Effects of Outreach Strategies on Quality of Pharmacotherapy

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Effects of Outreach Strategies on Quality of Pharmacotherapy

Effecten van Nascholingsmethoden op de Kwaliteit van Farmacotherapie

(met een samenvatting in het Nederlands)

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De Nederlandse samenvattingen bevinden zich steeds aan het begin van de hoofdstukken.

HOOFDSTUK 1
Data <> informatie, inleiding

Dit proefschrift is een evaluatie van methoden om het voorschrijven van artsen te verbeteren. Hiervoor is gebruik gemaakt van de declaratiegegevens van een zorgverzekeraar. We hebben de effecten gemeten van twee methoden om de kwaliteit van het voorschrijven te verbeteren – namelijk een individueel gerichte interventie (nascholing) en een groepsgerichte. Daarnaast hebben we ook de effecten van deze interventie op patiëntniveau gemeten.

Daarvoor hebben we ons steeds de volgende vier vragen gesteld:
1. Hoe wordt gedrag beïnvloed?
2. Wat kunnen we met declaratiegegevens doen?
3. Wat is eigenlijk goed voorschrijven? Hoe meet je dat?
4. Wat zijn effecten op patiëntniveau?

In de inleiding staan vier grote schema's waarin de kennis die we bij aanvang van het onderzoek hadden over de onderwerpen is samengevat. Gezamenlijk vormen zij achtergrondinformatie voor ons onderzoek.

Diagram 1 Gedrag veranderen, kenmerken van nascholingsprojecten
In dit diagram staan op de verticale as allerlei aspecten van nascholing genoemd. Horizontaal wordt daaraan een oplopende mate van intensiteit gekoppeld. Bij verticaal 'setting', komt horizontaal 'mass', 'group' en 'individual'. Wij denken dat hoe meer een nascholingsmethode voldoet aan alles wat in de rechter verticale kolom vermeld staat, hoe meer impact deze heeft. Bijvoorbeeld: Het in een grote zaal, eenmalig presenteren van multi-interpretabele onderzoeksresultaten, waarbij de aanwezigen niets kunnen inbrengen of vragen, zal veel minder impact hebben dan een persoonlijk bezoek, waarin vragen kunnen worden gesteld en waarin ruimte voor discussie is.
Hoe persoonlijker, hoe intensiever. Toch kan het werken met een groep een aantal voordelen bieden die één-op-één contacten niet hebben. In een groep kan discussie ontstaan, kan iemand díe vraag stellen die een ander niet durft te stellen et cetera. Hoe meer interactie, hoe beter informatie zal beklijven. Hoe intenser, hoe meer bindend en hoe meer kansen om het gedrag te beïnvloeden.

Diagram 2 Declaratiebestanden in geneesmiddelen gebruiksonderzoek
Gegevens van een zorgverzekeraar zijn een administratieve weergave van wat er de in werkelijkheid gebeurt. In dit diagram worden 'de werkelijkheid' en 'de administratieve werkelijkheid van de zorgverzekeraar' toegelicht.

'De werkelijkheid'; boven de diagonale lijn:
1. De patiënt is zich bewust van een klacht en gaat naar de dokter.
2. De dokter stelt een diagnose en doet een voorstel voor behandeling, schrijft eventueel een recept uit.
3. De patiënt besluit om naar de apotheek te gaan (of doet dat niet!).
4. De apotheker verstrekt het geneesmiddel en geeft voorlichting (of niet!).
5. De patiënt gebruikt het geneesmiddel (op een bepaalde manier).

'De administratieve werkelijkheid'; onder de diagonale lijn.
Apotheek en arts sturen gegevens naar de verzekeraar (HIC = health insurance company)

a) De arts levert gegevens over de patiënt (nummer en leeftijd), de verzekeraar betaalt het consult of het huisartsabonnement.
b) De apotheek levert gegevens over verstrekte medicijnen (patiënt, afleverdatum) en de verzekeraar betaalt op basis daarvan de factuur. Of er voorlichting is gegeven, is voor de vergoeding niet van belang en derhalve niet terug te vinden in deze administratie.

De verzekeraar heeft maar een beperkt aantal gegevens nodig, dit zijn dan ook de enige gegevens die terug te vinden zijn in zijn declaratiebestand. Deze 'administratieve weergave' geeft dus maar een beperkt, en niet altijd betrouwbaar, beeld van de werkelijkheid.

Diagram 3 Wat is goed voorschrijven?
Hoe kan 'kwaliteit van voorschrijven' gedefinieerd worden?
Er is bij voorschrijven altijd sprake van een aantal doelen:
- Maximaal effect en minimale bijwerkingen
- Minimale kosten en de keuzes van de patiënt respecteren.
- Korte- en langetermijneffecten

Kortom: men streeft naar veilig, effectief, economisch en passend voorschrijven. Deze doelen zijn niet altijd in overeenstemming, en vaak zelfs tegenstrijdig. Daarnaast is het belangrijk de korte- en langetermijneffecten op een rij te zetten. Afhankelijk van iemands verwachte levensduur kunnen deze anders wegen. Goed voorschrijven is het afwegen van al deze doelen per individuele situatie. Het meten van goed voorschrijven gebeurt meestal op groepsniveau en schept daarom extra uitdagingen.

Diagram 4 Effecten op patiëntniveau
Het is belangrijk het effect van een behandeling op patiëntniveau te meten. De gebruikersgroep (C) is meestal een andere dan de groep waarbij een behandeling is onderzocht (A). Zo weten we dat de gebruikerspopulatie vaak ouder is en meer vrouwen bevat dan de onderzochte populatie. Deze twee groepen zijn deels overlappende deelverzamelingen van de gehele populatie (B). Uiteindelijk gaat het echter om individuen (D) en die zijn allemaal anders.

OPZET VAN DEZE STUDIE

Deze kennis hebben we gebruikt bij het ontwerpen van het onderzoek dat in dit proefschrift wordt beschreven. Het doel van onze studie was om methodes om gedrag te beïnvloeden te vergelijken, waarbij declaratiegegevens gebruikt werden om de kwaliteit van farmacotherapie te meten en te beïnvloeden. Voor en na deze interventie hebben we vragenlijsten gestuurd naar gebruikers van antidepressiva ouder dan 60 jaar. Omdat het gebruik van declaratiegegevens voor dit onderzoek specifieke problemen kent gaat hoofdstuk 2 hierover. Hoofdstuk 3 beschrijft hoe we met behulp van deze gegevens het gebruik van antidepressiva bij ouderen hebben geanalyseerd. In hoofdstuk 4 staat beschreven welke klachten de gebruikers van antidepressiva hadden voor de interventie begon. Hoe moeilijk het is de diagnose depressie te stellen blijkt uit hoofdstuk 5. Om een wetenschappelijk verantwoorde interventie te kunnen doen wilden we de artsen goed over de interventiearmen verdelen. Wat we hiervoor hebben gedaan staat beschreven in hoofdstuk 6. Hoofdstuk 7 beschrijft de interventie en het effect van individuele en groepsgewijze nascholing over antidepressiva bij ouderen, bij artsen en apothekers. In hoofdstuk 8 onderzoeken we het effect van de interventie op patiëntniveau. Hoofdstuk 9, tenslotte, gaat over de toekomst; wat kunnen grote databases met gezondheidszorg gebruiksgegevens en de toegenomen mogelijkheden van de ICT (Informatie en Communicatie Technologie) betekenen voor medische nascholing en onze gezondheidszorg.

1
Scope of the thesis

One day when he was out walking, he came to an open place in the middle of the forest, and in the middle of this place was a large oak-tree, and, from the top of the tree, came a loud buzzing-noise. Winnie-the-Pooh sat down at the foot of the tree, put his head between his paws, and began to think.

First of all he said to himself: "That buzzing-noise means something. You don't get a buzzing-noise like that, just buzzing and buzzing, without its meaning something. If there's a buzzing-noise, somebody's making a buzzing noise, and the only reason for making a buzzing-noise that I know of is because you're a bee."

Then he thought another long time, and said: "And the only reason for being a bee that *I* know of is making honey."

A.A. Milne, Winnie-the-Pooh, 1926.
Chapter: We are introduced, page 3.

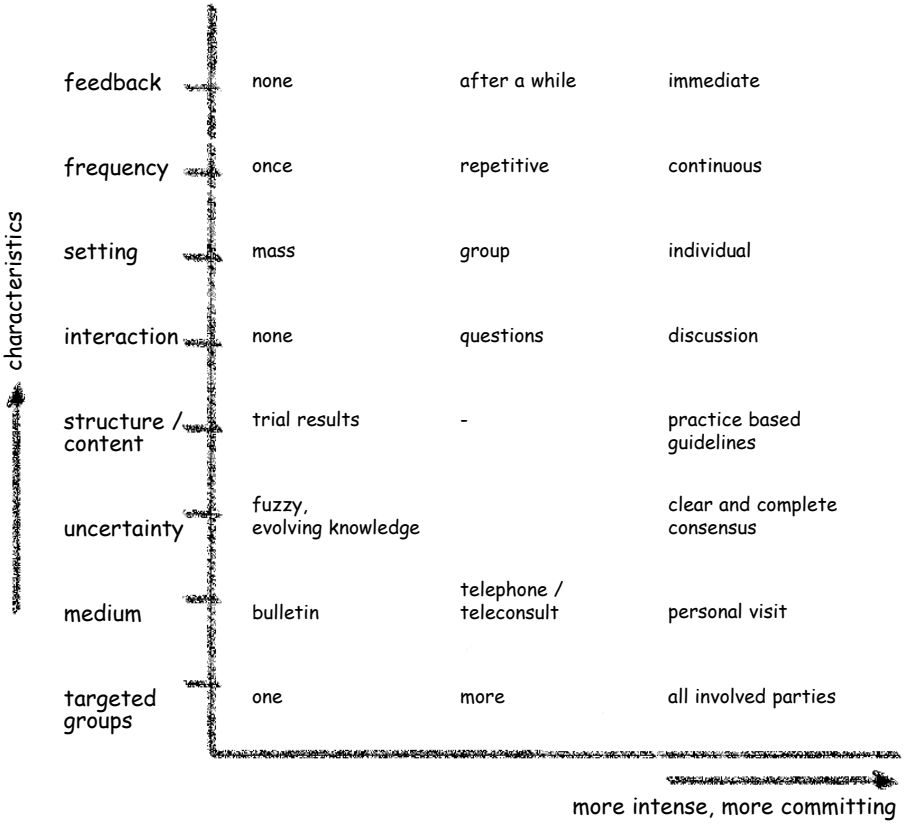
INTRODUCTION

The focus of this thesis is an evaluation of methods to influence prescribing with the aid of reimbursement data to improve the quality of pharmacotherapy. We have not only measured the effect of our outreach program on prescribing, but also monitored the effect on a patient level. As a result, this project addressed four main issues: influencing behavior, the use of health insurance company data to analyze the use of health care resources, how to define good prescribing, and measuring the effect of an intervention on a patient level.

Influencing behavior

The mere publication of trial results does not effectively change behavior, nor do meta-analyses or mailing evidence-based guidelines (1-7). In times of increasing demand for evidence-based medicine and effective use of resources, we still lack knowledge on the implementation of innovations (8,9). How does evidence from clinical trials and observational studies influence prescribing (10-13)? What happens during therapeutic decision-making (14-18), how can the decision-making process be improved, and which approaches are most effective in influencing behavioral changes (19-21)? Intensive ways to disseminate information and facilitate implementation are needed to achieve lasting behavioral changes (22-28).
We know that the pharmaceutical industry has a long history of effectively influencing doctors' prescribing behavior (29), yet non-commercial outreach programs haven't usually been so successful (30). What is known about outreach programs (31,32)? Which aspects of an outreach program stimulate the diffusion of innovations (33, 35)? How can it be most effective in improving the quality of prescribing?
Diagram 1 describes different characteristics of outreach programs. Several different qualities are defined on the vertical axis (4,24). The intensity of these qualities is represented on the horizontal axis. An increase in intensity indicates more commitment and therefore a greater likelihood of behavioral change.
Feedback is the first quality indicated on the Y-axis. It is increasingly popular when computerized practice support systems or reimbursement systems are being used. It becomes more intense when immediate, like a computer reminder that pops up every time a drug that is not in the formulary is prescribed (33). Increased frequency of information will also make the program more intense. An outreach program can take place within either an individual or group setting (36). Individual contacts are more intense than group contacts, which allow one to avoid participating. A classic one-way lecture requires less commitment than a discussion covering knowledge, barriers to change, possible consequences et cetera. This interaction is an important aspect of diffusion of innovations and can be stimulated in a peer group (37).

diagram 1
Influencing behavior; characteristics of continuous medical education strategies (chapter 7)



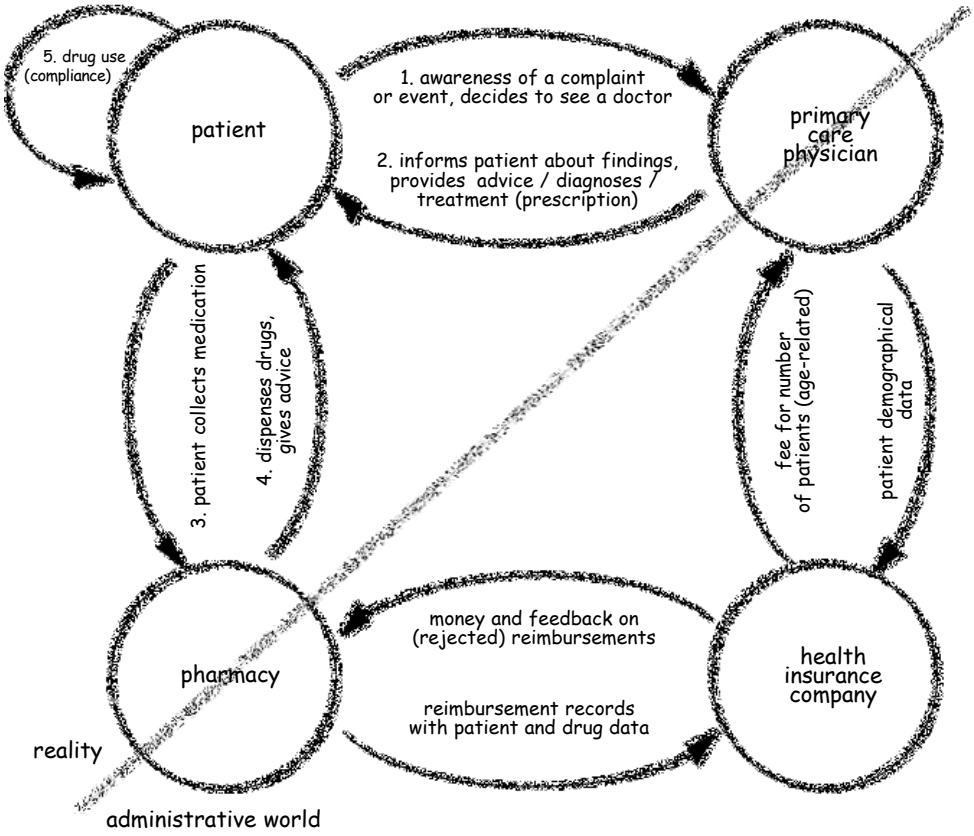
When the content is unapplied information, such as trial results, it is not so easy to implement as guidelines are. Computerized decision-making trees can enforce these guidelines. Besides the content, the uncertainty of the information is an important aspect: a complete consensus can give a clear message whereas in most issues there is still some discussion and some uncertainty remaining (21) (giving a third party that is harmed by the new consensus a chance to actively frustrate the diffusion of innovation, by presenting the information as being fuzzy.) Apart from characteristics that are related to the content of the information, there are characteristics that are related to how the information is presented. The medium used for the outreach program is an opportunity to make the program more effective; a drug bulletin is not as confronting as a personal visit. When the

educational program targets patients, schools, policymakers *and* paramedics as well, the program will be more likely to change behavior than a program targeting only one specific group (23).
Combinations of qualities can enforce or reduce the effectiveness; feedback will be more intense when it is immediate, personalized and more frequent. Feedback related to clear guidelines is more interesting than overall volume or costs figures are. In contrast, when the ball gets rolling in a group meeting, many barriers to behavioral change may be brought up than in a one-to-one discussion.
Academic detailing has effectively combined some of the characteristics mentioned, improving on the pharmaceutical industry's approach towards professionals. It consists of repeated personal visits, including feedback, presenting clear practice-relevant recommendations and anticipating any implementation problems (30). Not all characteristics of effective outreach visits have been identified (23). This diagram is not intended to be complete or without any redundancy. In the future we may discover other qualities that have a great impact on the effectiveness of an outreach program and the diffusion of innovations.
Apart from the above mentioned characteristics of outreach programs, quite some legislation has been designed and implemented to influence prescribing behavior. These laws vary from reimbursement regulations to limiting the amount of a drug allowed per prescription. This usually will effectively change behavior, but apart from the fact that it does not influence knowledge, it is also notorious for resulting in (often very creative) behavior which bypasses the legislation (38).

Analyzing reimbursement data to assess the use of health care resources

To properly use reimbursement data, we have to understand the process of data collecting in health care and be aware of the conflicting priorities that may influence this process. Diagram 2 simplifies some of the actions and parties involved in this process. The process starts when a person with a complaint decides to see a doctor (arrow 1). This doctor will then, after examining the patient, inform her about her findings and give some advice. In more than 60% of visits this consultation will result in a prescription (arrow 2) (39) Most patients will take this prescription to the pharmacy (arrow 3) to get the drugs dispensed (arrow 4). Now the patient has to decide and manage to take the drug according to the prescription (arrow 5), which is usually referred to as compliance. The above processes are what happens or should happen in the real world.
The administrative systems are only a reflection of what happens in this real world (40-42). Administration is an active process. It should be worth the effort to register what has been done (43,44). In the case of the pharmacy, this process of administration is rewarded because of the reimbursement requirements of most health insurance companies and pharmacy logistics (45). Most pharmacies do not keep records on the advice they dispense, as there is hardly an incentive to do so.

diagram 2
Data collecting in health care (chapter 2)



Physicians need to keep records as well, but in the Netherlands the financial incentive only requires the number of patients and some social-demographic data. For patients with public health service coverage, this fee is not influenced by the number of consultations that actually take place. For good clinical practice, short entries about consultations will usually be sufficient.
When analyzing reimbursement data or other medical records, one should keep in mind that these records are an administrative reflection of processes in health care. The availability and appropriateness of these data for research purposes is usually not the priority of the people who do the actual input and processing, nor of the management. Therefore the continuity of these data suffers a great deal from

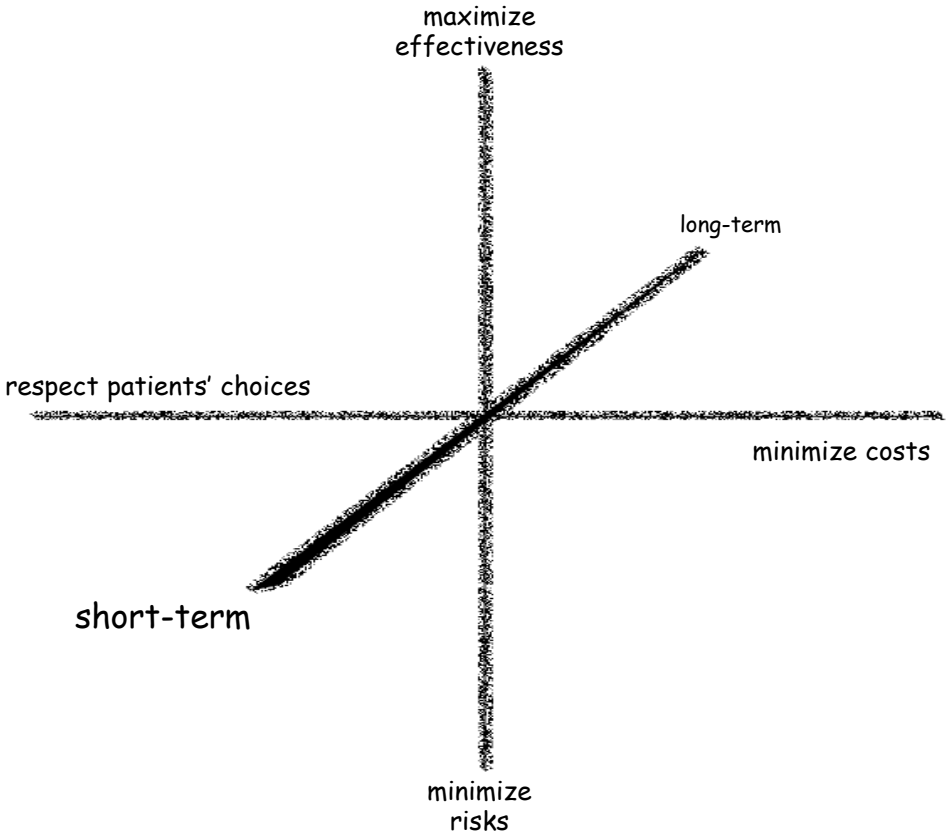
procedural changes, political decisions, takeovers and changes in hard or software (46,47).
The fact that most health care is publicly funded does not only justify pharmaco-economical analyses, it also frustrates these analyses. Minor changes in regulations (on reimbursement or organization of health care) can have strong effects on costs and the allocation of these costs (e.g. changing the possibilities to get a drug reimbursed affects the prescribing volume) (48). This is in contrast to commercial enterprises where it is (a teenyweenybit) easier to allocate costs.

How to define good prescribing

Before we can measure quality of pharmacotherapy, we have to ask ourselves what represents good prescribing exactly? What constitutes good prescribing is not easy to give and consequently to measure. In 1973, Parish published his oft-cited criteria: "appropriate, safe, effective and economic" (49). This tends to imply that there are right answers, rather than recognizing the complex trade-offs that have to be made between conflicting goals (50). During decision-making and monitoring, it is advisable to be aware that when we target good prescribing, there are more aims which can also be conflicting. Barber has grouped and visualized targets as shown in diagram 3: maximize effectiveness, minimize risks, minimize costs, and respect the patient's choice. This diagram clearly shows that good prescribing constitutes balancing harm and good done to the patient by the drug, the financial consequences of a treatment and patients' individual differences and preferences.
To maximize effectiveness we firstly want to alleviate a complaint or make it go away. The best strategy to achieve this is usually defined by the interpretation of study results. Sometimes these results are clear and unambiguous, but more often studies give conflicting results and consensus is only reached over a period of time as knowledge evolves. How to maximize effectiveness in treatment is therefore subject to change over time.
Another goal of good prescribing is to minimize risks. Here again, study results can be conflicting and non-informative. What is considered "safe" is a very complex (non-rational) individual decision, dependent on the beneficial effects. Risk minimization includes hazardous events and minor transient (but possibly uncomfortable) adverse events.
Registered side effects are not always causal, because all medical events will be registered in clinical trials even when they can be due to the underlying disease or other drugs used (51).
Part of the reason why study results on the effectiveness of a treatment are so difficult to interpret is that, when we are measuring the effects and adverse events of a treatment, we can focus on several things: effect on the disease (complaint), life expectancy (especially when the disease was life-threatening), adverse events or overall well-being using quality-of-life domains. Of course, a treatment should

firstly take away a complaint or a life-threatening condition. This goal is relatively easy to measure for a short time period, but measuring the long-term effect of blood pressure lowering medication on life expectancy is quite an extended project; we therefore have added this as an extra dimension in Barber's diagram. Measuring the extent of immediately presenting adverse events seems to be possible as well. But to assess the long and short-term side effect load, which should include summarizing visible and invisible adverse events, measurable and non-measurable side effects, immediate and later effects, minor, irksome or dangerous adverse events and those that are worse than the complaint, will not be easy. Ultimately we want to know how the patient feels, functions and survives.
The real aim of a medical intervention (and thus pharmacotherapy) is more than just improving life for the patient. Usually **the patient** desires the treatment to bring her back to the situation before the complaint or event ("Doctor, will I still be able to……?"). But everything else has changed as well (we have grown older etc.). It is usually not possible to completely return to the old situation. It is interesting to recognize that this is what is really aimed at in our culture. ("When will I be myself again?")
Minimizing costs and respecting patients' choices are in fact a pair of ethical matters where we have to balance between Utilism and Kant (society and the individual), as long as health care is funded from public resources (52). Budgets and fundholding have created a need for "health-economics", to be able to compare strategies (50). Assessing the costs and benefits of a (drug) treatment in financial terms is, however, still a very complex and difficult challenge. Information we have available on costs is usually extracted from clinical trials and can not always be applied to daily practice. (This is true for primary study results like the effectiveness of a drug, but is true in a stronger sense for secondary information extracted from a trial, such as costs (28,53-56).)
Alongside ethical and economical arguments there are many practical reasons why the patient's choices, particularly informed choices, must be part of good prescribing. One important practical reason to take a patient's choice into account is that the patient herself is going to choose whether or not to use the drug. Disclosing important barriers to follow a certain therapy may improve compliance and therefore the effect of a therapy. Ideally, a doctor will go through the available evidence with the patient, and thereafter make a well-informed choice **with** the patient. This kind of shared decision-making may result in the patient deciding to live with the complaint rather than to live with the burden of a treatment.
Because good prescribing includes several goals that can be conflicting, a definition of good prescribing is case dependent. Using this diagram helps us to communicate the possible conflicts in individual cases. To assess quality of prescribing on a larger scale, as often aimed at by researchers, policymakers and administrators, this diagram might help to understand decision-making in daily practice.

diagram 3
How to define good prescribing (chapters 3 and 8)



based on N. Barber

Measuring good prescribing
Each individual case requires balancing several, possibly conflicting, goals (57). This creates a great challenge when we are looking for criteria to operationalize rational prescribing (58-60). We need criteria that surpass the individual level and that are available, can be repeated, clear, comprehensible, fair and do not cause perverse incentives (40).
Some have developed complex algorithms to assess the quality of drug prescribing on a patient level (61-64). These usually require indications, which are not always

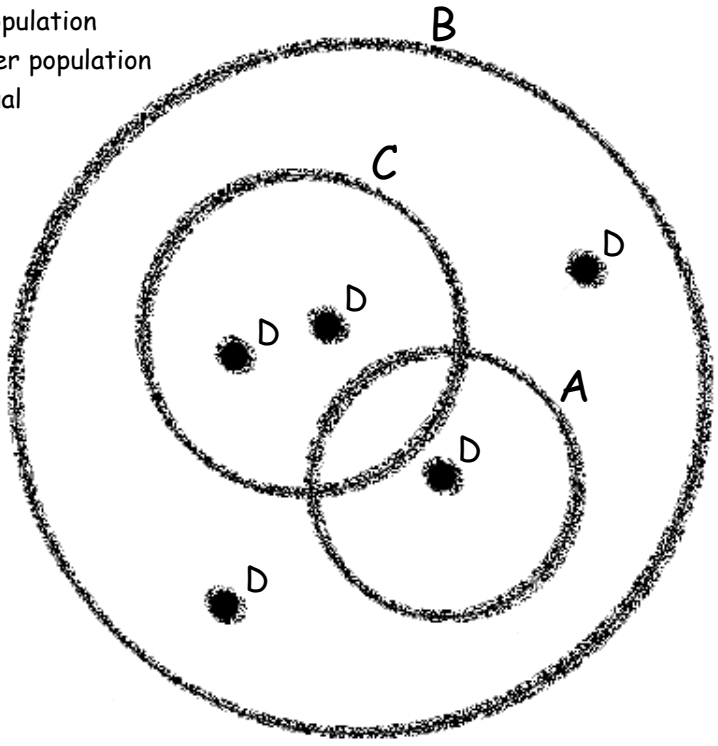
available. Because all patients are different, ranking systems that can be used for meso or macro level evaluation may become very abstract and are not easy to comprehend or relate to daily practice (65,66).
When evaluating prescribing on a disease level, instead of on a patient level, it is possible to choose the treatment of one condition and rank several treatments or to measure adherence to guidelines (standardizing) (65).
Quality of prescribing can also be evaluated on a drug level. One way is by measuring the volume of use of agents that are generally considered to be overused (e.g. antibiotics, expensive NSAIDs) (43). Another is to search for irrational combinations of drugs and drugs that are not optimal for certain sub-groups (e.g. anticholinergic antidepressants in the elderly). For our research, we chose to use a very simple restricted measure which enabled operationalization (67). Evaluating quality of prescribing on a drug level does not describe overall quality of pharmacotherapy.

