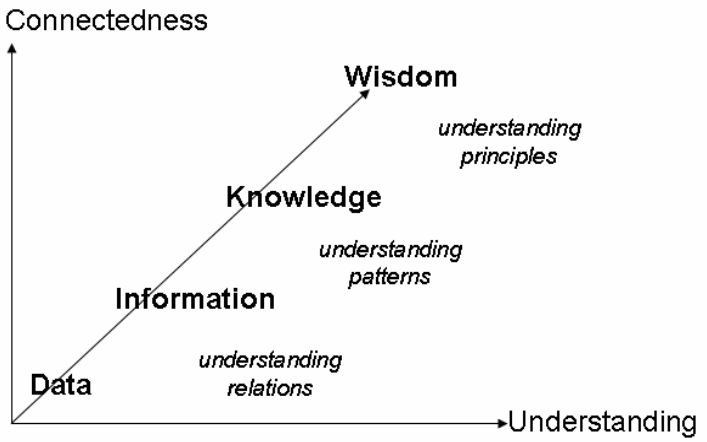


Figure 6. The cascade of Data, Information, Knowledge, and Wisdom (DIKW) after Gene Bellinger et al. [35]

The predominant difference between data and information would be that information should have some kind of meaning to humans—at least to some,

while data are merely representations without a meaning. Data are stored and processed in computers, while information is not.

eHealth

During the 1990s, as the Internet exploded into the public consciousness, a number of e-terms began to appear and proliferate.[e] The terms were useful: eMail brought new possibilities for people to communicate rapidly and share experiences; eCommerce proposed new ways to conduct business and financial transactions through the Internet. The introduction of eHealth, describing the interaction between man, machine, and medicine (*Figure 7*), represented the promise of ICT to improve health and the healthcare system.[150] In an eHealth Ministerial Declaration, 22 May 2003, ministers of the EU defined that "eHealth refers to the use of modern ICT to meet needs of citizens, patients, healthcare professionals, healthcare providers, as well as policy makers." [6]

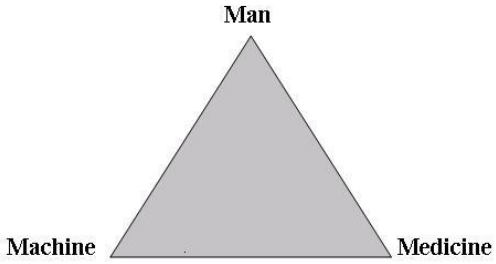


Figure 7. As an applied academic discipline, eHealth represents studies on the interaction between man, machine, and medicine. Man representing the single human individual (professionals or patients) as part of a professional and organizational context (Medicine) in which healthcare services are utilized, interacting in a system environment (Machine) built on ICT.

When the Swedish government in 2006, together with healthcare authorities and other national stakeholders, formed a new national strategy for eHealth the vision was to ensure adequate, safe, and secure healthcare, and good-quality services for all patients.[10] ICT was seen as a strategic tool to more efficiently and effectively utilize resources within the healthcare sector. The future agenda included better basic conditions for ICT in healthcare for the elderly by bringing laws and regulations into line with the extended use of ICT as well as creating a common information structure and technical infrastructure. Also, eHealth solutions needed to be improved and adapted to patient needs by facilitating interoperability between systems, access to information across organizational boundaries and easy access of information and services to citizens. Education, training, and research were seen as crucial to the development.

Another e-term, ePrescribing, is in the realm of the present thesis.

[e] 'e' is short for electronic, but has also been used as a prefix to indicate that something is Internet-based

Implementation of new technology

Organizational and sociological aspects

The implementation of new technologies not only involves the technological aspects, but entails organizational and sociological aspects as well.[129] To understand the intricate interplay, the triangle on man – machine – medicine has to be considered coordinated. Also, technical change must be seen as a process, not as an event.[44]

In a democratic society, man, as a social being, has the option to make a strategic choice to opt out,[52] or to take part and negotiate his/her participation in an innovation process.[44] Resistance may occur as a consequence of lack of involvement, knowledge, understanding, and education. New technology may also introduce a more complex process[137], which is harder to comprehend for the single individual for cognitive reasons. For the individual, the objective reality, attitude structures, social reality, and social norms have an impact on behavior.[136]

In the interaction between man and machine, the socio-technical perspective,[120, 128] the behavioural aspects and often resistance to new technology has been observed. Regularly, the resistance has been associated with the individuals' norms and values in an organizational and professional context.

The technical development of 'the machine' has been argued to be of minor importance,[49] but cannot be ruled out since it is mostly a prerequisite for change.[24, 137]

Diffusion of innovations

The process by which innovations are communicated through certain channels over time among members of a social system has been described as a diffusion process (*Figure 8*). *The innovators* (2.5%) are characterized by venturesomeness, with a desire for the rash, the daring, and the risky. They are followed by *the early adopters* (13.5%), who form a more integrated part of a local system than the innovators. They are esteemed colleagues, respected within their network, who decrease the uncertainty by their adoption of new ideas. *The early majority* (34%), making up one-third of the members of a system, adopt new ideas just before the average member of a system. They interact frequently with their peers, but they seldom hold an opinion leadership, deliberately extending the innovation-decision period. *The late majority* (34%) approach new ideas with a sceptical and cautious air. Last in the social system to adopt an innovation are *the laggards* (16%), possessing almost no opinion leadership, being near isolates in their social network. Their point of reference is the past, adopting a new idea when they are certain that it will not fail.[86, 157]

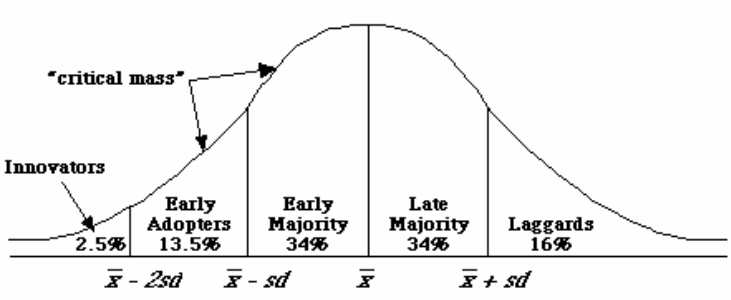


Figure 8. Adopter categorization on the basis of innovativeness, after Everett Rogers, Diffusion of Innovations.[157]

Leadership roles in change

Implementation of new technology in an organization may also require another kind of leadership.[167, 203] A traditional rational leadership, guided by rules and suited for incremental changes, may not be useful. Introduction of revolutionizing new technology that may change an entire business process needs a braver leadership, with a consistent and non-exhausted communication over time, a leadership that enthusiastically involves different stakeholders. Mostly, a complex change in a process involves several organizations, necessitating a multi-stakeholder approach, favouring a horizontal rather than a vertical integration.

Implementation of new technology in healthcare is an example of a complex web of interacting participants, where the same individual may play several roles in different circumstances. The same individual might both be a citizen, a politician, a patient, and a professional, and in those roles being a member of a political party, a patient organization, a professional organization, or holding an influential position within a healthcare body.

Also, it has been argued that the mismatch between the logical, linear, sequential way computer software is developed and the interpretative, interruptive, multitasking, collaborative, distributed, opportunistic, and reactive way healthcare is working, is bound to fail. The technological change takes place as a dynamic cycle; technology changes work practice, which in turn changes technology. Introduction of computerized tools in healthcare should be a guided organizational change by a process of experimentation and mutual learning, rather than one of planning, command, and control.[192]

Training has always been an essential part of any information technology project, even though the best applications are intuitive and self-evident.

History and status of ePrescribing

Pioneers of ePrescribing

The Swedish experience of ePrescribing began in 1981 with a national working party, in collaboration with the county hospital in Jönköping. A group of computer experts, physicians, and pharmacists were given the task of exploring the potential of having a computer in the doctor's office. ePrescribing was hypothesized as the start of a transformation with several interesting lines of e-development for the physicians office: appointment planning, healthcare records, prescribing, information retrieval, communication (laboratory, x-ray, pharmacy), statistics on diagnoses, and prescriptions with adverse drug event reporting. [148, 149, 211]

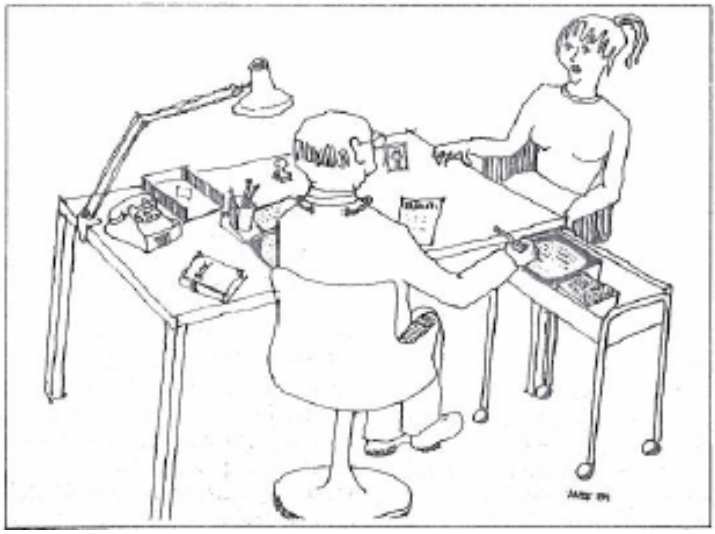


Figure 9. A computer in the doctor's office. From [Computer terminal in the physician's office to assist drug prescription], Lakartidningen, 1982. Reprinted with permission.[148]

The collaboration resulted in 1983 in the world's first Electronically Transferred Prescription (ETP) for outpatients between the computer systems in the doctor's office at a medical clinic and a nearby outpatient pharmacy (*Figure 9*). This happened the same year as the first eMail was transferred to Sweden; a great breakthrough came a decade later when the first e-mail between heads of state was exchanged in 1994 from Carl Bildt to Bill Clinton.[100, 169]

The pilot ETP system was run on a custom built multi-user computer system based on an Intel 8086 processor, with a Winchester disc (10 MB) for storage and touch-sensitive screens. The rationale behind the architecture was the anticipated shift in technology from mainframes to microcomputers, the physicians' lack of experience of keyboards and data entry, and the demand from the physicians not to let technical equipment disturb the patient-doctor relationship

during the consultation but rather to involve the patient in the actual prescribing process (Table 2).

