

## Geriatrics

### Drug–Drug Interactions in the Elderly

Ingeborg K Björkman, Johan Fastbom, Ingrid K Schmidt, Cecilia B Bernsten, and the Pharmaceutical Care of the Elderly in Europe Research (PEER) Group<sup>a</sup>

**OBJECTIVE:** To detect the frequency of potential drug–drug interactions (DDIs) in an outpatient group of elderly people in 6 European countries, as well as to describe differences among countries.

**DATA SOURCES AND METHODS:** Drug use data were collected from 1601 elderly persons living in 6 European countries. The study population participated in a controlled intervention study over 18 months investigating the impact of pharmaceutical care. Potential DDIs were studied using a computerized detection program.

**RESULTS:** The elderly population used on average 7.0 drugs per person; 46% had at least 1 drug combination possibly leading to a DDI. On average, there were 0.83 potential DDIs per person. Almost 10% of the potential DDIs were classified to be avoided according to the Swedish interaction classification system, but nearly one-third of them were to be avoided only for predisposed patients. The risk of subtherapeutic effect as a result of a potential DDI was as common as the risk of adverse reactions. Furthermore, we found differences in the frequency and type of potential DDIs among the countries.

**CONCLUSIONS:** Potential DDIs are common in elderly people using many drugs and are part of a normal drug regimen. Some combinations are likely to have negative effects; more attention must be focused on detecting and monitoring patients using such combinations. As differences in potential DDIs among countries were found, the reasons for this variability need to be explored in further studies.

**KEY WORDS:** drug–drug interactions, elderly.

*Ann Pharmacother* 2002;36:1675-81.

Drugs can be useful tools in the prevention and treatment of symptoms and diseases, but if not used properly, they may be harmful and cause new symptoms or produce suboptimal effects. A 1994 estimate of the costs to treat disorders caused by drug-related problems in the US was \$76.6 billion,<sup>1</sup> and a newly updated calculation using the same model showed that the estimated costs had increased to \$177.4 billion for the year 2000.<sup>2</sup> Publications describing similar studies conducted in Europe have not been found.

A number of studies<sup>3-6</sup> have demonstrated that adverse drug reactions (ADRs) are a significant cause of hospital admission. Some ADRs are caused by drug–drug interactions (DDIs). A review<sup>7</sup> from 1993 showed that up to 2.8% of hospital admissions were caused by DDIs. A study<sup>8</sup> conducted in Australia demonstrated that 4.4% of the drug-related admissions were due to DDIs and, in a study<sup>9</sup> carried out in the US, DDIs caused 4.6% of adverse drug events (ADEs) during hospitalization.

Most DDI studies examine the prevalence of potential DDIs in patients in emergency departments or on hospital wards. Since our article examines DDIs in outpatients, we searched for this kind of information in the literature, but only found a few relevant publications. Two studies from the US<sup>10,11</sup> and 1 from Sweden<sup>12</sup> found that 25–27% of the patients had drug combinations that could lead to moderate or major changes in therapeutic outcome. The US studies involved 400 and 100 patients, respectively, all of whom

Author information provided at the end of the text.

<sup>a</sup>See page 1680.

This study was supported by the National Corporation of Swedish Pharmacies (Apoteket AB). The PEER group was supported by the European Commission, under the BIOMED 2 program for medical research, and each country also had national contributors.

were  $\geq 60$  years old and visiting a family outpatient clinic or family practice. The Swedish study included 5125 outpatients. The majority of the patients were old, and all were in a specific drug-dispensing program. In Odense, Denmark, 4.4% of 26 337 patients aged  $\geq 70$  years old had at least 1 of 45 selected DDIs generally accepted as carrying a risk of serious drug reactions.<sup>13</sup> Two recent studies from Sweden found potential DDIs in 8–9% of all outpatients purchasing  $\geq 2$  prescribed drugs on 1 occasion during 1 month. One trial included patients 15–95 years old,<sup>14</sup> and the other studied patients from birth to 106 years of age.<sup>15</sup>

The primary goal of this article is to describe the prevalence and type of potential DDIs in a group of elderly people in 6 European countries, as well as to describe differences between countries.