Measuring the effect of an intervention on a patient level
The aim of our outreach program was to change prescribing for a very specific subpopulation, based on theoretical evidence: we asked PCPs not to prescribe anticholinergic antidepressants to the elderly, based on research demonstrating the vulnerability of elderly to these drugs (68-70). The primary outcome measures of the outreach program are prevalences and incidences of antidepressant prescribing retrieved from the reimbursement records. Thus rationalizing prescribing, the question remains whether the patients had benefited from the intervention program and really did feel better. There are only a few outreach programs that measure the effect of their intervention on the patients. This is relevant because most interventions are based on knowledge gathered from groups that have characteristics different from those of the patients addressed in the intervention (either directly or indirectly).
To gather information on what constitutes good prescribing we have to compare and interpret the effect of several treatments on groups of patients (71). Applying that treatment to another subpopulation or one specific individual will probably give different results from the treatment on the study population. Not rarely, relations are revealed that apply only for specific subpopulations of patients. We have to realize that the effectiveness for other (sub)groups remains unclear (57,72,73).
Diagram 4 demonstrates how research populations (A) can differ from consumer populations (C). A typical clinical trial population includes only fit male adults. The effect of a drug applied to the consumer population (which does not necessarily equal the targeted population), will therefore probably differ from the effect in the research population. The same can happen when study results are extrapolated to the total population or when the effect on a specific individual is expected to be

equal to that on the research population. This is a dilemma for doctors, policymakers and patients as well. New research techniques try to tailor treatment results by defining subpopulations in each treatment group, but no subgroup is an individual with all her individual characteristics.

diagram 4
The effect on a patient level (chapters 4 and 8)

A= research population
B= total population
C= consumer population
D= individual



OBJECTIVES AND OUTLINE OF THIS THESIS

Given what we know about the quality of pharmacotherapy, we set out to investigate methods to change prescribing, using reimbursement data to assess quality and to influence it. Before and after the intervention we sent out questionnaires to users and former users of antidepressants in order to be able to evaluate the effect of the academic detailing program on a patient level.
As we made extensive use of reimbursement data, we had to start examining the possibilities to perform research with these data, which had been collected for another purpose. This is described in chapter 2. We then used these data to define an area of suboptimal prescribing to target in our intervention. The prevalence and incidence of anticholinergic and non-anticholinergic antidepressant use in the elderly, as described in chapter 3, was in our opinion a relevant and suitable topic for the intervention. To be able to measure the effect of the intervention on the targeted population of antidepressant users we needed to send out a questionnaire to the over-sixty users of these drugs, including questions covering quality of life, complaints and medical consumption, mood and some basic statistics. One questionnaire was sent before and one was sent after the outreach program. The adverse events, possibly due to antidepressants, mentioned by this group prior to the intervention are described in chapter 4. As treatment starts with diagnosis, chapter 5 compares various scales to score depression in our research population. The outreach program was designed as a three-armed intervention (group approach, individual approach and a control arm) to evaluate the effect of two different approaches to influence the prescribing of PCPs: the impact of individual visits vs. group visits, both with the use of academic detailing techniques. As in the Netherlands PCPs and pharmacists work together in Peer Review Groups (PRGs) to improve the quality of pharmacotherapy, we took these groups as the unit of randomization. To be able to balance relevant characteristics of these groups over the treatment arms, we took an inventory of characteristics of these groups prior to the intervention. This inventory and the stratification of the PRGs is described in chapter 6. The aim of this intervention was to make general practitioners more aware of the vulnerability of elderly for the anticholinergic adverse events of most TCAs. The effect of this outreach program on the incidence of anticholinergic antidepressants in the elderly is described in chapter 7. Chapter 8 assesses the effect of the intervention on a patient level. Chapter 9 comprises the summary and final considerations. It describes what continuous medical education might look like in the future, and the role of very large medical information databases in quality assessment and continuous education. It aims to stimulate thinking and working on the implications of ICT (Information and Communication Technology) on health care.

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HOOFDSTUK 2
Passen de onderzoeksdoelen bij de beschikbare gegevens? Een checklist om dit systematisch na te gaan

Een schat aan gegevens, maar ook een goede onderzoeksbron?

Zorgverzekeraars voeren een uitgebreide administratie, bijvoorbeeld om de declaraties van apothekers en huisartsen te verwerken, en om verzekerden te registreren. Op deze manier bouwt een verzekeraar verscheidene, vaak enorme gegevensbestanden op: databases. Het is verleidelijk te denken dat je met een dergelijke verzameling gegevens onderzoek zou kunnen doen naar veel onderwerpen. In dit hoofdstuk is een methode beschreven om te beoordelen of een database geschikt is voor een specifieke onderzoeksvraag. Of dat zo is, hangt af van de gegevens in de database en van het onderzoeksdoel.

De ideale database

Als eerste stap hebben we gedefinieerd hoe 'de ideale database' voor farmaco-epidemiologisch onderzoek eruit zou moeten zien. In de ideale database is in principe álles opgenomen. Alle gebeurtenissen zijn zoveel mogelijk in detail vastgelegd: de arts, de patiënt, de laborant die heeft geprikt en de uitslag van de bloedtest, het geneesmiddel dat werd voorgeschreven, de apotheker die het verstrekte, de informatie die zij gaf enzovoorts. Iedere patiënt, iedere behandelaar, kortom iedereen die betrokken is bij de zorg, is uniek te identificeren. In de ideale database zijn de gegevens niet gegroepeerd, maar apart opgeslagen. De ideale database heeft een oneindige historie, en de structuur waarin de gegevens zijn verzameld verandert nooit. Aan de ene kant wil je dat de gegevens optimaal zijn beveiligd, aan de andere kant is goede toegankelijkheid een belangrijke vereiste (en dat is natuurlijk tegenstrijdig). Een ideale database is verder goed en foutloos aan andere bestanden te koppelen. En ten slotte: de gebruikte hard- en software mogen niet veranderen.
De ideale database bestaat dus niet: deze zou te onhandelbaar, te star en door niemand te onderhouden zijn. Een database wordt altijd gebouwd met een doel. De gebruiker wil bepaalde gegevens kunnen terugvinden, gebruiken of bewerken. Hoe een database eruit ziet, is daarvan het gevolg.

Vergelijking

De database die wij voor ons onderzoek gebruikten, was een declaratiebestand van OZ-zorgverzekeringen. Dit gegevensbestand bevatte declaraties van apothekers voor de geneesmiddelen die aan ziekenfondsverzekerden waren verstrekt op recept van de huisarts. Het bleek voor een niet-ingewijde bepaald niet makkelijk om de benodigde gegevens te ontrafelen.

We hebben 'onze' database vergeleken met de 'ideale' database. Hiervoor ontwikkelden we een tabel (tabel 1) waarmee het mogelijk is een database systematisch te onderzoeken op de geschiktheid voor een bepaald onderzoeksdoel. Uit die vergelijking bleek dat op basis van 'onze' database veel onderzoek wél mogelijk is, maar ook heel veel niet. In de declaratiebestanden was de code van de verstrekte geneesmiddelen opgenomen, plus de datum van levering, de naam van de apotheek, de naam van de patiënt en de code van de huisarts die het middel had voorgeschreven. Omdat de verzekeraar deze gegevens verzamelde met het doel betalingen te verrichten, was het aannemelijk dat ze zeer betrouwbaar en compleet waren. De gegevens hadden een historie van een paar jaar; oudere gegevens waren door veranderingen in hard- en software moeilijk te achterhalen. Over patiënten kon aanvullende informatie opgeroepen worden. Van de huisartsen was de naam te traceren in een papieren dossier.
Maar op een aantal vragen gaf de database uiteraard geen antwoord. Gaf de apotheker voorlichting bij het verstrekken van de medicijnen? Gebruikte de patiënt de geneesmiddelen wel goed? Welke medicijnen zijn voorgeschreven door een specialist?
Uit de analyse bleek dat we door middel van de declaratiebestanden wel goed zicht konden krijgen op wat wordt voorgeschreven in de eerste lijn, maar van wat in de tweede lijn gebeurt weten we veel minder.

CONCLUSIE

De methode die we ontwikkelden om databases te analyseren op geschiktheid voor farmaco-epidemiologisch onderzoek, kan ook worden gebruikt door anderen die een dergelijk onderzoek willen beginnen of moeten interpreteren.

2

Do the research goal and databases match? A checklist for a systematic approach

a revised version of this manuscript has been accepted for publication in Health Policy

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Suddenly Christopher Robin began to laugh…and he laughed…and he laughed…and he laughed. And while he was still laughing – *Crash* went the Heffalump's head against the tree-root, Smash went the jar, and out came Pooh's head again…

A.A. Milne, Winnie-the-Pooh, 1926.
Chapter: piglet meets a Heffalump, page 64.

Abstract

To test the appropriateness of a given database for specific research questions, we designed a checklist starting with the definition of an ideal database. This ideal database contains all relevant data on patients, providers and services. It is safe and accessible, input is always accurate, continuity is guaranteed and linkage with other information is easy. These features are often taken for granted, but are highly influenced by organizational processes in health care and prioritization. Starting with the characteristics of an ideal database, one can systematically list the required aspects for research goals and compare these with the available systems. This checklist can also be valuable to others to design or interpret studies based on claims databases.

Keywords: pharmaco-epidemiology, drug-utilization, record-linkage, benchmarking, reimbursementdata, administrative aids

INTRODUCTION

Due to the increased computerization of administrative work, a tremendous amount of health care data has become available for research in the last decades. Health insurance companies (=HICs) maintain administrative databases originating from systems that provide or finance medical care and contain computerized records of encounters between patients and health care providers (1). These so-called claims data (also known as reimbursement records or insurance data) contain information about patients, providers and their encounters. Claims data are increasingly used for drug utilization reviews, epidemiological research, policymaking and to support management (2-7). As HICs register the medical consumption of large numbers of people, the utility of these data is potentially enormous. One focus in the analysis of these databases is suboptimal prescribing. This is an issue of recurrent concern of many researchers and policymakers (8-11). With the availability of a wide variety of drugs and with the ongoing knowledge of effectiveness and the detection of new adverse drug reactions, the increasing demand for "evidence based medicine" and limited resources in health care, the analysis of quality of prescribing through these databases is of growing interest (12). Researchers have been using these databases for decades now and are still discussing the potency and pitfalls of using these data for drug utilization studies (1,2,5,13). We have designed an approach to match research goals with the qualities of a database. Claims data research design is often a process of balancing research question and available data (figure 1).

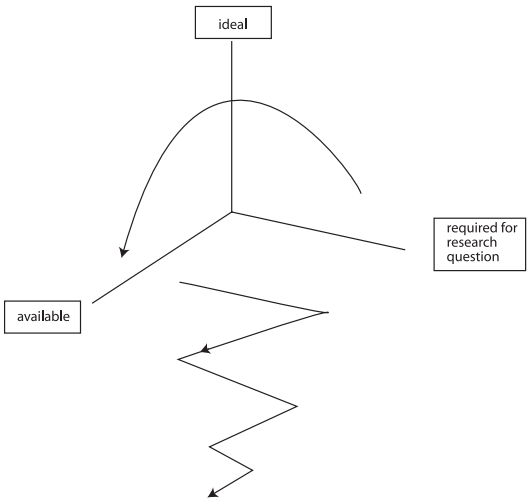

Figure 1: qualities of a research database

This process can be improved when using a checklist on an "ideal" database (table 1). Using this method, relevant qualities of databases will be taken in account. "Blueprint" assumptions about databases will be made explicit. It makes possible a systematic analysis of what is available and the discrepancies between different goals.
We use this method below to discuss whether a Dutch HIC (HIC-OZ: Health Insurance Company- Mutual Care) data set can be used to assess quality of prescribing. The required and available databases have been compared with the aid of this checklist, and the differences will be discussed. This method can be used by others to make inventory of the required and available data.

AN IDEAL DATABASE

Ideal: Research Goal

For each goal and each research question a different set of data is required, and other relations (between the data) need to be revealed. Furthermore, the necessary accuracy is dependent on the goal; resource planning requires a different degree of accuracy than does research on adverse (drug) reactions, where a one-in-a-million occurrence can be relevant. An ideal database can be used for scientific research, policymaking, resource planning, fraud control, benchmarking and so on.

Ideal: Data on Encounters

An ideal database for research provides the opportunity to follow persons (patients and providers) in time and registers all medical encounters and the identity of the provider(s) involved (table 1). This means a unique code is needed to identify persons. This code should not be subject to change, not in time and not between different sets of data. Alternatively, clear mapping must be provided to relate old codes to new ones. It must be possible to relate all medical services to a person and it must be unambiguous what service has been provided to whom and by which provider. An ideal research database gives the opportunity to relate to as many patient characteristics as needed. Depending on the research question one might also be interested in education, smoking attitudes and other health behavior, occupation, family relation or even sexual preference or gene mapping. Ideally, all health care providers (whether individual, clinic, hospital or other institutions) are uniquely identifiable and details about them are computerized.
An ideal database contains all relevant details about health care services (procedures), including details on results, diagnoses, time, place, costs and of course which patient and health care provider were involved. Encounters can result in more services ordered, possibly including other providers and procedures (referral). Each procedure needs a unique code and each diagnosis must be clear and includes

information on the severity of the disease. Relations between code numbers and disease entities should be evident through clearly defined mutually exclusive categories (14). Clustering is loss of information. The ideal database can be a collection of databases that are feasible for record linkage.

Ideal: Other Qualities

Other aspects of an ideal database include security, accuracy and continuity. An ideal database is safe; non-authorized persons should not have access to personal information. To assure safety advanced technology and procedural steps are needed. Despite advanced technology, there will always be a conflict between security and accessibility. Society will have to discuss the advantages of these databases to improve health care and find ways to avoid an invasion of privacy that might ensue as a byproduct (15,16). The ideal database is completely accurate; all input, independent of location, computer system or interpreter, is similar. All input should be swift and impeccable. Nothing should jeopardize continuity. All details and history are kept indefinitely. In this ideal database, all registrations can be linked smoothly. Prerequisites to realize linkage are proper coding and compatibility of computer systems.

REQUIRED FOR RESEARCH ON QUALITY OF PRESCRIBING

Required: Research Goal

Quality of prescribing means prescribing the right substance (in the correct dose, duration and form) for the right indication, with adequate information and instruction to the right person (WHO) in accordance with co-morbidity and other medication used. In 1973 Parish summarized the features of rational prescribing as appropriate, safe, effective and economical (10).

Required: Data on Encounters

For many forms of pharmaco-epidemiological research, unique codes to identify users and prescribers are needed (table 1). Details on the pharmaceutical products, costs, doses, duration and form are necessary. Information on indication and instructions provided is also desired. To evaluate appropriate prescribing it is required to know other patient characteristics, e.g. pregnancy, allergies, complaints and diseases, non-reimbursable medication used and non-pharmaceutical (para-) medical interventions. When prescribing was not according to protocol, the reason for this should be known.

Required: Other Qualities

The researcher desires good and swift access to all relevant information and does

not have a primary interest in security. Data relevant for research on the quality of prescribing should be completely accurate and computerized. All input should be up-to-date. An extended history needs to be available, preferably in the same format. Linkage between databases containing information on patients, providers and pharmaceutical products is necessary. Linkage with other services and diagnoses can be relevant to estimate the effect of different treatments on the use of other resources (e.g. physiotherapy or hospitalization) (17).

DATA AVAILABLE AT A DUTCH HEALTH INSURANCE COMPANY

Available: Goals

Claims data are primarily gathered for reimbursement purposes. This has to be done according to certain laws and regulations. Yet, the reality is that where prescriptions are handled, goals can conflict with each other. In pharmaceutical practice, for example, conflicting interests are: helping patients swiftly and accurately, and entering the right information, processing information for reimbursement, or for drug review. This is reflected in accuracy. At an HIC, conflicting goals can exist between several units. The financial department focuses on prompt payment, which contrasts with the goal of internal auditing, which is clear insight in processes. Account managers want a good relationship with the providers of care, but also want to prevent unnecessary reimbursements. Marketing wants as many customers as possible. Management wants information for policymaking. In addition, researchers want all data to be clean and accurate, easily accessible, linkable etc., allowing for all possible questions to be addressed (table 1).

Available: Data on Encounters

HICs keep family or personal codes for the insured population, a family number being sufficient for most reimbursement goals. Combining a family number with the date of birth and sex will identify most individuals, but will fail to recognize same-sex twins and all other multiple births. Next to that, the need to combine information creates an opportunity for errors. HIC-OZ registers personal details such as address, employer, occupation (not the history of these), religion, income and family structure.

Most health care providers in the Netherlands (including doctors and pharmacists) have a personal code. These codes are unique, not subject to change and are maintained at a national level. The practices and institutions where they work in also have a code of their own. This does not mean that all claims data contain the right provider code. In hospitals, the department head is often the provider whose code is used. Also, in primary care group practices and rota groups, codes can be used in several ways (for example, the doctor seen or the usual family doctor).

When a health care provider from outside the area is involved (not to mention locums and trainees), there is an increased chance the code used is not the legitimate personal code. Detailed information on the providers themselves (address, on-call group, age, university, training or special interests) is only partly available at HIC-OZ, most of which was not automated.
Data on procedures vary depending on the type of service. Reimbursement records on medication contain very detailed information, including the patient and provider codes, the pharmaceutical product, the form, amount and costs, the prescribed daily dose, and the time of dispensing (17). They do not include an indication or diagnosis, nor do they contain information on instructions given.

Available: Other Qualities

Security and access are organized and access is limited to a restricted number of people. Accuracy is strongly related to the goal of data collection –in everyday life people are often forced to set priorities. "The relationship of the claims to reimbursement can be both a blessing and a curse. The blessing is that such linkage ensures that diagnoses and procedures will in fact be recorded so the provider will be paid. The curse is that what is recorded may be merely enough to satisfy the minimal requirements for getting paid, or can even skew what is recorded so as to maximize cash flow rather than nosological purity." (5)
Input and maintenance in the real world are a product of many conflicting interests between and within organizations, endangering flawless input and maintenance (15) (18). In the Netherlands, information on medication is gathered and processed on a monthly basis and back-up tapes are available for at least five years. Because of the financial incentive to register all prescriptions, only a few will be missing. On the other hand, the same incentive only requires that the prescription is reimbursable. This requires no more than a valid insurance number, an existing doctor and a reimbursable item with a code and price that match (5). Extremes will be noted by the administrators, but it is hard to check which child needed the prescription and which doctor was actually the prescriber.
Takeovers or consolidation of companies and new developments in hard or software jeopardize continuity on a large scale. When companies merge, information technology is seldom a priority issue. Companies usually take over an existing system from one of the companies, or new systems are implemented. Continuity of data is further endangered by new legislation (e.g. shift from prescription-only to OTC drug or changing laws on reimbursement). Information on personal medical consumption is troubled when people change their HIC. This usually means that all data concerning them will be gathered in other databases at a different location, using another structure and other personal codes.
In most reimbursement databases, linkage is possible as most codes are unique, but troubled by hard and software incompatibility and minor differences in coding.

RESULTS COMPARING REQUIRED AND AVAILABLE DATABASES

Results: Goals

There are important differences between the research goal and the goal of data gathering at a HIC (table 1). For research on the quality of prescribing, very exact information on decision making and advice giving is needed. At a health insurance company, research is not the first goal of data collection. The reason that HICs gather these data is to allocate financial resources in health care. For reimbursement purposes it is not always relevant who did what, why, how, how often, and to whom. Bulk payments diminish administrative load and therefore save money, but do not serve researchers.

Results: Data on Encounters

Most people are uniquely identifiable, but researchers will not be able to track multiple births. When people change their HIC, they are usually out of sight of researchers. Most research needs providers to have unique personal codes. In group practices and during night calls there is quite some inadequate coding of actual prescribers. Details on form, dosage, costs and duration are available for researchers. Required information on a diagnosis or an indication for treatment is not available at a Dutch HIC, this can partly be retrieved by interpreting the medication history. Next to that, it is not known whether instructions for use have been given adequately or interpreted satisfactorily.

Results: Other Qualities

Data are not always easy to access and decipher for researchers, due to procedures and technical obstacles. Security is usually not an obstacle for authorized researchers.

Researchers prefer computerized data that are completely accurate, but accuracy is a problem in reimbursement data, partly due to conflicts of interest and putting priories.

Although back-up tapes are usually available to go back in time, this does not make historic information easily accessible due to incompliant computer systems and modified architecture. Research on quality of prescribing requires linkage of pharmacy records, patients and providers. This is possible with HIC-OZ data. Linkage with other resources (hospitalization, physiotherapy) is troublesome.

	Aspects / involving	IDEAL DATABASE	REQUIRED FOR RESEARCH GOAL	AVAILABLE DATABASE (Dutch HIC data)	COMPARING
Goal of data		Not relevant; everything is available and linkable.	Quality of prescribing	Data are gathered for reimbursement purposes.	Discrepancy of goals
Data on encounters					
	Population (people, patients)	Can be followed in time.	Unique persons	Unique persons, except for twins, triplets and so on	Problems with multiplets and changing of HIC
	Providers (like physicians and pharmacists)	Unambiguos coding at all locations, not subject to change.	Doctors and pharmacists uniquely coded	Doctors and pharmacists have unique codes, but group practices and night calls cause inadequate coding.	Good, but for group practices and night calls
	Procedures (health care services e.g. medication, hospitalization, physiotherapy)	No clustering of patients, providers or procedures. All thinkable details available.	Details on pharmaceutical products, substance, dose, duration and form. Information on indication and instructions given.	Dosing not always adequately available. No information on indication or instructions.	Quality of prescribing has to be assessed through indirect methods
Other qualities of databases					
	Security (and accessibility)	All information readily available for researchers. No access for unauthorized people.	Easily accessible for researcher	Security and access are organized and limited to a restricted number of people. Security is well organized.	Data are not always easy to access and decipher for researchers, due to procedures and technical obstacles.
	Accuracy (input)	All input swift and impeccable	Computerized and standardized data exchange required for reimbursement. Accurate input.	Not all providers are used to computer systems, and there is some tolerance towards inaccurate data.	Rather adequate
	Continuity Maintenance (history, matching formats and frequency)	Not jeopardized by reorganizations of any kind. No changes in format	Back-up tapes are kept for years. Compliant formats.	Back-up tapes are kept for years, but during those years there were many changes in hard and software and procedures.	Does not have enough priority.
	Linkage	In an ideal database all codes are unique and unambigous. Therefore linkage is no problem.	Good linkage possibilities between databases containing information on patients, prescribers, pharmacists and drugs.	Unique codes, but minor mistakes in input. Hard and software incompatibilities.	Adequate for most research

Table 1: framework to match research goals and databases

DISCUSSION

HIC data are a very good potential source for information on the use of health care resources and its outcomes. The direct linkage between drugs prescribed and prescribing physician offers the unique opportunity to examine physician prescribing patterns as well as patterns of recipient drug consumption. To extract information quite some issues have to be solved. Even within the primary process there are conflicting goals that have to be taken into account. Other problems concern the records themselves: they are not always what they seem. HIC have information available on the *reimbursement* of prescription drugs. Researchers and policymakers have to be aware that prescription drugs are firstly prescribed, secondly dispensed, then reimbursed. When a prescription is reimbursed, this does not necessarily mean that the right person is going to use the drug according to the instructions given (not to mention inter-individual differences in pharmacokinetics).
Moreover, the relevance of some details may change in time, new knowledge will create the need for other data. Therefore the answer to what is relevant will always be temporary.
Other issues concern the subjects of this information: patients and providers. How can society balance benefit and harm possibly done to them by the exploration of these data? Security and accessibility will always have to be balanced. Individual and social benefits and risks have to be weighed, after intensively examining short- and long-term consequences -a political issue. It might bring society to the conclusion that we do not want to keep all personal information in automated databases, whatever the potential benefits, whatever the safety procedures. Personal integrity has to be respected. Privacy should always be respected and data treated accordingly. Researchers should also respect security measures and not attempt to override them because of the importance of their research.
Continuity of data rarely receives enough attention. It is not a priority issue, but seems to be a problem that can be solved with technical and financial effort, like maintenance and swift input. Each goal and each process requires its own data architecture and data cleaning, therefore, each goal takes time and money of its own. This is also reflected in the back-up sets that are made. Most serve a specific goal. The more specialized the function of the (back-up) set, the less universally it can be used. Back-up sets take time to make and space to keep; therefore management and the IT department have to be convinced of the usefulness of each set. If goals are being balanced in a different way (e.g. due to management changes), this can be reflected in the databases. A change in the databases, whether minor or large, can jeopardize continuity of the data (19).
This approach provides a systematic approach for matching research goals and available data. Despite that the aspects mentioned are strongly entwined, this

checklist can help others to analyze the appropriateness of available data for their research goals. The systematic analyses of research question and available data through the use of a checklist on an ideal database will give better insight in the potencies and pitfalls of the databases.
Architecture, language, hard and software, and the frequency of registrations are not discussed in detail here. In an ideal database they are not relevant, but in reality can be important obstacles that have to be overcome. The relevance of some inadequacies in the databases can be increased or solved because of the above-mentioned aspects. For example, small errors in input can increase dramatically in magnitude depending on the number of linking and converting phases needed. Moreover, there is still lack of algorithms to identifying good prescribing using claims databases. What is the standard of rational prescribing? Simply listing profiles or ranking volumes and a distribution of providers according to these do not equal quality of care. There is a tendency to label heavy prescribing as inferior prescribing, but these measurements have limited value to help patients obtain the right drug in the right amount at the right time (15). Drug-drug incompatibilities per topic are relatively simple to assess. Analyses of certain types of patient drug profiles manifest utility. Yet meaningful interpretation still requires application of certain criteria. The design and validation of methods to assess quality of drug prescribing are still a field of quite some research (20, 21).

In conclusion, the use of a checklist on an ideal database for claims data research is a valuable tool in the design and evaluation of pharmaco-epidemiological research. Researchers, HICs, and policymakers should be aware of the potencies and pitfalls of these valuable sources and deal with them accordingly (22). At this moment, a substantial amount of claims data research is being done. In the future, the assessment of the quality of care will become increasingly important due to the increasing need for better understanding of the process and results of health care. The increasing role of claims data for research can be supported by the systematic analyses of the appropriateness of these databases for different research questions.

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HOOFDSTUK 3
Het gebruik van prevalentie- en incidentiegegevens om de invloed van leeftijd op het voorschrijven van antidepressiva met en zonder anticholinerge effecten te onderzoeken

'Oude' en 'nieuwe' antidepressiva

We hebben in de gegevens van de zorgverzekeraar naar een gebied gezocht waar de kwaliteit van voorschrijven verbeterd zou kunnen worden. Op dat gebied wilden we een interventie doen – letterlijk: een 'tussenkomst' – met het doel die kwaliteit te verbeteren. Met andere woorden: een actieve poging doen om het voorschrijfgedrag van artsen te veranderen.

Op het moment van studie was er een discussie gaande over de vraag wat de beste antidepressiva zijn: de 'nieuwe' antidepressiva of de 'oudere' antidepressiva. De 'nieuwe' zijn duurder dan de 'oudere', een niet onbelangrijk gegeven in de discussie rondom het geneesmiddelenbeleid.
Tegelijkertijd speelde er een discussie over de bijwerkingen van de zogenaamde anticholinerge geneesmiddelen. Ouderen blijken hiervoor veel gevoeliger te zijn dan jongere mensen. Tot de belangrijkste sterk anticholinerge geneesmiddelen horen een paar van de 'oude' antidepressiva.