The ICT-system was used during two years, 1983-1984, in regular outpatient healthcare. An evaluation of the eight physicians' attitudes, after the transfer of 3-4,000 prescriptions, concluded that the doctor, the patient and a computer could work very well together during a consultation.[211]

The first pilot project in Jönköping was followed by several others during the 1980's at different healthcare centres in Sweden: Lerum/Gråbo,[17] Jönköping/Bankeryd, Sollentuna, Sundbyberg, and at the medical clinic in Linköping; both with handheld and stationary computers; with stand-alone systems and integrated with EHRs at different healthcare organizations. Standardization of the ePrescription format, both information content and communication protocols, were also subject to several years of intense work, gaining approval from stakeholders, both nationally and internationally.

Table 2. *Rationale for the first pilot project with electronic transfer of prescriptions (ETP) for outpatients.*[148, 149, 211]

Actors	**Requirements and prerequisites**
Physicians	Speediness, ease-of-use, flexibility, uninterrupted patient relation, decision-support-system, and increased cost-consciousness. Inexperienced typewriters and computer users.
Pharmacists	Increased efficiency, expanded information role, and better customer service. Improved inter-professional teamwork.
Patients	New services and shorter waiting-time. No paper prescriptions. Personal integrity and security.
Technology	From mainframes to microcomputers, data communication.
Organizations	Agreements on costs and responsibilities. New cutting-edge technology.
Authorities	Regulations of ETP.

A computerized decision-support system

During the first pilot project, physicians were alerted by a CDSS for side effects and contraindications like kidney or liver disorders, breastfeeding and other vital patient information. The idea was that the information given to the patient at the doctor's office should be in line with information disseminated at the pharmacy. Other features tested for the first time in Sweden were the prescribing of small test packages, automated calculation of package sizes and amount based on the prescribed dose schedule and time period, and the presentation of the prescribing costs to the physician in an effort to establish a more cost-conscious attitude. For reasons of patient integrity, the storing of patient history was not assumed to be realistic.

Frequent prescriptions were presented as favourites with ready to use prescriptions for drugs; strength, dose schedule and treatment regimen or amount and days supply with fixed alternatives. For flexibility, entry of dose regimen

and treatment time was also allowed as discrete values (1×3), intervals (1-2×1-3) and free text. The system was based on two-tier diagnosis menus recommending appropriate therapy in concordance with the formulary of the Pharmacy & Therapeutics committee.

The first regulation of ETP

In 1984, Swedish authorities regulated for the first time the ETP, including the test package and dose schedule/time period prescribing features.

Lines of development

At an international conference on Human-computer communications in healthcare in Stockholm, Sweden, in 1985, two different lines of development were predicted, based on the experimental project in Jönköping: a) *small handheld*, touch-sensitive computers with large storage capacity but limited functionality and b) *large-scale integration* with healthcare information systems.[211] The second line of development came to predominate in Sweden. In the year 2006, sixteen EHR systems were approved to transfer ePrescriptions to pharmacies. An independent web site offered ePrescribing functionality too.

The first predicted line of development became a tool in every man's hand (cell phone, agenda, camera, communicator) about two decades later and is now being implemented as a prescribing tool in, for example, the US (*Figure 10*). With new technology, the two different lines may now be offered in a coordinated fashion, using the same software in different devices, depending on user preference and circumstances. The portable devices may be preferable in home care[42, 58], being in connection with large hospital information systems, with the same information resources available remotely as at hospitals or synchronized after docking the stationary system.

There are software products commercially available including features like ETP with refills and renewal of prescriptions, decision support for drug utilization review at the point-of-care to monitor drug interactions, prior adverse reactions, dosage, duplicate therapy, and drug-to-health state verification. These products also offer access to patients' medication history with patient allergy checks, to drug monographs and may check Pharmacy & Therapeutics formulary compliance and the availability of generic equivalents.

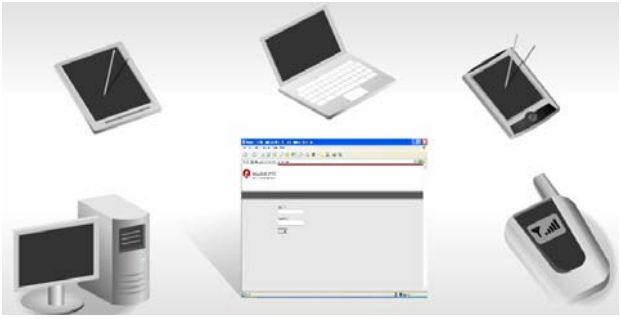


Figure 10. Example of commercially available web-based products for ePrescribing. Prescribers may connect to the same information source, from left to right, by a stationary personal computer (PC), a wireless tablet PC, a portable laptop PC, a handheld Personal Digital Assistant (PDA), or an internet enabled mobile phone, connected to the same software.[11]

Further implementation

The development of ePrescriptions in Sweden has increased rapidly since a new strategy was decided at the end of the 1990's (*Figure 11*), with an actual penetration rate of ETP of 65% (April 2007: 2.2 million ETPs *per* month) of all new prescriptions. This was the result of a decisive strategic action within the National Corporation of Swedish Pharmacies (Apoteket AB) in cooperation with the different regional healthcare bodies and national players. Carelink, a co-operating network for healthcare in Sweden, were instrumental in the deployment of the technical platform for secure communication, the Sjunet.[134] A national project organization was coordinating and supporting activities in regional teams.

A national mailbox for ePrescriptions allows the patient to have access to valid prescriptions at any pharmacy with the presentation of valid identification. Patients may also store their prescriptions in a national online repository, with no need for paper-prescriptions and with the introduction of new services, like mail-order prescription drugs.

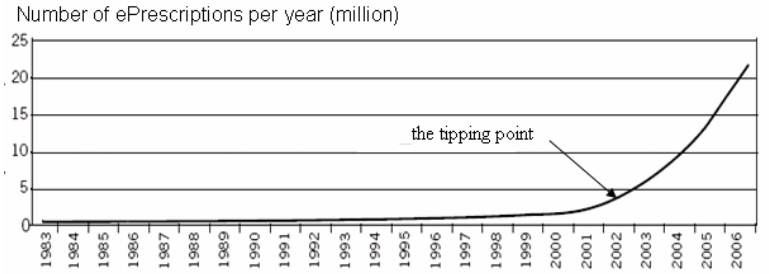


Figure 11. Number of ETPs *per* year in Sweden.[214] Twenty years after the first pilot project the tipping point for the new technology occurred. [83]

Storage of prescription data

One approach to improve the situation for prescribers has been to store information on the *prescribed* therapy in databases at institutions or within larger regional organizations, mostly as part of an EHR. When prescribing, the physician will be able to check the patient history for polypharmacy, interactions and different kinds of contraindications. Automated systems for interaction alert may also be integrated in these systems. Results of the alerts may be to refrain from prescribing, adjusting the dose or monitoring the plasma concentration of the drug. Discontinuation of previous prescriptions may also be relevant.

Another approach to provide prescribers with medication history has been the new legislations in Denmark (Medication Profile)[106] and Sweden (National Pharmacy Register) (II) allowing nationwide databases with information on *dispensed* prescriptions at the pharmacies. The information is accessible by the patients and with patients' conditioned consent to prescribers and dispensing pharmacists (*Figure 1*) for a limited period of time (Denmark 24 months and Sweden 15 months). These databases comprise a large proportion of the national population and are subject to strict security regulations to ensure individual confidentiality.

Both approaches have a need for common standards regarding identification of individuals, codification, classification, and nomenclature of terms and information, control for duplicates of information, information structure allowing aggregation of information and a process-oriented architecture. The information systems should be suitable for decision and process support at the point of care, for follow-up of individual patient care, and of healthcare activities, as well as for statistics and research (Table 3 and Table 4).

Table 3. *National registers of dispensed medications in Sweden since July 1, 2005.*

Registers (Host organization)	**Purpose**	**Accessibility**	**Some characteristics**
National Prescribed Drug Register[201] (National Board of Health and Welfare)	Statistics, epidemiology and scientific research	Researchers	By application only No time restrictions Data may be linked with other healthcare registers
National Pharmacy Register (II)[213] (National Corporation of Pharmacies)	Safer future prescribing	Individuals, prescribers and dispensing pharmacists	Secure digital signature for Internet 15 months storage Content limited to patient, drug and date of dispensing
Online Prescription Repository[214] (National Corporation of Pharmacies)	Prescription services	Individuals and dispensing pharmacists	Secure digital signature for Internet PIN-code for phone services 15 months storage

Epidemiologic research

The equivalent information to that in the National Pharmacy Register is collected and transferred to the Swedish National Prescribed Drug Register, intended for *statistical, epidemiologic,* and *scientific* purposes, whereby drug and disease associations and the risks, benefits, effectiveness, and health economical effects of drug use may be explored.[201] There is no time constraint for storing information in this database, which is hosted by the National Board of Health and Welfare.

The online prescription repository

The change in legislation in 2005 in Sweden also made an online prescription repository possible. Beginning in 2006, pharmacy customers were offered the option of storing their prescriptions in a national pharmacy database. The prescriptions are available online on the internet with a secure digital signature, by phone with a 7-digit numerical personal identification number (PIN), and at any Swedish pharmacy by presenting a legal personal identification document. New services were launched during 2006 with, for example, home delivery of prescribed drugs.[214]

Table 4. *Some features of different methods for storing of prescription data.*

	Local	**National**
Prescribed data	*Advantages:* Market oriented Easy to collect Controlled access; few users *Disadvantages:* No data on non-compliance Generalizability	*Advantages:* Unbiased and updated information on physicians' medication orders *Disadvantages:* Difficult to collect - low degree of standardization and interoperability No data on non-compliance
Dispensed data	*Advantages:* Mirrors primary non-compliance; closer to what is actually consumed *Disadvantages:* Small samples for research No data on changes in doctors' orders	*Advantages:* Relatively easy to collect due to financial requirements Entire national population – close to true exposure *Disadvantages:* Need for national systems for authentication and control of access No data on changes in doctors' orders

Ethical and legal considerations

In ePrescribing, modern technologies' capacity for making large population databases, with individual-based healthcare information, available, for a better utilization of drugs, introduces ethical and legal challenges.