## Methods

### PATIENTS AND DATA SOURCES

All patient data were obtained from a European controlled, longitudinal multicenter study on pharmaceutical care involving elderly people at community pharmacies. Participating countries were Denmark, Germany, the Netherlands, Northern Ireland, Portugal, the Republic of Ireland, and Sweden. The European Commission supported the coordination of the study (BIOMED 2 program). Ethical approvals were obtained in each country according to local practice. Detailed information about the study has been presented elsewhere.<sup>16</sup>

Patients were randomly invited to participate in the study. For inclusion, they had to be  $\geq 65$  years old, use  $\geq 4$  prescribed drugs, and live at home, taking care of themselves. In most of the countries, the recruitment was done by screening drug records in the pharmacy. In Sweden, where no drug records are available in the pharmacies, the patients were instead recruited from the general practitioners' records.

### COLLECTING DATA

The drug lists used in this analysis were created during interviews in the pharmacy when the patients were recruited. The lists reflect the drugs that patients reported they were using at the time of the interview. All drugs were classified using the Anatomical Therapeutic Chemical (ATC)-code system recommended by the World Health Organization (WHO)-Europe.<sup>17</sup>

### CLASSIFICATION OF DDIs IN SWEDEN

In Sweden, a classification system for potential DDIs has been available since the mid-1990s. The system is based on ATC codes and is described in the yearly publication *Pharmaceutical Specialities in Sweden* (FASS).<sup>18</sup> The classification is done at the Department of Pharmacology at Huddinge Hospital, Stockholm. All classifications are based on published data and documentation from drug companies.

The potential DDIs are classified in categories A, B, C, or D according to clinical relevance.<sup>a</sup> DDI categories A and B are of minor importance, whereas categories C (C-DDIs) and D (D-DDIs) are considered to be clinically significant.<sup>b</sup>

<sup>a</sup>If a drug is not classified in this system, it does not mean that it has no interactions, but that it has no published documentation on interactions. All DDIs are potential; they may, but do not necessarily, cause a therapeutic change.

<sup>b</sup>Potential DDI in category A indicates a documented interaction of no clinical importance. Category B indicates that the effect of the interaction has not yet been established. DDIs designated category C have documentation of possible changes in therapeutic effect or adverse effects, but this could be overcome by individual dosage adjustments. DDIs placed in category D have documented severe adverse effects or absence of therapeutic effects, or individual dosage adjustments of the drugs are difficult and are thus recommended to be avoided.

## ANALYZING DATA

All drug data were coded using ATC codes and entered in the statistical computer program, SPSS for Windows. The analysis was performed on patients from 6 of the participating countries, as drug data from the Netherlands were not available in this format.

Potential interactions were analyzed in a computerized program (constructed by Johan Fastbom), using the classification in FASS.<sup>18</sup> C-DDIs and D-DDIs were analyzed. ANOVA analysis was performed to test for differences among countries.

## CLASSIFICATIONS OF DDIs IN THE OTHER COUNTRIES

We decided to use the same computer program for detection and classification of potential DDIs for the whole group of patients. Some of the drug combinations used in the other European countries were not classified in the FASS system since they contained drugs that were not registered in Sweden. To minimize this problem, unregistered drugs were, if possible, replaced by an appropriate drug registered in Sweden. The author did this by studying the literature<sup>19</sup> and consulting 2 independent clinical pharmacologists.

The unregistered drug was reclassified to a substance included in the Swedish system if the substance had the same DDI profile as the Swedish drug according to available documentation or if group-specific DDI effects were documented. If neither of these criteria was fulfilled, the substance was not reclassified and was thus not included in the analysis.<sup>c</sup>

## Results

In the 6 European countries, 1601 patients with complete drug lists were recruited. Details are presented in Table 1.

Initially, 416 ATC codes could not be analyzed in the computer program. These codes corresponded to 1669 (15%) of the drugs used. After reclassification, as described above, 246 different ATC codes remained that were unable to be analyzed, corresponding to 789 (7%) of the drugs used. Approximately 100 of these ATC codes involved drugs with no DDIs, for example, dermatologic preparations (29 ATC codes), ophthalmologic agents (22 ATC codes), vasoprotective agents (17 ATC codes), and vitamins (8 ATC codes). The average number of drugs per patient that were not analyzed was 0.04 in Sweden, 0.2 in Denmark, 0.4 in the Republic of Ireland, 0.6 in Northern Ireland, and 1.2 in Germany and Portugal.

## PREVALENCE OF POTENTIAL DDIs

The 1601 patients used 11 180 prescribed drugs in 38 533 drug combinations, averaging 24 combinations per person.<sup>d</sup> Among these combinations, we found 1324 potential DDIs corresponding to 0.83 DDIs per person.

