Abstracts of Papers and Posters

Drug Utilization Research and Pharmacoepidemiology Meeting

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A HIGHER IMPACT OF DRUG FORMULARIES: DISCUSS THE CONTENTS WITH GPS

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Background: In September 1991, a drug formulary was introduced in the Groningen Province (the Netherlands). This year, the third edition of this formulary will be introduced. This led to a study of the impact of the Groningen Formulary.

Setting: A database is being maintained with pharmacy data from 12 pharmacotherapy discussion groups (19 pharmacies covering >180,000 patients) in order to study the effectiveness of pharmacotherapy discussion meetings. This database was used to study the impact of the Groningen Formulary.

Of some drugs or drug groups (e.g. offonax, macrolides, macrolitics), prescribing was studied in three regions: Groningen Province (region A), a region with another drug formulary (region B), and a region without any drug formulary (region C). Subsequently, prescribing within region A was audited to study differences in prescribing between GPs who had, and GPs who had not discussed the formulary in pharmacotherapy discussion meetings.

Results: of the macrolides, the incidence of prescribing of the 'drug of choice', erythromycin, was significantly higher in region A (73 per 100 prescriptions, n=666) than in the other regions (45 and 45 per 100 prescriptions in region B (n=380) and region C (n=381), respectively). Stratification by pharmacotherapy discussion group showed that this effect is mainly attributable to GPs who discussed the macrolides during pharmacotherapy discussion meetings. For the other drugs, a significant impact of the drug formulary could only be found after stratification by pharmacotherapy discussion group.

Conclusion: For a drug formulary, to be more effective, the contents of this formulary have to be discussed with GPs.

HEALTH INSURANCE DATABASES DRUG THERAPY ENABLING (HIDDEN) PRESCRIPTION DATABASES IN QUALITY ASSESSMENT AND QUALITY IMPROVEMENT

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Health Insurance companies collect an enormous amount of health care data. Prescribing data are provided by pharmacists for reimbursement of costs of pharmaceutical care and are a potential source for research in health care and health care management.

At the Health Insurance company OZ which is situated in the Southwest of the Netherlands an initiative was started to enable research with prescription data. The final goal is to provide feedback to pharmacotherapy discussion groups (PTDs) and the effect on drug prescribing.

Those data are gathered according to a defined structure. The KNMP and the VNz have agreed about the lay-out that all reimbursement-prescription data should have. Each record in the database is one prescription item. Potentially data are available on medication histories and demographic data per patient and prescriber and pharmacist characteristics.

Our first aim was to evaluate the completeness and accuracy of the available data of 240,000 patients.

From January 1993 on reimbursement data are available in the defined structure.

Our findings are as follows:

1993

<table>
<thead>
<tr>
<th>records that can be matched with the KNMP Taxe</th>
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<td>96%</td>
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records with an ATC code: 90,4 %
Incomplete information on prescription: 1,5 %
Incomplete information on patient: 1,0 %

On average in 1993 over 90 % of the records were accessible for research.

Procedures are now being developed to increase the percentage of usefull records.

Summary:

When using reimbursement data for the accessing the quality of pharmacotherapy, considerable effort has to be done to test the quality of the data used. Several procedures have to be developed to improve the quality of the data.

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1) can be due to pharmacy mode preparations or local codes
Background: In the Netherlands, pharmacists and general practitioners (GPs) participate in pharmacotherapy discussion meetings. The objective of these meetings is to improve prescribing, dispensing and pharmacotherapy for the individual patient. The meetings take place at a local level, on a one- or two-monthly basis.

Setting: An intervention study is being carried out with respect to the effectiveness of pharmacotherapy discussion groups. To this end, a database is being maintained with pharmacy data from 12 pharmacotherapy discussion groups (19 pharmacies; 100,317 patients). A case-study has been carried out in one pharmacotherapy discussion group that had a meeting about antihistamines. A longitudinal study of prescribing behaviour of the participating GPs (n=12) and a control group (n=18) has been carried out. Seasonal influences were taken into account. Regression lines were fitted to estimate differences in prescribing before and after the meeting.