From the society's perspective, often being responsible for the quality of healthcare and also being a major financier of drugs, both in hospitals and in ambulatory care, it may seem reasonable to use population-based resources of individuals' drug information, to control spending and improve public health.

From the individual's perspective it may be favourable too, to have individual drug information readily available in healthcare. Prescribers' and pharmacists' utilization of the new tools may provide a better basis for decision-making and may also detect and prevent unintended drug interactions and adverse drug events. Most individuals are truly interested in benefiting from modern medicine's progress but may, at the same time, be cautious about the confidentiality of one's personal health information. The risk for abuse, of just bad procedures, making sensitive personal information available for unauthorized personal in healthcare must constantly be controlled, if the individuals are expected to have confidence in the use of large databases in healthcare.

Internationally, two models, making personal health records available, have been presented; the opt-in and the opt-out model, where individuals have the choice to participate voluntarily or to reject to contribute to the collection of their personal information.[91, 177, 191] Another approach to solve this dilemma, in the national dispensing databases in Denmark and Sweden, has been to mandatorily allow the collection and registration of the information in the national databases and give the patient the right to restrict the accessibility of the information to certain individual healthcare professionals and also to permit the patient full transparency to whom has accessed the information. According to national laws, unauthorized access might be subject to a lawsuit.

For individuals to have a confidence in the use of new information technology in healthcare, a reasonable balance between benefits and risks is necessary.

For epidemiologic research, the large population databases offer enormous prospects to further evaluate the use of medications in the population, both regarding effects and side-effects. The linking of different healthcare databases might even provide new causal evidence for relations between exposure and disease.[97, 201] Still, the use of the individual-based research databases must be handled restrained, with strict regulations, to ensure public confidence. For scientists too, the ethical reflections are pivotal.[155, 185]

Aims of the thesis

The thesis aimed to study the developments, in the area of pharmacoinformatics, of the electronic prescribing and dispensing processes of drugs - in medical praxis, follow-up, and research.

More specifically, the objectives were

- to study a regional, individual-based prescription database as a model for a national pharmacy register, by examining the frequency, distribution, and determinants of potential drug interactions (I),
- to describe the information content in a new national pharmacy register for clinical medical praxis, follow-up, and pharmacoepidemiologic research (II),
- to analyze the co-variation between polypharmacy and potential drug interactions, and how it changes over three decades, and to examine the relative risk for actual drug combinations (III), and
- to assess the risk of prescribing errors for ePrescriptions compared to non-electronic prescriptions, by evaluating dispensing pharmacists' clarification contacts with prescribers (IV).

Materials and methods

A common denominator for the four studies (Table 5) in the thesis is the point of measure; the dispensing of prescribed medications at pharmacies. Data, collected either mandatorily (II), voluntarily with informed consent (I, III), or in a specifically designed study (IV), has been stored in large databases and been analyzed with epidemiologic measures and statistical methods. All data processing in the studies was done anonymously, without the personal identification number, and was hence not subject to ethical approval.

Table 5. *Overview of aims, materials, and methods of the studies in the thesis.*

Aims	Materials	Methods
I. Study a regional, individual-based prescription database as a model for a national pharmacy register	The Jämtland cohort 2003-04 n=8,214 individuals	Retrospective database study Frequency, Cumulative incidence, RR (95% CI) Interaction detection system t-test
II. Describe a national pharmacy register	The Swedish National Pharmacy Register 2005-06 n=6,424,487 individuals	Population-based database study Prevalence, Incidence, RR (95% CI)
III. Analyze the co-variation between polypharmacy and potential drug interactions over time	The Jämtland cohort 1983-04, 1993-04, 2003-04 n=8,318; 8,726; 8,214 individuals	Cross-sectional study Frequency, Cumulative incidence, RR (95% CI) Interaction detection system t-test, Kruskal-Wallis
IV. Assess quality aspects of ePrescriptions	Dispensing at three mail-order pharmacies 2006 n=31,225 prescriptions	Prospective direct observational study RR (95% CI)

Study design

A regional individual-based prescription database

Detection of drug exposure, potential drug interactions, and polypharmacy

To detect potential drug interactions in a general population, a regional individual-based prescription database, as a model for a national pharmacy register, was studied (I). The cross-sectional study (III), was also designed to make a historical comparison of drug exposure during a three decade study period

(1983-1993-2003), analyzing the co-variation between polypharmacy and potential drug interactions. Individuals were enrolled from the Jämtland cohort study.[45-48]

The Jämtland cohort study

Jämtland is a small county (1.4% of the Swedish population) in the northwest part of Sweden. The proportion of the population aged 65 and above was 20% in Jämtland in 2004, as compared to 17% in all of Sweden.[12] The county of Jämtland is mainly rural with one large town. The cohort contained all inhabitants born on the same 4 days each month. All individuals included are informed and may have left the cohort whenever desired. However, the drop-out from the cohort is very low. Since 1970, all ordinary prescriptions dispensed at pharmacies within the county are registered. Medications dispensed for individuals residing in hospitals or in nursing homes, without ordinary prescriptions, are not registered. The register does not contain information on sales of over-the-counter (OTC) drugs or herbal remedies. Data recorded included the social security number (giving age and gender), the drug and amount dispensed, the dosage and the time of dispensing. Data were recorded through Apoteket AB.[198]

A model study

The chosen study variables and the length of the study period were intended to mimic the new National Pharmacy Register (II), which makes prescriptions of an individual available for 15 months to prescribers, pharmacists, and the registered individual. By including similar information as the National Pharmacy Register, the design of the study (I) was intended to provide a model for the new register.

The National Pharmacy Register

A study (II) was conducted to describe the information content of the National Pharmacy Register.

Prevalence of dispensed drugs in Sweden

The National Pharmacy Register is individual based and contains data from all dispensed out-patient prescriptions at all Swedish pharmacies from July 1, 2005, including multi-dose dispensed prescriptions and legal internet sales. Data collection from about 900 pharmacies and the National Pharmacy Register is administered by Apoteket AB.

The registered information is available for the registered individual at the pharmacy counter, with valid identification, and on the Internet, with a secure digital signature. After conditioned consent from the registered individual, the register will be accessible on-line for prescribers and dispensing pharmacists. The registration is mandatory and includes the name and the personal identifi-

cation number (social security number) of the registered individual along with day of dispensing, drug name, prescribed amount and dosage (Table 6). The information is stored in the register for a period of 15 months and thereafter cleared. All prescriptions dispensed at pharmacies, including multi-dose dispensed drugs at pharmacies, but not drugs dispensed in hospitals and OTC sales, have been stored in the National Pharmacy Register since July 2005. Use of the medication history in this register is, by a special law, restricted to clinical use and documentation (II).[213]

Table 6 *Information content in the National Pharmacy Register.*

Object	Variable
Patient	Name
	Personal identification number (including birth and gender data)
Drug	Name
	Amount
	Dose
Pharmacy	Date of dispensing

Quality assessment of ePrescriptions

To assess how the implementation of ePrescriptions has changed the quality (accuracy, completeness, correctness) of the prescribing process, a prospective direct observational study (IV) was performed at three of four Swedish mail-order pharmacies with a large proportion (38-75%) of ePrescriptions.

Mail-order pharmacies

The same regulations and operating procedures apply to the mail-order pharmacies as to the other about 900 outpatient pharmacies in Sweden; all run by Apoteket AB. However, different from other pharmacies, the pharmacists cannot communicate with the patient face-to-face at the pharmacy counter. Also, dispensed prescriptions emanate not only from prescribers in the same neighborhood, so pharmacists generally do not have personal knowledge about physicians' prescribing habits. Pharmacies in Sweden do not have access to automated software for prospective Drug Utilization Reviews (pDUR).[53, 75, 77] Hence, all prescriptions were manually examined by the pharmacists. At the time of study, iterated ePrescriptions in Sweden were printed as paper prescriptions at the pharmacies after first being dispensed, and delivered to the patient for subsequent refilling (IV).

The study was conducted during three consecutive weeks in February-March 2006, in the natural setting, by five trained, final year pharmacist students observing all pharmacists' interventions; non-disguised and in real time. The dispensing process was aligned between the three pharmacies, to reduce differences depending on variation in operating procedures. The structured observations were recorded and classified by means of an internationally developed

protocol, adapted and modified in Swedish (Appendix 2).[92, 117, 118] In order to have a consistent reporting and classification, one of the authors supervised the reporting process.

The outcome measures in the study (numbers and frequencies of prescription errors, causes of clarification contacts, and time and results of interventions) were related to statistics of dispensed prescriptions, collected from Apoteket AB for February 2006 for the three studied pharmacies. The collected statistics were adjusted for number of workdays (15/20), due to different time periods for our study (15 workdays) and the collected statistics (20 workdays) (IV).

Study subjects

The Jämtland cohort

In the retrospective database study (I), all individuals in the Jämtland cohort who collected two or more ordinary prescriptions at pharmacies within the county of Jämtland during the period October 2003–December 2004 were included. The age distribution in the Jämtland cohort was 0–14 (10%), 15–64 (64%), 65–84 (22%), and 85+ (3%) years as compared to 0–14 (9%), 15–64 (61%), 65–84 (26%), and 85+ (4%) years for the study population (Table 7).

Each individual included in the studies was at risk of receiving one or more potential drug interactions by two or more drugs in combination. An individual could have filled prescriptions with the same generic entity several times during each study period. Also, one single drug combination might have caused multiple interactions by different mechanisms. The above mentioned interactions were registered as one single potential interaction for each individual and each study period. Individuals residing in hospitals or in nursing homes without ordinary prescriptions were not included in the studies (I, III).