Forty-six percent of the patients had  $\geq 1$  potential DDIs, and  $\geq 2$  potential DDIs were identified in 22% of the patients. As shown in Table 2, potential DDIs were more

<sup>c</sup>For instance, acetyldigoxin (C01AA02) was changed to digoxin (C01AA05); phenprocoumon (B01AA04) to dicoumarol (B01AA01), low-ceiling diuretics (C03EAXx) to hydrochlorothiazide (C03EA01), and selective  $\beta$ -blocking agents (C07ABxx) were substituted with atenolol (C07AB03).

<sup>d</sup>The number of drug combinations was calculated as the binomial coefficient of the number of drugs; for example, if a patient uses 7 drugs, the number of combinations would be  $6+5+4+3+2+1 = 21$ .

common in the Republic of Ireland and Germany and less common in Northern Ireland and Portugal.

### POTENTIAL DDIs AND THEIR POSSIBLE EFFECTS

A total of 1324 potential DDIs were found. Among C-DDIs, 549 could increase the risk of ADRs and 639 could lower the therapeutic effect. In D-DDIs, most of the combinations increased the risk of adverse drug reactions. In all potential DDIs, 50% of the combinations could result in an adverse drug reaction and 50% in a suboptimal therapeutic effect. The most common combinations are presented in Tables 3 (C-DDIs) and 4 (D-DDIs). When appropriate, drugs are grouped according to therapeutic effect and/or chemical structure.

### DDIs THAT MIGHT REQUIRE DOSE ADJUSTMENTS

Approximately 90% of the potential DDIs were combinations that could be handled by dose adjustments (C-

DDIs). Cardiovascular drugs were commonly involved, with many of the combinations part of a normal drug regimen (Table 3). Five therapeutic groups accounted for 88% of all C-interactions: diuretics were involved in 46%, angiotensin-converting enzyme (ACE) inhibitors in 37%, digitalis glycosides in 27%, nonsteroidal antiinflammatory drugs (NSAIDs) or high-dose acetylsalicylic acid in 26%, and  $\beta$ -blocking agents in 11%.

A total of 108 unusual potential C-DDIs were found (defined here as a potential interaction occurring in <10 pts.). Examples of unusual but important possible C-DDI combinations are amiodarone/metoprolol (risk of severe bradycardia), diltiazem/carbamazepine (risk of carbamazepine intoxication), and NSAID/lithium (lithium excretion decreased).

### DDIs THAT SHOULD BE AVOIDED

Almost 10% of the potential DDIs were classified as combinations to be avoided (D-DDIs) (Table 4). The most common D-DDI occurred with concomitant ipratropium bromide and  $\beta_2$ -agonists, a combination that is important to avoid in the few patients predisposed for angle-closure glaucoma. This combination represented 29% of the D-DDIs. The second most common D-DDI was potassium combined with potassium-sparing agents in 18% of the interactions, and antithrombotic agents (i.e., warfarin, dicoumarol, or ticlopidine) combined with NSAIDs or acetylsalicylic acid, also in 18%. Pooling all combinations affecting antithrombotic agents, these combinations represent 22% of all D-DDIs.

### DIFFERENCES AMONG COUNTRIES

The distribution of C-DDIs in the 6 countries was as follows: Denmark 351 (523 pts.), Germany 291 (291), Northern Ireland 112 (189), Sweden 244 (334), Portugal 79 (137), and the Republic of Ireland 118 (127). The 10 most common combinations represented >82% of all potential C-DDIs in Denmark, Germany, Sweden, and the Republic of Ireland; this proportion was lower in Portugal (76%) and in Northern Ireland (67%). In Germany, patients were more often prescribed digitalis glycosides with diuretics (23%) and verapamil (9.6%) compared with patients in the other countries. German patients were also using more drugs for diabetes combined with ACE inhibitors (occurrence comparable with that in Portugal), and ACE inhibitors with an NSAID or high-dose acetylsalicylic acid.

Patients in all of the countries used drugs that had potential interactions with antithrombotic agents. This finding was most common in the Republic of Ireland (7.1% of pts.), followed by Portugal (2.9%), Sweden (1.8%), Northern Ireland (1.1%), Germany (1.0%), and Denmark (0.8%).

**Table 1.** Demographics on Study Patients in the Six Countries

Country	Patients (n)	Age (y) mean $\pm$ SD	% of Women	Drugs (n) mean $\pm$ SD <sup>a</sup>
Denmark	523	74 $\pm$ 6	57	6.8 $\pm$ 2.3
Germany	291	74 $\pm$ 6	60	7.5 $\pm$ 2.7
Northern Ireland	189	74 $\pm$ 6	62	6.2 $\pm$ 2.0
Portugal	137	73 $\pm$ 6	50	6.5 $\pm$ 2.0
Republic of Ireland	127	75 $\pm$ 6	54	6.6 $\pm$ 2.2
Sweden	334	76 $\pm$ 6	62	7.6 $\pm$ 2.9
Total	1601	74.7 $\pm$ 6	58	7.0 $\pm$ 2.5

<sup>a</sup>ANOVA used. Differences among countries concerning average number of drugs used:

Denmark, Northern Ireland, and Portugal differ from Germany and Sweden.