Een rationele keuze?

Op basis van deze feiten stelden we vast dat het rationeel zou zijn als bij ouderen alle sterk anticholinerge middelen zouden worden vermeden. We hebben onderzocht of deze redenering bevestigd werd in de gegevens van de zorgverzekeraar. Klopte het dat aan oudere patiënten minder vaak een sterk anticholinerg middel werd voorgeschreven dan aan jongere? Om dit te onderzoeken hebben we in de database de patiënten geselecteerd die antidepressiva slikten. Na vergelijking van jongere en oudere gebruikers van antidepressiva bleek dat aan oudere mensen juist méér anticholinerge middelen werden voorgeschreven. In de grafieken is dit duidelijk te zien. De donkere kolommen betreffen de sterk anticholinerge middelen. Het gebruik hiervan neemt toe met de leeftijd, terwijl het gebruik van minder anticholinerge middelen (lichte kolommen) eerder afneemt.

Nieuwe gebruikers

Als mensen al langere tijd een geneesmiddel slikken, en daar tevreden over zijn, is het voor een arts niet gemakkelijk hen te overtuigen dat een nieuw, ander middel beter is. Vaak zal een arts kiezen voor voortzetting van de bestaande medicatie. Daarom hebben we niet alleen naar bestaande gebruikers – prevalentie – gekeken, maar ook naar nieuwe gebruikers – incidentie. We hebben gekeken naar ouderen

aan wie, voor het eerst of na een interval van ten minste zes maanden, een recept voor antidepressiva werd uitgeschreven.
Dit zogenaamde incidente voorschrijven is een belangrijk beslismoment; hier maakt de arts opnieuw afwegingen. Wat schreven artsen voor aan patiënten die voor het eerst een antidepressivum kregen? Oude mensen bleken ook bij nieuwe (incidente) recepten vaker een anticholinerg middel te krijgen.

CONCLUSIE

Uit het voorgaande blijkt dat aan het voorschrijfbeleid van antidepressiva aan ouderen inderdaad wat te verbeteren leek. Daarom werd dit het onderwerp voor onze interventie.

3

The use of prevalence and incidence measures to describe age related prescribing of antidepressants with and without anticholinergic effects

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"Pooh," he said, "where did you find that pole?"
Pooh looked at the pole in his hands.
"I just found it," he said. "I thought it ought to be useful. I just picked it up."
"Pooh," said Christopher Robin solemnly, "the Expedition is over. You have found the North Pole!"
"Oh!" said Pooh.
A.A. Milne, Winnie-the-Pooh, 1926.
Chapter: Expotition to the North Pole, page 113.

Abstract

To evaluate whether physicians avoid the prescribing of highly anticholinergic antidepressant (highly AAD) in the elderly, a population-based retrospective data analysis was performed, using databases from a Dutch health insurance company. Data collected on approximately 240,000 persons covered the period from 1 July 1993 to 1 January 1996. The prevalence and the incidence (number of new starters) of antidepressant use was measured over 1994 and 1995. Use of highly AAD was proportionally higher in the elderly in terms of both prevalence and incidence rates; the ratio of starters of highly AAD versus starters of less AAD in 1994 increased steadily with age (from 0.54 in the age-group 20-29 to 1.15 in the age-group 60-69). In 1995 these incidence ratios decreased (0.41 to 0.99, respectively); however, the decrease was higher in the younger age groups.

The data indicate that in the population studied, physicians do not refrain from prescribing highly anticholinergic agents to older patients despite their potential adverse drug reactions in this age group. Moreover, this study indicates that prevalence and incidence rates can be extracted from reimbursement data and give insight into actual prescribing practices.

Keywords: antidepressive agents, aged, drug utilization (review), pharmaco-epidemiology, prevalence and incidence

INTRODUCTION

Quality of prescribing has become more and more an issue of concern for policy makers and health insurance companies. To use resources more efficiently, the process of prescribing is increasingly subject to various types of quality assurance activities. Analyses of prescription data can provide the basis for reviewing prescribing practices and developing measures to promote the rational use of drugs and to avoid drug-related problems (1). We used prescription data at a health insurance company (HIC) level to identify and characterize areas of suboptimal prescribing.
One group of drug-related problems of special interest is the category of anticholinergic side effects. These include dry mouth, blurred vision, constipation, urinary dysfunction, hypotension, tachycardia, and cognitive impairment (2,3) which all reduce the patient's quality of life and can cause substantial morbidity and even mortality. Among the agents with these adverse reactions, antidepressants are important because of their high levels of consumption, their increasing use and the availability of alternatives with a more favorable side effect profile.
Antidepressants are prescribed in elderly patients to a great extent (4,5). The elderly are marked by a higher sensitivity to anticholinergic effects which might worsen pre-existing symptoms (6-11). Some authors therefore recommend avoiding the use of highly anticholinergic agents in the elderly completely (12-15). Recently, in the Netherlands, two consensus reports on the treatment of depression have been published. The consensus report published on behalf of the Dutch association of general practitioners ('NHG-standaard'), concludes that the serotonine re-uptake inhibitors (SSRI) are not superior in term of efficacy, but more expensive. Therefore the tricyclic antidepressants amitriptyline and imipramine are recommended as first choice drugs in the treatment of depression (16). In contrast, the consensus report on the treatment of depression which was prepared by consultants of different disciplines (psychiatrists, geriatricians etc.), places the selective serotonin re-uptake inhibitors as first choice compounds (17). They conclude that for ambulant patients these are safer and better tolerated. In neither report is age presented as a criterion in clinical decision-making. It is not yet known to what extent physicians in the Netherlands avoid the prescribing of antidepressants with anticholinergic effects in elderly patients.
Most drug utilization studies evaluate plain volumes of drug use (number of prescriptions, DDD, costs) instead of measures on a patient level (how many people are on the drug and how many people have started the drug).
The aim of this study was to evaluate the prescribing of antidepressant with or without highly anticholinergic effects in different age groups, using prevalence and incidence measures, in order to evaluate to what extent physicians consider the risk of anticholinergic drug reactions in elderly patients when prescribing an antidepressant.

MATERIALS AND METHODS

Prescription Data

The data used for this study were obtained from the Dutch HIC "OZ zorgverzekeringen" and consisted of complete drug dispensing histories of a defined population from 1 July 1993 to 1 January 1996. The population consisted of 98% of those in the South Holland islands area who were required by law to be insured under the national health insurance system (the so-called "Sickness Fund"). The Sickness Fund insures the lower income brackets comprising approximately 65% of the population of the Netherlands.
The data were collected in the pharmacies and sent to the health insurance company on either diskette or magnetic tape for the purpose of reimbursement. Back-up tapes of the reimbursement system were used for this research. The data did not include the patient's name, but gave the family insurance number, the date of birth and sex. This information was used to combine prescription records so that individual medication histories could be obtained. The drug-related information consisted of the drug identification number, the dispensing date, the number of units dispensed and the prescribed daily dose.

Drug Classification

The antidepressants were classified with regard to their in vitro and in vivo anticholinergic effects. This classification was based on standard literature (3,18,19) and a literature review on anticholinergic side effects (8,20-23). In addition, the evaluations as published in the Dutch National Formulary ('Farmacotherapeutisch Kompas' by the Health Insurance Executive Board) were used, as this reference book is the most frequently consulted formulary in the Netherlands.
The following agents marketed in the Netherlands were classified as highly anticholinergic antidepressants (highly AAD): amitriptyline, clomipramine, doxepin, imipramine, trimipramin and maprotiline. Although there is some controversy in the literature about the anticholinergic effects of maprotiline, this compound was nevertheless included as it is classified as highly anticholinergic in the Dutch National Formulary. All other agents belonging to the group of antidepressants according to the ATC classification were classified as causing fewer or no anticholinergic effects and were called less anticholinergic antidepressants (less AAD).

Prevalence and Incidence Measures

The extent of prescribing of highly AAD versus less AAD was determined by calculating the prevalence and incidence of drug exposure by age group. Prevalence represents the proportion of patients treated by an antidepressant at a given time point ("How many people are using an antidepressant today?"), while incidence

provides the number of new starters of antidepressants during a specific time frame ("How many persons started on antidepressant last month?").
For the analysis, prescriptions of antidepressants as selected from ATC-codes N06A (antidepressants only) and N06CA (combination of antidepressants with neuroleptics) were used. To calculate the extent of prescribing, the database covering 1994 and 1995 was used. Prescriptions from 1993 were used to complement missing values in prescribed daily doses over 1994 and 1995 and to help define the new starters of an antidepressant in the first half of 1994 (see under incidence estimations).

Legend duration of use
For each prescription of an antidepressant in the database we created a time window of probable use. This legend duration of use was calculated by dividing the number of units dispensed by the number of units prescribed per day. This was multiplied by 1.1 in order to take into account that patients often get their prescriptions some days before they actually start the new package and to compensate for some extent of non-compliance (24). In the event that information regarding the prescribed dose was not available (9.3% of all antidepressant prescriptions), it was obtained from the closest preceding prescription for the same patient (3.9%) and if this was not successful (5.4%), the average prescribed dose for that trade product in the database was used.

Prevalence estimation
The prevalence of antidepressant use was determined for 1994 and 1995 by counting the number of patients having a prescription with a legend duration of use including the third of October in each year and dividing these numbers by the number of insured patients per age group in the respective year. The third of October was chosen because this day falls within a time period during which most people are presumed to not be on vacation. Advanced prescribing as a result of vacations spent abroad is therefore less likely. In order to validate this date, the analysis program was also run for several other random dates and the results were similar.

Incidence estimation
Besides the prevalence rates, the incidence rates of new starters of antidepressants were estimated over 1994 and 1995. A patient was defined as a new starter when he or she started an antidepressant during this period and there was no valid prescription for an AD in the half-year prior to this starting date. A patient is counted as an incident user every time (s)he starts using an antidepressant after an interval of more than a half year, as calculated above. (e.g. a prescription issued on March 1st with tablets for 60 days, would be valid until March 1st plus 66 days:

May 6th. Therefore, the first prescription that would classify this patient as an incident user would be after May 6th plus 180 days: after Nov. 2nd). Increasing the 180 day-interval did not change results dramatically nor did changing the factor 1.1. The ratio of prevalences and the ratio of incidences with their 95% confidence intervals of highly AAD versus less AAD were calculated.

RESULTS

The average number of persons insured at the health insurance company OZ during 1994 and 1995 was 236,207. Of the total population, 54% was female. Age distribution was 23%, 38%, 22% and 18% for men and 19%, 35%, 25% and 21% for women for the age groups under 20, 20-39, 40-59 and over 59 respectively. As only the lower income brackets are subject to compulsory insuring by the national health insurance system, the number of females is higher than the number of males in the older ages groups because women more often work part-time or receive welfare. The patients were registered with 160 general practitioners.
The total number of prescription records was 1,907,931 in 1993, 1,768,310 in 1994 (a substantial decrease because homeopathic and phytotherapeutic compounds were no longer reimbursable) and 1,852,660 in 1995 which comprised approximately 92% of the number of pharmacy records originally reimbursed by the pharmacies. The 8% of records that were discarded consisted mainly of extemporaneous products (pharmacy made products; mainly dermatological ointments).
The total number of antidepressant prescriptions used for analysis were 34,776 for 1993, 39,637 for 1994 and 46,962 for 1995. The size of the insured population did not change substantially during those years. The number of patients receiving highly AAD in 1995 increased by 6% compared to 1994 (1636 highly AAD users in 1994, 1730 highly AAD users in 1995) while the increase for less AAD was 37% (1489 in 1994, 2034 users in 1995) (Table 1). Amitryptiline was the most frequently prescribed highly AAD; paroxetine was the most common less AAD. The absence of exposure of patients to the combination preparation of amitriptyline and neuroleptics in 1995 is due to the withdrawal of these products from the market in 1994. Sertraline, on the other hand, was introduced on the market in 1995, which is reflected in Table 1.
The prevalence of patients treated with an antidepressant in 1994 increased from 0.54% for the age group 20-29 to 2.75% for the age group >69. The same pattern was observed over 1995; however, these prevalences were on average 30% higher (Table 2). Incidence rates over 1994 and 1995 demonstrated a similar pattern to the prevalence data. Stratified for age, it appeared that less AAD were prescribed preferentially for younger patients while highly anticholinergic compounds were mainly prescribed for older patients in 1994 and in 1995 (Figures 1[a] and 1[b]).

Highly anticholinergic antidepressants	1994	1995	less anticholinergic antidepressants	1994	1995
Tricyclic derivatives			**Tricyclic derivatives**		
Amitriptyline	653	866	Desipramin	4	3
Clomipramine	461	516	Opipramol	26	24
Doxepin	57	53	Nortriptyline	25	11
Imipramine	112	123	Dosulepin	42	38
Maprotilin *	174	172	Dibenzepine	1	0
Amitriptyline and psycholeptics	179	0	Trimipramine	2	0
			SSRIs		
			Sertraline	0	54
Total	1636	1730	Fluoxetine	442	555
			Fluvoxamine	286	288
			Paroxetine	474	814
			MAO inhibitors		
			Tranylcypromin	0	5
			Moclobemide	43	33
			Nialamide	4	0
			Others		
			Trazodone	23	31
			Venlafaxine	0	40
			Mirtazapine	0	9
			Mianserine	117	129
			Total	1,489	2,034

*Tetracyclic derivative

Table 1: number of patients with a legimate prescription for the various highly anticholinergic antidepressants and less anticholinergic antidepressants on the third of October in 1994 and 1995

The ratio of prevalences of highly AAD versus less AAD in 1994 increased steadily with age from 0.54 in the age group of 20-29 to 1.73 in the group 69 years and older (Table 3). In 1995 these age-specific prevalence ratios were all lower than in 1994. However, the decrease was higher in the younger age groups (Table 3). The

incidence rates and their ratios demonstrated a similar pattern to the prevalence and prevalence ratios in 1994 and 1995 (Figures 1[c] and 1[d] , Table 2 and 3). Interestingly, again the decrease in incidence rate ratios (IRRs) between 1994 and 1995 was more pronounced in the younger age groups than in the older. This indicates that the elderly age groups were more likely to receive a highly AAD than the younger ones, not only for repeat prescriptions, but also for new starters. Moreover comparing 1994 and 1995 the portion of highly AAD decreased more for the younger incident users than for the elderly. Separate analysis of females and males demonstrated that the above described differences were found in both sexes.

Years	Prevalence (%)		Incidence rate (per 1000 person years)	
	1994	1995	1994	1995
<20	0.06	0.10	2.9	3.4
20-29	0.54	0.69	13.8	14.7
30-39	1.28	1.69	21.8	24.6
40-49	2.05	2.56	28.0	30.4
50-59	2.21	2.67	28.2	28.6
60-69	2.44	2.71	26.6	25.5
>69	2.75	3.06	27.2	26.7

Table 2: prevalence and incidence rates of antidepressant use for different age categories

	1994		1995			1994		1995		
	PR	(95% CI)	PR	(95% CI)	Decrease in PR (%)	IRR	(95% CI)	IRR	(95% CI)	Decrease in IRR (%)
<20	3.14	(1.34-7.36)	0.92	(0.52-1.62)	71	2.40	(1.68-3.45)	1.52	(1.12-2.07)	37
20-29	0.54	(0.42-0.70)	0.40	(0.31-0.50)	26	0.54	(0.46-0.64)	0.41	(0.35-0.49)	24
30-39	0.73	(0.61-0.87)	0.58	(0.50-0.68)	21	0.64	(0.55-0.73)	0.44	(0.39-0.51)	32
40-49	1.00	(0.86-1.16)	0.70	(0.61-0.80)	30	0.75	(0.66-0.86)	0.56	(0.49-0.64)	25
50-59	1.13	(0.95-1.35)	0.93	(0.80-1.09)	18	0.85	(0.73-0.99)	0.73	(0.62-0.85)	14
60-69	1.40	(1.18-1.67)	1.10	(0.94-1.30)	21	1.15	(0.97-1.35)	0.99	(0.83-1.17)	14
>69	1.73	(1.48-2.02)	1.50	(1.30-1.73)	12	1.03	(0.89-1.20)	1.03	(0.89-1.20)	0
Total	1.14	(1.07-1.23)	0.85	(0.80-0.91)	25	0.81	(0.77-0.86)	0.65	(0.61-0.69)	20

The high incidence rate ratios in the youngest age group is caused by the use of amitriptyline and imipramine for enuresis nocturna.

Table 3: prevalence ratios (PR) and incidence rate ratios (IIR) of highly anticholinergic antidepressants versus less anticholinergic antidepressants for different age categories

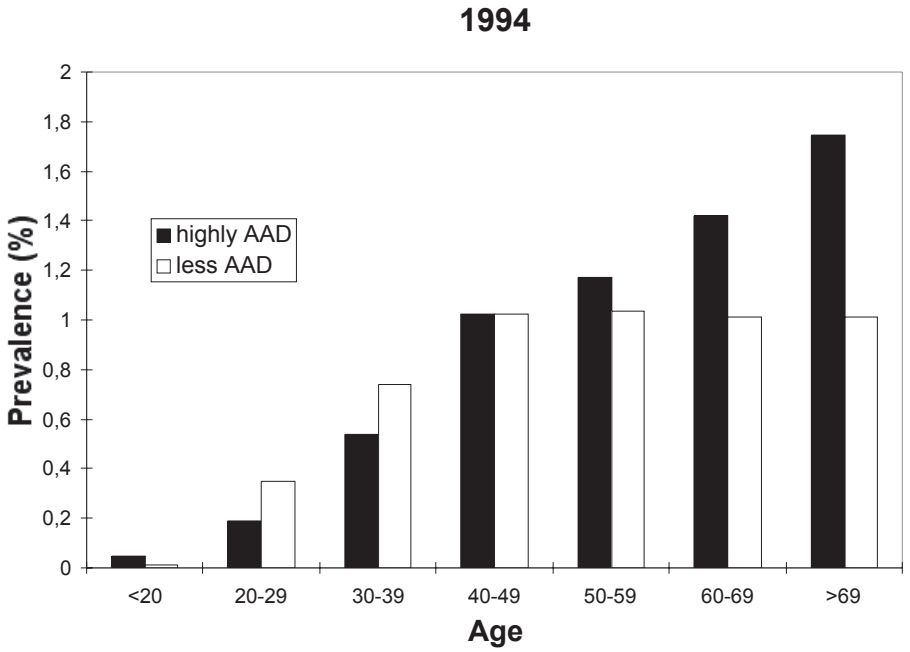

Figure 1a

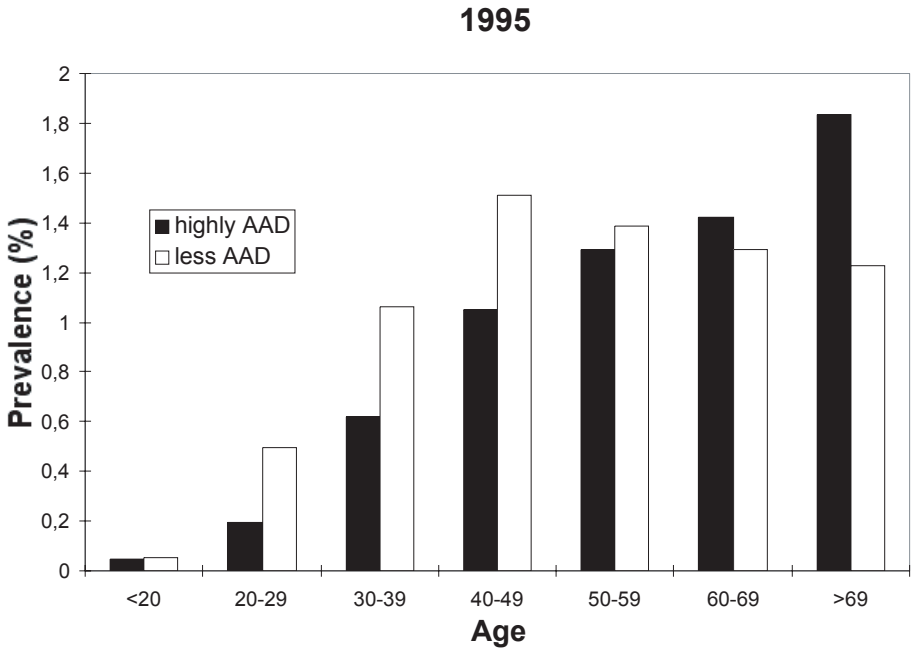

Figure 1b

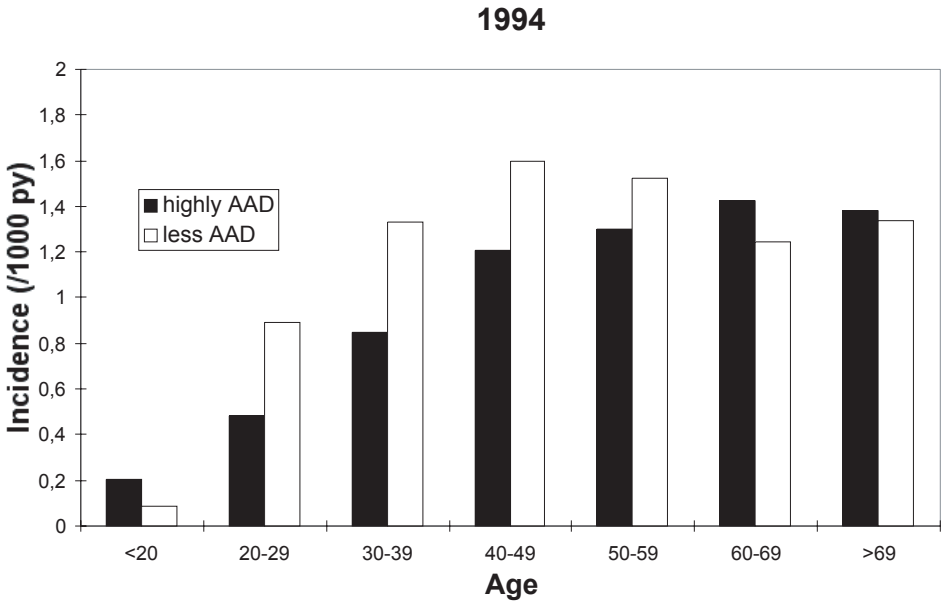

Figure 1c

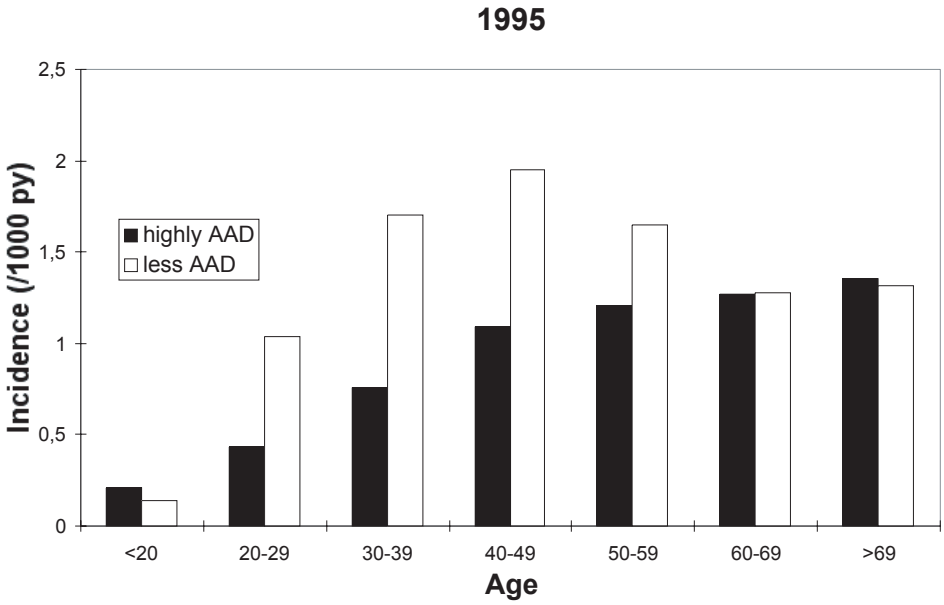

Figure 1d

DISCUSSION

These data indicate that elderly patients in the Netherlands are more likely to be prescribed highly AAD than less AAD, whereas for younger patients the opposite was true. Compared to 1994, the increased prescribing of less AAD in 1995 was mainly observed in younger age groups.

Prior to interpretation of the results several points need to be discussed. In our data we had no information as to indication. This information gap does not allow us to accurately assess the alternatives for this fraction of anticholinergic exposure in the elderly, but there are alternatives for each indication. In a recent survey among 142 patients using antidepressants, 75% were prescribed for depression, 19% for anxiety disorders, 11% for sleeping disturbances, and 8% for neurologic pain (25). We think, however, that despite the lack of clarity about the indication of antidepressant use, suboptimal prescribing seems to be identified. Beers et al. (12) and Salzman (15) recommend against prescribing any highly anticholinergic agents for the elderly.

Pharmacy data as used for the present study are very well validated in the Netherlands (24) and allow reliable evaluation of medication prescribed to individual patients. An important problem in collecting pharmacy records directly from pharmacies is that when patients visit more than one pharmacy, medication histories on a patient level may not be complete. By using data from an insurance company, however, the medication histories are likely to be complete as all prescriptions will be sent to the company the patient is insured at for reimbursement purposes. It might be questioned whether our results are also representative for the higher socio-economic classes which are not covered by the national health insurance system. However, as there are no reimbursement limitations for antidepressants in both the national health insurance system and the private insurance companies, differences between socio-economic classes are not expected.

An important strength of the present study is that we used prevalence and incidence of drug prescribing to measure prescribing practices for antidepressants in the population. Most drug utilization studies use the number of prescriptions or 'Defined Daily Doses' (DDDs) prescribed in a population. The DDDs of drugs are defined by the WHO with the aim of representing the average dose of a drug per day when prescribed for its primary indication. The latter parameters give information on the extent of prescribing in populations and allow a comparison between the prescribing of different drugs in one class. These parameters, however, do not provide insight into the fraction of people that are exposed to specific drugs or drug classes nor do they give insight into the number of new drug starters.

The prevalence data give insight into the percentage of the population exposed to each antidepressant, but do not reflect very well the drug preferences of prescribers at that moment. Although a doctor may have a preference for certain compounds,

she may still prescribe less-preferred compounds because of unwillingness to change medication a patient is satisfied with. Incidence measures, representing new episodes of drug use, give more insight into the drug preferences of doctors during the period the data are collected. Therefore, incidence is a sensitive measure to evaluate the influence of an intervention.
In our study we observed that the fraction of the population that was exposed to highly AAD versus the fraction that was exposed to less AAD in 1994 demonstrated a decrease in 1995. At least part of this change was caused by an increase in the preference to prescribe less anticholinergic compounds (especially SSRIs) from 1994 to 1995 as shown by the incidence data. Also, this change may have been induced by an increased switching of highly AAD prescribing to less AAD prescribing.
Our study demonstrated that there was an increase of 20% in the number of patients that were prescribed antidepressants when 1995 was compared with 1994. This increase was mainly caused by an increase in the prescribing of less AAD (37% increase compared to 6% increase in the highly AAD), mainly by the prescribing of SSRIs. Although the tolerability of the SSRIs appears to be superior to that of the older generation antidepressants (21), there is still discussion about the benefit/risk ratios, partly in relation to their costs. In the Netherlands this uncertainty is expressed in the different preference statements for antidepressants in two recent consensus reports (16,17). It may be clear that the benefit/risk ratio of the SSRIs increases in the elderly. It is interesting to see that in times of controversial guidelines, those who, in theory could have benefited most from a new development (the elderly) have not. Possible explanations are that these side effects are not so striking in daily practice or that the elderly do not complain of these side effects. Furthermore some people may experience side effects and stop taking their medication without informing their physician. Further research is needed to establish the side effect burden of different antidepressants.
This study indicates, using HIC data to obtain prevalence and incidence figures of antidepressant prescribing, that physicians do not refrain from prescribing highly anticholinergic antidepressants to older patients despite their potential adverse drug reactions in this age group and the availability of safer alternatives.
We used these findings as a starting point for an intervention on antidepressant prescribing in the elderly.