Table 7. *Study variables in study I.*

Variables	All	Men	Women
N	8,214	3,467	4,747
Age, mean years ±SD	50.1±22.9	49.9±22.6	50.5±23.3
No. of prescriptions (mean)	119,923 (14.60)	49,590 (14.30)	70,333 (14.82)

The cross-sectional study

In the cross-sectional study, we included all individuals in the Jämtland cohort who collected two or more ordinary prescriptions at pharmacies within the county of Jämtland, during any of the three periods October 1983-December 1984, October 1993-December 1994, and October 2003-December 2004 (III).

The individuals included in the cross-sectional study were about 8,000 for each study period. 45% of the individuals in the 1993-1994 period were present in the 1983-1984 period. 16% of the individuals in the 2003-2004 period were present in the 1993-1994 period, and 16% were present in both the earlier study periods (Table 8).

Table 8. *Study variables in study III.*

Variables		1983-1984	1993-1994	2003-2004
N		8,318	8,726	8,214
	Men	3,490	3,666	3,467
	Women	4,828	5,060	4,747
Age, mean years ±SD	All	46.2±24.0	46.7±24.3	50.1±22.9
	Men	46.5±24.9	46.8±23.7	49.9±22.6
	Women	46.0±23.4	46.5±25.1	50.5±23.3
No. of prescription (mean)	All	75,263 (9.05)	92,380 (10.59)	119,923 (14.60)
	Men	30,731 (8.81)	36,631 (9.99)	49,590 (14.30)
	Women	44,532 (9.22)	55,749 (11.02)	70,333 (14.82)

The National Pharmacy Register

To study the National Pharmacy Register, all individuals (6,424,487) filling prescriptions at Swedish pharmacies during the first 15 month period (July 2005 – September 2006) were included (II) (Table 9). The study population was stratified by gender and age (10-year classes) on July 1, 2005. Results were compared to statistics on the number of individuals by gender and age group in the Swedish population on December 31, 2005.

Table 9. *Study characteristics in study II (15 months July 2005 – September 2006) (unpublished observations, Apoteket AB).*

Variables	All	Men (%)	Women (%)
N	6,424,487	2,829,335 (44.0)	3,595,152 (56.0)
- dose dispensed excluded	6,265,246	2,772,287 (44.2)	3,492,959 (55.8)
No. of prescriptions	112,417,146	42,989,315 (38.2)	69,427,831 (61.8)
- dose dispensed excluded	76,004,043	30,793,733 (40.5)	45,210,310 (59.5)
Mean number of prescriptions *per* individual	17.5	15.2	19.3
- dose dispensed prescriptions excluded	12.1	11.1	12.9

The prospective direct observational study

In the observational study (IV), all prescriptions (31,225) dispensed during three weeks at the three studied mail-order pharmacies were included. Pharmacist's clarification contacts with prescribers were used during the dispensing

process as the point of measure. All attempts to contact the prescribers were included, whether or not leading to a contact or an intervention during the dispensing process. The frequencies of contacts and contact causes were recorded and evaluated in relation to all other dispensed prescriptions (Table 10).

Table 10. *Number (%) of prescriptions dispensed during three weeks in February 2006 at the studied mail-order pharmacies (IV).*

	New ePrescriptions	**New non-electronic prescriptions**	**All new prescriptions**	**Refill prescriptions**	**All prescriptions**
	7,532	6,833	14,365	16,860	31,225
	(52.4) [a]		(46.0) [b]		
Pharmacy 1	2,055	698	2,753	3,127	5,880
	(74.6) [a]		(46.8) [b]		
Pharmacy 2	3,058	2,182	5,240	5,232	10,472
	(58.4) [a]		(50.0) [b]		
Pharmacy 3	2,419	3,953	6,372	8,501	14,873
	(38.0) [a]		(42.8) [b]		

Only ordinary drug prescriptions dispensed for humans were included. Monthly statistics were adjusted (15/20) for the three week period.

[a] % of all new prescriptions

[b] % of all prescriptions

Prescribing errors detected in the first-line were escalated to a second-line, for further investigation and clarification contact with prescribers. During the second-line, some of the prescribing errors were resolved by pharmacists' own appraisal, after consulting the patient, their relatives and different information sources.

Methods

Interaction detection

Potential drug interactions were detected with a specifically designed computerized detection system (developed by Sten-Erik Öhlund), based on an interaction database (Pharmaceutical Specialties in Sweden, 2003). The drugs were matched by the Anatomical Therapeutic Chemical (ATC) Classification System for each subject using an interaction classification system. Each potential interaction was classified according to the clinical relevance (Table 11)(I, III).[175]

During each study period of 15 months, the included subjects' prescriptions were recorded with date of sales, the drugs named by trade name, and by the ATC, along with information about the individual, including blinded individual number, gender, and age. We registered the above mentioned interactions as one potential interaction for each individual.

Table 11. *Drug interactions classified by clinical relevance.*[175]

Drug classification	Clinical relevance
Type A	Probably no clinical relevance
Type B	Clinical relevance not completely assessed
Type C	The interaction may modify the effect of the drug, however this can be mastered by individual dose adjustment, and/or by determination of the plasma concentration of the drug
Type D	The interaction may have serious clinical consequences, such as severe adverse effects, no effects, or the modified effects may be difficult to control by individual dose adjustment

Potential drug interactions

The term 'potential drug interaction' was referred to as 'the possibility that one drug may alter the intensity of the pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of a new effect that is not seen with either drug alone'.[102] The definition of the general expression 'drug', was defined as the chemical entity or substance, which is the fifth level in the ATC classification.[188]

Polypharmacy

The concept of polypharmacy might both refer to the use of multiple medications (many drugs) and to the excessive use of concomitant drugs (too many drugs).[20] We referred to the concept of polypharmacy in the general sense of many drugs, without any standpoint regarding appropriateness or number of drugs (I, III). We did not evaluate whether or not the drugs were in fact consumed concomitantly. Drugs dispensed during each study period of 15 months were considered as part of the polypharmacy.[61, 204]

Epidemiologic measures

Traditionally, epidemiology is the scientific discipline that studies the frequency, distribution, and determinants of a particular disease. We have studied the occurrence of *potential* drug interactions, not the actual outcome, by using the epidemiologic measures frequency, cumulative incidence and relative risk (I, III).

Frequency

A frequency distribution was used to compare counts of potential drug interactions related to the number of individuals in each group (gender, age, and type of interaction). Counts were based on the individual subjects and related to the number of individuals in the population at risk at each study period. The distribution of potential drug interactions was stratified for age groups, gender, and number of drugs on an individual basis. If not stated otherwise, the age strata used were 0-14, 15-64, 65-84, and 85 years and above (I, III).

Cumulative incidence

The cumulative incidence was used as a measurement of the occurrence of potential drug interactions in the study population (I, III). The cumulative incidence can be regarded as a measurement of the average risk on an individual level, conditioned that the risk is defined as the probability of an individual having a potential drug interaction during the study period. The cumulative incidence was calculated as cumulative incidence = n/N, where n denotes the number of individuals receiving drugs with potential interactions during the study period and N denotes all the subjects at risk. The cumulative incidence always ranges from 0 to 1. It should be noted that the cumulative incidence was applied to each time period of 15 months.

Relative risk

The relative risk (RR) for one group compared to another was estimated by the rate ratio between cumulative incidences, RR = cumulative incidence$_1$/cumulative incidence$_0$. Cumulative incidence$_1$ denotes the cumulative incidence of a potential drug interaction in the observed group, and cumulative incidence$_0$ refers to the cumulative incidence in the population at risk, less the observed group. The RR was used as an effect measure of the strength of the association. When RR equals unity (=1) there is no difference between the compared groups.[161] For comparison between different study periods, the RR was calculated as a ratio between risks for the two compared groups; RR = cumulative incidence$_1$/cumulative incidence$_2$ (III). RR was also employed to compare rates of prescribing errors between two groups (IV).

Prevalence

The prevalence was defined as the proportion of individuals filling prescriptions in the Swedish population during 15 months (II).

Incidence

The incidence was defined as the total number of new individuals filling prescriptions in the Swedish population *per* month, after a wash-out period of 12 months (waiting-time distribution) (*Figure 12*) (II).[96, 98]

Incidence rate

The incidence rate was defined as the number of new individuals filling a prescription x 1,000/number of individuals at risk (the entire Swedish population) after a wash-out period of 12 months (II).[96, 98, 179]

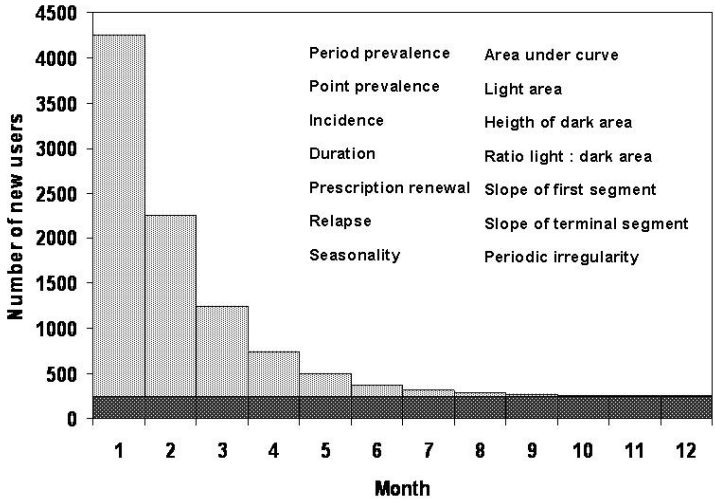


Figure 12. Hypothetic waiting-time distribution. From "Drug utilization statistics for individual-level pharmacy dispensing data", Jesper Hallas, Pharmacoepidemiology and Drug Safety, 2005. Copyright John Wiley & Sons Limited, 2004. Reproduced with permission. [98]

Statistics

P-values were derived for two-sample t-tests. The Kruskal-Wallis non-parametric test (III) was used to compare sample distributions of unpaired, not normally distributed groups. Direct standardization (III) was employed for age adjustment. RRs with a 95% confidence interval (95% CI) including 1 were considered not statistically significant.

Microsoft Excel (Microsoft Corp. Redmond, WA, USA) 2003, Statistix 8 (Analytical Software, FL, USA), and SPSS 14.0 for Windows (SPSS Inc. Chicago, IL, USA) were used for descriptive statistics. Episheet (http://members.aol.com/%20krothman/episheet.xls) was used to calculate RRs with 95% CI.