Germany differs from Denmark, Northern Ireland, and Portugal.

Republic of Ireland differs only from Sweden.

Sweden differs from all countries except Germany.

**Table 2.** Occurrences of Potential DDIs

Country	Patients (n)	Number of DDIs		Patients with	
		DDI/Patient <sup>a</sup>	Range	$\geq 1$ DDIs (%)	$\geq 2$ DDIs (%)
Denmark	523	0.75	0–9	43	19
Germany	291	1.04	0–8	51	28
Northern Ireland	189	0.67	0–6	39	17
Portugal	137	0.62	0–4	43	13
Republic of Ireland	127	1.05	0–5	57	29
Sweden	334	0.84	0–6	47	24
Total	1601	0.83	0–9	46	22

DDIs = drug–drug interactions.

ANOVA used. Differences among countries concerning average frequency of potential DDIs:

Denmark and Northern Ireland differ from Germany.

Germany differs from Denmark, Northern Ireland, and Portugal.

Republic of Ireland differs only from Portugal.

Portugal differs from Germany and Republic of Ireland.

Sweden does not differ from any country.

## Discussion

This is the first study investigating the frequency of potential DDIs in an elderly outpatient population in 6 European countries. The results of the study demonstrate that potential DDIs are common in elderly patients using many drugs, and that approximately half of the potential DDIs could result in ADRs and the remaining half in reduced therapeutic effects.

### FREQUENCY OF POTENTIAL DDIs

Almost half of the patients had experienced at least 1 potential DDI; this is a higher prevalence than in other outpatient studies we identified in the literature.<sup>10-15</sup> This finding is not surprising, as our DDI classification system includes some commonly used recommended combinations. Also, our patients used more drugs on average than patients in the other studies, and it has been shown<sup>20</sup> that the number of DDIs correlates with the number of combinations of drugs used. In a Danish study,<sup>13</sup> 45 drug combinations with known high risk were detected in elderly patients using  $\geq 2$  drugs. In that investigation, 4.4% of the patients had  $\geq 1$  of these selected combinations. We tested the Danish method and found DDIs in 13% of our patients. As half of their patients were taking 2 or 3 drugs and all of our patients were taking  $\geq 4$  drugs, these results seem to be comparable. Two recent studies<sup>14,15</sup> from Sweden used the same computer-based program to detect DDIs as we did. Both were using data from the Swedish Health Care Database on Pharmaceutical Agents. This database gives information on drugs dispensed in the pharmacy to 1 person, prescribed by 1 physician, and purchased on 1 occasion. Investigators in those trials found potential DDIs in 8–9% of the population. However, they were not focusing on elderly people and, furthermore, we assessed all drugs that patients were using and not only what they purchased on 1 occasion.

### DIFFERENCES AMONG COUNTRIES

Notable differences in both frequency and type of interactions among the 6 participating countries were found. The numbers of potential DDIs were highest among patients in Germany and the Republic of Ireland (~1 per pt.) and lowest among patients in Portugal and Northern Ireland (~0.6 per pt.).

Potential DDIs involving digitalis glycosides were much more common in Germany than in other countries. Furthermore, potassium chloride combined with potassium-sparing agents was found among patients in Denmark (17), Germany (only 1), and Sweden (5), but not among patients in the other countries. The combination of ipratropium bromide and  $\beta_2$ -agonists was fairly common in Sweden, while this combination was not found in Germany. Such differences are likely to reflect different therapy traditions as well as different policies regarding, for example, the use and implementation of clinical guidelines among the European countries. These findings call for future research in this area.

### CLINICAL CONSEQUENCES

Studies investigating potential DDIs in patients often analyze combinations leading to ADRs and, less frequently, combinations potentially leading to lowered therapeutic effects.<sup>21</sup> In our study, it was interesting to note that risks of subtherapeutic effects were as common as risks of ADRs. This means that some of the elderly people might have used drugs that provided insufficient or no effect.