Results: During the meeting, several guidelines for the prescribing of antihistamines were established. After the meeting, a significant increase of the incidence of the prescribing of ‘drugs-of-choice’ is demonstrated in the group of participating GPs (p<0.005). Significant differences existed between the participating GPs, however.

In a similar longitudinal study of prescribing by GPs from the control group, no significant differences in prescribing behaviour before or after the date of the meeting could be demonstrated.

Conclusion: Pharmacotherapy discussion meetings can be an effective way to improve pharmacotherapy. For optimum results, agreements about guidelines for prescribing and dispensing have to be made in a very clear and unequivocal way.

Setting: an intervention study is being carried out with respect to the effectiveness of pharmacotherapy discussion groups. Setting -

Subjects -

Methods:

Objectives: To assess the frequency and the kind of adverse drug reactions (ADR) which were presented in general practices with a source population of approximately 330,000 patients included in a 3-month period.

Design: A descriptive study in a dynamic population

Results: Ninety-four percent of respondents had no objection against the reporting of ADR to the Inspectorate for Health Care by their medical practitioner or pharmacist. In a multivariate analysis the following co-factors were positively associated with the reporting of ADR in a significant way: visiting the pharmacist fewer than five times a year (p<0.05), regarding the computerisation of pharmacies non-threatening to privacy (p<0.01) and full employment (p<0.05). Seventy-seven percent of respondents did not object to the use of their medical data, even if these data were not anonymous, as long as the data were kept strictly confidential. Most patient were of the opinion that such data could be used without asking permission. Males would more readily give their permission than females (p<0.05).

Conclusions -

Implications: Although adverse drug reactions are commonly encountered in general practice, the majority of these are known and not serious.

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The feasibility of constructing an indication-related medication database in primary health care is assessed. A 'simple model to establish such a database is the registration of indication-related medication by the General Practitioner (GP). However, in the Netherlands most GPs who make active use of computerised medical records only register indication and/or prescriptions separately and it is not expected that, in the near future, GPs will register indication-related medication. Therefore in this project it is studied whether indication data registered in general practices can be reliably linked to medication data from health insurance claims which are routinely collected from pharmacy records. This is evaluated in a sample of 12 GPs covering about 20,000 patients. The GPs work together in the Registration Network Groningen (RNG) and since 1989 they all use the same software. The GPs of the RNG register both medication and indication. The data can be retrieved in 3 different files; the 'medications-file' where the events of a face-to-face contact between GP and patient are registered, the 'problem-file' which represents chronic health problems and the 'medication-file' where the RNG registers medication and the indication. The first 2 files are used to link to the diagnosis to the medication claims. The medication-file is used to validate this linkage. The linkage is done first at the patient level with the unique coded (VHKenn) insurance number and secondly at the level of the prescription using date of prescribing/dispensing as an extra linkage criterion. However, this results in unsolvable linkages since 1 patient can have comorbidity and can present themselves to the GP at 1 date so that it is unclear which indication is related to the medication. For instance for antimicrobial drugs (Anatomical Therapeutic Chemical (ATC) group J) and heart/vascular drugs (ATC-group C) the percentage unsolvable linkages was 68% and 72%. Two methods to reduce the unsolvable linkages were examined:

1) before linkage, the use of another linkage criterion i.e. the theoretical logical relation between dispensed medication and diagnosis. It should be stressed that regular update of the theoretical logical relation is required because, in practice, indications can change.
2) after linkage, acceptance of an indication for a medication only if the frequency of the indication exceeds a certain minimum

Preliminary results show that both methods reduce the percentage unsolvable linkages significantly (method 1: ATC-group J to 16%, ATC-group C to 19%, method 2; ATC-group J to 10%, ATC-group C to 38%) and can be used in the linkage process.

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The field of medical and pharmaceutical sciences can be divided into many subdisciplines which are more or less related amongst each other. The resulting scientific literature of these subdisciplines has strong intra-subdisciplinary connections, but weak inter-subdisciplinary connections. This means that knowledge from the one subdiscipline is not always connected in the scientific research of another subdiscipline. This situation can be illustrated with the following example: An antiepileptic drug is known to cause hypotension as an ADR. This knowledge is of potential interest for researchers developing an antihypertensive drug. However, at this moment there is no structural methodology to connect knowledge from one discipline to another. In this study we intend to contribute to innovation in the medical sciences by offering a theoretical model and the computational tools that provide a way to obtain new hypotheses from existing literature, by connecting knowledge from the different subdisciplines.