Results and comments

A regional individual-based prescription database

Drug exposure and risk of potential drug interactions with polypharmacy

The 15 month (2003-04) retrospective study of a regional individual-based prescription database (n=8,214) in the county of Jämtland was designed as a model for a national pharmacy register (I). On average, each individual filled 14.6 prescriptions and 3.6% of the individuals filled more than 15 different drugs. The risk of receiving a potential drug interaction type A-D was estimated as a cumulative incidence of 0.26 overall (0.22 for men and 0.29 for women). Of the more severe type D interactions, relatively few potential drug interactions were present; only 2 *per* 100 individuals (*Figure 13*). The age adjusted risk for women was 1.30, but after excluding the group G Sex hormones and modulators of the genital system, no elevated risk was shown. The risk of receiving a combination of potentially interacting drugs was positively correlated with age and polypharmacy.

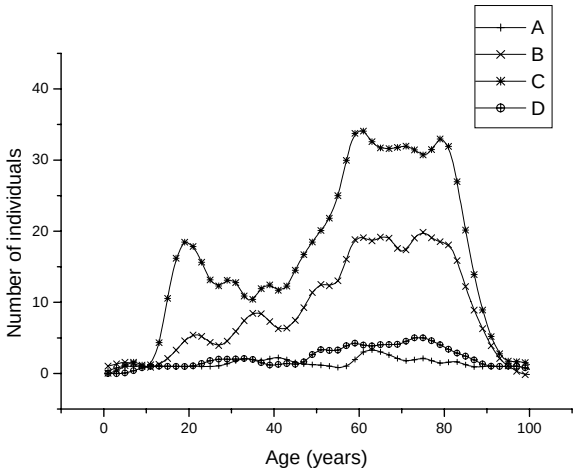


Figure 13. Frequency distribution of potential drug interactions for type A, B, C and D according to age (I).

The National Pharmacy Register

Prevalence of dispensed drugs in Sweden

The prevalence of dispensed drugs was studied with the new Swedish National Pharmacy Register; a national database intended for clinical purposes that includes information for the majority of the population with the objective to improve drug utilization (II). In this population-based database study, the National Pharmacy Register (6.4 million individuals) for clinical use was described; the prevalence of individuals with dispensed drugs in the Swedish population (9,047,752) was 71.0% (women 78.8% and men 63.1%), during the 15 month study period (2005-06) (*Figure 14*). For the elderly, the prevalence was 92.1%, 94.9%, and 94.3% respectively, in the age groups 70-79, 80-89, and 90 and above. For children 0-9 years of age, the prevalence was 62.8%. For women, the prevalence was 77% or more for all age groups 20 years and above (*Figure 15*). The incidence rate for individuals with dispensed drugs was estimated as 12.4 *per* month and 1,000 inhabitants, after a 12 month wash-out period. The mean number of dispensed prescriptions was 12.1 (median 6, Q1-Q3 2-15) *per* individual. For elderly individuals (age group 80-89), the mean number of dispensed prescriptions was 27.8 during the study period (median 24, Q1-Q3 13-38). The RR of having prescriptions dispensed for women *vs.* men was 1.25.

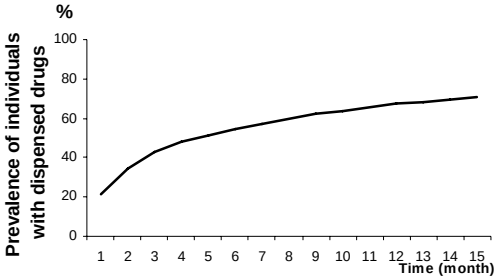


Figure 14. Prevalence of individuals with dispensed drugs in the National Pharmacy Register during the first 15 months.

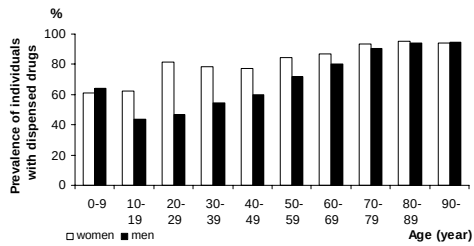


Figure 15. Prevalence of individuals with dispensed drugs according to age groups and gender in the National Pharmacy Register during the first 15 months.

Co-variation between polypharmacy and potential drug interactions

Increase in prescriptions over three decades

To evaluate the change in risk over time of receiving potentially interacting drugs and to examine the RR for actual drug combinations, a cross-sectional study (III) was designed as a historical comparative study, during three decades (1983-1993-2003). The RR of receiving potentially interacting drugs increased for type C interactions, RR 1.177, and decreased for type D interactions, RR 0.714, from the period 1983-84 to 2003-04. Polypharmacy increased by 61% (number of prescriptions) during the same time period. The risk of receiving potentially interacting drugs was strongly correlated to the concomitant use of multiple drugs (*Figure 16*). The best fit of equations to data displayed linear relationships for the potential type C interactions and exponential relationships for the potential type D interactions. The pronounced increase in polypharmacy over time implies a growing reason for prescribers and pharmacists to be aware of drug interactions. A few interacting drug combinations were responsible for a large proportion of the risk.

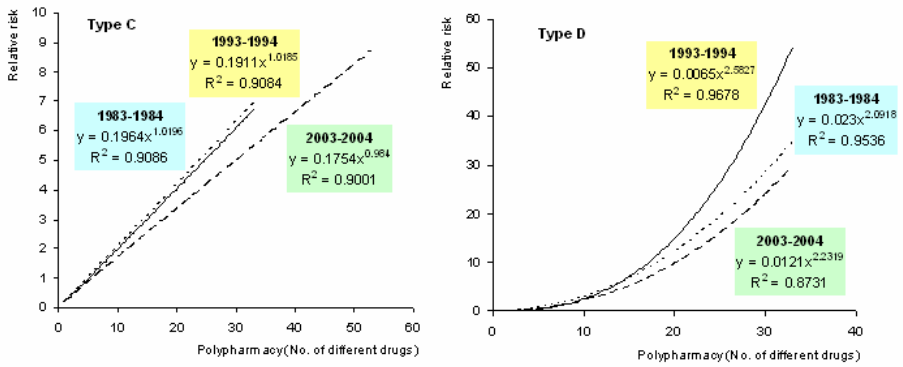


Figure 16. Relative risk of potential interactions type C and D, respectively, correlated with polypharmacy. R^2 are coefficients of correlations for the respective years.

Quality assessment of ePrescriptions

Risk for prescription errors with ePrescriptions

In the observational study (IV), conducted to assess the risk of prescribing errors for ePrescriptions compared to non-electronic prescriptions, we found that new ePrescriptions were associated to a greater extent with pharmacists' clarification contacts, RR 1.69 (95% CI 1.29-2.21); seemingly contrary to the expectation that ePrescribing could have a positive impact on safety, quality, efficiency, and cost-effectiveness. The main reasons for clarification contacts were missing or ambiguous information for 'Dosage and directions for use', RR 7.60 (95% CI 2.83-20.4), compared to other clarification contacts. While prescribing errors necessitating a prescriber contact only occur in the range of one in one hundred, ePrescriptions overall might still be more efficient and cost-effective than non-electronic prescriptions, also taking into account the lower process time for contacts with prescribers for ePrescriptions compared to handwritten prescriptions, which could depend on shorter access time to electronic patient records at the healthcare setting. However, to fulfil the potential of ePrescriptions, quality aspects have to be more persistent in future deployment.

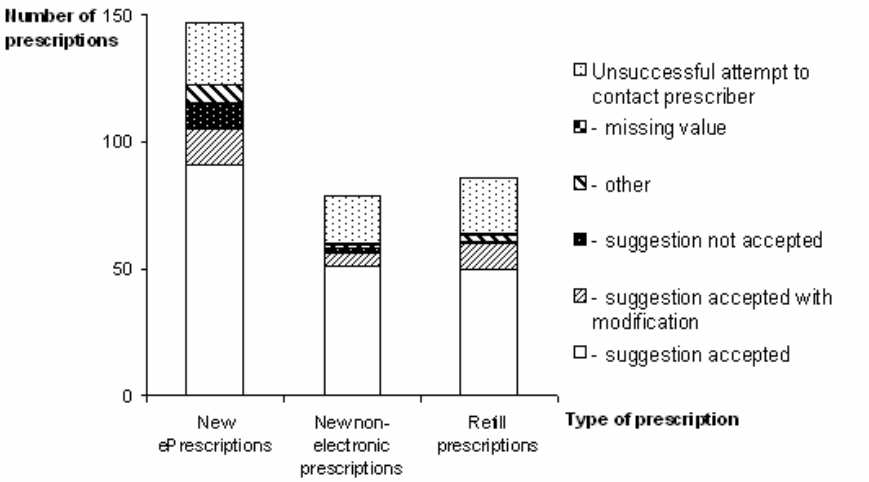


Figure 17. Results of pharmacists' clarification contacts *per* type of prescription (IV).

The pharmacists' clarification contacts with the prescribers resulted in a very high degree of acceptance (90%) (*Figure 17*); supporting the benefit of pharmacists as gatekeepers, to prevent the patient from prescription errors. On the other hand, the different EHRs should be designed to minimize primary errors, so the need for pharmacist intervention will be reduced.

Limitations

For the accuracy of scientific studies, questions of reliability (consistency) and validity (internal and external) have to be taken into consideration, both in design and analysis. To what extent could the results of a study have been affected by systematic or random errors?

A bias is a *systematic error* (not affected by study size) afflicting the design, thus affecting the validity of the study, by confounding, selection or measurement error (information bias and misclassification). A scientific study should attempt to control for and thereby reduce the sources of error.[43]

Studies utilizing large databases might have problems with *information bias*, resulting in a non-differential misclassification; is the exposure information reliable? Are all individuals that have been exposed to drugs registered? How can that have influenced the results of a study?

Internal validity

In study III, we controlled for age, but the estimates of polypharmacy and potential drug interactions were only slightly reduced, indicating that the detected differences seem to be dependent on changes in the market and prescribing patterns.