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HOOFDSTUK 4
Bijwerkingen van verschillende soorten antidepressiva bij ambulante ouderen

Wat vonden de ouderen er zelf van?
In dit hoofdstuk wordt beschreven wat de resultaten waren van ons onderzoek naar de aard en de ernst van klachten die ouderen hebben bij het gebruik van antidepressiva. We wilden vooral de verschillen in kaart brengen tussen de bijwerkingen die optreden bij het gebruik van minder anticholinerge en sterk anticholinerge middelen. Welke klachten meldden de patiënten in de dagelijkse praktijk zelf?

We hebben dit onderzocht met behulp van een vragenlijst. Alle mensen boven de 60 jaar in de onderzoeksgroep die in 1995 een antidepressivum slikten, ontvingen een vragenlijst; in totaal ging het om 2.359 patiënten. We vroegen in deze enquête naar hun geneesmiddelengebruik en de klachten die zij daarvan ondervonden. In een bijgevoegde uitgebreide lijst konden zij aankruisen waar zij last van hadden. 945 mensen retourneerden een ingevulde vragenlijst, waarvan er 876 geschikt waren voor analyse.

Bij de analyse bleek dat een grote groep mensen gestopt was met het slikken van antidepressiva. In eerste instantie vonden we dat erg teleurstellend. Tot we ons realiseerden dat 'de gestopte groep' juist een goede controlegroep was. We hebben de vragenlijsten in drieën gedeeld: één groep van gestopte gebruikers, één groep van gebruikers van sterk anticholinerge antidepressiva, en een groep die minder anticholinerge antidepressiva slikte.

Tot onze verbazing meldden gebruikers van antidepressiva niet meer klachten dan niet-gebruikers. Ook meldden de mensen die een sterk anticholinerg geneesmiddel gebruikten niet meer bijwerkingen dan zij die een minder anticholinerg middel slikten. Doordat de klacht 'een droge mond' wel significant meer voorkwam bij de groep gebruikers van sterk anticholinerge middelen, wisten we dat we wél goed aan het meten waren; aan het onderzoek lag het niet.
Hoe kan dit kleine verschil in klachten verklaard worden? Wellicht houden artsen bij het voorschrijven van medicatie rekening met al bestaande klachten, bijvoorbeeld obstipatie. We hadden bijvoorbeeld verwacht dat veel mensen die sterk anticholinerge middelen slikken verstopping zouden noemen als klacht. Er was echter geen sprake van een significant verschil.

CONCLUSIE

Over het geheel genomen bleek uit ons onderzoek niet dat gebruikers van sterk anticholinerge middelen meer klachten hebben dan gebruikers van minder anticholinerge antidepressiva. Dit kan mogelijk verklaard worden doordat artsen rekening houden met de specifieke bijwerkingen van de sterk anticholinerge middelen.

4

Adverse events in community-dwelling elderly using highly-anticholinergic versus less-anticholinergic antidepressants

submitted for publication

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"Rabbit's clever," said Pooh thoughtfully.
"Yes," said Piglet, "Rabbit's clever."
"And he has Brain."
"Yes," said Piglet, "Rabbit has Brain."
There was a long silence.
"I suppose," said Pooh, "that that's why he never understands anything."
A.A. Milne, The house at the Pooh corner, 1928.
Chapter: A very grand thing, page 127.

Abstract

Objective: To compare the prevalence of adverse events in users of highly-anticholinergic versus less anticholinergic antidepressants, in a typical population of elderly patients.
Design: Cross-sectional survey with questionnaires
Setting: South Holland Islands, 1995
Participants: Elderly patients (age between 60-95 years) who used antidepressants in 1995 were identified using a health insurance prescription database.
Main outcome measure: Prevalence of reported adverse events, expressed as odds ratios (and 95% confidence intervals) in elderly using two categories of antidepressants as well as former users.
Results: Of 867 respondents, 429 patients had stopped antidepressant use at the time of the questionnaire. These patients served as controls. Adverse events in users of highly-anticholinergic antidepressants (n=268) varied from 5% (difficulties with urination) to 51% (dry mouth). Users of less anticholinergic antidepressants (n=170) had a different pattern of adverse events, but about the same number of symptoms; rates ranged from 3% (constipation) to 40% (difficulty falling asleep). The frequency of symptoms reported by both groups were similar to those seen in former users. Evaluation of the association of anticholinergic adverse events in the two groups of antidepressant users compared with former users revealed two significant associations: dry mouth and incontinence occurred more often in users of highly anticholinergic antidepressants than in former users (odds ratios 1.8 (1.3-2.5) and 1.5 (1.0-2.2), respectively). Evaluation of mood and quality of life demonstrated no differences between both groups of users, in contrast to the control group, which scored better for both.
Conclusions: The number of adverse events reported by community-dwelling elderly using highly-anticholinergic antidepressants as well as less-anticholinergic antidepressants are both high, and similar to complaints mentioned by former users of antidepressants; only dry mouth and incontinence were reported significantly more often in users of highly anticholinergic antidepressants. Confounding by contraindication may explain these findings.

Keywords: antidepressants, side effects, adverse events, anticholinergic, questionnaire, community dwelling elderly

INTRODUCTION

The advantages and disadvantages of the various types of antidepressants are a source of continuing debate. Most of this is focused on the costs and the benefit-risk ratio of tricyclic antidepressants (TCA) and selective serotonin re-uptake inhibitor (SSRI) agents (1-4). The overall impression from trials is that the efficacy of both groups of antidepressants is more or less equal, but there is widespread belief that SSRI seem to have fewer side effects. The anticholinergic side effects of older TCAs may play an important role in the differences between both groups of antidepressants. Much research has emphasized the side effects of highly-anticholinergic drugs in this class, and the vulnerability of the elderly to these adverse events. Some authors even advise against prescribing any highly anticholinergic compounds to the elderly if alternatives are possible. (5-7). In a former study of ours we have shown that the elderly still use many highly-anticholinergic antidepressants (8), despite the availability of less-anticholinergic compounds. As most knowledge of adverse events is generated in trials, in which the elderly are often underrepresented (9-12), we wanted to assess the prevalence of antidepressant adverse events among elderly in daily practice. The aim of this study was to describe the prevalence of adverse events in community-dwelling elderly using highly-anticholinergic antidepressants and less-anticholinergic antidepressants.

METHODS

Study Design

The relationship between antidepressant use and adverse events in an ambulatory setting was evaluated with a cross-sectional study design. We compared elderly using highly-anticholinergic antidepressants and those using less-anticholinergic antidepressants with a control group of former users of antidepressants.

Population

The study population consisted of antidepressant users between 60 and 95 years old who were insured at health insurance company "OZ zorgverzekeringen" (Mutual Care health insurance) in the Netherlands. The insured population consisted of 98% of those in the South Holland Islands area that were compulsorily insured by the national health insurance system. This so-called "Sickness Fund" insures patients in the lower income brackets, comprising approximately 65% of the population in the Netherlands. Of the approximately 240,000 persons insured at "OZ zorgverzekeringen" in this area, approximately 56,150 persons were between 60 and 95 years old. Users were defined by use of at least one antidepressant (table

1) reimbursed in 1995. We identified 2,359 different users of antidepressants in the prescription databases.

Highly-Anticholinergic Antidepressants (Highly-AAD)	Less or Non-Anticholinergic Antidepressants (Less-AAD)	
Tricyclic derivatives	**Tricyclic derivatives**	**MAO-inhibitors**
Amitriptyline	Desipramin	Tranylcypromin
Clomipramine	Opipramol	Moclobemide
Doxepin	Nortriptyline	Nialamide
Imipramine	Dosulepin	**Others**
Maprotilin *	Dibenzepine	Trazodone
Trimipramine	**SSRI's**	Venlafaxine
	Paroxetine	Mirtazapine
	Sertraline	Mianserine
	Fluoxetine	
	Fluvoxamine	

*Tetracyclic derivative

Table 1: Drug Classification

Prescription Data

The drug reimbursement database used for this study was obtained from the health insurance company "OZ zorgverzekeringen" and consisted of complete drug dispensing histories of the insured population from 1 July 1993 to 31 December 1996. These drug-dispensing records were collected in pharmacies and sent to the health insurance company on either diskette or magnetic tape for reimbursement purposes. The data did not include the person's name, but included the family insurance number, the date of birth and sex. Unique combinations of family insurance numbers, birthday and sex identified individual users. The drug-related information consisted of a unique product code, the prescriber, the dispensing date, the number of units dispensed and the prescribed daily dose. Linking the product code to other databases gives access to information on ATC, total DDDs (defined daily doses) in the package, brand name, dispensing unit and costs (13).

Drug Classification

The antidepressants were classified with regard to their in vitro and in vivo anticholinergic effects, based on standard literature and publications found by a literature review using Medline (14-19). In addition, the evaluations as published in

the 'Farmacotherapeutisch Kompas' (a Dutch equivalent of the British National Formulary) were used.
The following agents, which are marketed in the Netherlands, were classified as highly-anticholinergic: amitriptyline, clomipramine, doxepin, imipramine, maprotiline and trimipramine (8). All other agents belonging to the group of antidepressants according to the ATC classification were classified as causing fewer anticholinergic effects and were considered less-anticholinergic agents. (table 1)

Questionnaire

The questionnaire sent to patients comprised questions on basic characteristics (sex, age, marital state, household, religion, education, occupation, smoking, coffee and alcohol use), current medication use, symptoms (including a list of known antidepressant side effects and complaints), health care utilization in the former year, the Geriatric Depression Scale (GDS) and the COOP-WONCA Health charts (20-22). The questionnaires were sent out in March 1996.

Procedures

After identifying the users of antidepressants in 1995 from the prescription reimbursement databases, their codes were further processed at the health insurance company. Address labels were made at "OZ zorgverzekeringen" and questionnaires were sent from there. A stamped return envelope was enclosed. When questionnaires were returned they were coded and the consent form (the only sheet including the respondent's name) was removed and filed at a different location.

Exposure Definition

Exposure assessment was done using the answers in the returned questionnaires. To examine adverse events experienced by elderly using anticholinergic antidepressants we divided users into two groups: those using highly anticholinergic antidepressants and those using an antidepressant not having a strong anticholinergic component (see *drug classification* and table 1). Respondents who did not report antidepressant use were used as a control group of former antidepressant users, as selection criterion for the questionnaire had been the reimbursement of at least one antidepressant prescription in the preceding year.

Statistical Analyses

Data were processed using FoxPro ® and SPSS ® (for Windows, release 6.1.3). Frequencies of adverse events were calculated in each of the three patient groups. Odds ratios and their 95% confidence intervals were calculated to estimate the risk of specific adverse events in users of highly-anticholinergic antidepressants and less-anticholinergic antidepressants, using a logistic model. All associations with

adverse events were assessed in separate models. For the exposure variable, users were categorized as highly-anticholinergic antidepressant users, less-anticholinergic antidepressant users and controls (subjects who did not report antidepressant use). Crude odds ratios were obtained, only coding for antidepressant use. Adjustment for potential confounders was accomplished by entering other prognostic factors (sex, age, mood and pain) into the model. All variables were entered into the model after categorization (with age treated as a continuous variable).

RESULTS

We sent 2,359 questionnaires, of which 945 were returned. Eighteen responses had too many missing values to evaluate, and another sixty were answered by a family member other than the patient addressed. 867 (37% of 2,359) questionnaires were used for the current report. There were no material differences between the response and the non-response population concerning sex and age distribution and antidepressant use (average age 71.8 vs. 73.2 years old; women: 74.2% vs. 74.7%). Population characteristics are presented in table 2. Of these 867, 429 respondents reported no antidepressant use. Highly anticholinergic antidepressant use was reported by 268 respondents. Of the 173 respondents reporting use of less-anticholinergic antidepressants, three also reported use of a highly anticholinergic antidepressant. These three were allocated to the highly-anticholinergic antidepressant users. The other 170 respondents were analyzed as less-anticholinergic antidepressant users.

	Highly-Anticholinergic Antidepressant Users Number (Percentage)	Less-Anticholinergic Antidepressant Users Number (Percentage)	Control (Former Antidepressant Users) Number (Percentage)
Number	268	170	429
Sex Male	71 (26.5)	52 (30.6)	144 (33.6)
Female	196 (73.1)	118 (69.4)	283 (66.0)
Age (mean, stand.dev.)	71.1 (7.4)	70.5 (7.5)	71.6 (7.4)
Diabetes	37 (13.8)	15 (8.8)	62 (14.5)
Hypertension	84 (31.3)	50 (29.4)	142 (33.1)
History of coronary disease	35 (13.1)	20 (11.8)	92 (21.24)
Parkinson's disease	11 (4.1)	3 (1.8)	9 (2.1)
History of depression	133 (49.6)	115 (67.6)	113 (26.3)
COPD	20 (7.5)	17 (10.0)	60 (14.0)
Cancer in history	12 (4.5)	14 (8.2)	28 (6.5)

Table 2 Population Characteristics (baseline)

Tables 3a and 3b list the reported adverse events. When comparing crude rates, elderly using anticholinergic antidepressants were likeliest to report the known side effects of these drugs (dry mouth, constipation, dyspepsia and incontinence).

Antidepressant use	Frequencies								Logistic Regression			
	Highly-Anticholinergic		Less-Anticholinergic		Control		All		Highly-Anticholinergic versus control		Less-Anticholinergic versus control	
total questionnaires	268	(%)	170	(%)	429	(%)	867	(%)	RR	(95%CI)	RR	(95%CI)
Dry Mouth	138	51%	67	39%	159	37%	364	42%	1.80	(1.32-2.46)*	1.10	(0.77-1.59)
Falling more often	18	7%	12	7%	38	9%	68	8%	0.74	(0.41-1.33)	0.78	(0.40-1.53)
Blurred Vision	61	23%	38	22%	111	26%	210	24%	0.84	(0.59-1.21)	0.82	(0.54-1.26)
Nausea	18	7%	25	15%	65	15%	108	12%	0.40	(0.23-0.70)*	0.97	(0.59-1.59)
Impaired concentration	51	19%	44	26%	96	22%	191	22%	0.82	(0.56-1.19)	1.21	(0.80-1.83)
Dyspepsia	64	24%	31	18%	91	21%	186	21%	1.17	(0.81-1.68)	0.83	(0.53-1.30)
Palpitating	45	17%	26	15%	76	18%	147	17%	0.94	(0.63-1.41)	0.84	(0.52-1.36)
Memory problems	80	30%	53	31%	118	28%	251	29%	1.12	(0.80-1.57)	1.19	(0.81-1.76)
Constipation	39	15%	14	8%	53	12%	106	12%	1.21	(0.77-1.89)	0.64	(0.34-1.18)
Unstable gait	89	33%	60	35%	144	34%	293	34%	0.98	(0.71-1.36)	1.08	(0.74-1.57)
Reaction time increased	50	19%	34	20%	58	14%	142	16%	1.47	(0.97-2.22)	1.60	(1.00-2.55) *
Dizziness	52	19%	45	26%	103	24%	200	23%	0.76	(0.52-1.11)	1.14	(0.76-1.71)
Difficulties with urination, yes:	101	38%	64	38%	147	34%	312	36%	1.10	(0.79-1.51)	1.08	(0.74-1.56)
Hesitation	22	8%	16	9%	34	8%	72	8%	1.04	(0.59-1.82)	1.21	(0.65-2.25)
Dripping	28	10%	25	15%	49	11%	102	12%	0.90	(0.55-1.48)	1.34	(0.80-2.25)
Incontinence	59	22%	32	19%	69	16%	160	18%	1.47	(1.00-2.17) *	1.21	(0.76-1.92)
Other / various	14	5%	6	4%	18	4%	38	4%	1.26	(0.62-2.57)	0.84	(0.33-2.14)
Constipation < 2 /week	19	7%	5	3%	17	4%	41	5%	1.85	(0.94-3.62)	0.73	(0.27-2.02)

Table 3a: Questionnaire Results: Anticholinergic Effects Frequency Table

Antidepressant use	Frequencies								Logistic Regression			
	Highly-Anticholinergic		Less-Anticholinergic		Control		All		Highly-Anticholinergic versus control		Less-Anticholinergic versus control	
total questionnaires	268	(%)	170	(%)	429	(%)	867	(%)	RR	(95%CI)	RR	(95%CI)
Coughing	70	26%	44	26%	122	28%	236	27%	0.89	(0.63-1.25)	0.88	(0.59-1.31)
Diarrhea	15	6%	16	9%	26	6%	57	7%	0.92	(0.48-1.77)	1.61	(0.84-3.08)
Irritable	30	11%	20	12%	52	12%	102	12%	0.91	(0.57-1.47)	0.97	(0.56-1.67)
Feeling numb	35	13%	28	16%	39	9%	102	12%	1.50	(0.93-2.43)	1.97	(1.17-3.32) *
Anxiousness	63	24%	41	24%	74	17%	178	21%	1.47	(1.01-2.15)*	1.52	(0.99-2.35)
Sleepiness	46	17%	39	23%	76	18%	161	19%	0.96	(0.64-1.44)	1.38	(0.89-2.14)
Difficulty falling asleep	113	42%	68	40%	182	42%	363	42%	0.99	(0.73-1.35)	0.90	(0.63-1.30)
Eczema	26	10%	16	9%	43	10%	85	10%	0.96	(0.58-1.61)	0.93	(0.51-1.71)

Table 3b: Questionnaire Results: Non-Anticholinergic Effects Frequency Table

	Measure	Highly-Anticholinergic antidepressant users	Less-Antichlolinergic antidepressant users	Control (former antidepressant users)
GDS Outcome	Normal / not depresssed	107 (40.0)	68 (40.0)	206 (48.0)
	Slightly depressive	124 (46.3)	79 (46.5)	178 (41.5)
	Moderate-serious depr.	36 (13.4)	23 (13.5)	44 (10.3)
COOP/Wonca: Overall Health lately	Mean *	3.64	3.63	3.73

* In the COOP/Wonca charts a higher number stands for a better overall health lately

Table 3c: Questionnaire Results: Population Benefits

By contrast, while users of less-anticholinergic antidepressants had lower frequencies of these adverse events, they complained more of nausea, dizziness, impaired concentration and dripping. The crude rate of occurrence of adverse events ranged from 3% (stool freq.< 2/week) to 40% (difficulty falling asleep) for less-anticholinergic antidepressants and from 5% (various difficulties urinating) to 51% (dry mouth) for highly anticholinergic antidepressants (Table 3a and 3b). Difficulty urinating as well as constipation were each mentioned by 4% of the non-users. Among controls, 42% mentioned difficulty falling asleep.
The crude rate differences of complaints between the two groups of drugs ranged from 12% more dry mouth with highly-anticholinergic antidepressants to 8% more nausea with less-anticholinergic antidepressants. Table 3a and table 3b also present the estimated ORs of all adverse events. Significant increased risks were found for dry mouth and incontinence for users of highly-anticholinergic antidepressants. However, users of less-anticholinergic antidepressants were significantly more likely to report emotional numbness and an increased reaction time. Adjusted ORs did not differ considerably from the unadjusted ORs and are not presented here.
Table 3c lists the effectiveness of drug therapy. Our results demonstrate that users of both classes of antidepressants show similar scores on the GDS depression scale and perception of overall health lately. Whereas the control group showed better scores for both mood and overall health lately.

DISCUSSION

In this population-based survey of typical elderly patients taking antidepressants, we found a different pattern of adverse events in users of highly-anticholinergic antidepressants when compared to users of less-anticholinergic antidepressants. However, the number of adverse events reported was similar in both groups, and similar to the number reported by former users of antidepressants. Clinical trials tend to include selected patients under clearly defined circumstances. As a result, their findings cannot always be extrapolated to daily practice. The effectiveness of a therapy and its adverse events may be different when a therapy is applied to another population under different circumstances. This is especially true for the elderly. (12).
In addition to trials, observational studies can provide information about the effectiveness and unintended effects of drugs in specific populations in daily practice. Adverse events may have an effect on compliance and can be a cause of additional health care costs (23) (24). Much observational research involving the elderly is done in nursing homes and similar settings. The majority of these studies focus on one adverse event or lack controls (7,15,25-28). Our study compared a wide range of adverse events reported by a population of typical ambulatory elderly using

antidepressants, including a control group of former users of antidepressants. Former users of antidepressants were expected to be more comparable with current users than a control group of which antidepressant use is unknown. A problem might be that non-users in our study in reality are non-reporters of current use. However, comparison with pharmacy records showed that most of them indeed had stopped using antidepressants. Antidepressants are used for several indications and the distribution of indications will certainly not be equal in the former user, less-anticholinergic antidepressant and highly-anticholinergic antidepressant user groups. Although our data show an equal distribution of population characteristics, mood scores and recent overall health, confounding by indication across the treatment categories cannot be excluded with certainty.

Confounding by contra-indication may explain our finding that the anticholinergic adverse events were not dramatically higher in the highly-anticholinergic antidepressant users compared to the less-anticholinergic antidepressant users. For instance, when a patient has constipation or urinary problems, doctors may discontinue the offending drug and prescribe less-anticholinergic antidepressants. Thus there may be more patients already suffering anticholinergic-like complaints in the less-anticholinergic antidepressant user group. We do not have information on the start of the complaints in relation to the start of the drug. Thus, although there are no indications that the adverse event burden for users of highly-anticholinergic antidepressants is substantially higher, this could be explained by confounding by contraindication.

Another explanation of our findings can be that because patients with adverse events had stopped their antidepressants, resolving the adverse events. Alongside that, many of the adverse events reported may not have been caused by the antidepressants.

The frequency of adverse events does not reflect how patients experience the seriousness of these events. This could be assessed using quality of life scales and needs further research. Our results show no difference in effectiveness of either group of antidepressants on depression or overall quality of life.

Lack of significance can be due to small sample size. However, this study comprises a large population compared to most previous studies of typical elderly. Response bias could have caused under or overestimation of adverse events.

Although in theory the elderly are prone to suffer anticholinergic adverse reactions and should therefore not be prescribed highly-anticholinergic antidepressants, this could not be confirmed in our research population. Community-dwelling elderly using highly-anticholinergic antidepressants did not report more adverse events than elderly using less-anticholinergic antidepressants. Moreover, the number of adverse events in the antidepressant users was comparable with that seen in former users of antidepressants.

Conclusion

The elderly patients we studied reported a substantial number of adverse events during the use of both highly-anticholinergic antidepressants and less-anticholinergic antidepressants. These differed in nature, but not in frequency between the older and newer drug classes. In addition the number of symptoms reported by current antidepressant users of both types was similar to that seen in former users of antidepressants. The small differences in occurrence of anticholinergic adverse events in both antidepressant groups may be caused at least in part by confounding by contraindication, as would be expected if prescribers were aware of drug-specific adverse event risks and avoided or discontinued use of problematic drugs in patients with such symptoms.

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HOOFDSTUK 5
Een vergelijking van verschillende depressiescorelijsten bij ambulante ouderen

Een lastige diagnose

Depressie bij ouderen is een belangrijk probleem. Een depressie leidt tot veel verlies van de kwaliteit van leven voor de patiënt. Daarnaast doen depressieve ouderen doorgaans een groot beroep op de gezondheidszorg; er is dus waarschijnlijk veel geld mee gemoeid.

Depressie is moeilijk te diagnosticeren. Er bestaan verschillende scoringslijsten om depressiviteit te meten. Wij hebben hiervan een aantal met elkaar vergeleken in één populatie van ambulante (min of meer zelfstandig wonende) ouderen. Het is belangrijk om een goede diagnose van depressie te kunnen stellen. Wanneer er een behandelprotocol voor depressiviteit bij ouderen bestaat, is er uiteraard ook een indicatie nodig. Want: wanneer valt iemand onder dat protocol? Daarom was het voor de hand liggend om in deze studie ook de uitkomsten van verschillende scoringslijsten met elkaar te vergelijken.

De enquête die we rondstuurden aan ouderen die antidepressiva gebruikten, bevatte vier verschillende scoringslijsten om (de mate van) depressiviteit te meten. Dus op vier verschillende manieren werd de mensen gevraagd informatie te geven over hun gemoedsgesteldheid en over hun – doorgaans aan depressie gerelateerde – lichamelijke klachten. Dit hoofdstuk beschrijft de mate van depressiviteit die mensen scoren bij de verschillende lijsten. De depressiescores die deze lijsten opleverden, hebben we met elkaar vergeleken. Behalve dat er sprake was van een behoorlijke overlap, bleek bij analyse ook dat waar de ene lijst een ernstige depressiviteit aangeeft bij maar liefst 60% van de ondervraagden, de andere slechts bij 24% van de ondervraagden tot die conclusie komt.

CONCLUSIE

We denken dat het belangrijk is dat hulpverleners weten dat deze lijsten grote verschillen in uitkomst kunnen opleveren, en dat depressie bij ouderen moeilijk te diagnosticeren is.

5

Comparison of various depression scales in a group of ambulatory elderly

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submitted for publication

"Tigger is all right, really," said Piglet lazily.
"Of course he is," said Christopher Robin.
"Everybody is really," said Pooh. "That's what I think," said Pooh. "But I don't suppose I'm right," he said.
"Of course you are," said Christopher Robin.
A.A. Milne, The house at the Pooh corner, 1928.
Chapter: Eeyore joins the game, page 105.

Abstract

Background: Depression in the elderly is a major public health problem, resulting in a loss of quality of life and high demands on health services. One problem is that depression is underdiagnosed and undertreated. There are several validated scales available to score depression. However, these scales have not been compared with each other in the same population.

Methods: we invited a group of 2,359 elderly patients (60 years of age and older), who had used an antidepressant in the year prior to our investigation, to participate in a questionnaire. The patients were identified by a pharmacy record database of a health insurance company in the Netherlands. The questionnaire contained questions about general patient characteristics, the Geriatric Depression Scale (GDS), the VROPSOM list, part of the COOP/WONCA questionnaire. Correlations between the different rating scales were calculated by Pearson's correlation coefficient.

Results: 945 questionnaires (40%) were returned of which 867 (37%) could be used for statistical analyses. Correlations between different rating scales varied between 0.43 and 0.55 (all estimates $p<0.0001$). There were substantial differences in the percentages of patients with signs of depression when different scales were compared: GDS 55%, VROPSOM 24%, COOP/WONCA 81% and the question "Do you feel sad?" 35%.

Conclusion: Our study shows that health care workers who use depression rating scales should be aware of substantial differences in their potential to detect signs of depression.

Keywords: depression rating scales, elderly, primary health care, healthy insurance company

INTRODUCTION

The prevalence of depression in elderly people varies strongly in different surveys but is often reported to be 12-15% (1,2). As is the case in many other countries, in the Netherlands depression is a public health problem among the elderly. The prevalence of major depression in primary care is reported to be 8%, and of minor depression 17% (3).
One problem in primary care is that not all cases of depression are recognized; several studies have shown substantial underdiagnosis and undertreatment of depression in the elderly (4). There are several factors that may be an obstacle to detecting depression in the elderly. First, some general practitioners may possess an inadequate diagnostic capacity (5,6). This might be caused by a reluctance to discuss feelings, a lack of knowledge of the prevalence of depression in the elderly and confusion about the role and use of self-report questionnaires to detect depression. Second, comorbidity might lead to misinterpretation of symptoms of depression (1).
The use of rating scales for depression in daily practice is potentially helpful to detect depression when such a diagnosis is suspected. Although rating scales are sometimes used, this is still not common practice (7).
Validated depression scales are the Geriatric Depression Scale (GDS) (4), the Depression Adjective Check Lists (DACL = VROPSOM lists) (8) and part of the Dartmouth COOP Functional Assessment Charts WONCA (COOP/WONCA) (the emotional condition component) (9). Although these rating scales are all validated, not necessarily in the elderly, they have not been compared directly with each other in a population of elderly subjects. As each scale uses different criteria to detect depression, differences in the scoring of depression might occur.
The aim of our study was to perform a direct comparison of different rating scales for depression in a group of elderly people.