All DDIs we detected could require precautions according to the classification system; almost 10% were to be avoided (D-DDIs). However, the most common possible D-DDI was a combination that is recommended in the treatment of chronic obstructive pulmonary disease — inhaled ipratropium bromide combined with  $\beta_2$ -agonists. This combination was also the most common possible D-

**Table 3.** The Ten Most Common Combinations that Might Need Dose Adjustment (C-DDIs)<sup>a</sup>

Most Common C-DDIs	Total (n = 1601) %	Denmark (n = 523) %	Germany (n = 291) %	Northern Ireland (n = 189) %	Portugal (n = 137) %	Republic of Ireland (n = 127) %	Sweden (n = 334) %
Digitalis glycosides/diuretics	13.6	13.8	23.4	7.4	9.5	13.4	10.2
Diuretics/NSAIDs	9.6	9.9	5.8	6.9	5.8	14.2	13.8
Furosemide/ACE inhibitors	9.4	10.1	10.0	6.3	3.6	14.2	9.9
ACE inhibitors/low-dose ASA	7.0	4.2	4.8	9.5	5.8	15.0	9.3
Drugs used in diabetes/ACE inhibitors	6.1	2.9	16.5	0.5	12.4	3.9	3.3
ACE inhibitors/NSAIDs or high-dose ASA	5.0	5.2	15.1	0	5.1	0.8	0.3
$\beta$ -blocking agents/NSAIDs	4.3	3.8	1.4	4.2	1.5	7.1	7.8
Digitalis glycosides/verapamil	3.1	2.3	9.6	0.5	0	0.8	2.4
Diuretics/sotalol	1.7	2.3	0	0.5	0	3.1	3.0
Codeine, combinations/antidepressants	1.6	1.5	0.3	3.7	0	3.9	1.2

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; DDI = drug–drug interaction; NSAID = nonsteroidal antiinflammatory drug.  
<sup>a</sup>Figures represent the percentage of patients using the specific drug combination.

DDI in the 2 Swedish studies<sup>14,15</sup> using the same classification system. In persons predisposed to angle-closure glaucoma, this combination must be avoided, but such patients are few. The second and third most common combinations were antithrombotic agents combined with NSAIDs or acetylsalicylic acid, and potassium chloride combined with potassium-sparing agents. Some combinations (e.g., low-dose acetylsalicylic acid and warfarin or potassium chloride and amiloride) are sometimes used with success in individual patients. However, these patients need careful monitoring since these combinations always are a risk and fatal events have occurred.

Most of the potential DDIs could be overcome by dose adjustments (C-DDIs). These drug combinations present no negative effects to patients if the clinical effects are evaluated regularly and dosages adjusted if needed. Evaluation must be done when important changes in a drug regimen have been made; for example, introducing new drugs or changing dosages. There are also reasons for reevaluating drug therapy in elderly patients, as physical changes could alter the pharmacokinetic disposition of drugs.

Since many of the combinations identified as potential DDIs are well known and also are recommended in clinical therapy, one can question whether they should be included in the classification system of interactions. Obviously, a different classification system would dramatically change our results. The number of potential DDIs in our study decreases by almost 50% if 5 recommended, commonly used combinations are removed from the list (ipratropium bromide with  $\beta_2$ -agonists, digitalis glycosides with diuretics, ACE inhibitors with furosemide, ACE inhibitors with low-dose as-

pirin, ACE inhibitors with drugs used in diabetes). However, it is important to increase awareness and knowledge regarding the possible clinical consequences of drug combinations classified as potential C-DDIs. Thus, this system supports the effort toward optimizing drug therapy and points to the importance of careful monitoring even when recommended drug combinations are used. A French study<sup>22</sup> showed that hospital admissions related to combinations comparable to C-DDIs were as common as admissions related to combinations comparable to D-DDIs. This could mean that, although C-DDIs seldom lead to significant clinical changes for the individual patient, they may result in problems of the same magnitude as D-DDIs since so many patients use these combinations. The same study also found that the frequency of potential DDIs correlated with the frequency of ADRs.

Unusual potential DDIs probably are more difficult for clinicians to keep in mind. However, in our study, most of these unusual combinations included known metabolic inducers or inhibitors (e.g., cimetidine, erythromycin, phenobarbitone) or drugs known to have narrow therapeutic indices (e.g., theophylline, lithium, warfarin). Since the effects of these DDIs are commonly known, it is more likely that physicians did make proper dose adjustments while prescribing these combinations; another possibility is that such combinations already had been noted and addressed by pharmacists.