We have chosen ADRs as a starting point for the analysis. ADRs are knowledge about aspects of a drug which are considered to be unwanted or dangerous. Furthermore this knowledge is context-dependent. A pharmacological ADR can only be described in combination with the drug and the indication. We think that this knowledge, connected to another context, can be a very useful trigger for innovative research.

Our case study is the angiotensin-converting enzyme inhibitors. One of the ADRs observed in the early years of Captopril, was proteinuria. Recently diabetic nephropathy has become an indication for Captopril. The strength of innovations is of main interest for researchers developing new drugs. The recent development of the new indication through qualitative analysis of literature from the period 1978 to 1984. The results show that a connection between Captopril and diabetic nephropathy can actively be made, in which proteinuria serves as the connecting link.

We use this test case for further exploration and refinement of an automatic literature-based drug discovery system. The system can be used as a contributing tool in the process of drug innovation.

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HYPOGLYCAEMIA ASSOCIATED WITH THE USE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS

The use of angiotensin converting enzyme inhibitors has been associated with an increased insulin sensitivity in diabetic patients. Although such an effect could be of benefit when treating hypertension or congestive heart failure in diabetic patients, several reports underly the hypothesis that this mechanism might be responsible for precipitating severe hypoglycaemia. To test this hypothesis we performed a nested case-control study - using data of the Dutch PHARMO system (1986-1992) - among diabetic patients treated with either insulin or oral antidiabetics with hospitalisation for hypoglycaemia as the major outcome. Adjusted for a wide range of potentially confounding factors, hypoglycaemia was significantly associated with current use of ACE-inhibitors (OR: 2.8, 95% CI 1.4-5.7). Both among users of insulin and users of oral antidiabetics, the use of ACE-inhibitors was significantly associated with an increased risk for hospitalisation for hypoglycaemia (OR: 2.8, 95% CI 1.2-6.4 and OR: 4.1, 95% CI 1.4-12.2 respectively).

Although ACE-inhibitors have several advantages over other antihypertensives among diabetic patients, the risk of developing hypoglycaemia should be considered. Further elaboration of the mechanism is needed as up to 13.8% of all hospitalisations for hypoglycaemia might be attributed to the use of ACE-inhibitors.

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DETERMINANTS OF SUMATRIPTAN-INDUCED CHEST PAIN

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Background: There are several reports on serious cardiac adverse reactions including myocardial infarction attributed to the anti-migraine drug sumatriptan. Chest pain is considered to be a relatively common adverse reaction to sumatriptan. We examined risk factors for chest pain following use of sumatriptan.

Design: Cohort study among sumatriptan users.

Patients and methods: The study is a part of a national cohort study on adverse reactions to sumatriptan, performed with assistance of drug dispensing general practitioners in The Netherlands. In part of this study, all participating general practitioners had at least one patient with chest pain attributed to sumatriptan. 94% of the consumers of sumatriptan were visited at home for validation of the questionnaires, physical examination and collection of blood samples. "Cases" were defined as consumers of sumatriptan who reported chest pain attributed to intake of sumatriptan. They were compared to consumers of sumatriptan with the same general practitioner, who did not report any type of chest pain or pressure after use of sumatriptan.

Results: The participating drug dispensing general practitioners in this part of the study, had dispensed sumatriptan to a total of 420 patients. Of these patients, 372 (88%) responded to the questionnaires, of which 358 had indeed used sumatriptan. A total of 137 "cases" were identified. After multivariate analysis, low age, hypertension, general complaints of abdominal pain, and a family history of myocardial infarction were associated with an increased risk of chest pain attributed to sumatriptan.

Conclusions: Several determinants of chest pain attributed to sumatriptan were observed. The results may have consequences for both prescribing and understanding of the possible mechanism of this adverse reaction.