MATERIALS AND METHODS

The data used for the present study were part of a larger project in which intervention strategies were evaluated for their potential to influence the prescribing of antidepressants in primary care (10). The project was performed in a research area that is part of the area of the health insurance Company 'OZ zorgverzekeringen' in the Southwest Netherlands. Approximately 240,000 people (60% of the population in the research area) were insured through 'OZ zorgverzekeringen' of which 50,000 were 60 years of age or older.
Prior to this intervention, a questionnaire was sent in 1996 to all elderly people (60-95 years of age) in the research area who had used an antidepressant in 1995.

Patients were identified using the reimbursement databases that pharmacists send to the health insurance company. The questionnaire contained questions about general patient characteristics (including morbidity), the GDS (30 yes/no questions) (11) the VROPSOM list (34 yes/no items) (8), and the COOP/WONCA, which includes five pictorial choice charts assessing functioning in emotional condition areas (9).
Furthermore, the closed-ended question "Do you feel sad?" (Yes /no answer) (4) was included in the questionnaire. We used Dutch translations of the different rating scales. The questionnaires were sent to patients with postage paid return envelopes.

Analysis

After applying internationally accepted cut-off values to diagnose depression for the various rating scales (GDS: no depression <11 questions yes, mild depression 12-20 questions yes and severe depression >20 questions yes (11); VROPSOM: no depression >=7 items yes and depression <=7 items yes (8)), the scales were compared to each other by Pearson's correlation coefficient (SPSS) and by comparing the prevalence of depression as scored by the different scales.

RESULTS

In the pharmacy records of the health insurance company, 2,359 elderly patients who had used an antidepressant in 1996 were identified. A total of 945 questionnaires (40%) were returned and of these, 867 (37%) could be used for statistical analysis. Seventy-eight questionnaires were excluded because of errors in completion of the questionnaire.
The population in this study consisted of 68% women and 32% men, with a mean age of 71 years (standard deviation 7.4). All respondents were using antidepressants at the time of completion of the questionnaire. The most frequently self-reported medical problems are presented in Table 1.
The Pearson's correlation of the different rating scales and the question "Do you feel sad" varied between 0.43 and 0.55 (all correlation estimates $p<0.0001$) (Table 2). Although there was a reasonable correlation between rating scales, the prevalence of depression as scored by the different scales showed substantial differences. According to GDS, VROPSOM, COOP/WONCA and the closed-ended question, slight to severe depression was present in 55%, 24%, 81% and 35% of respondents, respectively. In 123 patients (14% of the total group) all rating scales scored positive for depression. Sixteen percent (141 respondents) rated as not depressed across all rating scales and the question "Do you feel sad?"

Sex			
	Male	277	32%
	Female	590	68%
Age			
	60-69	408	47%
	70-79	324	37%
	80-89	127	15%
	>90	8	1%
Co-Morbidity			
	Diabetes	109	13%
	Hypertension	269	31%
	Coronary disease	149	17%
	Nephropathology	26	3%
	Parkinson's disease	21	2%
	Asthma/COPD	98	11%
	Cancer	55	6%
	Rheumatism	90	10%

Table 1: General Characteristics of Patients

	GDS	COOP/WONCA	VROPSOM	Sad feeling
GDS	1	0.55	0.52	0.43
COOP/WONCA		1	0.52	0.51
VROPSOM			1	0.48
Sad feeling				1

Correlation is significant at the $p<0.0001$ level

Table 2: Pearson's Correlation of COOP/WONCA, GDS and VROPSOM rating scales and the question "Do you feel sad?"

		Depression	
		Number	Percentage
GDS			
	No	387	44.6%
	Mildly	379	43.7%
	Severely	101	11.6%
VROPSOM			
	No	662	76.4%
	Yes	205	23.6%
COOP/WONCA			
	No	167	19.3%
	Slightly	220	25.4%
	Moderately	246	28.4%
	Seriously	177	20.4%
	Extremely	57	6.6%
Sad Feeling			
	No	563	64.9%
	Yes	304	35.1%

Table 3: Outcome of four depression rating scales in a group of 867 patients

DISCUSSION

Although there is a reasonable correlation between the different rating scales for depression, our study demonstrated that there are substantial differences in the number of patients detected as depressed when applying the different scales in the same patient group. As we had no 'gold standard' (psychiatric interview) in our study, it is not possible to conclude which rating scale performed best. There may be both overdiagnoses and underdiagnoses (false positives and false negatives) for the different scales.

The prevalence of depression that was estimated in our study cannot be extrapolated to the entire population of elderly. Our study used a group of patients that were treated with an antidepressant the year prior to our investigation. Although antidepressants are used for other indications as well, the prevalence was expected to be high in our population. This was confirmed by our data. We found prevalence of signs of depression varying from 24% to 81%. Although our group was not representative for the elderly in the Netherlands, this does not jeopardize

our comparison of the different rating scales. In fact, it is helpful that there is a large variation in the level of depression in our patient group, increasing the power of our statistical comparisons. We also do not expect that the low response rate has influenced our results since we have no reason to assume that the comparison of the different rating scales in the non-responders will be different.
Early diagnosis and treatment of depression in the elderly remains challenging to the clinician, but ultimately provides opportunities to reduce suffering and increase the quality of life, to prevent suicide, to restore optimal levels of functioning and independence, and to decrease the societal costs of health care (1).
Although we cannot say which rating scale performed best, one important conclusion, which can be drawn, is that the chance of a patient to be diagnosed as depressed depends heavily on the rating scale being used. These results stress the importance for further research into the value of different depression rating scales in the elderly.

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HOOFDSTUK 6
Kenmerken van FTO-groepen: betekenis voor stratificatie in een gerandomiseerde interventie

FTO-groepen

In Nederland werken huisartsen en apothekers in groepen samen om kennis uit te wisselen, te discussiëren en afspraken te maken over de kwaliteit van farmacotherapie. Deze zogenaamde farmaco-therapie-overleggroepen (FTO's) bestaan al geruime tijd.
De Nederlandse aanpak is uniek in de wereld, en staat model voor soortgelijke initiatieven in andere landen. Deze werkvorm is namelijk een heel goede manier gebleken om in de eerste lijn samen te werken. Artsen die deel uitmaken van een FTO-groep blijken rationeler en goedkoper voor te schrijven.
Omdat FTO-groepen zo belangrijk zijn, wilden wij deze groepen ook betrekken bij onze interventie. We wisten dat deze groepen van grote invloed zijn op de kwaliteit van voorschrijven. Daarom vonden we het belangrijk om vóór de interventie al te kijken hoe de FTO-groepen in de onderzoeksregio samenwerkten, èn om ervoor te zorgen dat de groepen die intensief samenwerkten gelijkelijk verdeeld zouden worden over de interventiearmen (de drie onderzoeksgroepen, zie hoofdstuk 7).

Veel Verschillen

Dit hoofdstuk beschrijft de resultaten van telefonische interviews die we hebben gehouden onder de FTO-groepen in de onderzoeksregio. In deze interviews vroegen we naar allerlei kenmerken van de FTO-groepen, zoals de organisatiestructuur en de doelstellingen. Maar ook welke voorbereiding er aan een FTO voorafgaat, welke lesvormen er worden gebruikt en of er afspraken worden gemaakt. Hoe bindend zijn deze? (zie appendix Questionnaire)
Uit de interviews bleek dat er sprake is van enorme verschillen (zie tabellen 1 tot 3). Sommige groepen werkten al lang samen, andere nog maar kort. Sommige kwamen regelmatig bij elkaar, andere maar zeer incidenteel. Soms bestond de groep uit niet meer dan vier artsen en een apotheker en soms wel uit zestien artsen en vijf apothekers. Verder hanteerden de groepen zeer verschillende werkvormen.

Criteria voor Randomisatie en Stratificatie

Om het effect van de interventie goed te kunnen meten moesten we FTO-groepen met belangrijke kenmerken willekeurig (gerandomiseerd) en gelijkelijk (gestratificeerd) verdelen over de interventiearmen. Daarom moesten we kiezen welke kenmerken relevant zouden zijn voor een gewogen verdeling van de FTO-groepen over deze interventiearmen. Allereerst vonden wij het van belang of de groep werkte met een formularium. Een formularium is een 'voorkeurslijst van

geneesmiddelen' die de arts hanteert, waarin omschreven staat welk geneesmiddel in welke situatie de meeste voorkeur geniet. Het gebruik van een gezamenlijk formularium is een teken dat de groep streeft naar het rationaliseren van het voorschrijfbeleid. Verder vonden we het belangrijk of een groep ervaring had met prescriptieterugkoppeling (overzichten van het eigen voorschrijfgedrag). Ten slotte vonden we het relevant of een groep te kennen gaf naar consensus te streven, en dus in principe 'bindende' afspraken wilde maken.

CONCLUSIE

Na de interventiestudie en de analyse van resultaten konden we bevestigen dat deze kenmerken inderdaad effect hadden op het effect van de interventie.

6

Characteristics of Dutch peer review groups: implications for stratification in a randomized trial

submitted for publication

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"How would it be?" said Pooh slowly, "if, as soon as we're out of sight of this Pit, we try to find it again?"
"What's the good of that?" said Rabbit.
"Well," said Pooh, "we keep looking for Home and not finding it, so I thought that if we looked for this Pit, we'd be sure not to find it, which would be a Good Thing, because then we might find something that we *weren't* looking for, which might be just what we *were* looking for, really."
A.A. Milne, The house at the Pooh corner, 1928.
Chapter: Tigger is unbounced, page 121.

Abstract

Background: In experimental studies, stratification prior to randomization is a well-known technique to prevent imbalance between treatment groups in factors that may strongly influence prognosis or treatment responsiveness. Although such stratification is often used in trials in which patients are randomized, it is seldom performed when groups are randomized. This study reports on the process of selection of characteristics of peer review groups (PRGs; groups of primary care physicians and community pharmacists) thought on theoretical ground to be relevant for the responsiveness to an educational outreach program aimed to change prescribing. After the outreach program was tested in a controlled trial in which PRGs following stratification were randomized over treatment arms, we evaluated whether the selected characteristics indeed modified the effect of our intervention.

Methods: Representatives of 61 PRGs in our research area were asked to participate in a telephone interview. The interview consisted of questions on organizational structure of the PRG, how meetings were prepared and presented, and the level of binding agreements on pharmacotherapy. Changes in prescribing within strata thought to be relevant for the effect of our outreach program were evaluated by estimation of incidence rate ratio's (Poisson regression)

Results: Forty representatives of PRGs (66%) participated in our study. Based on responses and theoretical considerations we found the aim of the group (information exchange (n=14) versus binding consensus on pharmacotherapy (n=26)), the use of a formulary (22 PRGs did and 18 PRGs did not) and the use of feedback data (22 PRGs did and 18 PRGs did not) most relevant to use for stratification. After evaluation of our educational outreach program it appeared that the characteristics we had selected strongly modified the effect of our program, on prescribing behavior. While the overall effect was that prescribing was significantly changed by our program this change was not observed when PRGs were selected on the basis of working with binding consensus, not using feedback and not using a formulary.

Conclusion: Based on theoretical considerations and inventory of characteristics of PRGs we were able to define factors to be used for a stratified randomization of PRGs which in retrospect indeed strongly modified the effect of an educational outreach program directed to change prescribing.

Keywords: stratification, randomization, peer review groups, educational visits, rational drug use, continuing medical education

INTRODUCTION

When organizing an experimental intervention in natural populations, stratification prior to randomization offers an opportunity to prevent imbalance between treatment groups in factors that may strongly influence prognosis or treatment responsiveness. Control of such variability can lower the occurrence of type l errors and improves power for small trials. While it is important to define stratification factors that have a relevant effect on prognosis or treatment responsiveness, it is also important to avoid creating too many strata (1). Most literature on stratification strategies is based on interventions at an individual (e.g. patient) level. Although educational interventions are often organized at a group level, there is hardly any literature on the role of stratification of groups within a group approach intervention (2).
Recently we performed a three-arm randomized controlled trial to compare the effect of individual educational visits and group visits versus no visits on the prescribing of highly anticholinergic antidepressants in the elderly (3) As unit of randomization we used peer review groups (PRG). In the Netherlands the expression 'peer review group' (PRG) is used for regular meetings of groups of primary care physicians and pharmacists to discuss pharmacotherapy and improve the quality of pharmacotherapy. This type of interdisciplinary groups are increasingly popular in other countries as well (4). For our trial we performed a stratified randomization of PRGs as we expected based on literature review that certain characteristics of PRGs would modify the effect of our intervention on prescribing.
Characteristics of PRGs that support dissemination of knowledge have been described by several authors (5-11). The qualities mentioned can be divided into those concerning organizational structure, those on goals and consensus, and those on preparation and presentation.
This paper describes the process of how we selected characteristics of PRGs that were used to perform the stratified randomization and reports whether these characteristics indeed modified the effect of our intervention (changing of prescribing behavior).

METHODS

Study Design and Participants

We contacted representatives of all PRGs in the primary working area of the health insurance company "OZ zorgverzekeringen" in the Southwest Netherlands (61 Peer Review Groups, insured population approximately 600,000 persons). These representatives were primary care physicians and pharmacists. Within two weeks

after being sent a letter of introduction, these representatives were approached to make an appointment for a structured telephone interview. The interviews were completed by the same person (MM) in a period of four months.

Questionnaire

The questionnaire contained questions about characteristics of the PRGs: the organizational structure, attitudes towards achieving consensus, and the way topics to discuss were prepared and presented (7,8).

Organizational Structure

Most literature on PRGs is based on the paradigm that highly structured consultations will produce better results (5). A better structure facilitates problem-solving collaboration and improves the results of the meeting (9). Structured cooperation results in more cooperation between primary care physicians and other first-line disciplines and leads to changes in drug therapy (12). The minimal requirements of structural organization are generally considered to be: group size between 5 and 15 professionals, frequency of gatherings between 5 to 10 per year, duration of 90-120 minutes per meeting and good attendance rate. It also involves making commitments concerning the chairman, collaboration with pharmacists, preparation, agenda and minutes (9) (Table 1).

Questions	Average	SD	Min-max
Meeting since	4.5 yr.	5.5	0.5 - 25
Number of members	9.9 persons	4.4	4 – 21
Attendance rate	85 %	18	60 – 100
Number of meetings per year	6.2	1.9	4 –10
Duration per meeting	1.5 hours	0.6	0.5 – 3
	Yes (n)	(%)	
Is the peer review group also the on-call group?	34	(85)	
Are the minutes discussed?	21	(53)	
Has a chairman been appointed?	31	(78)	
Is this a rotating position?	16	(41)	
Is there contact with other groups?	7	(18)	
Is there contact with hospital specialists?	13	(33)	
Are minutes being recorded?	25	(62.5)	
Is audiovisual support used?	27	(67.5)	
Is advertising material used?	6	(15)	
Are speakers invited?	10	(25.6)	

Table 1: Characteristics of peer review groups related to organizational structure

Goals and Consensus

Another important issue is a common goal and the intention of reaching consensus. This may seem easy; a major goal of each PRG is to improve pharmacotherapy, but the interpretation and intensity can be very different (from merely exchanging information to developing binding consensus on therapy and testing adherence to guidelines). PRGs are generally considered to evolve from information exchange towards more binding agreements, (5,9) and the goals of each are related to how long the peer review group has been in existence (10). The more binding the meetings and the agreements are, the more effective (5). In our questionnaire we inquired as to the goals of the PRGs and about attitudes regarding consensus of prescribing (Table 2).

Questions	Yes	
	n	(%)
Goals:		
To exchange information regarding pharmacotherapy	38	(95)
To discuss current prescribing	32	(80)
To give advice regarding pharmacotherapy	31	(78%)
To arrive at a consensus	26	(65)
Testing these agreements	10	(25.6)
Are the goals explicitly discussed?	32	(80)
Are personal prescribing attitudes discussed?	29	(73)

Table 2: Characteristics of peer review groups related to goals and consensus

Preparation and Presentation

Style of presentation influences the outcome of PRG meetings. The use of complaints, diagnoses and cases as topics appears to work better than theoretical lectures that cannot easily be implemented in practice (9). The use of feedback data (prescription audit) or a formulary is important aspects of preparation and presentation to achieve behavioral change. Questions on how groups actually prepare and present meetings are summarized in Table 3.

Analyses

Starting with the PRG characteristics thought to be most relevant for the modification of effects of our intervention we used the results of the questionnaire to model combinations of stratification factors on the total number of strata and the number of PRGs in each stratum. Finally, we made a choice of stratification factors based on relevance and distribution.

Questions	Yes	
	n	(%)
Is the group working on a formulary?	9	(23)
Does the group use an existing GP formulary?	22	(55)
What is being prepared?		
Theoretical lecture / presentation	31	(78)
Case	23	(58)
Conceptual advice on first choice medication	15	(38)
Prescription feedback / numbers	22	(55)

Table 3: Characteristics of peer review groups related to preparation and presentation

After completion of our randomized trial the Poisson regression model was used to estimate Incidence Rate Ratios (IRRs) of anticholinergic antidepressants in the intervention arms versus the control arm. These IRRs were estimated for six different strata. These strata were formed by dichotomizing the whole data set three times. First, a stratification of PRGs based on the presence or absence of binding consensus. Second, stratification on the use of feedback data or not. Finally, a stratification on the presence or absence of a formulary. In Egret, IRRs were estimated after correcting for sex and baseline incidences, using baseline incidences as an offset variable.

RESULTS

Response

Of the 61 PRG representatives that were contacted, 40 (66%) cooperated. Six preferred to fill out the questionnaire at home, four of which were returned. Nine did not want to participate because of lack of time or interest, six were on holiday, two could not be reached for other reasons and two did not want to mention why they declined to cooperate.

Questionnaire

Organizational Structure

There was great variance in how long groups existed (0.5-25 yrs.) and the number of members (4-21). There was less variation in the attendance rate (60-100%) and the number of meetings per year (4-10). Most PRGs sprung forth from groups that shared night calls (85%). Some PRGs had contact with other PRGs (18%), invited speakers (26%) or had contact with hospital specialists (33%) (Table 1).

Goals and Consensus
More than one answer could be provided for the question on goals. Ninety-five per cent (95%) defined one of the goals as the exchange of information regarding pharmacotherapy. Eighty percent reported discussing current prescribing, 78% giving advice, and 65% making agreements on pharmacotherapy. Only 26% reported testing these agreements (Table 2).

Preparation and Presentation
Lectures were the most popular format for meetings, followed by case discussion and the use of prescription data (Table 3). Over half (22 PRGs) used an existing primary care physicians formulary, but only nine were working towards a formulary of their own. Feedback data of any kind were used by 22 PRGs. Sixteen groups reported to use both an existing formulary and feedback data.

Stratification
Characteristics of PRGs potentially influencing the effect of an educational outreach program were thought to be related to organizational aspects, the aim of the group and preparation and presentation.
The results of the questionnaire showed that minimal requirements for structure as described in Dutch literature on PRGs (5-8) were fulfilled. Therefore, we decided not to use this part of the questionnaire for stratification.
Besides organization, the aim of a group is potentially relevant for stratification. Based on theory and responses we decided that the stated aim of the groups might be an important PRG characteristic that might influence the outcome of the intervention. We therefore dichotomized the PRGs into those which did not go further than information exchange versus those which worked with binding consensus. All groups that indicated that the aim was to make agreements were considered to be on the level of binding consensus (26 PRGs). The rest was allocated to the level of information exchange.
We chose the use of a formulary and the use of feedback data as two other characteristics warranting stratification. We interpreted the use of a formulary as an intention to rationalize prescribing. We considered experience with feedback data relevant for our intervention, as the outreach program would include feedback of prescription data.
At this point we had 8 (2*2*2) strata. After distribution of PRGs into these groups, all but one stratum would contain at least three PRGs (Table 4).
To evaluate the characteristics we used for our stratified randomization we compared the outcome of the educational outreach program for groups with and without these characteristics (Table 5). The effect estimates show that all three characteristics modified the effect of our outreach program. Although our overall analysis showed that our outreach program influenced prescribing (a reduction of

anticholinergic antidepressants of 31%, 95% confidence interval 5-50%, p=0.022) (3) this reduction was not observed when PRGs were selected on the use of binding consensus, no use of feedback data and no use of a formulary.

Binding consensus	Use of feedback data		Use of existing formulary	
Yes : 26	Yes:	17	Yes:	13
			No:	4
	No:	9	Yes:	3
			No:	6
No : 14	Yes:	5	Yes:	3
			No:	2
	No:	9	Yes:	3
			No:	6

Table 4: number of peer review groups after distribution over selected characteristics of PRGs thought to be relevant for the effect of an educational outreach program on prescribing behavior

PRG characteristic	Yes/ No	IRR	95% C.I.
Level of binding	Yes	1.3558	0.7276-2.5264
consensus	No *	0.2583	0.1210-0.5515
Use of feedback	Yes	0.6436	0.3401-1.2179
data	No	1.4505	0.7034-2.9913
Use of existing	Yes *	0.4327	0.2271-0.8245
formulary	No	1.6634	0.7342-3.7685

#: An IRR lower than 1 means that the prescribing of anticholinergic antidepressants in the intervention group compared to the control group was decreased. *: p<0.05

Table 5: incidence rate ratios (IRR)# of anticholinergic antidepressants of the intervention arms versus the control arm within characteristics of PRGs which were used for the stratified randomization

DISCUSSION

This study reports on the selection process of characteristics of PRGs thought on theoretical ground to be relevant for the responsiveness of an educational outreach program on prescribing behavior and the control afterwards whether the selected characteristics modified the effect of our intervention. Our results show retrospectively that it was indeed relevant to distribute the characteristics we had selected equally over the treatment arms. However, this study does not show that these were the most relevant characteristics to select. There may be other known or unknown characteristics, which have an important modifying effect on our intervention.

Literature about the qualities of PRGs that might facilitate goal achievement (improvement of quality of pharmacotherapy) is scarce. We therefore used research and theories on the effectiveness of PRGs to assess and distribute potential relevant characteristics. More general theories on the diffusion of innovations conclude that diffusion is fundamentally a social process, and emphasize the importance of network interconnectedness (affiliation with a hospital, office-sharing and sociometrical position) (13).

Some limitations to our approach should be considered. Response to the telephone interview was 66%. Thirteen representatives did not want to be interviewed. They may have caused response bias, as most of these (nine) indicated a lack of interest. This was partly because their group had not yet started or had only just started. Another reason brought up was that PRGs were too much in focus; some professionals claimed to be tired of all this attention. Interviews were conducted with group representatives, who may have been more motivated and more enthusiastic about the meetings than other group members.

Because not all groups wanted to or were able to cooperate with the prior inventory of characteristics of PRGs, the stratification was based on available information. For our randomized trial we randomly assigned groups that had not been interviewed over the intervention arms.

Despite the emphasis on organizational structure of PRGs in the literature, we thought it not necessary to use it for our stratification. In most PRGs, basic requirements for structure were fulfilled. This may be due to the fact that accreditation for post-academic training has been attached to the organization of PRG meetings in the Netherlands.

We found that groups that work on the level of binding consensus were less receptive to our intervention strategy. An explanation may be that these groups take more time to change prescribing because they first have to reach a new consensus on the subject. As we have no data on the long-term effect of our intervention, we could not evaluate this hypothesis.

The use of a formulary indicates an intention to rationalize prescribing, but it can

also cause a different effect: there are already guidelines on the subject of intervention. This may make it more difficult to influence prescribing. Unexpectedly, we observed that we were not able to change prescribing in groups that did not work with a formulary.
Experience with feedback data was not only relevant because it was part of our intervention strategy to change prescribing, but it can also be considered as an intention to arrive at a consensus. Anticholinergic antidepressant prescribing in the elderly decreased more strongly in groups familiar with feedback data. Further research is needed to find out whether this is an important factor for groups to be maximally receptive to educational programs.
Our findings indicate that for future educational interventions it may be necessary to use several tailored strategies depending on the characteristics of the PRGs Although we realize that our choice is partly subjective, we think that in an educational outreach program on a group level, stratification is superior to plain randomization. We chose factors that seemed relevant for our outreach program. Other interventions or PRGs with other characteristics may require another set of factors for stratification.
We conclude that although many aspects of continuing medical education are not yet well understood it is possible and relevant to do a stratified randomization in an educational outreach program where the level of intervention is a group of professionals. In this paper we used characteristics of PRGs found in the literature. It is important to further identify relevant characteristics by comparing groups in which prescribing altered versus groups in which this was not the case.

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HOOFDSTUK 7
Het voorschrijven van sterk anticholinerge antidepressiva bij ouderen verminderen: een gerandomiseerde interventie van individuele en groepsgewijze nascholing

Doel van de interventie

In dit hoofdstuk wordt de interventie beschreven. Verbetering van de kwaliteit van het voorschrijven van antidepressiva aan ouderen door huisartsen, dat was wat we met deze interventie wilden bewerkstelligen.
Maar waarom? Dat we gekozen hebben voor 'antidepressiva bij ouderen' was min of meer toeval, zoals wordt toegelicht in hoofdstuk 2 en 3. De database van de zorgverzekeraar kon ons de benodigde gegevens verschaffen, de discussie over 'oude' en 'nieuwe' antidepressiva was actueel, en er leek inderdaad wat te verbeteren aan het voorschrijfgedrag.
Maar een ander motief lag aan deze doelstelling ten grondslag. We leven in een snel veranderende wereld waarin nieuwe kennis en veranderde inzichten met betrekking tot behandelwijze en farmacotherapie elkaar razendsnel opvolgen. Artsen en apothekers moeten op de hoogte zijn van deze ontwikkelingen, én de veranderingen implementeren in hun beleid. Er worden verschillende methoden toegepast om nieuwe kennis aan artsen en apothekers over te brengen. Er wordt postacademisch onderwijs gegeven, er worden kwaliteitsprojecten geïnitieerd en er worden richtlijnen geformuleerd. Maar wat blijkt? Het publiceren van resultaten van studies of het rondsturen van richtlijnen is nauwelijks effectief. In de praktijk leiden al deze inspanningen niet tot het gewenste resultaat, namelijk gedragsverandering van behandelaars.
Welke aanpak is dan wel effectief? De farmaceutische industrie heeft een lange staat van dienst als het gaat om gedragsbeïnvloeding van artsen. De farmaceutische bedrijven investeren er veel geld in, en ze zijn er goed in. Maar de industrie heeft uiteraard zo haar eigen belangen. Een door de farmaceutische industrie veel gebruikt instrument om producten 'in de pen te krijgen', kortom: om artsen te beïnvloeden, is 'de artsenbezoeker', die in een één-op-één contact de dokter probeert te overtuigen van de voordelen van een bepaald geneesmiddel.
Een andere effectieve manier om een doelmatig voorschrijfbeleid tot stand te brengen is de werkwijze van FTO-groepen: huisartsen en apothekers bespreken gezamenlijk hun kennis en inzichten en verbinden daar in veel gevallen consequenties aan voor de uitoefening van hun praktijk.
Het eigenlijke doel van onze interventie was te onderzoeken hoe voorschrijfbeleid beïnvloed kan worden. Daarvoor ontwikkelden we deze campagne: de interventie. Het verbeteren van het voorschrijfbeleid van antidepressiva aan ouderen was daarbij middel, en geen doel op zich.

Utvoering van de interventie

We wilden een vergelijking maken tussen de effecten van een campagne op individueel niveau (analoog aan de activiteiten van een artsenbezoeker) en op FTO-niveau (dus het geven van groepsgewijze voorlichting).