#### STUDY LIMITATIONS

Our study has limitations. First, as discussed above, the classification system includes well-known and recom-

**Table 4.** Combinations Recommended to Be Avoided (D-DDIs)<sup>a</sup>

Most Common D-DDIs	Total n	Denmark n (%)	Germany n (%)	Northern Ireland n (%)	Portugal n (%)	Republic of Ireland n (%)	Sweden n (%)
Ipratropium bromide/selective $\beta_2$ -adrenoreceptor agonists	37	10 (1.9)	0	3 (1.6)	1 (0.7)	5 (3.9)	18 (5.4)
Potassium chloride/potassium-sparing agents	23	17 (3.2)	1 (0.3)	0	0	0	5 (1.5)
Antithrombotic agents <sup>b</sup> /high-dose ASA or NSAID	15	3 (0.6)	3 (1.0)	0	4 (2.9)	0	5 (1.5)
Antithrombotic agents <sup>b</sup> /low-dose ASA	8	1 (0.2)	0	1 (0.5)	0	5 (3.9)	1 (0.3)
Antithrombotic agents <sup>b</sup> /propafenone, amiodarone, or cimetidine	5	0	0	1 (0.5)	0	4 (3.2)	0
Codeine, combinations/antipsychotics	13	2 (0.4)	1 (0.3)	8 (4.2)	0	0	2 (0.6)
Methotrexate/ASA or NSAID	6	4 (0.8)	0	0	0	0	2 (0.6)
Verapamil/ $\beta$ -blocking agents	4	1 (0.2)	2 (0.7)	0	0	0	1 (0.3)
Verapamil/ $\beta$ -blocking agents (eye drops)	4	1 (0.2)	0	0	1 (0.7)	0	2 (0.6)
Various combinations <sup>c</sup>	14	3	5	1	0	1	4
TOTAL D-DDIs	129	42	12	14	6	15	40

ASA = acetylsalicylic acid; DDI = drug–drug interaction; NSAID = nonsteroidal antiinflammatory drug.

<sup>a</sup>Figures show actual numbers and percentages (within brackets) of patients having the specific combination.

<sup>b</sup>Warfarin, dicoumarol, ticlopidine.

<sup>c</sup>ASA with acetazolamide (3 cases), antacids or quinapril with tetracyclines or norfloxacin (3 cases), antacids with ursodeoxycholic acid (2 cases), cimetidine with theophylline (2 cases), dextropropoxyphen with alprazolam (2 cases), cimetidine with metformin (1 case), and propafenone with metoprolol (1 case).

mended therapeutic combinations that are often used in a population such as ours, that is, elderly people with hypertension and cardiac disorders. Thus, our incidence values of DDIs are expected to be high. Second, as some drugs used outside Sweden were not detected by our computer program and since the number of drugs strongly affects the number of interactions, the values from the other countries could have been underestimated. Third, in some of the countries, the study population was rather small, especially in Portugal and the Republic of Ireland; subsequently, the results from these countries are more uncertain.

## Summary

Drug combinations possibly leading to interactions are common in an elderly population using many drugs. A large proportion of these combinations is likely to be part of a normal drug regimen. However, some of the combinations are likely to have negative effects, and more attention must be focused on detecting and monitoring patients using such combinations.

Differences in potential DDIs among countries were found. The reasons for this variability need to be explored in further studies.

**Ingeborg K Björkman** MScPharm, Pharmacist, Apoteket AB (Swedish National Corporation of Pharmacies), Stockholm; PhD Student, Department of Public Health and Caring Sciences, Uppsala, Sweden

**Johan Fastbom** MD PhD, Associate Professor, Neurotec, Doge, Karolinska Institutet and Stockholm Gerontology Research Center, Stockholm

**Ingrid K Schmidt** PhD, Senior Analyst, The National Board of Health and Welfare, Stockholm

**Cecilia B Bernsten** PhD, Department Director, The National Board of Health and Welfare, Stockholm; Associate Professor, Department of Public Health and Caring Sciences, Uppsala, Sweden

### The PEER group:

**Cecilia B Bernsten** PhD, The National Board of Health and Welfare, Stockholm, Associate Professor, Department of Public Health and Caring Sciences, Uppsala, Sweden

**Ingeborg K Björkman** MScPharm, Apoteket AB (Swedish National Corporation of Pharmacies), Stockholm

**Margarida Caramona** PhD, Faculdade de Farmacia, Laboratorio de Farmacologia, University of Coimbra, Coimbra, Portugal

**Grainne Crealey** PhD, Pharmacy Practice Research Group, The School of Pharmacy, the Queen's University of Belfast, Medical Biology Centre, Belfast, Northern Ireland