The risk for misclassification in observational studies (IV) also has to be taken into account. We used independent observers documenting the interventions to ascertain a high degree of capture. Other studies with self-reported interventions have had 10-fold variation in reported error rates, indicating low validity. The alignment of the operating procedures and the supervision of the protocol employed, aimed at promoting a consistent reporting, minimized the inter-individual variation. We do not think that misclassification in the study influenced our results to any considerable extent. However, the risk for a misclassification in the *collected statistics* cannot be ruled out. The risk for misclassification was evaluated in a small sample (1 pharmacy, 2 days) and revealed that, in some cases, refill prescriptions (<5%) could have been recorded as new prescriptions. A sensitivity analysis revealed that the risk estimate for ePrescriptions, RR 1.69, could be slightly overestimated; an assumed differential misclassification of 5% of the non-electronic prescriptions yielded a RR of 1.48 (95% CI 1.13-1.94).

External validity

As a true measure of the occurrence and the risk of receiving drugs with potential interactions, the results in studies I and III were probably slightly *underestimated*, since only prescribed medications were included and not illicit Internet sales, OTC non-prescription medications, herbal, and/or home remedies. Furthermore, drugs dispensed in hospitals and nursing homes without ordinary

prescriptions were not included in the study. On the other hand, the study may also have *overestimated* potential interactions, as the time relationship for the concurrent use of drug combinations was not evaluated during the study period.[39] As a clinical tool, an interaction classification system may be questioned as some interactions by clinicians may be found to be safe in daily use. In our study, we used the classification 'as is' and did not evaluate clinical relevance.

The prevalence and incidence of dispensed drugs may be viewed as indicators of the health status of a population. However, drugs are not only used for curing and alleviating diseases but also for prevention, contraception, and more rarely, diagnosing. Moreover, we did not measure the actual consumption of the drugs, only the prescriptions dispensed at the pharmacy (I-IV).

That the population in the Jämtland cohort is older than in Sweden in general might also imply an overestimate of the cumulative incidence of potential interactions among the elderly. However, this circumstance did not have any effect on the risk estimates. The validity of the Jämtland cohort was explored by comparing the 20 most common classes of drugs, at the second level in the ATC system, measured as defined daily doses, DDD/1,000 inhabitants/day in the cohort with the 20 most common classes for all of Sweden. The same groups were the most common in both cohorts but some differences in the level of use were found.

The magnitude of prescribing errors was in the range of 0.5-1.6% for new prescriptions (IV). The proportion of prescription errors in other studies varies between 0.86-8.7%, the largest value detected at a mail-order pharmacy.[50, 75, 81, 103, 165, 195] The wide range of frequencies in different studies may depend on definitions, methodology, culture, legislation, and available technical solutions. One major reason for the relatively low frequency in the present study may be that we included only prescribing errors that were found to be severe enough by dispensing pharmacists to necessitate a clarification contact with the prescribers. For example, the 'dosage and directions for use' texts are corrected by pharmacists for readability and accuracy to a much greater extent than reported. This may have influenced the low estimates in our study compared to other studies.

General discussion

The present thesis has demonstrated a growing exposure to drugs in the Swedish population, with a correspondingly increased risk for potential drug interactions associated with polypharmacy and age. With this rising trend of medication, associated with medical risks and possible adverse events, the urge for new tools for research and clinics seems justified (II). However, new electronic tools may also introduce new risks (IV), which have to be controlled, not to harm patients.

Empowerment of individuals

In healthcare, a prevailing idea is that individuals increasingly want to participate in their own treatment and medication. This phenomenon has been described as citizen or patient empowerment. With access to the National Pharmacy Register, patients have a new opportunity to get a good overview of their own medication, and to allow prescribers and dispensing pharmacists' access to the information in order to perform a more quality assured drug prescribing in the future.

Also, half a million pharmacy customers (August 2007; one year after launch) were electronically storing their active prescriptions nationally, with the prospect to utilize new pharmacy services like home delivery. Patients might in the future have access to new personalized electronic services like my medication library, my health record, and my healthcare contacts, with automated alerts and reminders. Also, web-based interactive knowledge-based services like 'Ask the doctor' could be followed by 'Ask your pharmacist'.[186]

Physicians

In Sweden, almost all physicians in primary care and a growing number in secondary care are using computers and EHRs as a daily means for documentation, information retrieval and communicating decisions on, for example, the use of drugs. Considering the increase in prescribing of drugs, questions on efficacy and efficiency may be raised; would it be possible to write all those prescriptions by hand? Is the growing prescribing trend dependent on easy access to computers? Is it efficient to produce as many prescriptions as possible during a specified time-unit? These questions warrant further studies.[93]

Considerable efforts have been directed towards the lack of compliance, or adherence, to the prescribed therapy. On the other hand, the pronounced poly-

pharmacy, with accompanied risk increase (I, III), raises questions whether or not a high degree of compliance is always in the interest of the individual patient? A more critical attitude towards prescribing seems relevant. To make modern specific and potent drug therapy cost-efficient, better monitoring and continuous follow-up of patient outcome seems to be beneficial. The National Pharmacy Register could be *one* of several tools for better quality and control in medical praxis (II).

Pharmacists

Since the mid-80's, all dispensing pharmacists in Sweden have used the same software in a national client-server network. Most applications were previously deployed in local servers without external communication, except for batch oriented collection of statistical data. With time, more and more applications have been centralized, accessing nation-wide databases for, *e.g.,* the national mail box for ePrescriptions, the national drug reimbursement insurance, the online prescription repository, and the National Pharmacy Register for medication history. Knowledge-based databases are increasingly web-based, like drug interaction databases.

Still, relatively few applications are available for automated dispensing control, like the pDUR-systems available in other countries. During coming years, it is assumed that this development with more knowledge-based interactive systems will expand, aiming at increased quality assurance and control. Automated checks of all prescriptions with patient specific information, medication history, and knowledge databases might constitute a safe and updated alert system, with, *e.g.,* drug-food idiosyncrasies, drug interactions, maximum doses, and duplicate use of generic substances. This may be done as an automated transfer check, refuting ePrescriptions and alerting prescribers on prescriptions lacking required and appropriate information, thereby reducing the amount of clarification contacts between pharmacists and prescribers.

Personal information on drug exposure, like the National Pharmacy Register, need to be available in healthcare for consulting pharmacists as it is for physicians. With that kind of knowledge-based interactive systems, the interaction between physicians and pharmacists need to develop and mature. Otherwise, the risk for professional conflicts is imminent. Increasingly, pharmacists have to develop their professional role as drug experts in teamwork with other healthcare professionals.[140]

Quality of data

Data is increasingly collected, stored, and retrieved in healthcare. Prescribing data, originally produced to transfer a message from the doctor's office to the pharmacist, may be reused for research or clinical purposes, without being critically examined. To control the accuracy of stored healthcare data, the quality assurance process need to be carefully examined (II, IV).

Collection of personal prescription information

Large-scale collection of personal prescription information has been developed for dispensed prescribing data. What, in Sweden, started as data communication of prescriptions between local healthcare units and local pharmacies, has developed to a national service embracing more than 65% of all new prescriptions. The long tradition of paper prescriptions seems soon to be fully replaced by electronic communication.

Also, repeat prescriptions may now be stored as a service for customers; a service expected to grow considerably during the next coming years.

By means of the new national dispensed prescription databases, all prescription data for outpatients are now collected electronically and may be used for further decisions in clinical consulting as well as in pharmacoepidemiologic research (II).[73, 74, 201]

Storage of data

The storage of personal prescription information is subject to laws and regulations to protect the individual. On the other hand, large amount of sensitive information is expected to be updated instantaneously and readily available, which requires both efficient and secure solutions. Information need to be stored in an original form, not being destroyed or changed, in redundant and mirrored system architectures. Large storage capacity is not a problem with presently available technology, and is not expected to be a constraint in the future. However, efforts to protect personally sensitive data always need constant attention, to ensure availability of essential information in healthcare.

The advantages of the new national dispensed prescription databases (II) compared to the regional cohort in Jämtland, that we studied as a model for the National Pharmacy Register (I) and for historical comparisons (III), are obvious; the new databases are mandatory, comprising *all* individuals filling prescriptions on a *national* level, probably constituting one of the largest and most comprehensive prescription databases in the world. To further develop these databases, exposure to drugs within hospitals and OTC-sales (presumably voluntarily) should be added.

The regional Jämtland cohort study was a pioneering effort that has brought inspiration to the new national databases. Still, the Jämtland cohort is well suited for historical, pharmacoepidemiologic research and needs to be preserved for that purpose.

Retrieval of data – a role model?

The retrieval of personal drug information needs to be both fast and reliable. Users are increasingly familiar with 'instant' web-based systems. Both professionals and citizens require fast, interactive, and useable healthcare services.

ICT, with the expansion of broadband communication, has revolutionized our way of living in many ways. Still, the adoption of ICT in healthcare and for

individuals, with the potential to reduce traditional obstacles like time and distance, is waiting for a break-through all over the world. It seems that the pharmaceutical arena is a forerunner, making healthcare services available for individuals and professionals on a broad scale. With this in mind, the Swedish experience, with an almost full electronic flow of prescribing information, could be a role model internationally.

Integrity and availability

The question of how to balance issues of personal integrity with the demand for safe prescribing is subject to discussion. The two models presented internationally, making personal health records available, are the opt-in model and the opt-out model.[91, 177, 191] While new legislation in Sweden and Denmark, allows mandatory collection of all dispensed prescriptions, but also gives the patient the right to restrict the accessibility of the information to certain individual healthcare professionals and also to permit the patient full transparency as to who has accessed the information. Remarkably few public concerns have been recognized so far. The Scandinavian approach seems well-balanced, with public support.