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BENZODIAZEPINES AND THE RISK OF FALLING LEADING TO FEMUR FRACTURES: DOSAGE MORE IMPORTANT THAN ELIMINATION HALF-LIFE

RMC Herij1, BHC Stricker2, A de Boer3, A Bakker4, E Sturman2

Background: The past decade the use of benzodiazepines has been identified as a major independent risk factor for accidental falls. We studied the role of dosage, timing, elimination half-life and type of benzodiazepine in relation to the occurrence of accidental falls leading to hospitalisation for femur fractures.

Methods: A 1.5-year, sex and pharmacy-matched case-control study was performed using data from the Dutch PHARMO system (N=300,000). Cases included 493 patients (55%), newly admitted for a femur fracture resulting from an accidental fall (1986-1992).

Relative risk estimates were calculated using conditional logistic regression analyses to control for the potential confounding effects of concomitant drug use and presence of a wide range of underlying disorders.

Results: Falls were significantly associated with current use of benzodiazepines (OR=1.6, 95%CI: 1.2-2.1) and in particular with short half-life benzodiazepines (OR=1.5, 95%CI: 1.1-2.0), sudden dose increases (OR=3.4, 95%CI: 1.0-11.5) and concomitant use of several benzodiazepines (OR=2.5, 95%CI: 1.3-4.9). A strong dose-response relationship (p<0.0001) and dose-response patterns among users of either short- or long half-life benzodiazepines, suggest that these increased risks are explained primarily by dose.

Conclusions: Benzodiazepines are a major, independent risk factors for falls leading to femur fracture and that the increased risk is probably explained by prescribing too high doses to the elderly.

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DIURETIC MISUSE AND COMPLICATIONS OF CONGESTIVE HEART FAILURE

Elbert R. Heerdink MD, Hubert G. Lutfiyan PhD, Bruno HC Stricker PhD, E. Gribnau MD, John UG Koitl MD

Introduction: We sought to determine whether poor patient compliance plays an appreciable role in recurrent hospitalisations for congestive heart failure. We used the PHARMO system that links community pharmacy dispensing records to hospital admission and discharge data of 300,000 people.

Methods: A case-control study was employed to assess whether evidence for poor compliance is a risk factor for recurrent hospitalisation for complications of CHF. We compared 174 patients with multiple admissions for CHF with matched controls with only one hospital admission.

Results: After adjustment for confounders, we found an increased risk for a second hospitalisation for CHF in patients with lack of refill of their loop diuretic therapy (OR [Cl95%]: 2.0 [1.1-3.8]). We also found an increased risk in patients with a recent dosage change of loop diuretic therapy, both in lowered dosage (OR [Cl95%]: 2.6 [1.2-5.7]) and a increased dosage (OR [Cl95%]: 3.0 [1.6-5.8]).

Conclusions: The two-fold risk we found may be an underestimation of the actual risk, because intervals between prescription refills cannot reveal occasional 'drug holidays' that, though they represent the omission of only a small percentage of prescribed doses, can still lead to acute fluid retention.

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DISCONTINUATION OF DIURETIC THERAPY IN GERIATRIC PATIENTS

D.J.W. van Knaap, E. Brujinke, W. M.M. Jansen, F.W.J. Gribnau, W.H.L. Houttagels

Introduction: Approximately 25-40% of the elderly aged 65 and older uses diuretics. This use increases further with age and is mostly longterm. Adverse effects of diuretics in the elderly in particular include electrolyte disorders, dehydration, hypotensive episodes and incontinence. Small controlled studies suggest that discontinuation of diuretic therapy in the elderly is often possible.

Aim of study: To determine the frequency of discontinuation of diuretic therapy and its determinants in geriatric patients.

Methods: We retrospectively collected data on demographics, history, physical examination, diagnoses, and medications in all patients aged 75 years and older, seen at two geriatric departments (GAUZ, Nijmegen and GAAZ, Arnhem) in the years 1990 through 1993. Indications for diuretic use and reasons for discontinuation were recorded.