Zowel tijdens de individuele bezoeken als in de FTO-groepen hebben we aan de artsen verteld dat het ons doel was hen alert te maken op de kwetsbaarheid van ouderen voor anticholinerge geneesmiddelen. Vooral bij de behandeling van depressiviteit is het belangrijk daar rekening mee te houden, omdat antidepressiva die veelvuldig aan ouderen worden voorgeschreven vaak sterk anticholinerg zijn.

Tijdens de individuele bezoeken en bij de FTO-groepen zijn dezelfde punten besproken, gedurende twee bijeenkomsten met ongeveer drie maanden tussenpoos. Afhankelijk van de tijd en de reactie bespraken we het volgende: Eerst de veranderde manier waarop ouderen op geneesmiddelen reageren, de verhoogde gevoeligheid van ouderen voor bijwerkingen en waarom het belangrijk is om anticholinerge middelen bij ouderen te vermijden. Verder hoe lastig het kan zijn om een depressie te herkennen bij ouderen en dat er op dit moment in hun regio (het onderzoeksgebied, de Zuid-Hollandse eilanden) meer anticholinerge antidepressiva aan ouderen dan aan jongeren worden voorgeschreven.

Om het effect van de individuele bezoeken en het bezoeken van FTO-groepen goed te vergelijken, hebben we de eenentwintig FTO-groepen over drie armen verdeeld, elk met zeven FTO-groepen. Door loting werd bepaald, welke groep op welke manier benaderd zou worden.

Uit de eerste arm van zeven FTO-groepen is niemand benaderd, er is geen interventie gedaan. De artsen uit deze arm fungeerden als controlegroep. De artsen uit de tweede arm zijn allen individueel bezocht. De artsen uit de derde arm zijn in hun FTO-groepen benaderd. Op deze manier zijn 43 huisartsen en 14 apothekers individueel bezocht. Daarnaast zijn 52 huisartsen en 9 apothekers via het FTO gezien. Hiervoor waren meer dan 110 visites nodig, waarvan slechts 7 aan FTO-groepen.

CONCLUSIE

Het resultaat van de interventie was, dat de bezochte artsen na het bezoek daadwerkelijk minder anticholinerge middelen voorschreven aan ouderen. Uit de analyses bleek geen duidelijk verschil in effect tussen de individuele en de groepsbezoeken. Een groepsbezoek is dus een efficiënte manier van nascholing.

7

Reducing highly anticholinergic antidepressant use in the elderly: a randomised trial of group vs. individual "academic detailing"

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So he bent down, put his head into the hole, and called out:
"Is anybody at home?"
There was a sudden scuffling noise from inside the hole, and then silence.
"What I said was, 'Is anybody at home?'" called out Pooh very loudly.
"No!" said a voice; and then added, "You needn't shout so loud. I heard you quite well the first time."
"Bother!" said Pooh. "Isn't there anybody here at all?"
"Nobody." …….
A.A. Milne, Winnie-the-Pooh, 1926.
Chapter: Pooh goes visiting, page 21.

Abstract

Context: With the development of ever more effective and costly medical technologies, more needs to be known about the best methods to disseminate and implement that knowledge.

Objective: To compare the effect of individual educational visits versus group visits on prescribing, using academic detailing. For this comparison our focus was to reduce the use of highly anticholinergic antidepressants in the elderly.

Design: Randomized controlled trial with three arms (individual visits, group visits and a control arm).

Setting and Participants: General Practitioners (190) and pharmacists (37) organized in 21 Peer Review Groups in the Southwest Netherlands were studied using a database covering all prescriptions to persons insured by national health insurance in this area (approx. 240,000).

Intervention: All General Practitioners and pharmacists in both intervention arms were offered two educational visits. For physicians randomized to the individual visit arm, 43 of 70 General Practitioners participated; in the group visit intervention arm, 5 of 7 groups (41 of 52 General Practitioners) participated.

Main Outcome Measures: Incidence (starters) of highly anticholinergic antidepressants and less anticholinergic antidepressants by treatment arm.

Results: Using an intention-to-treat analysis, we found a 26% reduction in the incidence of initiation of highly anticholinergic antidepressants in the elderly (95% CI, -4%-48%) in the individual intervention and 45% (95% CI, 8%-67%) in the group intervention arm. In addition, the use of less anticholinergic antidepressants in the elderly increased by 40% (95% CI, 6%-83%) in the individual intervention and by 29% (95% CI, -7%-79%) in the group intervention arm.

Conclusions: Both the individual and the group visits decreased the incidence of initiating highly anticholinergic antidepressants and increased the incidence of less anticholinergic antidepressant use in the elderly. These approaches are practical means for continuing medical education to improve prescribing.

Keywords: health care peer review, randomized controlled trials, data collection, drug therapy, continuing medical education, drug utilization review, antidepressive agents, aged

INTRODUCTION

In the face of an increasing need to improve rational prescribing, many questions still remain unanswered on how best to achieve this goal (1-3).
Educational visits have been proven effective to modify professional behavior (4,5). They should consist of repeated personal visits, including feedback, presenting clear practice-relevant recommendations and anticipating any implementation problems (6-9). Not all characteristics of effective visits have been identified (4,10).
Collaboration of doctors and pharmacists in regional groups is an increasingly well accepted method of improving prescribing in several countries (1,11-13) and can be a cost-effective platform for the dissemination of new knowledge and guidelines.
The purpose of this study was to evaluate the effect of these two different approaches to influence the prescribing of physicians: the impact of individual visits vs. group visits, both with the use of academic detailing.
Antidepressants in the elderly was selected as a focus for the study because former analyses of dispensing data (14) and other studies (15) have shown that a substantial portion of patients over the age of sixty were prescribed highly anticholinergic antidepressants, despite their potentially greater risk of hazardous side-effects such as dry mouth, blurred vision, constipation, urinary dysfunction, hypotension, tachycardia, and cognitive impairment(16-23). We wanted to increase the awareness of the vulnerability of the elderly to anticholinergic side effects and decrease the prescribing of highly anticholinergic antidepressants in this group (e.g.tertiary amine tricyclics), while encouraging the use of less anticholinergic antidepressants when indicated, such as secondary amines or selective serotonin re-uptake inhibitors.

METHODS

Study Design

We conducted a randomized controlled design to compare the effect of individual vs. group educational visits on the prescribing of higly anticholinergic antidepressants in the 60+ population. To organize the group visits we used an existing system of Peer Review Groups which foster collaboration between Dutch pharmacists and General Practitioners. These groups of professionals, practicing in the same region, meet regularly to discuss treatment, pharmacotherapy and patient management. Similar initiatives are seen in other countries and are known as quality circles, pharmacotherapy discussion groups or pharmacotherapy consultation groups. The goals of these groups include: exchanging information, policy advising, agreement on guidelines, and using feedback methods to measure adherence to these(11-13). Prior to the intervention these groups were surveyed on

factors thought to be relevant for the intervention (see below). Based on this survey, groups were matched prior to randomization. Matching variables were: (a) stated goals of the group (binding consensus vs. other goals) and (b) the use of a formulary or feedback data vs. neither. We used a block randomization to assign all groups to one of three intervention arms. In the individual intervention arm each General Practitioner was offered individual educational visits. In the group visit intervention arm this was offered to each Peer Review Group as a whole. The control arm received no visits.

Research Area

The research area (the South Holland Islands) is part of the area of the health insurance company 'OZ zorgverzekeringen' (Mutual Care health insurance) in the Southwest Netherlands. This region is a mix of semi-rural and rural areas. The population is approximately 400,000, 60% of which (240,000) are insured through 'OZ zorgverzekeringen'.

Research Population

The research population comprised all people over 60 years old (approximately 50,000 elderly), living in the Southwest Netherlands health district and insured through 'OZ zorgverzekeringen'(table 1).
We performed a pre-study sample size calculation and found that 7 peer review groups (with an average 2,000 patients over 60 per peer review group and 22 patients starting an anticholinergic antidepressant over a time period of 1 year) per treatment arm were enough to demonstrate with 80% power a statistically significant ($p<0,05$) reduction of 30% in prescribing of anticholinergic antidepressants.

Databases

Prescribing of antidepressants was measured using the reimbursement databases that pharmacists send to the health insurance company monthly. These contain information on all drugs dispensed to insured patients: amount, dosage, costs, and date of issue, as well as information about the user's insurance number and birthday and the prescribers' code. All reimbursable drugs for the insured population, are registered this way(14,24).

Drug Classification

We classified the following agents marketed in the Netherlands as highly anticholinergic antidepressants: amitriptyline, clomipramine, doxepin, imipramine and maprotiline (table 2).

	Individual visit Intervention arm			Group visit Intervention arm			Control arm		
Age (in yrs.)	**male**	**female**	**(%fem.)**	**male**	**female**	**(%fem.)**	**male**	**female**	**(%fem.)**
60-69	3399	4144	(55)	2853	3367	(54)	3362	4026	(54)
70-79	2422	3593	(60)	1809	2499	(58)	2410	3296	(58)
80-89	1035	2041	(66)	650	1274	(66)	943	1736	(65)
90-96	133	376	(74)	84	198	(70)	114	314	(73)
Subtotal	6989	10154	(59)	5396	7338	(58)	6829	9372	(58)
Average age	70.5	72.2		69.8	71.3		70.3	71.84	
Total 60-96		17143			12734			16201	
Baseline incidence rates (/1000 person-years) of antidepressant use									
60+ Highly Anticholinergic antidepressant users		8.02			6.36			5.82	
60+ Less Anticholinergic antidepressant users		11.80			12.72			10.32	

Table 1: Baseline Characteristics of the Population

Highly Anticholinergic Antidepressants	Less or Non-Anticholinergic Antidepressants	
Tricyclic derivatives	**Tricyclic derivatives**	**MAO-inhibitors**
Amitriptyline	Desipramine	Tranylcypromin
Clomipramine	Opipramol	Moclobemide
Doxepin	Nortriptyline	Nialamide
Imipramine	Dosulepin	**Others**
Maprotiline *	Dibenzepine	Trazodone
	Trimipramine	Venlafaxine
	SSRIs	Mirtazapine
	Sertraline	Mianserine
	Fluoxetine	
	Fluvoxamine	
	Paroxetine	

*Polycyclic derivative

Table 2: Drug Classification

Intervention

The intervention was designed following theories and experience usually referred to as social marketing or academic detailing (4-6,10). It is a framework for dissemination and implementation of prescribing improvement activities and refers to a combination of adult learning theories and the marketing experience of the pharmaceutical industry, but directed at improving the rationality of prescribing. All doctors and pharmacists from groups assigned to the individual visit intervention arm were individually contacted by telephone. They were told of the aim of the study (to improve antidepressant prescribing in the elderly and measure the effectiveness of an educational program), and they were invited to participate in the program. For those who agreed, an appointment was made for a twenty-minute visit with the lead investigator (MvE), a physician. This session emphasized the unique therapeutic difficulties of the aged and the problems of anticholinergic side effects in the elderly, using a hand-out flyer containing an evidence-based summary of the most important information.

To decrease the use of highly anticholinergic antidepressants in the elderly, all sessions were based on a priority list for issues to be discussed. Depending on the length of the visit and the responses of the professionals, these items were discussed in order: 1/ altered pharmacodynamics and kinetics in the elderly (18,19) 2/ increased vulnerability for side-effects in the elderly (20,21) 3/ the need to avoid anticholinergic antidepressants in the elderly (22) and 4/ difficulties in diagnosing depression, especially in the elderly (17). Overall data of antidepressant prescribing

in the former year in the area were shown during the visit to illustrate that most anticholinergic antidepressants are prescribed to people over 60 (14). The initial visits included no further comment on personal performance. At the end of each visit another appointment was made for approximately four months later. During the second visit a graph was provided showing personal performance and the fraction of anticholinergic antidepressant prescriptions versus less anticholinergic antidepressant prescriptions in three age categories: under 60, 60-70 and over 70 years old.
For the group intervention arm all group co-ordinators were contacted to ask permission to use one full meeting for the educational program. The content of these presentations was essentially the same as in the individual contacts. At the end of the first visit, permission to use part of another meeting was requested. In this second meeting, a graph of accumulated prescribing in the group was shown and personal graphs were handed out.
All contacts for both intervention arms were performed by one of the authors (MvE). The control arm was not contacted.

Study Outcome

The effectiveness of this intervention is best reflected in antidepressant choice for patients initiating therapy.
To define starters (incident users) of antidepressants, we used the prescription reimbursement records described above. For each prescription we calculated the number of days the prescription would cover using the PDD (prescribed daily dose) and the package size (14). In this way, a time window of probable use was created. We assessed all antidepressant prescriptions from July 1995 on. If there was no former antidepressant prescription or if the interval exceeded 180 days, the patient was considered an incident user (a starter) of either a highly anticholinergic antidepressant or a less anticholinergic antidepressant (14).
In the Netherlands all persons under National Health Insurance are allocated to a general practitioner. Pre-, inter-, and post-visit periods were calculated for each general practitioner in the region to allocate each starter to the right period per general practitioner, to determine whether the start of the antidepressant was before, between or after the sessions. In order to calculate incidence rates (number of new starters / person years), the number of patient days per period was calculated to determine the denominator. For the control arm and for non-participating general practitioners (in the individual and group intervention arms), average visiting dates were calculated for physicians not actually visited, based on those actually visited and used to create a pre-, inter-, and post intervention period.
The incidence rates of highly anticholinergic antidepressants use and less anticholinergic antidepressants use were calculated per General Practitioner per period.

Statistics

We used a Poisson regression model to estimate Incidence Rate Ratios (IRRs) of starting highly anticholinergic antidepressants and less anticholinergic antidepressants for the elderly in both intervention arms in relation to the control arm. The evaluation was done on an intention-to-treat basis, so as not to overestimate the effect of the intervention by including only the most responsive physicians. Since randomization was performed on a group level and correlated outcomes (within a group) can influence precision (95% CI) (25), we studied IRRs with and without correction for correlated outcomes (exchangeable correlation matrix), using a longitudinal data analysis (Spida). This did not materially influence outcome. Point estimates were virtually identical and 95% confidence intervals changed less than 3% (there was no change in statistical significance of effects estimates).
Since it was not possible to correct for baseline incidences in Spida, we used Egret, although in this program it is not possible to analyze correlated Poisson outcomes. In Egret, IRRs were estimated after correcting for sex and baseline incidences, using baseline incidences as an offset variable. The effect of the first and second visits and of both visits together were estimated. The effects in each intervention arm and of both interventions together were also measured.

RESULTS

Overall, 190 general practitioners and 36 pharmacists were working in the research area. Sixty-nine per cent of the general practitioners and 100% of the pharmacists in the intervention arms were visited (table 3). In the individual visit intervention arm, 86% of the professionals visited were visited twice. The request for a second appointment after the first visit was always granted, but did not take place on seven occasions, because the first possible date was after the closing date of the intervention. The average time spent per person was 14.6 minutes in the individual visit intervention arm. In the group visit intervention arm only one group (14%) was visited twice. Most groups first wanted to decide together whether and when they were going to join the program. Well organized Peer Review Groups had their agenda planned for the entire season, while other groups were glad to have one (or two) meetings organized by an academic researcher. This caused large differences between groups in contact time (from 15 min. once to a full hour twice). Further details on general practitioners, pharmacists and visits are listed in Table 3.
The total number of 60-96 year-olds in the research area was 46,078, 58% of whom were female. Baseline incidence rates of highly anticholinergic antidepressant use were lower than the incidence rate of less anticholinergic antidepressants (Table 1).

	Individual Approach Intervention Arm	Group Approach Intervention Arm	Control Arm
Number of groups	7	7	7
General practitioners (female GPs)	70 (4)	52 (6)	68 (3)
General practitioners visited (%)	43 (61%)	41(79%)	-
visited twice	36 GPs	6 GPs, (from 1 group)	-
average visit time (min)	14.5 (5-30) per GP	62.5 (15-105) per group	-
Pharmacists (female)	14 (3)	9 (2)	13 (2)
Pharm. visited (%)	14 (100%)	9 (100%)	-
Visited twice	13	1	-
Average visit time in minutes (range)	18.8 (7-30)	62.5 (15-105) per group	-

Table 3: Baseline Characteristics of General Practitioners and Pharmacists

Baseline incidences differed between treatment arms. In both intervention arms the incidence of anticholinergic antidepressants for patients aged ≥ 60 decreased during the study period, while in the control arm the incidence actually increased (Figure 1). Table 4 shows IRRs of anticholinergic antidepressants after correction for baseline incidence rates and sex. All estimates showed a reduction in the prescribing of highly anticholinergic antidepressants in the intervention arms compared to the control arm. This reduction was more than 30% after two visits in the individual visit intervention arm (A) and more than 40% in the group visit intervention arm (B). This decrease was significant for the group approach and for the combined effect of both interventions.

In both intervention arms the incidence of less anticholinergic antidepressants for patients ≥ 60 years increased during the study period, while in the control arm the incidence decreased (Figure 2). In the individual visit intervention arm, elderly subjects were 100% more likely to start antidepressant treatment with a less anticholinergic antidepressant in the post-intervention period (Table 4). In the group visit intervention arm this was almost 70%.

Effect on Incidence of	Individual Visits		Group Visits		Both Intervention Arms	
Highly Anticholinergic Antidepressants	IRR (95%CI)	p-value	IRR (95%CI)	p-value	IRR (95%CI)	p-value
INTER period	0.77 (0.50-1.20)	0.248	0.48 (0.22-1.02)	0.057	0.70 (0.46-1.07)	0.098
POST period	0.68 (0.39-1.18)	0.169	0.56 (0.28-1.15)	0.114	0.63 (0.38-1.07)	0.084
INTER & POST together	0.74 (0.52-1.04)	0.082	0.55 (0.33-0.92)	**0.023**	0.69 (0.50-0.95)	**0.022**
Less-Anticholinergic Antidepressants	IRR (95%CI)	p-value	IRR (95%CI)	p-value	IRR (95%CI)	p-value
INTER period	1.16 (0.83-1.61)	0.385	0.66 (0.43-1.01)	0.635	1.14 (0.84-1.56)	0.401
POST period	2.02 (1.24-3.30)	**0.005**	1.66 (0.97-2.85)	0.066	1.87 (1.18-2.96)	**0.008**
INTER & POST together	1.40 (1.06-1.83)	**0.016**	1.29 (0.93-1.79)	0.127	1.36 (1.05-1.75)	**0.018**

Intention-to-treat analyses
IRRs were corrected for sex and baseline incidence rates of antidepressants.
The difference between the group and individual arm was not statistically significant.

Table 4: Results, Incidence Rate Ratio (IRR) of the Intervention Groups versus the Control Group for Highly Anticholinergic antidepressants and Less Anticholinergic antidepressants

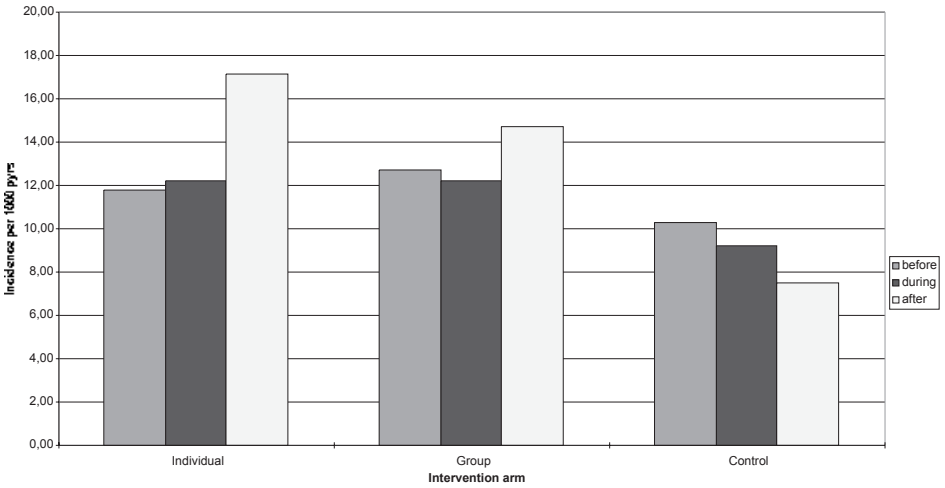

Figure 1: incidence of initiation of less anticholinergic antidepressants in te 60+ population, before, during and after educational visits (intention to treat)

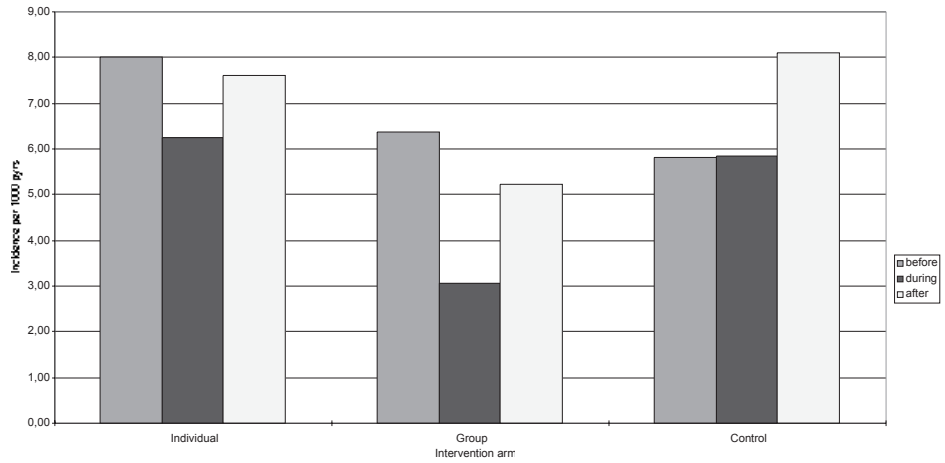

Figure 2: incidence of initiation of highly anticholinergic antidepressants in te 60+ population, before, during and after educational visits (intention to treat)

DISCUSSION

We have shown that both individual visits and group visits can effectively improve the clinical appropriateness of prescribing behaviour in an area of suboptimal prescribing: the treatment of depression in the elderly. Both interventions had a similar effect not seen in the controls: elderly people starting antidepressant treatment received less anticholinergic medication more often. The group visits significantly decreased the use of highly anticholinergic antidepressants and the individual visits significantly increased the incidence of less anticholinergic antidepressants in older patients. The combined effect of both intervention arms was also significant.
Reasons for non-participation were diverse. For the group intervention it was mainly a time problem. Most finally agreed, but in some cases the intervention period had already ended. For the individual visits reasons mentioned were; shortage of time, this study should be initiated by the medical faculty instead of the faculty of pharmacy, just not motivated.
The data reported probably represent a lower-bound estimate of the potential of this approach. Anticholinergic versus non-anticholinergic antidepressant prescribing remained a topical issue in the given time period (26-29). Despite the fact that we focused our intervention on anticholinergic antidepressant use in the elderly, this controversy might have diluted the effect (30).
We think the observed changes over time are not due to a "regression to the mean" effect. The statistical analyses adjusted for the different baseline incidence rates. Next to that, for regression to the mean to occur, it usually requires the selection of a sample because it has an unusually high (or low) set of values for a given variable. The groups studied were not defined or chosen on this basis.
Tricyclic antidepressants are used not only for depression, but other indications as well, such as chronic pain syndromes. Their use for other such indications may also have had a diluting effect on our intervention. The effectiveness of the intervention was probably also diluted by prescriptions initiated by psychiatrists or other specialists who were not part of the intervention, since we allocated all incident cases to their General Practitioner.
This study contains no long-term evaluation of the effectiveness of our intervention, yet other studies have shown that repeated interventions are needed, for sustained behavioral changes. It can be assumed this approach will also be effective for other drug categories. In groups, two opposing processes can influence the effect of an outreach programme on prescribing. Groups can be more effective in accomplishing tasks (31), and to publicly announce behavioral changes results in more commitment than to do so privately. In this way, behavioral changes can be facilitated by the group approach. Psychological research into group behavior has produced an inventory of factors that influence conformity with group standards

(32). Unanimity provides more pressure to conform, while privacy makes it easier not to. On the other hand, as there is rarely unanimity in medicine, obstacles can be expressed easily in these meetings, and more barriers against the new strategy might be expressed in a group than in a one-to-one setting. The implementation of new knowledge is facilitated by expressing and discussing how to overcome obstacles to its acceptance. This may occur more intensely in groups than in an individual learning setting.
Further research in group learning processes in health professional groups may reveal valuable information on factors that facilitate the dissemination and application of new knowledge about pharmacotherapy.
Audit and feedback are becoming increasingly important to help professionals keep up with evolving knowledge and to actively implement it in their practices. The present study adds to our knowledge of educational programmes in daily practice. Group approaches are likely to be a useful and cost-effective addition to the arsenal of academic detailing approaches used to improve evidence-based prescribing.

CONTRIBUTORS

Martine van Eijk initiated and coordinated the formulation of the primary study hypothesis, designed the protocol and was responsible for data collection, interpretation, analyses, and writing of the paper. Jerry Avorn participated in the protocol design, interpretation of the data, and editing of the paper. Arijan Porsius initiated the research project, participated in the design of the study protocol, discussed core ideas and interpretation of the findings, and editing the paper. Anthonius de Boer participated in the design and execution of the study- particularly quality control and statistical analyses- and contributed to the paper. Both Martine van Eijk en Anthonius de Boer are guarantors for this study.

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COMPETING INTERESTS

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HOOFDSTUK 8
Effect van de interventie op patiënt niveau gemeten

Wie werd er beter van deze interventie?

Onze interventie had succes: in de interventiearmen was het voorschrijven van anticholinerge middelen aan patiënten boven de zestig sterk verminderd.
In dit hoofdstuk wordt beschreven wat het effect van de interventie op patiëntniveau was. Het gaat tenslotte om de patiënt: het beïnvloeden van het voorschrijfgedrag van artsen is bedoeld om het leven van patiënten aangenamer te maken.
Er zijn weinig studies waarbij niet alleen de effecten van een interventie op het voorschrijfgedrag van de arts onderzocht is, maar waarbij ook is gekeken is naar patiënten. Waren die er eigenlijk wel bij gebaat?

We gebruikten hiervoor dezelfde vragenlijsten als beschreven in hoofdstuk 4 en 5. Om te weten hoe het met de gebruikers van antidepressiva ging nadat wij de artsen benaderd hadden, verstuurden we nog een enquête. Met behulp van de ingevulde vragenlijsten hebben we na de interventie onderzocht of patiënten uit de interventiearmen ook daadwerkelijk minder last van bijwerkingen hadden in vergelijking met patiënten in de controlearm, waar geen interventie had plaatsgevonden.
De gemelde bijwerkingen in de interventie- en de controlearmen voor en na de interventie evaluerend, kwamen we tot de conclusie dat de patiënten niet beter, maar ook niet slechter zijn geworden van de veranderingen in het voorschrijven van artsen. Dit kan liggen aan geringe respons of aan de schaal van het onderzoek of aan gebrekkige indicatoren. Misschien hadden we andere vragen moeten stellen.

CONCLUSIE

We denken dat het zinvol is de effecten van een interventie op patiëntniveau te meten. In ons onderzoek wijst niets erop dat patiënten er slechter van zijn geworden.

8

Evaluation of patient outcomes in an area in which the prescribing of anticholinergic antidepressants was successfully reduced by academic detailing

submitted for publication

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By the time it came to the edge of the Forest the stream had grown up, so that it was almost a river, and, being grown up, it did not run and jump and sparkle along as it used to do when it was younger, but moved more slowly. For it knew now where it was going, and it said to itself, "There is no hurry. We shall get there some day."

A.A. Milne, The house at the Pooh corner, 1928.
Chapter: Eeyore joins the game, page 89.

Abstract

Objective: To evaluate, on a patient level, the effect of an intervention that successfully reduced anticholinergic antidepressant prescribing in the elderly.

Design: Cross sectional surveys with questionnaires send prior to and after our intervention

Setting: South Holland islands, the area in which we performed in 1996 a randomized controlled trial to study the influence of an intervention on prescribing behavior.