**Bente Frøkjær** MScPharm, Pharmakon, Danish College of Pharmacy Practice, Hillerød, Denmark

**Erika Grünberger** BSc, Apoteket AB (Swedish National Corporation of Pharmacies)

**Tove Gustafsson** PhD, Pharmakon, Danish College of Pharmacy Practice

**Martin Henman** PhD, Trinity College, School of Pharmacy, Dublin, Republic of Ireland

**Hanne Herborg** MScPharm, Pharmakon, Danish College of Pharmacy Practice

**Carmel Hughes** PhD, Pharmacy Practice Research Group, The School of Pharmacy, the Queen's University of Belfast, Medical Biology Centre

**James C McElney** PhD, Pharmacy Practice Research Group, The School of Pharmacy, the Queen's University of Belfast, Medical Biology Centre

**Maeve Magner** MScPharm, Trinity College, School of Pharmacy  
**Foppe van Mil** PhD, Rijksuniversiteit Groningen, Subfaculteit Farmacie, Werkgroep Social Farmacie in Farmacoepidemiologie, Groningen, the Netherlands

**Marion Schaeffer** PhD, Humboldt University Berlin, Fachbereich Pharmazie, Berlin, Germany

**Sonia Silva** MScPharm, Faculdade de Farmacia, Laboratorio de Farmacologia, University of Coimbra

**Birthe Søndergaard** MScPharm, Pharmakon, Danish College of Pharmacy Practice

**Ian Sturgess** PhD, Pharmacy Practice Research Group, The School of Pharmacy, the Queen's University of Belfast, Medical Biology Centre

**Dick Tromp** PhD, Rijksuniversiteit Groningen, Subfaculteit Farmacie, Werkgroep Social Farmacie in Farmacoepidemiologie

**Lisa Vivero** MScPharm, Trinity College, School of Pharmacy

**Almut Winterstein** PhD, Humboldt University Berlin, Fachbereich Pharmazie

**Reprints:** Ingeborg K Björkman MScPharm, Project Coordinator, Apoteket AB, Expeditionsapoteket, Södersjukhuset, Sjukhusbacken 10, S-118 83 Stockholm, Sweden FAX + 46 8 616 1492, E-mail ingeborg.bjorkman@sos.se

We acknowledge Timothy Oké PhD for statistical support and Professor and Clinical Pharmacologist Rune Dahlqvist MD PhD for assistance in initiation of the analysis. We also thank Apoteket AB for supporting this research in Sweden, and EU-Commission (BIOMED 2) for supporting the European OMA study. Finally, thanks to all coresearchers in the PEER group and to pharmacists and patients who participated in the study.

## References

1. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. *Arch Intern Med* 1995;155:1949-56.
2. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc* 2001;41:192-9.
3. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990;150:841-5.
4. Beard K. Adverse reactions as a cause of hospital admission in the aged. *Drugs Aging* 1992;2:356-67.
5. Dartnell JG, Anderson RP, Chohan V, Galbraith KJ, Lyon ME, Nestor PJ, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. *Med J Aust* 1996;164:659-62.
6. Manneke CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing* 2000;29:35-9.
7. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Saf* 1993;9:51-9.
8. Stanton LA, Peterson GM, Rumble RH, Cooper GM, Polack AE. Drug-related admissions to an Australian hospital. *J Clin Pharm Ther* 1994;19:341-7.
9. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. *JAMA* 1997;277:301-6.
10. Kurffees JF, Dotson RL. Drug interactions in the elderly. *J Fam Pract* 1987;25:477-88.
11. Costa AJ. Potential drug interactions in an ambulatory geriatric population. *Fam Pract* 1991;8:234-6.
12. Bergendal L, Friberg A, Schaffrath AM. Potential drug-drug interactions in 5,125 mostly elderly out-patients in Gothenburg, Sweden. *Pharm World Sci* 1995;17:152-7.
13. Rosholm J-U, Bjerrum L, Hallas J, Worm J, Gram LF. Polypharmacy and the risk of drug-drug interactions among Danish elderly. *Dan Med Bull* 1998;45:210-3.
14. Merlo J, Liedholm H, Lindblad U, Björck-Linné A, Fält J, Lindberg G, et al. Prescriptions with potential drug interaction dispensed at Swedish pharmacies in January 1999: cross sectional study. *BMJ* 2001;323:427-8.
15. Läkemedel i användning – Förändringar och tendenser (Drug use — changes and trends). Stockholm, Socialstyrelsen (The National Board of Health and Welfare), 2000. Kvartalsrapport 2000:4 (Quarterly report 2000:4).
16. Bernsten C, Björkman I, Caramona M, Crealey G, Frøkjær B, Grünberger-

