

## IDENTIFYING AND PREVENTING ADVERSE DRUG EVENTS IN ELDERLY HOSPITALISED PATIENTS: A RANDOMISED TRIAL OF A PROGRAM TO REDUCE ADVERSE DRUG EFFECTS

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**Abstract:** *Objectives:* Evaluate the impact of educational intervention in decreasing ADEs in elderly patients in a hospital setting. *Design:* Randomised prospective study. *Setting:* The study was performed in France in the Paris area, in 16 rehabilitation geriatric centres of APHP (Assistance Publique – Hôpitaux de Paris). Patient capacity per centre varied from 15 to 57 with a total of 526. *Participants:* All the patients  $\geq 65$  years hospitalized during the 4 week study period were included. *Measurements:* During a first 2 week phase without intervention ADE's were recorded in all centres. Then units were then randomised for an educational intervention or not. The educational phase lasted 1 week, without ADE tracking. Then, both types of units (I+ and I-) recorded ADEs for 2 weeks. Possible drug-related incidents were detected using a standardized check list (nurses) and a weekly review of all charts by investigators. Possible drug-related incidents were analysed by a group of reviewers selected from the authors to classify them as ADE or not. *Results:* 576 patients (mean age:  $83.6 \pm 7.9$  years) were consecutively included. The mean number of drugs at inclusion was  $9.4 \pm 4.24$  drugs per patient. 223 out of 755 events were considered "probable" ADEs (29.5%). Among the 223 ADEs, 62 (28%) could have been prevented. The main outcome of this trial was the change in the proportion of ADEs in elderly patients in the intervention-units, compared to the control group. The main errors were: to high a dose (26%), double therapy (21%), under dose (13%), inappropriate drug (13%), drug-drug interaction (6%), previous same adverse drug reaction (3%) and miscellaneous (11.18%). After a specific educational intervention program, there were fewer ADEs in the intervention group ( $n = 38$ , 22%) than in the control group ( $n = 63$ , 36%;  $p = 0.004$ ). *Conclusion:* Educational programs could help reduce the prevalence of ADEs by 14% and encourage physicians to change outdated prescription habits.

**Key words:** Adverse drug event, elderly, inpatients.

Elderly patients often take a variety of medications to treat multiple chronic conditions. Suboptimal prescriptions are common and problematic in this group (1, 2). First, aging causes a change in drug metabolism (pharmacokinetics) and target organ sensitivity (pharmacodynamics) (3, 4). Generally, the results of these changes in elderly patients are a longer drug activity, greater or lesser effect of the drug, and an increase in the incidence of drug toxicity. Because of these changes, the benefits of medication in elderly patients must be carefully weighed against the potential associated risks. Second, in the past decades, there has been a greater tendency to treat symptoms and increase the number of drugs prescribed to elderly patients, increasing the risk of drug interactions.

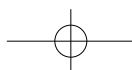
The World Health Organization (WHO) defines an adverse drug event (ADE) as a detrimental response to medication that is undesired and unintended, excluding therapeutic failure, poisoning, and intentional overdose (5).

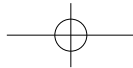
The rate of inappropriate drug use varies from 14% in community-dwelling to 40.3% in nursing home residents (6). Improvement of prescription patterns in medical practice is a

challenging task.

In practice, all providers and professionals who care for elderly adults play an important role in the process of managing medications. For example, nurses must identify potential ADEs. Drug withdrawal is sometimes necessary in elderly patients, and although their quality of life may be improved by stopping these drugs, doing it is not always easy for practitioners.

The prevalence of inappropriate prescriptions is particularly high in rehabilitation care settings, where ADEs are also frequent. The use of unnecessary, ill adapted or even contraindicated drugs is the cause of many ADEs. Admission to a rehabilitation care unit, with its consolidation of care, provides an ideal opportunity to review and improve a patient's drug regimen. It is a good structure for trial discontinuation and monitoring medications that may not be beneficial. Drugs prescribed for an acute illness may no longer be required once the condition is cured or controlled, and many drugs prescribed in the hospital can often be reduced after a few days or weeks. Drug therapy may be continued unnecessarily in patients in





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hospital if a competent senior member fails to review the prescription chart, if more than one doctor prescribes for the patient or if no one questions the duration of the prescriptions.

Evidence suggests that a thorough evaluation of diagnostic indications for drug treatment in the elderly and/or a reduction of potentially inappropriate drugs may provide significant clinical benefits. However, few data are available on what percentage of ADEs may be prevented, and which strategies may be used to prevent them (1). Our hypothesis is that an educational intervention program will be effective in decreasing ADEs in elderly patients in hospital settings.

### Methods

#### Study settings

The study was performed in France, in the Paris area, in 16 geriatric centres of the APHP (Assistance Publique – Hôpitaux de Paris). The main activity of these centres was rehabilitation care in elderly patients. Patient capacity per centre varied from 15 to 57 with a total of 526.

#### Procedures

ADEs were recorded during a first phase without intervention, including all centres and lasting 2 weeks. The units were then randomised to receive educational intervention or not. The educational phase lasted 1 week, without ADEs tracking. Then, both types of units (I+ and I-) recorded ADEs for 2 weeks. The study lasted 5 weeks in all centres (fig. 1)

The intervention included a physician and a nurse who both made oral and written recommendations to the rehabilitation care team (physicians, nurses and pharmacists) to adapt prescription habits. The control group didn't receive any recommendations about their prescription patterns in the elderly.