Prerequisites for the deployment of the Swedish ePrescribing process

The deployment of electronic processes for prescription information in Swedish healthcare has been dependent on the following prerequisites

- The early shared learning experiments in different organisations
- The high penetration of EHR in primary care
- The determination by strong and enduring national/regional stakeholders, expressed as shared local/regional implementation teams
- The confidence in a secure handling, with a virtual private network for communication, with secure identification for personal integrity
- The national registers allowing secure identification of drugs, prescribers, pharmacists, and prescriptions
- Standardization of terminology, nomenclature, and communication protocols
- The low degree of detailed regulations, giving high responsibility to stakeholders, beneficial for the entrepreneurial development of the new technology
- The new legislation allowing national databases, independent of reimbursement form, but with high degree of patient consent and transparency
- The high public penetration rate for mobile phones, personal computers, and the Internet
- The high degree of public and professional acceptance

From data to improved performance – a challenge for pharmacoinformatics

We now have data on drug utilization available that can be recognized as useful information by answering questions on "who", "what", "where", and "when". By an increased degree of connectedness to that information, our knowledge on "how" medications are used may be expanded. Evaluating the underlying patterns and principles may convey a better wisdom in medical praxis.

Nevertheless, in not being willing to perform what is known by changing behaviour, the single individual will not prosper from all efforts in healthcare.

Pharmacoinformatics, being the discipline where ICT intersects with any aspect of drug delivery, will have a challenging role to play, for the research and for the clinical use of medications in individuals and populations, improving the drug utilization, for individuals and for the society.

Conclusions and implications

Conclusions

The main conclusion of the studies, in the area of Pharmacoinformatics, was that ePrescribing with communication of prescribed drug information, storing and retrieving dispensed drug information, offers new opportunities for clinical and scientific improvements.

- In the general population, there were relatively few severe potential drug interactions. The risk of receiving a combination of potentially interacting drugs was positively correlated to age and polypharmacy. As a model, the new national pharmacy register is expected to provide health care professionals with a powerful tool to systematically review all prescriptions (I).
- The Swedish National Pharmacy Register provides prescription dispensing information for the majority of the population. The medication history in the register may be accessed online, to improve drug utilization, by registered individuals, prescribers, and pharmacists in a safe and secure manner. Lack of widespread secure digital signatures in health care may delay general availability. To clinically evaluate individual medication history, the relatively high prevalence of dispensed drugs in the population, seems to justify the National Pharmacy Register (II).
- The risk of receiving potentially interacting drugs was strongly correlated to the concomitant use of multiple drugs. A few interacting drug combinations were responsible for a large proportion of the risk. The pronounced increase in polypharmacy over a three decade period implies a growing reason for prescribers and pharmacists to be aware of drug interactions (III).
- The detected increased risk of prescribing errors, for ePrescriptions compared to non-electronic prescriptions, indicated the need for an increased focus on quality aspects in ePrescribing deployment. To increase the safety and quality for patients, as well as developing the efficiency and cost-effectiveness in health care, the technology of ETP should be developed towards a two-way communication between the prescriber and the pharmacist, with automated checks of missing, inaccurate, or ambiguous information (IV).

Implications

How far have we come?

The hypothesis, three decades ago, that ICT could have a positive impact on healthcare delivery and also have a favourable influence on individuals' life and health, is still to be corroborated. The development has not yet to any considerable extent been used to improve the utilization of medications, neither on an individual, clinical level nor on the population, epidemiologic level; neither by individuals nor by professionals. What can be recognized as emerging eHealth technologies is merely the beginning of what may be achieved in the future. The technological requisites, like fast and reliable computers, efficient user-interfaces, large storing capacity, wired and wireless broadband communication, have not only fulfilled but exceeded all expectations. However, individuals and organizations ability to adapt to and benefit from the technological revolution seems to take much longer. Still, after more than 20 years of experience of ETP in Sweden, scientific papers are written internationally on 'early experience'.[94]

What will the future bring?

The new national Swedish eHealth strategy is building on the above-mentioned foundation, with the intention to introduce new national healthcare services for individuals and healthcare professionals, independent of organizational and technological boundaries.[10] Also, internationally considerable efforts are focused on health information technology as a tool to transform healthcare delivery and refocusing around the consumer.[184]

The interaction between man and machine

On a human level, the introduction of a computer in the doctor's office is an intriguing example of how the interaction between man and technology needs to be well considered. In the experimental ePrescribing project at the county hospital in Jönköping, the combination of a latest cutting-edge technology with a novel hardware device, the touch-screen, and a menu-driven software programme, with the finger as a pointing device, was developed to span the bridge between man-machine-medicine.

When will ICT improve quality in healthcare?

In a nation like Sweden, where the penetration of mobile phones, personal computers, and the use of the Internet is among the highest in the world, the information model of ePrescribing is in action. Presently, information on all prescriptions dispensed are stored nationally, all pharmacy dispensing is computerized, most doctors in primary care are using EHRs, a majority of prescriptions are transferred electronically, even patients take advantage of their personal information on the Internet for more comprehensive compilation of drug prescription information and extended pharmacy and healthcare services.

The introduction of new technology in healthcare has proved to be a dynamic cycle of experiments, publications, and reporting to be approved by professionals and organizations before taking off; the time factor always seeming to be underestimated. The technological inventions surviving, on the other hand, have to be robust, beneficial, and evidence-based, gaining approval in healthcare.

What to improve?

The increased exposure of drugs of a national population warrants a vigilant attitude from all healthcare professionals.

Increasingly, communication between prescribers and pharmacists has to be improved, on a personal and professional level but also in regard to technical communication. The developing of more intuitive user interfaces, standardization to alleviate interoperability between different ICT systems, and quality assurance of e-processes in healthcare, are all aspects in constant need of improvement.

ePrescriptions holds a potential to increase safety and quality compared to paper prescriptions. ICT offers a unique opportunity to systematically improve the prescribing and dispensing processes. If the full potential for ePrescribing, to improve, not only efficiency and cost-effectiveness, but also safety and quality in healthcare, these opportunities for systematic improvements, must be adopted horizontally by all involved.

Questions of safe authentication, to ensure personal security and integrity, must also be attained properly, making available information useable in healthcare.

Promises for the future

Maybe the most promising evolution so far are all those hundreds of individuals, daily taking part in their medication history online, storing their prescriptions electronically, and using new electronic services.

Let us hope that the single individual will be in the realm of our future endeavour.

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Appendices

Appendix 1

Literature review on papers related to ePrescribing, sorted by year of publication.

First Author, Nation	Year	Titel	Main content
Nilsson, S, Sweden	1982	Computer terminal in the physician's office to assist drug prescription [148]	Prospects
Nilsson, S, Sweden	1983	A computer in the physician's consultancy [149]	Evaluation, status
Åstrand, B, Sweden	1985	Doctor's use of VDUs for medical prescriptions [211]	Implementation, evaluation
Anderberg, G, Sweden	1987	Swede*star – ett läkemedelssystem vid Gråbo vårdcentral [17]	Implementation, prospects
Peterson, C, US	1995	On-line prescribing: keystrokes for quality [153]	Implementation, patient safety, efficiency
Siwicki, B, US	1995	Electronic prescriptions: just what the doctor ordered [173]	Prospects, barriers
Wynn, P, US	1996	Get ready! Electronic prescriptions are coming [209]	Patient safety, prospects
Schiff, GD, US	1998	Computerized prescribing: building the electronic infrastructure for better medication usage [170]	Status, prospects, barriers
Simmons, D, US	1998	Electronic prescriptions [172]	Pharmacy
Anderson, KJ, US	1999	Electronic prescriptions in pharmacy [18]	Pharmacy
Bates, DW, US	1999	The impact of computerized physician order entry on medication error prevention [29]	Patient safety
Demkjaer, K, Denmark	1999	Third generation electronic pharmacy communications. Recommendations based on ten years' experience [63]	Pharmacy

Keet, R, US	1999	Essential characteristics of an electronic prescription writer [116]	Prospects
Venot, A, France	1999	Electronic prescribing for the elderly: will it improve medication usage? [193]	Prospects, obstacles, patient safety
Teich, JM, US	2000	Effects of computerized physician order entry on prescribing practices [182]	Patient safety, cost-effectiveness, inpatients
Bates, DW, US	2001	Reducing the frequency of errors in medicine using information technology [30]	Patient safety
Cornell, S, US	2001	Electronic prescribing. New technology can reduce errors and save time [57]	Patient safety, Cost-effectiveness
Kilbridge, P, US	2001	E-Prescribing [119]	Report, status
Papshev, D, US	2001	Electronic prescribing in ambulatory practice: promises, pitfalls, and potential solutions [151]	Literature survey, prospects, obstacles
van der Kam, WJ, the Netherlands	2001	Effects of electronic communication between the GP and the pharmacist. The quality of medication data on admission and after discharge [190]	GP, pharmacy, quality, cooperation
Altman, SH, US	2002	Controlling spending for prescription drugs [15]	Cost-effectiveness
Parker, PL, US	2002	E-scribing: more realistic than ever [152]	Patient safety, prospects
Adler, JH, US	2003	E-prescribing technology can improve patient care. The handwriting on the wall [14]	Improvement
Bartlett, G, Canada	2003	Evaluation of standardized tasks for primary care physicians using the MOXXI electronic prescribing and integrated drug management system [27]	Evaluation, primary care
Bates, DW, US	2003	Improving safety with information technology [31]	Patient safety

Corley, ST, US	2003	Electronic prescribing: a review of costs and benefits [56]	Cost-effectiveness, benefits
Bastholm, Rahmner, P, Sweden	2004	Physicians' perceptions of possibilities and obstacles prior to implementing a computerised drug prescribing support system [28]	Physician's attitudes prior to implementation
Greenberg, MD US	2004	Electronic prescribing and HIPAA privacy regulations[84]	Privacy, security
Hammond, WE, US	2004	The role of standards in electronic prescribing [99]	Evaluation, barriers, standards
Tanne, JH, US	2004	Electronic prescribing could save at least 29bn dollars [181]	Cost-effectiveness
Cubi Montfort, R, Spain	2005	Electronic prescription in Spain: feasibility. [60]	Feasibility
de Clieppele, F, Belgium	2005	The law on e-Health: draft proposal for an electronic medical prescription [62]	Legal aspects, privacy
Kohli, M, US	2005	Electronic prescribing at Johns Hopkins Community Physicians: a success story [122]	Evaluation, implementation
Kristensen, N, Denmark	2005	Danish pharmacies have a safe and quick electronic service [125]	Pharmacy
Ross, SM, US	2005	Effects of electronic prescribing on formulary compliance and generic drug utilization in the ambulatory care setting: a retrospective analysis of administrative claims data [160]	Formulary compliance, generic utilization
Teich, JM, US	2005	Clinical decision support in electronic prescribing: recommendations and an action plan: report of the joint clinical decision support workgroup [183]	Patient safety, quality, action plan
Wears, RL, US	2005	Computer technology and clinical work: still waiting for Godot [192]	Organizations, new technology
Eggert, C, Canada	2006	Clinical electronic communications: a new paradigm that is here to stay? [66]	Clinical electronical communication