Participants: Elderly patients (age between 60-95 years) who used antidepressants in 1995 and 1996 in our research area according to a Health Insurance prescription database.

Main Outcome Measures: Prevalence of adverse events related to antidepressant use, severity of depression and quality of life have been compared in users living in the intervention and control areas.

Results: Prior to our intervention we send 2359 questionnaires of which we could use 827 (35%) for analysis. At baseline, there were no statistically significant differences between the intervention and control areas. After the intervention 3375 questionnaires were send of which 939 (28%) could be used. The occurrence of dry mouth and coughing and the amount of pain were lower in the intervention area compared to the control area ($p<0.05$).

Conclusion: We found no indications that adverse events, severity of depression and quality of life was changed in an unfavorable direction, when comparing patients living in an area in which the prescribing of highly anticholinergic antidepressants was successfully reduced to patients living in an area in which the prescribing of antidepressants was not intentionally changed.

Keywords: patient outcome measures, questionnaires, adverse events, depression, elderly, COOP/WONCA charts

INTRODUCTION

Most programs that intend to rationalize prescribing evaluate their effectiveness by looking at prescribing volumes. There is increasing attention for economic evaluation of treatment strategies and interventions to rationalize prescribing (1-3). The need to include patient outcome measures has been mentioned before, but is not often practiced (4-6). Recently we published the results of a randomized controlled trial in which we compared the effect of individual educational visits and group visits versus no visits on prescribing of antidepressants in primary care (7). The focus of the study was to reduce the use of highly anticholinergic antidepressants in the elderly in which we succeeded. During the study the prescribing of anticholinergic versus non-anticholinergic antidepressants remained a topical issue (8-10). On the one hand there was a consensus report published on behalf of the Dutch association of general practitioners ('NHG-standaard') (11) in which tricyclic antidepressants were presented as first choice drugs for the treatment of depression. On the other hand, there was a consensus report which was prepared by consultants of different disciplines (psychiatrists, geriatricians, etc) ('CBO-consensus report') (12) in which serotonin re-uptake inhibitors were presented as first choice compounds. Given the controversy on the subject, and the lack of information on how elderly react to these drugs (13)we decided, next to the collection of prescription data, also to collect data on patient outcomes. This manuscript reports on the effects on a patient level of our successful intervention: reduction of the prescribing of highly anticholinergic antidepressants in the elderly.

MATERIALS & METHODS

Design

To measure patient outcomes we performed two cross sectional surveys. Questionnaires were sent to elderly antidepressant users living in the area where we performed the randomized controlled trial, (7). Questionnaires were sent prior to and after the performance of the trial.

Short details of the trial

The participants in the study were 190 general practitioners and 37 pharmacists organized in 21 Peer Review Groups in an area covering approximately 50,000 elderly. The 21 Peer Review Groups were equally divided in an individual intervention arm, in a group visit intervention arm and a control arm (no visits). Our intervention followed theories and experience usually referred to as academic detailing. The focus of the study was the reduction of highly anticholinergic antidepressants in the elderly. The outcome of the study was that in both the

individual and group arm the prescribing of highly anticholinergic antidepressants was reduced (26% and 45%, respectively) while the prescribing of less anticholinergic antidepressants was increased (40% and 29%, respectively) compared to the control arm.

Setting

The project was performed in a research area that is part of the area of the health insurance company 'OZ zorgverzekeringen' in the Southwest Netherlands. Approximately 240,000 people (60% of the population in the research area) were insured through 'OZ zorgverzekeringen' of which 50,000 were 60 years of age or older.

Participants

During the first survey (prior to the intervention study) all elderly people (60-95 years of age) in the research area who had used an antidepressant during the year prior to the survey (1995) were invited to participate in our questionnaire survey. During the second survey (after the intervention) all elderly who were selected for the first survey were again asked to participate. Furthermore, during the second survey we invited all elderly who had newly started an antidepressant during the year of the intervention study, 1996, (and thus were not asked to participate during the first survey) to participate. Of this last group of elderly only one questionnaire (after the intervention) is available.

Questionnaire

The questionnaire contained questions about general patient characteristics (sex, age, marital state etc.), medical state (including a list of known side effects and complaints, related to antidepressants and depression), medical consumption, the Geriatric Depression Scale (14) and the COOP-WONCA Health Charts (15).

Procedures

Patients were identified using the reimbursement databases that pharmacists send to the health insurance company. Patients who had at least one prescription of an antidepressant (defined as a drug with ATC code N06A or N06CA01) reimbursed in 1995 were selected (16). Questionnaires were send to patients by the health insurance company with pre-stamped return envelopes. For the second survey all patients invited to participate in the first survey were again asked to participate. Furthermore, patients who had newly started an antidepressant in the reimbursement databases during the intervention study were also send a questionnaire after completion of the trial.
A short letter in which the aim of the survey was explained accompanied the questionnaire. The aim mentioned was the evaluation of drug use in elderly,

adverse events and well being of elderly using drugs. We emphasized the limited information that is collected from experimental drug trials and the importance of surveys on the effects of drugs in the elderly in daily practice. No special attention was given to antidepressants nor to the prescribing interventions we performed in the research areas.

Analysis

Our intervention (to reduce the prescribing of highly anticholinergic antidepressants in the elderly) was directed at prescribers and pharmacists. This report focuses on the outcome of patients (adverse events, symptoms related to depression and general well being) in the areas in which the intervention was performed versus the control area. We decided to perform an intention-to-treat analysis. Thus, not only the patients of the most responsive physicians were included in the analysis but all patients of all physicians in the intervention areas and control area.

The reduction of the prescribing of highly anticholinergic antidepressants, as intended by our intervention, could occur in two ways. First, the reduction could occur in patients newly prescribed an antidepressant. Second, in patients already using highly anticholinergic antidepressants, a switch to less anticholinergic antidepressants could take place. So far, we only evaluated the effect of our intervention on the incidence of initiating highly and less anticholinergic antidepressants and not the effect on switching of antidepressants (7). The latter is expected to occur less or later than the effect on new starts of antidepressants ("Never change a winning team").

In the light of this, and the fact that of the patients newly started on an antidepressant no baseline questionnaires were available, we decided not to compare the change in patient outcomes (post intervention minus baseline outcomes). We compared post-intervention patient outcomes separately for all patients in the intervention areas versus all patients in the control area and for patients newly started on an antidepressant in the intervention areas versus patients who newly started an antidepressant in the control area.

Descriptive statistics of the baseline questionnaire are presented in order to be able to evaluate whether possible post-intervention differences were already present prior to the intervention.

Dichotomous patient outcomes (e.g. the presence of adverse events) were evaluated by logistic regression. Effect estimates were adjusted for age and sex differences in the intervention versus the control groups.

Ordinal patient outcomes (scores of COOP/WONCA) were analyzed by linear regression (adjustment for age and sex differences) and expressed as mean difference and 95% confidence intervals.

Results

In our first survey in 1996, prior to the intervention study, we sent questionnaires to 2,359 users of antidepressants in 1995 of which 945 were returned (40%). Fifty-eight of these questionnaires had too many missing values and 60 were answered by another family member than the one addressed, leaving 827 (35% of 2,359) questionnaires that could be used for our data analysis.

For the second survey in March 1997, after completion of our intervention study, the patients that were sent a questionnaire during the first survey (n=2,359) and the patients that used an antidepressant in 1996 and not in 1995 (new starters of an antidepressant; n=1,016) were sent a questionnaire. Of these groups the response rates were 719 (30% of 2,359) and 314 (31% of 1016), respectively. For our data analysis on the level of all patients we were able to use 939 (28% of 2,359 plus 1,016) questionnaires and for the analysis of new starters of antidepressants, 101 (9.9% of 1016) questionnaires. Reasons for the reduction of 1,033 questionnaires to 939 were major omissions in the answers of the questionnaire (n=64) and answering of the questionnaire by another family member (n=30). The reduction of the 314 questionnaires to 101 was caused by answering the questionnaire by a family member (n=18) and the start of the antidepressant prior to the date on which the patient's general practitioner was visited for the intervention meeting (aimed to change the prescribing of antidepressants) (n=195). In the patients of the control area, the mean date of the visited general practitioners in the intervention areas was used.

Tables 1 to 3 show the number of adverse events and complaints related to depression and antidepressant use reported by the (former) users of antidepressants in the research area, before and after the intervention. Table 3 relates to the new starters of antidepressants in the research area. Prior to the intervention, there were no statistically significant differences in baseline characteristics. After the intervention only dry mouth, coughing and amount of pain was reported significantly less ($p<0.05$) in the intervention area, compared to the control area. Other patient outcome measures, including overall well being and quality of life questions from the COOP/WONCA charts post-intervention showed no significant differences between the control and intervention area (Table 4).

N=827	Control Area	Intervention Area
Number (female)	296 (204)	531 (368)
Complaints	n (%)	N (%)
Coughing	81 (27.4)	149 (28.1)
Dry mouth	129 (43.6)	211 (39.7)
Falling more often	19 (6.4)	44 (8.3)
Blurred vision	74 (25.0)	128 (24.1)
Nausea	27 (9.1)	70 (13.2)
Impaired concentration	62 (20.9)	111 (20.9)
Dyspepsia	70 (23.6)	111 (20.9)
Palpitating	43 (14.5)	93 (17.5)
Sleepiness	64 (21.6)	96 (18.1)
Memory problems	85 (28.7)	141 (26.6)
Sad feelings	101 (34.1)	176 (33.1)
Constipation	36 (12.2)	66 (12.4)
Diarrhea	17 (5.7)	39 (7.3)
Feeling numb	36 (12.2)	57 (10.7)
Irritable	35 (11.8)	55 (10.4)
Anxiousness	55 (18.6)	103 (19.4)
Unstable gait	99 (33.4)	180 (33.9)
Reaction time increased	51 (17.2)	83 (15.6)
Dizziness	69 (23.3)	121 (22.8)
Difficulties falling asleep	124 (41.9)	224 (42.2)
Eczema	20 (6.8)	61 (11.5)
Serious pain	91 (30.7)	155 (29.2)

* No statistically significant differences (logistic regression)

Table 1: baseline characteristics of patients living in an area in which a randomized controlled trial was performed to reduce the prescribing of highly anticholinergic antidepressants*

N=939	Control	Intervention
Number (female)	337 (230)	602 (426)
Complaints	n (%)	n (%)
Coughing	93 (27.6)	152 (25.2)
Dry mouth *	146 (43.3)	220 (36.5)
Falling more often	20 (5.9)	44 (7.3)
Blurred vision	75 (22.3)	133 (22.1)
Nausea	45 (13.4)	62 (10.3)
Impaired concentration	56 (16.6)	122 (20.3)
Dyspepsia	66 (19.6)	105 (17.4)
Palpitating	61 (18.1)	115 (19.1)
Sleepiness	68 (20.2)	119 (19.8)
Memory problems	97 (28.8)	165 (27.4)
Sad feelings	101 (30.0)	203 (33.7)
Constipation	40 (11.9)	64 (10.6)
Diarrhea	28 (8.3)	43 (7.1)
Feeling numb	48 (14.2)	68 (11.3)
Irritable	40 (11.9)	79 (13.1)
Anxiousness	66 (19.6)	127 (21.1)
Unstable gait	114 (33.8)	203 (33.7)
Reaction time increased	62 (18.4)	96 (15.9)
Dizziness	68 (20.2)	130 (21.6)
Difficulties falling asleep	122 (36.2)	252 (41.9)
Eczema	30 (8.9)	66 (11.0)
Serious pain	111 (32.9)	168 (27.9)

* p=0.041

Table 2: outcome of patients in an area in which the prescribing of highly anticholinergic antidepressants was successfully reduced (intervention) compared to a control area (control)

N=101	Control	Intervention
Number (female)	35 (23)	66 (43)
Complaints	n (%)	n (%)
Coughing *	13 (37.1)	11 (16.7)
Dry mouth	12 (34.3)	17 (25.8)
Falling more often	1 (2.9)	6 (9.1)
Blurred vision	12 (34.3)	18 (27.3)
Nausea	3 (8.6)	6 (9.1)
Impaired concentration	5 (14.3)	13 (19.7)
Dyspepsia	3 (8.6)	8 (12.1)
Palpitating	5 (14.3)	15 (22.7)
Sleepiness	11 (31.4)	17 (25.8)
Memory problems	9 (25.7)	21 (31.8)
Sad feelings	10 (28.6)	22 (33.3)
Constipation	5 (14.3)	6 (9.1)
Diarrhea	3 (8.6)	9 (13.6)
Feeling numb	5 (14.3)	6 (9.1)
Irritable	5 (14.3)	10 (15.2)
Anxiousness	10 (28.6)	14 (21.2)
Unstable gait	12 (34.3)	19 (28.8)
Reaction time increased	6 (17.1)	9 (13.6)
Dizziness	6 (17.1)	18 (27.3)
Difficulties falling asleep	13 (37.1)	24 (36.4)
Eczema	5 (14.3)	8 (12.1)
Serious pain	11 (31.4)	17 (25.8)

* p= 0.024

Table 3: outcome of patients who newly started an antidepressant in an area in which the prescribing of highly anticholinergic antidepressants was successfully reduced (intervention) compared to a control area (control)

	Baseline (all patients)		Post-intervention (all patients)		Post-intervention (new starters)	
	intervent.	control	intervent.	Control	intervent.	control
N	531	296	602	337	66	35
COOP/ WONCA item	mean (std dev)	mean (std dev)	mean (std dev)	mean (std dev)	mean (std dev)	mean (std dev)
Physical fitness	3.79 (1.06)	3.87 (0.94)	3.79 (1.00)	3.88 (0.98)	3.64 (0.98)	3.73 (0.98)
Change in health lately	3.12 (0.82)	3.17 (0.81)	3.11 (0.77)	3.15 (0.75)	3.02 (0.84)	3.18 (0.67)
Overall health lately	3.68 (0.74)	3.68 (0.70)	3.64 (0.71)	3.74 (0.71)	3.60 (0.76)	3.94 (0.50)
Feelings of depression	2.62 (1.22)	2.73 (1.15)	2.68 (1.21)	2.64 (1.14)	2.71 (1.26)	2.66 (1.21)
Daily activities	3.00 (1.24)	3.02 (1.22)	2.98 (1.21)	3.01 (1.25)	2.89 (1.32)	3.03 (1.05)
Social activities	2.49 (1.41)	2.46 (1.34)	2.45 (1.36)	2.41 (1.33)	2.40 (1.40)	2.42 (1.30)
Amount of pain	2.85 (1.19)	2.89 (1.17)	2.83 (1.17)	3.00(1.16) *	2.73 (1.12)	3.18 (1.16)

*mean difference -0.178 (95%CI -0.34 to -0.02) p=0.028

Table 4: COOP/WONCA prior to and after the performance of a randomized clinical trial in which the prescribing of highly anticholinergic antidepressants was successfully reduced in the intervention area (intervention) compared to the control area (control)

DISCUSSION

Due to the low response rate of patients, our study results have to be interpreted cautiously.
When we assume that there is no to minor selection bias. This study demonstrated that in an area in which the prescribing of antidepressants in the elderly was intentionally changed towards less prescribing of highly anticholinergic antidepressants and more prescribing of less anticholinergic antidepressants, the well-being of patients who used or recently had used antidepressants was comparable to similar patients in an area in which this prescribing intervention was not executed. Except for less complaints of dry mouth, coughing and amount of pain in patients in areas in which the intervention took place compared to the control area, the occurrence of adverse events, complaints related to depression, the seriousness of depressed feelings and the scores of different domains of quality of life were comparable.

Response rates in both surveys were low (28-35%). These rates were lower than expected when compared with similar surveys. In retrospect there may be several reasons for low response besides the general tendency of more and more people to refuse to participate in questionnaire surveys. First, the questionnaire was relatively long, especially for an elderly group (60-95 years in our surveys). It is possible that, the explanation of the total study (including our intervention study) and more information about other projects by our institute, would have increased response rates; however, this information might also have influenced patient responses (information bias).
Our comparison of responders and non-responders revealed no important differences for several general patient characteristics. Although this might point at minor selection bias in our study results, this interpretation is speculative. Furthermore, the relative small sample size and the uncertainty of confounding bias (not all prognostic factors of different outcomes were available) further limits the interpretation of the study results.
Although our statistically significant differences can be due to type I error (we performed 90 statistical comparisons), an interesting finding was that in the intervention areas the occurrence of dry mouth was lower that in the control area. This finding was in accordance with the reduction in the prescribing of highly anticholinergic antidepressants in the intervention areas. This finding was statistically significant when all patients were analyzed together and not when the analysis was restricted to the patients newly started on an antidepressant, although the same tendency (less occurrence of dry mouth) was observed.
Our study design and the way we analyzed the data show the difficulties one encounters when patient outcomes are to be evaluated in a study in which the

intervention was directed at the prescribing of general practitioners. Decisions have to be made concerning intention-to-treat versus a per protocol analysis, correction or not for baseline findings, evaluation of only patients using antidepressants at baseline and post-intervention or also including patients that recently have used antidepressants, evaluating post-intervention data of only patients that newly started an antidepressant during the intervention period versus evaluation of all patients that used at baseline or have recent past use of antidepressants et cetera. Prior to the start of the study we thought the most relevant patient data would be baseline and post- intervention data of patients that newly started an antidepressant during the intervention period. However, a simple and practical solution for the collection of the baseline questionnaire was obviously not possible, especially in the control area in which the general practitioners and pharmacists were not contacted.

Conclusion

Although this study has methodological limitations and a low response rate, we have no indications that the well-being, adverse events, severity of depressive feelings and quality of life was changed in an unfavourable direction, when comparing patients living in an area in which the prescribing of highly anticholinergic antidepressants was successfully reduced to patients living in an area in which the prescribing of antidepressants was not intentionally changed.

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HOOFDSTUK 9
Samenvatting en algemene overwegingen

Er is een groeiende behoefte aan wetenschappelijk verantwoord medisch handelen. Om dit te ondersteunen worden richtlijnen opgesteld met behulp van de resultaten uit onderzoek. Dat dokters deze richtlijnen gebruiken, is echter niet vanzelfsprekend. Er wordt dan ook veel aandacht besteed aan manieren waarop artsen gestimuleerd kunnen worden deze richtlijnen te volgen. Dit proefschrift beschrijft diverse aspecten van dit proces. Het laatste hoofdstuk speculeert over hoe nascholing er in de toekomst uit zou kunnen zien. Wat zou de rol kunnen zijn van de grote databases bij kwaliteitsanalyses, medische besluitvorming, kennismanagement en voortdurende nascholing? Met dit hoofdstuk willen wij een aanzet geven tot het denken en discussiëren over de rol van grote gegevensbestanden en de Informatie Communicatie Technologie (ICT) binnen de gezondheidszorg.

In de toekomst zal er steeds meer informatie beschikbaar zijn over artsen en patiënten. Dit kan ernstige inbreuk maken op onze privacy en veel ellende veroorzaken. Het kan echter ook de gezondheidszorg ondersteunen, wanneer we daarvoor kiezen.
Uit onderzoek naar het gebruik van vernieuwingen blijkt dat deze nieuwe structuren nodig maken. Elke nieuwigheid beïnvloedt de bestaande processen. Zo volgde op de uitvinding van de auto een behoefte aan betere wegen, vervolgens kwam er de mogelijkheid om verder van het werk te wonen en veranderde uiteindelijk onze hele houding ten opzichte van mobiliteit. Zo zal ook nascholing veranderen en kunnen overgaan in voortdurende nascholing door de enorme toename van (beschikbare) informatie. Niet iedere keer dat uit onderzoek blijkt dat de behandeling van een aandoening verbeterd kan worden, zal hierover een programma worden opgezet. Er moet een soort continu proces van samenwerking, communicatie, kwaliteitsanalyse en kennismanagement ontwikkeld worden. Er zullen interdisciplinaire platforms van steeds wisselende samenstelling ontstaan, waarin voortdurend informatie beheerd en gewogen wordt. Hoe deze er precies uit gaan zien, weten we nog niet, maar het zal belangrijk zijn dat alle partijen (patiënten, zorgverleners, universiteiten, zorgverzekeraars et cetera) hieraan deelnemen en dat ieders belangen bekend zijn en gewogen kunnen worden. We zullen anders moeten omgaan met informatie, communicatie en samenwerking. We zien nu al dat ICT de wereld zal veranderen. Het internet forceert deze vernieuwingen; medische kennis en hulp, overal vandaan, zijn beschikbaar als nooit tevoren. Hoe de nieuwe gezondheidszorg er precies uit zal zien, zal blijken in de volgende decennia. Wat zijn de kansen en uitdagingen van deze nieuwe tijd? In de kakofonie van informatie waarin we terecht zijn gekomen, zullen behandelaars en patiënten hun onderlinge relatie moeten veranderen. Met behulp van richtlijnen, losse informatie

en individuele kenmerken moet steeds een passend behandelplan gekozen worden. Artsen en patiënten zullen samen, in een open dialoog, een keuze maken. Apothekers kunnen hier een belangrijke rol in gaan spelen. Hoe kunnnen we in de toekomst alle informatie wegen? Iedereen kan zijn of haar ideeën via het internet beschikbaar stellen. Dat is één van de uitdagingen die er ligt in de toekomst: welke informatie is betrouwbaar? In dit verband is het in ieder geval een voorwaarde dat er geen verborgen belangen zijn. Daarnaast zullen de medische en de farmaceutische opleidingen zich minder moeten richten op het leren van feiten en meer op het leren wegen van informatie, en het ontwikkelen van een attitude van voortdurende reflectie en verbetering.
Hoe kunnen we zorgen dat ICT de gezondheidszorg ondersteunt? In de toekomst hebben we mensen nodig die graag informatie delen en met kritiek kunnen omgaan. Daarnaast moeten we een enorme hoeveelheid technische problemen oplossen; systemen moeten beter kunnen communiceren, gegevens en kennis moeten beschikbaar zijn voor iedereen, maar privé-informatie moet privé kunnen blijven. We moeten leren met een enorme hoeveelheid informatie om te gaan en goede zoekstrategieën te ontwikkelen. Als dat lukt kunnen kwaliteitsanalyse, communicatie, kennismanagement en het maken van een behandelplan samen gaan vallen.

Hoe is de relatie tussen grote databases, kwaliteit van zorg en het implementeren van vernieuwingen? Diagram 5 laat zien hoe we een overvloed aan informatie uit registraties kunnen gebruiken in een soort continu proces van 'inzoomen' en 'uitzoomen' om kwaliteitsprojecten te ondersteunen. Allereerst kan er op macroniveau gekeken worden wat er gebeurt en wat er opvalt. Vervolgens kunnen we zoeken naar gebieden waar kwaliteitsverbetering mogelijk is en deze specificeren. Daarna kunnen we het probleem kwantificeren en zo op de agenda van de betrokkenen proberen te krijgen. Daarbij kunnen we met behulp van data concrete doelen formuleren om een interventie te ondersteunen. Ook kunnen we de informatie voor de betrokkenen inzichtelijk maken op individueel niveau (zoals bijvoorbeeld prescriptieterugkoppeling, maar iets dergelijks kan ook voor patiënten gemaakt worden). Dit laatste kunnen we dan ook gebruiken om te (laten) zien of de gestelde doelen bereikt zijn. Daarnaast kunnen we onderzoeken waarom we onze doelen al dan niet gehaald hebben, wat het effect op andere variabelen is en wat we van dit project kunnen leren voor toekomstige projecten.

Er zijn nog veel vragen over alle aspecten van kwaliteitsprojecten in de zorg. Hoe definiëren we optimale zorg? Op welke manier stimuleer je die? Hoe kunnen we de grote medische registraties onderhouden zonder de privacy in gevaar te brengen? Wat is de ideale interventie?

Laten we hier nog lang en kritisch over discussiëren.

9
Summary and Final Considerations

"When you wake up in the morning, Pooh," said Piglet at last,
"what's the first thing you say to yourself?"
"What's for breakfast?" said Pooh. "What do you say, Piglet?"
"I say, I wonder what's going to happen exciting to-day?" said Piglet.
Pooh nodded thoughtfully.
"It's the same thing," he said.
A.A. Milne, Winnie-the-Pooh, 1926.
Chapter: We say Good-bye, page 144.

SUMMARY

There is a general trend to work towards a more evidence based medical practice. To support this, an increasing number of guidelines are being developed to translate new evidence to medical practice. The implementation of guidelines, however, is a complex process described in various behavioral models. These models have influenced health behavioral projects and pharmaceutical marketing and so found their way into academic detailing as used in this research. Still, doctors' compliance to guidelines varies widely and there is no general agreement about the most effective way to support doctors implementing new guidelines. This thesis compares two methods (individual visits versus group visits) aimed at improving the quality of pharmacotherapy. Reimbursement data were used to provide quantitative information to support the methods. We used the regionally organised, typically Dutch, peer review groups (PRGs) of primary care physicians and pharmacists to address professionals. In addition we included patient outcome measures to evaluate the effect of our program on both doctors' performance and patients' well being. Chapter 1, the introduction, describes the state of the art in the diffusion of innovations, the use of reimbursement data for research, and how to define –and how to measure– the quality of prescribing and how to measure patient outcomes. To optimally design the diffusion of an innovation, many aspects have to be taken in account. Chapter 2 is about the assessment of the quality and suitability of our data. We describe a systematic tool to test the appropriateness of a given database for specific research questions. It gives insight into data collecting and data quality, relevant for both researchers and interpreters of similar investigations. We describe in particular the potency and the pitfalls of reimbursement data and express our belief that these data need to be protected and valued more and should be handled with care. This is the challenge: striking the balance between reckless utilism and respect for the individual. Chapter 3 is the description of how we used the reimbursement data to assess the quality of prescribing of antidepressants to the elderly. At the time, much discussion went on about the advantages and disadvantages of the newer antidepressants and the vulnerability of the elderly to anticholinergic drugs. We used reimbursement data to assess whether physicians avoid prescribing highly anticholinergic antidepressants to the elderly. We therefore analyzed the drug choice for new users of antidepressants only (incident users) to avoid contamination of the results with patients that are "happy" with a drug, as it can be difficult for physicians to change medication for these patients. We have demonstrated that the elderly are still prescribed highly anticholinergic antidepressants and that it is possible to assess incident prescribing with reimbursement data. We decided to designate this a benchmark for our intervention on prescribing behavior. The incidence rates would be more illustrative for physicians than basic prescribing volumes. Chapter 4

compares the prevalence of complaints mentioned by users of anticholinergic antidepressants to a control group of former users of antidepressants in a population of ambulant elderly, in order to relate prescribing to patient outcome. Because there is evidence that highly anticholinergic drugs can be harmful to the elderly, we decided to assess patient related outcome measures prior to the intervention. We sent a questionnaire to all users of antidepressants over 60 years in the research area. This questionnaire inquired as to basic characteristics (sex, marital state, smoking, alcohol use etc.), medical condition and medical consumption. The Geriatric Depression List, the VROPSOM, Rand-36 and the COOP-WONCA Health charts were also included. Could we confirm results from randomized controlled trials in our study of the elderly? To our surprise, we found no evidence that elderly using highly anticholinergic drugs suffer more adverse events. Community-dwelling elderly using highly-anticholinergic antidepressants did not report more adverse events than elderly using less-anticholinergic antidepressants. Moreover, the number of adverse events in the antidepressant users was comparable with what can be seen in former users of antidepressants. Confounding by contraindication may explain these findings, as would be expected if prescribers were aware of drug-specific adverse event risks and avoided or discontinued use of problematic drugs in patients with such symptoms. In Chapter 5 we compared several rating scales to assess depression, since inclusion criteria are considered to be an essential element of good guidelines. (Under-)diagnosis of depression is mentioned to be a problem in several studies; therefore, we also used the questionnaires of the preceding chapter to evaluate depression scales. We were able to establish a comparison of various validated rating scales scoring depression in a group of ambulant elderly. The results show that the chance of a patient to be diagnosed as depressed depends heavily on the rating scale being used. It remains a challenge for future research to find new solutions as early diagnosis and treatment of depression is important to restore optimal levels of functioning, quality of life and independence, and to reduce societal costs. Chapter 6 describes another essential factor for the intervention: How are PRGs functioning in the area? The intervention design included validating the effect of individual visits versus PRG visits. Using the existing knowledge on PRGs, we designed a questionnaire including different aspects of organization, goals and preparation. We selected and evaluated characteristics of PRGs that were thought to be relevant for the effect of our outreach program. After the intervention we were able to demonstrate that these factors (use of feedback data, use of a formulary, level of binding consensus) did indeed modify the effect of our educational outreach program. When groups are addressed in an intervention, it is relevant to assess basic characteristics of these groups, either to use these for a block randomization or for correction in the subsequent analyses. Chapter 7 describes the intervention we undertook to reduce the prescribing of highly anticholinergic antidepressants in the elderly and its effect

on incident prescribing. The intervention was designed following insights usually referred to as academic detailing, an approach that has proven to be effective to influence prescribing, which is usually used in an individual setting. We added a group versus individual approach design, using PRGs. We have demonstrated that a group approach can effectively change prescribing as well. In our intervention, we found a 31% reduction in the incidence of initiation of highly anticholinergic antidepressants in the elderly and a 36% increase of the use of less anticholinergic antidepressants. Many countries are looking for models for continuous medical education. Addressing groups may be an important tool to support acceptance of new guidelines. More research in group-learning processes is needed to improve our understanding of continuing medical education. Chapter 8 compares the questionnaires of elderly using anticholinergic antidepressants, living in the intervention and control areas, to measure the effect of our intervention on a patient level. Besides the patient questionnaire mentioned above, we sent a similar questionnaire after the intervention. We found no indications that well-being, adverse events, severity of disease and quality of life had been changed unfavorably in patients living in the intervention arm areas, compared to patients living in the control arm area. Unfortunately, neither did we observe an increase in quality of life for patients in the intervention arm area. The scale of the study might not have been large enough to measure such a result on a patient level. Besides this summary, Chapter 9 includes some final considerations, in which we speculate on what continuous medical education might look like in the future. What will be the role of very large medical information databases in quality assessment and continuous education? It aims at stimulating to think ahead –and to take action– on employing ICT (Information and Communication Technology) for the benefit of health care.