Results: The records of 1547 patients (459 men and 1088 women, median age 82 (range 75-102), were studied. 593 Patients (38%) were using diuretics. In 210 of these 593 diuretic therapy was discontinued (33%), in another 34 cases advised to stop was given. Resumption of diuretic therapy was reported in 48 of 210 stoppers (23%). Discontinuation was more often performed in inpatients (57% vs 19%) and at the GAAZ (40% vs 24%). Diuretics for unknown indications or hypostatic edema were discontinued more often than diuretics for heart failure or hypertension (48% and 41% vs 20% and 33%). Reasons for discontinuation were doubts on the indication (45%) and adverse effects (43%).

Conclusion: Diuretic treatment was discontinued in 35% of this population of geriatric patients. Diuretic treatment was not only discontinued if prescribed for unknown reasons or unspecified edema but also in 29% of patients with heart failure and 33% of patients with hypertension. Doubts on indication and adverse effects were the main reasons for discontinuation.

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DRUG-DRUG INTERACTIONS IN MULTIPLE DRUG USERS--AGE IS NOT A RISK-FACTOR

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Introduction: Interactions between drugs are a major source for complications in multiple drug users. The objective of this study is to provide prevalences of drug-drug interactions in patients with multiple drug use. Possible risk factors associated with the occurrence of drug-drug interactions will be studied, including age as a possible independent factor.

Methods: Point prevalence of clinically important, potential drug-drug interactions were estimated in 4,737 patients using 4 or more drugs from different therapeutical categories. Patients with drug-drug interactions were compared to patients with no drug-drug interactions in a case-control design and possible risk factors were identified.

Results: An overall of 17.3% of all patients showed one or more drug-drug interactions. After adjustment for the number of prescriptions and the number of different drug groups, no increased risk in higher age groups could be found. Interactions with cardiovascular drugs were most often seen.

Conclusions: Patients, using drugs from multiple therapeutical categories, and showing cardiovascular disease have been shown to be at the highest risk for potential drug-drug interactions. Patients fitting this profile should be the prime target for reassessment of their medication.

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GENDER-DIFFERENCES IN SELF-REPORTED ANTIHYPERTENSIVE DRUG USE IN THE NETHERLANDS.

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Introduction: The Monitoring project on cardiovascular disease risk factors in The Netherlands has been carried out from 1987 to 1991 and examined over 36,000 men and women aged 20-59 years. In this project blood pressure, serum lipid levels, weight and height were assessed and calculated (3-point scale, with higher score indicating more unstable therapy pattern) from their prescription drug history.

Methods: Antihypertensive drug use was assessed by self-report of 546 hypertensive patients in 1994. But the same debate is going on in the UK. In this context it is important to know how GPs actually treated depression and prescribed antidepressives before the publication of the standard. Further developments can then be assessed in relation to such "pre-standard" patterns. This question is approached by looking at 1. the treatment of depression; 2. the indications that are being used for antidepressives; and 3. the difference in indication for 'modern' antidepressives (SSRIs) and classical antidepressives (tricyclic agents).

Methods: Data are taken from a continuous registration network of 3 general practices with 12 GPs in the North of the Netherlands covering approximately 20000 patients; episodes of morbidity as well as indication (ICPC code) and medication (ATC-code) are being registered for every practice-patient contact (including tel and contacts with practice assistants). The data concern 1993.

Results: In total 286 patients with depression were identified, of whom 125 (44%) received an antidepressive (AD) at least once in 1993. In addition 279 patients received an AD for other indications. Of the 404 patients receiving an AD 125 (31%) did so for depression. Other indications were anxiety (19%) and other psychological problems and 21% for chronic pain. Overall 62% of the AD users received a classical AD. A wide variation was found between practices regarding all indications than depression for some time, mainly so the so-called 'classical' ADs. The SSRI's were in 1993 still primarily for the treatment of depression, although the latter being used more often for chronic pain as well as other psychological problems. The results suggest a difference in treatment policy between the practices. One practice combining a relatively high use of AD for depressive patients with a relatively high use of AD for other indications, in particular so in case of the classical AD.

Conclusion: The results suggest that AD's have been used widely for other indications than depression for sometime, mainly so the so-called 'classical' ADs. The SSRIs were in 1993 still primarily for the treatment of depression, although the first signs of a broadening indication were found also here. In view of these results the use of AD in pharmacoepidemiological studies as an indicator of depression (as has been done in earlier studies) is not possible.