Halamka, J, US	2006	Early experiences with E-prescribing [94]	Evaluation, patient safety
Halamka, J, US	2006	E-Prescribing collaboration in Massachusetts: early experiences from regional prescribing projects [95]	Evaluation, barriers
Rosenbloom, ST, US	2006	Approaches to evaluating electronic prescribing [158]	Evaluation
Schade, CP, US	2006	Effects of electronic prescribing on formulary compliance and generic drug utilization in the ambulatory care setting: a retrospective analysis of administrative claims data [168]	Implementation of EHR and ePrescribing, primary care
Schneck, LH, US	2006	E-prescribing can be new tool in quality-care arsenal [171]	Prospects
Sjöborg, B, Sweden	2006	Design and implementation of a point-of-care computerized system for drug therapy in Stockholm metropolitan health region-Bridging the gap between knowledge and practice [174]	Implementation, prospects, barriers
Smith AD, US	2006	Barriers to accepting e-prescribing in the U.S.A. [176]	Pharmacy, barriers
Ridinger, MH, US	2007	The electronic prescription conundrum: why "e-Rx" isn't so "e-Z" [156]	Patient safety, implementation
Nilsson, JL Sweden	2007	Electronically transferred prescritions: faster picked up than paper prescritions[147]	Patient behaviour
Åstrand, B, Sweden	2007	ePrescribing current and future processes [212]	Implementation, history, prospects
Åstrand, B, Sweden	2007	ePrescribing [In Swedish: Elektronisk recepthantering] [214]	Implementation, history, prospects

Appendix 2

Swedish version of the protocol used to assess quality aspects of ePrescriptions (IV).

Schema 2: SCHEMA FOR REGISTRERING AV INTERVENTIONER I APOTEK

Ett schema fylls i för varje ordination som det interveneras på - ett per ordination på resp. resept. Använd vb baksidan.

FEL OCH BRISTER, ORSAKER TILL EVENTUELL INTERVENTION (flera alternativ kan vara aktuella)

Förskrivningsfel
100 Fel läkemedel
101 Fel styrka
102 Fel beredningsform
103 Fel dosering
105 Fel mängd forskriven eller fel behandlingstid
106 Fel patient
109 Fel indikation/användningsområde
110 Annat fel (specificera):

Interaktioner
120 Läkemedel-läkemedel
125 Annat (specificera):

Brister i ordinationen
140 Läkemedel eller vara saknas
141 Styrka saknas
142 Beredningsform saknas
143 Dosering saknas
144 Behandlingstidens längd oklar
145 Mängd läkemedel eller vara saknas
146 Ofullständig bruksanvisning
148 Brister i förskrivaruppgifter
149 Brister ang patientuppgifterna
150 Fel och brister ang. rabattering
152 Annat (specificera):

Kontraindikationer
160 Nedsatt njurfunktion
161 Allergi
163 Graviditet
164 Amning
165 Annat (specificera):

Andra orsaker
180 Biverkningar / toxicitet
184 Läkemedlet avregistrerat/ restnoterat/ tillhandahålls ej
185 Annat (specificera):
200 Oläsligt
201 Datum saknas
202 Förfalskat
203 Patientens bekymmer/frågor
205 Annat (specificera):

INTERVENTIONER, FÖRSLAG TILL ÅTGÄRD OCH RESULTAT (flera alternativ kan vara aktuella)

Interventioner
300 Kontaktat forskrivaren
301 Kontaktat eller intervjuat patienten
302 Kontaktat eller intervjuat anhörig/annan
303 Granskat patientens läkemedelsprofil
304 Konsulterat källa till läkemedelsnformation (specificera):
305 Uteslutande farmaceutens egen bedömning (används undantagsvis)
306 Annat (specificera):
307 Fick inte kontakt med förskrivaren (Vad gjorde man istället - specificera):

Förslag til åtgärd
400 Lägga till läkemedel
401 Utsättning av läkemedel
402 Ändra eller förtydliga läkemedel
403 Ändra eller förtydliga styrka
404 Ändra eller förtydliga adm. form
405 Ändra eller förtydliga dosering
406 Ändra förtydliga behandlingstid
407 Ändra eller förtydliga mängd
408 Expediera som angivet på receptet
409 Inte expediera läkemedlet
410 Annat (specificera):

Resultat
510 Förslaget accepterat
511 Förslaget modifierat (specificera):
512 Förslaget inte accepterat
513 Annat

DEMOGRAFI OCH BESKRIVNING AV HÄNDELSEN

Recepttyp
600 Nyutskrivet
601 2.a eller senare exp. på itererat recept
602 Handskrivet

Läkemedelsförmån
603 rabatterat
604 kostnadsfritt
605 utan rabatt

Forskriver
620 Primärvårdsläkare
621 Sjukhusläkare
622 Tandläkare
623 Veterinär
624 Sjuksköterska
625 Distriktssköterska
626 Barnmorska
627 Okänt
628 Annan (specificera):

Receptformedling
640 Lämnat av patienten
641 Lämnat av anhörig /annan
642 Fax-recept
643 Förvaras på apoteket
644 E-recept
645 Telefonrecept
646 Post från förskrivaren
649 Annat (specificera):

Patientens kön
660 Man
661 Kvinna

Patientens födelseår
680 .....

700 **Beskrivning av händelsen**
Inkludera en beskrivning av problemet och namnen på de läkemedel som var involverade. Använd baksidan eller lägg till ett extra blad ark om nödvändigt. (häfta ihop)

800 **Total tidsåtgång (ca)** _____ min

Omarbeidet av Institutt for apotekforskning AS, 2004 etter tillatelse fra A. G. Kennedy and B. Littenberg, University of Vermont , USA (IJPP **12**(2004) 13-19.

English translation of the protocol used to assess quality aspects of ePrescriptions (IV).

Pharmacist Intervention Report

REASON FOR INTERVENTION

Prescribing Error	Prescribing Omission	Other reasons
100 ☐ Inappropriate drug / indication	140 ☐ Drug not specified	180 ☐ Side effects / Toxicity
101 ☐ Inappropriate dose	141 ☐ Dose not specified	
102 ☐ Inappropriate form / route	142 ☐ Form / route not specified	184 ☐ Drug taken off the market/ not in stock at wholesaler
103 ☐ Inappropriate schedule	143 ☐ Schedule not specified	
105 ☐ Inappropriate quantity or duration	144 ☐ Duration not specified	
106 ☐ Incorrect patient	145 ☐ Quantity not specified	185 ☐ Other (specify):
	146 ☐ Incomplete directions for use	
109 ☐ Incorrect indication/directions of use	148 ☐ Incomplete information about prescriber	
110 ☐ Other (specify):	149 ☐ Incomplete information about patient	
	150 ☐ Errors and omissions regarding reimbursement	
	152 ☐ Other (specify):	
Interactions	**Contraindications**	200 ☐ Illegible
120 ☐ Drug-drug	160 ☐ Reduced kidney function	201 ☐ Not dated
	161 ☐ Allergy	202 ☐ Fraud
		203 ☐ Patient concern / question
	163 ☐ Pregnancy	
125 ☐ Other (specify):	164 ☐ Nursing	205 ☐ Other (specify):
	165 ☐ Other (specify):	

INTERVENTIONS, RECOMMENDATIONS, AND OUTCOMES

Interventions	Pharmacist recommendations	Outcomes
300 ☐ Contact prescriber	400 ☐ Add drug	
301 ☐ Contact or interview patient	401 ☐ Discontinue drug	510 ☐ Recommendation accepted
302 ☐ Contact patient family/others	402 ☐ Change or clarify drug	511 ☐ Recommendation modified (specify):
303 ☐ Patient profile reviewed	403 ☐ Change or clarify dose	
304 ☐ Consult drug info source (specify):	404 ☐ Change or clarify form / route	512 ☐ Recommendation NOT accepted
305 ☐ Pharmacist own judgement only	405 ☐ Change or clarify schedule	513 ☐ Other (specify):
306 ☐ Other (Specify):	406 ☐ Change or clarify duration	
307 ☐ Unable to get in touch with prescriber What was done (specify):	407 ☐ Change or clarify quantity	
	408 ☐ Dispense Rx as written	
	409 ☐ Do not dispense Rx	
	410 ☐ Other (specify):	

DEMOGRAPHICS AND EVENT DESCRIPTION

Prescription Status	Prescription Source	700 Event Description
600 ☐ New Rx	640 ☐ Patient brought Rx in	**Include a description of the problem and the name of the drugs involved. Attach additional sheets if necessary (staple)**
601 ☐ Refill Rx	641 ☐ Member of family/other brought Rx in	
602 ☐ Handwritten	642 ☐ Fax-prescription	
Prescription category	643 ☐ Prescription kept at pharmacy	
603 ☐ Partly reimbursed	644 ☐ Electronic prescription	
604 ☐ Fully reimbursed	645 ☐ Phone prescription	
605 ☐ Not reimbursed	646 ☐ Sent by mail by prescriber	
	649 ☐ Other (specify):	
Prescriber Type	**Patient Sex**	
620 ☐ MD community	660 ☐ Male	
621 ☐ MD hospital	661 ☐ Female	
622 ☐ Dentist		
623 ☐ Veterinary	**Patient year of birth**	800 **Time spent**_____min
624 ☐ Nurse	680 ☐	
625 ☐ District nurse		
626 ☐ Midwife		
627 ☐ Unknown		
628 ☐ Other (Specify):		

Adapted after A. G. Kennedy University of Vermont, USA (IJPP **12** (2004)9 13-19)

Papers I-IV