FINAL CONSIDERATIONS

Future perspective; accumulated accessible information

New technological developments will open up opportunities to assess and analyze accumulated information on patients and doctors. This accumulated, accessible information can change the world into a nightmare of loss of privacy and intimacy, can result in inequality, and can make us alienated, cold and distant. But it can also support equal and accessible health care for everyone, if we want it to (1-4).

New insights require new organizations

Research on diffusion of innovations has evolved from examining natural diffusion of innovations through supporting diffusion and acceptance of innovations to individuals, to the organizational consequences of innovations. There is an increasing awareness that organizational variables act on innovation behavior in a

manner over and above that of the aggregate of individual members of the organization (5,6). The implementation of (technical) innovations in an organization amounts to a mutual adaptation of the innovation and the organization. Typically, each one changes during the subprocess of the implementation (7). "Innovations not only adapt to existing organizational and industrial arrangements, but they also transform the structure and practice of these environments" (Van de Ven, 1986).

From continuous to ongoing medical education

In the future we do not want to plan and design an intervention for each area of sub-optimal prescribing, or each time new knowledge or evidence results from research. We need to reorganize health care in such a way that health care providers and users (patients, clients) work together continually. We need to communicate, to share knowledge and to work on quality assessment and improvement of care as an ongoing process of information management (8,9). Interdisciplinary platforms of medical cooperation may communicate and work together rapidly in constantly changing platforms. Anybody can be the center of a platform at some time. Different people will be actively involved, depending on the topics discussed. Patients and doctors will be able to make well-informed, shared decisions (8-10). The exact structure and organization of these platforms will probably evolve over the next few decades. The role played by patients, insurance companies, the pharmaceutical industry and the government is not yet clear. All conflicts of interest (as there are always conflicts of interest) need to be revealed and handled in a systematic and open way (11,12).

ICT will change the world

A new attitude towards cooperation, communication, information and knowledge sharing will be accelerated by new developments in Information and Communication Technology (ICT). Already we can see some of the impact that ICT will have on medical care. In the decades to come we will have to shape and build this new style health care. It is not clear yet what it will look like, but the ICT revolution has passed its point of no return and will have an enormous impact on every aspect of our lives in the near future. The Internet creates transparency and equality and challenges historically grown hierarchical structures. Patients already have access to online medical journals and can exchange information and experiences. This has made medical information available to laymen as never before (13). This, combined with vanishing distances (consulting doctors from the other side of the world or discussing with patients suffering the same complaints wherever they are is easy), will change the patient-doctor relation dramatically (3). Any patient, certainly the one with the means to pay, will be able to withdraw herself from governmental control or the agreements and guidelines of the medical profession in her physical environment (13).

Opportunities and challenges

This new situation of total equal access to information will force a change in the doctor-patient relation (3). They have landed on a planet of cacophony, where they will need each other to decide on the best possible treatment strategy for each specific situation. This wil include going through a complex process of risk assessment, taking into consideration ones set of genes, environment, character, social network, lifestyle and history (14). Computer-assisted execution of guidelines (including personalized patient information leaflets, checklists, prescriptions, documentation and laboratory protocols being processed after putting in a tentative diagnosis) and availability of information will change medical work into a combination of rapid routine jobs and advanced case management that will continuously update a doctor's medical knowledge (8,15). We will have to redefine what constitutes good medical care (including pharmacotherapy) in a world where everybody is an individual. At times, patient and doctor will be searching for and evaluating evidence and other information together and come to shared decision-making in an open dialogue (15). Even for lots of routine problems, this process will keep the doctor constantly alerted to new information and new guidelines (8,9). Some of this may seem scary; as we all know, anyone (any fool, idiot or professor) can find someone to agree with her or him. In the future there will be a website to support any awkward opinion. This will be one of the challenges before we can maximize the potential benefits of ICT to health care: we need ways to define and to give insight to credibility of (online) health information (13) (9). This requires at least a completely open system of decision-making where no hidden conflicts of interest are tolerated. In addition to the integrity of available information, we need tools to find our way in times of chaotic information overload (13). Every medical school, every patient organization and every governmental and non-governmental health organization will set up an online library of guidelines, key lectures, publications, discussion platforms and benchmarks (10). We need special medical search tools to find relevant and reliable information quickly (15). We need professionals that can help people to find their way. Pharmacists can play an important role here. Following this online consumer health information will not only bring difficult questions to the doctors' office; it can also bring us a well-informed and motivated patient. We need to shift the emphasis of medical training from learning data to learning to weigh information, to communicate, to achieve an attitude of continuous learning, self-reflection, collaboration and a desire for self-improvement (16).

A clear advantage of online education will be the accessibility of this information for doctors, pharmacists and patients in remote areas. An important condition to meet this advantage is equitable access across the globe. Everyone should be able to get online and all relevant information should be available online.

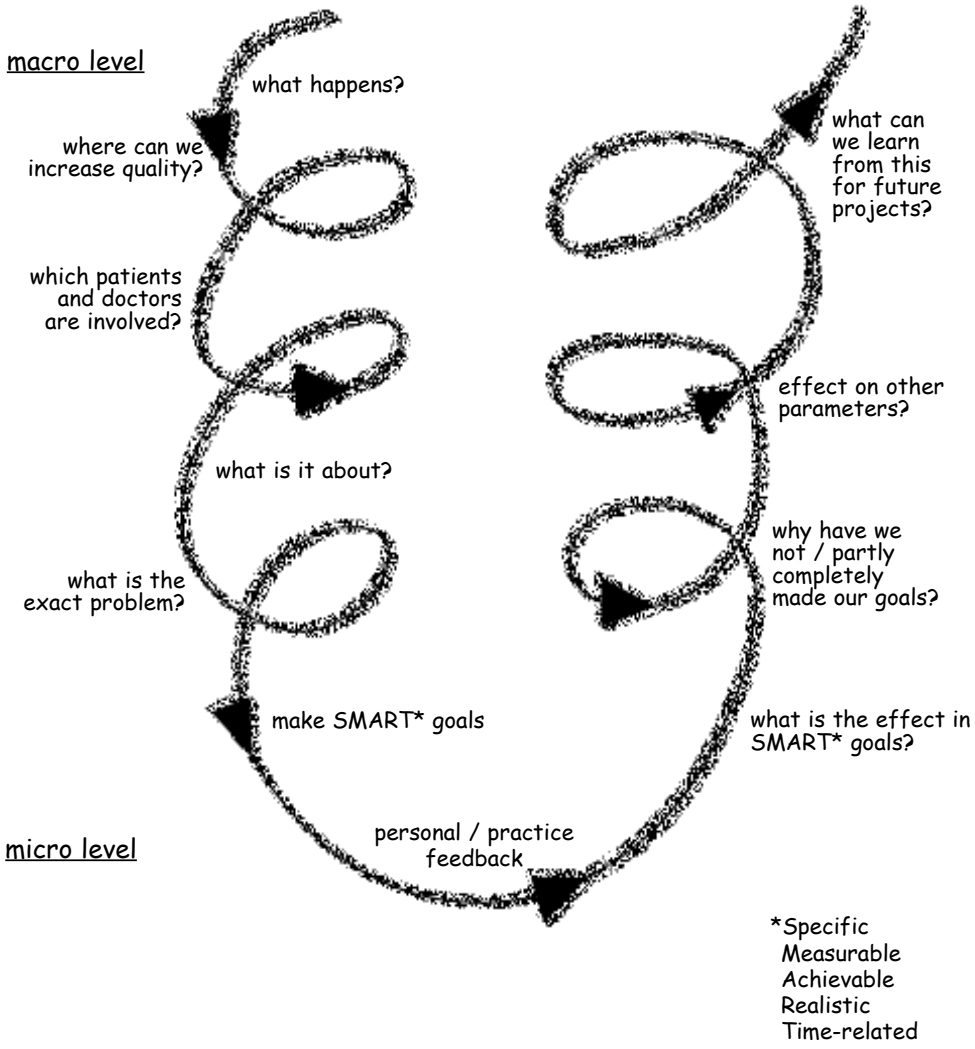
Tele-consultation will be another opportunity created by new communication

techniques, to combine improved patient care and continuous medical education. Another important challenge will be to balance privacy and connectivity, to protect the individual and support the community. Techniques that will enable secure and mobile data processing in health care have to be improved. We need quality control and intellectual property agreements. This will require new laws with international validity.
It may happen that online professionals will relieve the practitioner from some routine jobs, but differences between virtual and face-to-face interaction will never make a physician jobless.

How can we make ICT support health care?
In the future, good health care will be provided and supported by people with an open attitude towards information sharing and criticism. The speed of new developments, the complexity of medical decision-making and the high economic and emotional value of possible conflicting interests, all require a revolution to be able to provide rational health care for everyone in the near future (15).
Our great challenges are that: We will have to solve an enormous number of technical problems and to agree on definitions to make systems able to communicate. It is possible that in the future, all systems will be integrated. We have to find ways to make individual information accessible for all that are eligible to use this information and none that are not, balancing utilism and respect for individual privacy. We need to share health care and knowledge with the rest of the world (including all the poor). We have to find ways to deal with the information overload that will be a direct result of these developments and we will have to solve problems on credibility of information. We need new techniques for the retrieval of relevant and reliable medical information rapidly.
The greatest challenge of the new millennium will be to bring about a change of attitude that will make health care providers and consumers emphasize long-term goals and believe in equality of all parties involved. In this changing world, post-academic training will finally be continuous medical education in a true sense, where quality assessment, communication, case and knowledge management and shared decision-making meet.

Large databases, quality of care and diffusion of innovations
One of the initiating questions of this research was; how can we support quality of pharmacotherapy with the aid of reimbursement records? To achieve optimal medical care (including optimal prescribing) we need (among many things) good guidelines, which are evidence based, regularly updated ànd good programs for continuous medical education (17-36).
Medical registration, whether reimbursement data, questionnaires or other registrations, can support this in several ways. Diagram 5 sketches the relation of

diagram 5
The relation of large databases and diffusion of innovation



large databases and diffusion of innovations as a continuous multilevel quality project that requires drilling down and drilling up again and again, shifting between macro- and microlevel. Firstly, data can help us to monitor prescribing and analyze pharmacotherapy (what happens). Secondly, we can detect areas of sub-optimal care and locate specific problem domains (where can we increase quality and who is involved?) (8,37-43). After this, we can use these databases to help to quantify the problem and put it on the agenda of involved parties. Following that, we can use data to define SMART (= specific, measurable, achievable, realistic and time-related) goals and support an intervention by giving feedback (24) and to assess the effect of an intervention, on prescribing, on a patient level or on other parameters (44-48). Our study demonstrates that these data can support quality of care, but also that we need to protect our data to make this possible (carefully balancing the possible harm and benefit that can be done with these data) (49-67).
Alongside the reimbursement data, we used questionnaires to assess quality of prescribing at a patient level. This may add valuable information on the effects of medication when used in "real life". After assessing quality of prescribing both at a patient and a doctor level (expressed in SMART goals), why should we include patient outcome measures if the intervention is evidence based and scientifically proven to be the best for patients (effect on other parameters)? The evaluation on a patient level of an intervention to increase evidence based prescribing is in a way an evaluation of the guidelines themselves. Is this necessary? Yes- we think one should aim at evaluating the guidelines as well in an ideal intervention. Reasons for this are that constantly new knowledge will evolve, patient benefits can be measured on an endless number of levels, consumer populations are different from trial populations, and circumstances are constantly changing. All this may force us to update guidelines. Further, what is beneficial for individuals can be in conflict with what is best for all, as is the case for short and long-term goals. We need to aim at projects that will include quality assessment at all levels (8,68-77). How do the doctors, patients *and* the guidelines perform (what can we learn from this project)?
We conclude that many questions still remain on all aspects of the process of diffusion of innovations. What is the best way to improve quality of care? What actually is to be defined as optimal prescribing, in individual cases, on a population level, on the long and short term? Which methods of feedback are most effective? How do we maintain large medical databases without jeopardizing privacy? How can we use these databases in a preventive way (e.g. post-marketing surveillance)? What constitutes an ideal intervention?

Please enjoy my unfinished thoughts.

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10
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This would be my present to you, my friends,
If it weren't your gift to me.
(vrij naar A.A. Milne)

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ik deel van een eigen gezin. Lambert, Lizette en Charlotte, voor jullie is het regelmatig opschuiven en inschikken door mijn ambities. Dat ging altijd zonder mokken of grote problemen, dat is een wonder, want het pad was heel zwaar de laatste tijd. Ook ik neem me als zoveel promovendi voor dat het anders zal zijn na de grote dag. Ik denk dat dat moet. Jullie aanwezigheid is een geschenk.

Op deze plek wil ik verder graag gebruik maken van de mogelijkheid om mijn familie, vrienden, buren, behulpzame schoolmoeders, mijn schoonmoeder (dank voor heel veel praktische, logistieke en morele steun), mijn broers Peter en Jeroen en schoonzus Rinske (die er onder andere voor zorgde dat mijn kinderen goed in de kleren zaten) en sommige toevallige passanten te bedanken. Jullie hebben allemaal grote en kleine daden verricht door af en toe een handje uit te steken en vooral met heel veel oppaswerk dit boekje helpen realiseren. Als promoverende moeder kun je nu eenmaal niet alleen je partner bedanken, maar moet je hele sociale systeem op het ereplateau. Er gaat niets boven een luisterend oor en samen lachen of huilen (en ja natuurlijk heb ik jullie verwaarloosd.....). Sommige van jullie ken ik al mijn hele leven, anderen volg ik pas sinds ik in de Braamstraat woon. Soms zijn het de buren waarmee je je zorgen en plezier deelt, of die een handje uitsteken, soms je familie. Samen zorgen jullie voor kwaliteit van leven in dit aardse bestaan.

Dit boekje was er echt nooit gekomen als niet heel veel mensen me geholpen hadden. Op het laatst nog schoten Ellen en Annemieke te hulp om mij te helpen in gewoon Nederlands uit te leggen waar ik al die tijd mee bezig ben geweest. Dat was een hele uitdaging. Zonder jullie was het niet zo goed gelukt. Ellen Wiggemansen heeft op het laatst wonderen verricht door het DTP-en op zich te nemen, IOU!

De meeste promotieprojecten zijn te groot om iedereen te bedanken die van essentiële waarde is geweest. Hoe meer mensen ik bedank, hoe meer mensen ik onterecht oversla. Hoe minder ik zeg, hoe meer recht ik doe aan alle onbenoembare elementen. Sommigen weten wellicht zelf niet eens hoe en wanneer hun aanwezigheid en steun van essentieel belang was. Truus en Ellen, jullie zijn vandaag mijn paranimfen en iedereen kan zien hoe jullie mij fysiek bijstaan. Dat is wat mij betreft symbolisch voor het gevoel dat jullie mij altijd hebben weten te geven; achter mij te staan. Obrigado! Wie ik onterecht vergeten ben te noemen, nodig ik uit me op te bellen. Dan gaan we een borrel drinken om te vieren dat deze monomane marathon eindelijk uitgelopen is.

Onderweg heb ik ook nog een belangrijke vriend verloren. Ik had helemaal op jouw aanwezigheid gerekend, Peter. We hebben elkaar leren kennen toen dit project net begonnen was. Helaas heb ik voor het afronden afscheid moeten nemen van je. Dat is onvoorstelbaar, maar toch waar. Bedankt voor al je hulp en lieve humor. "Never

make anything simple and efficient when a way can be found to make it complex and wonderful".

Ik wil ook niet nalaten om alle patiënten, artsen en apothekers die mij belangeloos hebben geholpen te bedanken voor hun aandacht en tijd. Het is altijd maar de vraag wat eruit komt als je je subject stelt voor een onderzoek, ik hoop dat ik jullie niet heb teleurgesteld (behalve in tempo). Verder kan ik het niet nalaten alle medewerkers van andere betrokken organisaties zoals de softwarehuizen, andere universiteiten, andere zorgverzekeraars, belangenverenigingen, koepels et cetera te bedanken. Zij richtten hun blik op de kracht van samenwerking en kennisdelen in plaats van op de macht van het alleen doen en alleen weten.

Tenslotte mijn nieuwe werkgever, DGV, het is fantastisch om alles waar ik de afgelopen jaren mee bezig ben geweest nu vanuit een andere invalshoek te mogen gebruiken. Die kans kon ik niet laten liggen. Wat ik terugkreeg was een team van professionals die een gezamenlijk doel voor ogen hebben; ondersteuning van het rationaliseren van de kwaliteit van farmacotherapie in Nederland. Jullie hebben de laatste hobbels helpen nemen, ALLEMAAL heel erg bedankt. Ik zie uit naar werken bij DGV zonder "dat boekje" als last op mijn schouders.

Wat kan een mens in 8 jaar overkomen: 7 chefs, 6 computerssystemen, 5 adreswijzigingen, 4 bevallingen (Lizette, Charlotte, Lambert's proefschrift en het mijne), 3 contracten, 2 keer naar een uitvoering van "L'Incoronazione di Poppea" in de Stopera en gelukkig slechts één man: Lambert. While I run around in a Tiggerish kind of way, you simply love me.

Curriculum vitae

Martine van Eijk werd geboren op 23 juli 1962 te Rotterdam. Na het behalen van haar VWO diploma aan het Strabrecht College te Geldrop in 1983, werd aanvang gemaakt met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam. Het doctoraal examen werd afgelegd in 1989 en het artsexamen in 1991. In de periode februari 1992 – oktober 1993 was zij werkzaam als arts van het GeneesmiddelTeam voor VWS. Van november 1993 tot februari 1999 werkte zij voor OZ zorgverzekeringen en aan het in dit proefschrift beschreven onderzoek bij de disciplinegroep farmacoepidemiologie en farmacotherapie van de faculteit farmacie te Utrecht (begeleiders prof. dr A.J. Porsius en dr A. de Boer). Sinds augustus 1999 werkt zij bij DGV Nederlands instituut voor verantwoord medicijngebruik.

Enquête FTO-groepen

Naam huisartsengroep .....

Naam FTO-groep .....

Naam contactpersoon .....

Samenstelling FTO-groep			
Naam	Huisarts	Apotheker	Anders, namelijk
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			

1. *In welk verband vindt het FTO plaats?*
   - ❑ huisartsengroep
   - ❑ deel huisartsengroep, nl. gezondheidscentrum
   - ❑ anders, nl. .....

2. *Hoe lang komt de FTO-groep al bij elkaar?*
   - ❑ < 1 jaar
   - ❑ 1-2 jaar
   - ❑ 2-4 jaar
   - ❑ 4-6 jaar
   - ❑ > 6 jaar

3. *Uit hoeveel personen bestaat de FTO-groep op dit moment?*
   ..... personen

4. *Wat is de gemiddelde opkomst van de deelnemers?*
   - ❑ < 50%
   - ❑ 50-70%
   - ❑ > 75%

5. *Wat is de frequentie van de FTO-bijeenkomsten?*
   - ❑ minder dan 5 keer per jaar
   - ❑ 5-9 keer per jaar
   - ❑ 10 keer per jaar of meer

6. *Wat is meestal de duur van een FTO-bijeenkomst?*
   - ❑ 0,5-1 uur
   - ❑ 1-1,5 uur
   - ❑ > 1,5 uur

7. *Is er in de groep expliciet gesproken over de doelstelling van het FTO?*
   - ❑ nee, reden: .....
   - ❑ ja

8. *Welke algemene doelstelling heeft uw FTO?**
   - ❑ informatie uitwisselen over geneesmiddelen en voorschrijfgedrag
   - ❑ kritische reflectie op (eigen) voorschrijfgedrag
   - ❑ elkaar adviseren over voorkeursbeleid
   - ❑ afspraken maken over voorkeursbeleid
   - ❑ toetsen van gemaakte afspraken
   - ❑ anders, namelijk .....

9. *Door wie wordt het FTO voorbereid?*
   - ❑ apotheker(s)
   - ❑ huisarts(en)
   - ❑ huisarts en apotheker samen
   - ❑ wisselend door apotheker of huisarts
   - ❑ geen voorbereiding

* meerdere antwoorden mogelijk

*10. Wat wordt er voorbereid?**
- ❑ theoriestuk/voordracht
- ❑ casus
- ❑ concept-advies t.a.v. voorkeursmedicatie
- ❑ prescriptiecijfers
- ❑ anders, nl. .....

11. Maakt uw FTO een planning voor langere termijn?
- ❑ nee, reden: .....
- ❑ ja
  - voor hoe lang?
    - ❑ half jaar
    - ❑ 1 jaar
    - ❑ > 1 jaar
  - wat wordt gepland?*
    - ❑ data
    - ❑ onderwerpen
    - ❑ de voorbereiders
    - ❑ de gespreksleider
    - ❑ evaluatie van het overleg
    - ❑ anders, nl. .....

12. Bespreekt u het verslag van de FTO-bijeenkomst?
- ❑ nee, reden: .....
- ❑ ja
- ❑ geen verslag gemaakt

13. Is er voor het FTO een gespreksleider aangesteld?
- ❑ nee
- ❑ ja
  - ❑ huisarts
  - ❑ apotheker
  - ❑ anders, nl. .....

14. Is het gespreksleiderschap vast of wisselend?
- ❑ vaste persoon
- ❑ wisselend per keer
- ❑ wisselend per jaar
- ❑ anders, nl. .....

*15. Wat wordt er in uw FTO **regelmatig** behandeld?**
- ❑ indicaties en bijbehorende geneesmiddelen
- ❑ (plaatsbepaling) nieuwe geneesmiddelen
- ❑ NHG-standaarden
- ❑ een Formularium, namelijk dat van .....
- ❑ automatisering
- ❑ substitutiebeleid of afleverbeleid
- ❑ patiëntenvoorlichting
- ❑ therapietrouw
- ❑ medicatiebewaking
- ❑ omgaan met druk van de patiënt om een middel
- ❑ doorverwijzingspatroon
- ❑ magistrale receptuur
- ❑ (overheids)maatregelen (incl. zorgverzekeraars)
- ❑ anders, nl. .....

16. *Welke criteria spelen een rol bij de keuze van een onderwerp?**
    - ❑ actualiteit
    - ❑ interesse van de huisartsen
    - ❑ interesse van de apothekers
    - ❑ complexiteit van een onderwerp
    - ❑ prescriptieverschillen
    - ❑ te behalen kwaliteitswinst (goedkoper,minder,beter)
    - ❑ bestaan NHG-standaard
    - ❑ beschikbaarheid deskundigheidsbevorderingspakket WDH

17. *Welke bronnen gebruikt u voor het FTO?**
    - ❑ Geneesmiddelenbulletin
    - ❑ Pharmaceutisch Weekblad
    - ❑ Nederlands Tijdschrift voor Geneeskunde
    - ❑ Huisarts en Wetenschap
    - ❑ Medisch Farmaceutische Mededelingen
    - ❑ Farmacotherapeutisch Kompas
    - ❑ NHG-Standaarden
    - ❑ Informatorium Medicamentorium
    - ❑ "Adviezen voor farmacotherapie"
    - ❑ Farmaceutische industrie

18. *Welke geneesmiddelengroepen/indicaties zijn het **afgelopen jaar** besproken?*

Geneesmiddelen/indicaties	Doelstelling

19. *Wordt er in het FTO gewerkt aan een eigen formularium?*
    - ❑ nee, reden: .....
    - ❑ ja

20. *Wordt er in het FTO gewerkt met een bestaand formularium?*
    - ❑ nee
    - ❑ ja, nl. .....

21. *Geven de artsen tijdens het FTO een beschrijving van het eigen voorschrijfpatroon, als dit van toepassing is?*
    - ❑ nee, reden: .....
    - ❑ ja
    - ❑ soms
    - ❑ niet van toepassing

22. *Worden de FTO-bijeenkomsten vastgelegd d.m.v. :*
    - ❑ verslagen
    - ❑ besluiten-/afsprakenlijst
    - ❑ niet

23. *Hoe komt men tot een concrete afspraak?*
    - ❑ de voorzitter deelt mee wat er gedaan wordt
    - ❑ na discussie wordt gekomen tot een (meestal) unaniem besluit
    - ❑ anders, nl. .....

24. *Is het altijd duidelijk of, en zo ja wat, er is besloten?*
    - ❑ nee, reden: .....
    - ❑ ja

25. *Wordt er tijdens het FTO gebruik gemaakt van:*
    - ❑ een notulist(e)
    - ❑ audiovisuele hulpmiddelen
    - ❑ reklame materiaal
    - ❑ presentatie van derden
    - ❑ anders, nl. .....

26. *Zijn er bepaalde zaken te benoemen die uw FTO-groep nodig heeft of kan gebruiken om de kwaliteit van het overleg te verbeteren?*
    - ❑ nee
    - ❑ ja, nl. .....

27. *Wat verwacht uw FTO-groep van het terugkoppelen van prescriptie gegevens?**
    - ❑ prikkeling
    - ❑ startpunt voor een discussie
    - ❑ inzicht van de arts in eigen prescriptie
    - ❑ presenteren van spiegelinformatie over het voorschrijfgedrag ter ondersteuning van het FTO
    - ❑ toetsen van het werkelijke gedrag aan de voornemens

28. *Op welke manier bent u van plan prescriptieterugkoppeling gegevens te gebruiken?*
    - ❑ start discussie/illustratie/prikkeling
    - ❑ vergelijken van artsen
    - ❑ bespreken van het effect
    - ❑ anders, nl. .....

29. *Is er contact met andere FTO-groepen?*
    - ❑ nee, reden: .....
    - ❑ ja, op welke manier .....

30. *Is er contact met de tweede lijn?*
    - ❑ nee, reden: .....
    - ❑ ja, op welke manier .....