- er E, et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care. *Drugs Aging* 2001; 18:63-77.
17. Anatomical Therapeutic Chemical (ATC) classification index Oslo. WHO Collaborating Centre for Drug Statistics Methodology. Oslo, Norway: World Health Organization, 1997.
  18. FASS (Pharmaceutical Specialities in Sweden). Stockholm: LINFO Läkemedelsinformation AB (Drug information), 1997. Available from: URL: <http://www.fass.se> (Swedish).
  19. Stockley IH. Drug interactions. 4th ed. London: Royal Pharmaceutical Society of Great Britain, The Pharmaceutical Press, 1996.
  20. Köhler GI, Bode-Böger SM, Busse R, Hoopmann M, Welte T, Böger RH. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. *Int J Clin Pharmacol Ther* 2000;38:504-13.
  21. Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. *Drugs Aging* 1998;12:485-94.
  22. Doucet J, Chassange P, Trivalle C, Landrin I, Pauty MD, Kadri N, et al. Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients. *J Am Geriatr Soc* 1996;44:944-8.

## EXTRACTO

**OBJETIVO:** Detectar la frecuencia de las posibles interacciones entre drogas (DDIs) en un grupo de personas de edad en 6 países Europeos. Describir las diferencias entre los países.

**FUENTES DE INFORMACIÓN:** Información de utilización de drogas fue reunida de 1601 pacientes mayores viviendo en 6 países Europeos. Todos los sujetos en la población estudiada participaron en un estudio de 18 meses investigando el impacto del cuidado farmacéutico. Se evaluaron las interacciones utilizando un programa computarizada para detectar interacciones.

**RESULTADOS:** Los sujetos mayores utilizaron un promedio de 7.0 drogas por persona. Cuarenta y 6 por ciento tenían por lo menos una combinación de drogas que podía resultar en una interacción. El promedio de potenciales interacciones de drogas fue 0.83 por persona. Casi 10% de las interacciones potenciales fueron clasificados "debe evitarse," según el sistema sueco de interacciones, pero casi un tercio de éstas se encontraron sólo en pacientes predispuestos a reacciones adversas. El riesgo de efectos sub-terapéuticos, como resultado de una

interacción potencial, fue tan común como el riesgo de una reacción adversa. Además encontramos diferencias entre la frecuencia y el tipo de interacciones potenciales entre los países.

**CONCLUSIONES:** Las interacciones entre drogas son comunes en pacientes de edad usando muchas drogas. Algunas de las combinaciones pueden tener efectos negativos, y se debe prestar mas atención a la detección y monitoreo de pacientes utilizando estas combinaciones. Se encontraron diferencias en cuanto a la frecuencia y el tipo de interacciones entre los diferentes países. Estudios futuros deben evaluar las razones para esta variabilidad.

Christina Dalmady-Israel

## RÉSUMÉ

**OBJECTIF:** Déterminer la fréquence d'interactions médicamenteuses potentielles (IMP) dans un groupe de patients âgés dans 6 pays Européens et décrire les différences entre ces pays.

**SOURCE DE DONNÉES ET MÉTHODES:** L'utilisation de médicaments a été recueillie chez 1601 personnes âgées. Les sujets ont participé dans une étude de 18 mois visant à mesurer l'impact des soins pharmaceutiques. Les IMP ont été étudiées à l'aide d'un programme de détection informatisé.

**RÉSULTATS:** Les sujets consommaient en moyenne 7 médicaments. Quarante-six pour cent des sujets présentaient au moins une association pouvant mener à une IMP. En moyenne, chaque sujet présentait 0.83 IMP. Environ 10% des IMP étaient classées "à éviter" selon le système de classification suédois mais seulement le tiers d'entre elles ont été retrouvées chez des patients prédisposés. Le risque d'effet sous-thérapeutique et d'effets indésirables associés aux IMP se sont avérés de fréquence équivalente. La fréquence et le type des IMP variaient d'un pays à l'autre.

**CONCLUSIONS:** Les IMP sont communes chez les personnes âgées qui consomment plusieurs médicaments régulièrement. Certaines associations peuvent mener à des conséquences négatives et devraient recevoir davantage d'attention afin d'augmenter leur détection et d'assurer un meilleur suivi. Il existe des différences entre les IMP d'un pays à un autre et cette variabilité devrait être étudiée dans des études ultérieures.

Nicolas Paquette-Lamontagne