Possible drug-related incidents were detected with a standardized check list (nurses) and a weekly review of all charts by investigators. Nurses and residents were asked to report incidents to investigators. An investigator visited each unit on weekdays and obtained information from nurses and residents. Instructions were also given on how to complete data collection forms. The investigator reviewed all charts weekly.

To discover the causes of preventable events, the results of the investigation were analysed by a multidisciplinary team of physicians and pharmacists (CT, CV, AMM, PhD). Possible drug-related incidents were analysed by a group of reviewers selected among the authors to classify them as ADEs or not. Reviewers considered the temporal relation between drug exposure and the event, as well as whether the event reflected a known effect of the drug. For all events classified as ADEs, reviewers also determined preventability.

Cases included anyone aged 65 or older who experienced an ADE during the study period. In individuals with multiple ADEs, only the first ADE was included. When there was disagreement about the classification of an event, reviewers met and reached a consensus.

#### Educational intervention

For one week, I+ rehabilitation care teams received specific information about prescribing in the elderly, ADEs, how to prevent them and how to identify them.

The teaching staff emphasized the risks associated with several classes of medications: nonsteroid anti-inflammatory drugs, benzodiazepines, and anticholinergic medications. These are associated with adverse outcomes when taken by elderly adults and should be taken with caution. They also discussed the use of opioid medications in seniors. Although they are not without risk, opioids are generally safe with slow titration, precautions, and a bowel regimen to prevent constipation. Finally, prescribers were told to consider estimating creatinine clearance when prescribing medications that require dose adjustment due to renal insufficiency.

#### Outcome measures

All patients  $\geq 65$  years hospitalized during the period study were included. The main outcome of this trial was the change in the proportion of ADEs in elderly patients in the intervention-units compared to the control group.

#### Diagnosis of ADEs

A sign or symptom caused by one drug or a drug combination was considered a "probable" adverse effect if: (i) there was a reasonable temporal sequence from the beginning of the drug combination treatment, (ii) there was a known response pattern, (iii) the signs or symptoms were improved by discontinuation of the drugs, (iv) the signs and symptoms could not reasonably be explained by the known characteristics of the patient's clinical condition (7).

#### Preventable ADEs

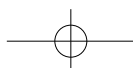
Some ADEs can be considered preventable, for example, excess doses of a drug; interfering chronic diseases that were not taken into account; and preventable drug-drug interactions. Preventable drug-drug interactions were defined based on absolute or relative contraindicated drug combinations. Reference data were taken from the Vidal dictionary (8), which corresponds to the Physician's Desk Reference, and is the reference book used for drug prescriptions by French physicians; it is updated annually by the French Health Department.

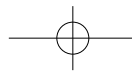
#### Statistical analysis

Data were recorded and analysed using the Statview statistical package. Qualitative values were compared using Chi-square test. A p-value below 0.05 was considered statistically significant.

### Results

16 geriatric centres participated in the study and 576 patients (mean age:  $83.6 \pm 7.9$  years) were consecutively included. The mean number of drugs at inclusion was  $9.4 \pm 4.24$  drugs per





patient. Patient characteristics are presented in table 1. Patients did not differ between the intervention (I+) and control groups (I-) at inclusion in the centres. The most prevalent chronic diseases were: cardiovascular (71.5%), musculoskeletal (47.9%), gastrointestinal (35.9%), genitourinary (29.2%), neurological (26%), ophthalmologic (21.9%), respiratory (21.2%) and dementia (18.9%). 223 out of 755 events were considered “probable” ADEs (29.5%), 122 during period 1 and 101 during period 2. The most frequent signs or symptoms of ADEs were (table 2): biological anomalies (20.6%), sleepiness (10.8%), falls (9%), diarrhoea (7.2%), constipation (6.7%), hemorrhage (6.7%), vomiting (4.5%), and shortness of breath (2.7%).

**Table 1**

Demographic and clinical features of 576 patients presenting a possible drug-related event (Mean ± SD or percentage).

	Total
Age (years)	83.6 ± 7.9
Gender (% female)	72%
Weight (kg)	59.2 ± 13.7
<i>More prevalent clinical chronic diseases (%)</i>	
Cardiovascular	71.5%
Muskuloskeletal	47.9%
Gastroenteric	35.9%
Genitourinary	29.2%
Neurological	26.0%
Ophthalmological	21.9%
Respiratory	21.2%
Dementia	18.9%
Cancer	17.7%
Diabetes	14.8%
Number of drugs	9.4 ± 4.24 (Range: 0-20)

**Table 2**

Recorded symptoms possibly due to ADEs

Type of event	Period 1		Period 2		Total N (%)
	Intervention units	Control units	Intervention units	Control units	
Biological anomaly	9	15	10	12	46 (20.6%)
Sleepiness	10	8	1	5	24 (10.8%)
Fall	9	4	0	7	20 (9%)
Diarrhoea	5	5	2	4	16 (7.2%)
Constipation	6	7	0	2	15 (6.7%)
Hemorrhagic	2	5	5	3	15 (6.7%)
Vomit	4	2	3	1	10 (4.5%)
Shortness of breath	0	2	1	3	6 (2.7%)
Other	11	18	16	26	71 (31.8%)
Total	56	66	38*	63*	223 (100%)

\* p = 0.004

The 223 ADEs were caused by 315 drugs, either alone or combined. The drugs were mainly cardiovascular (19.8%), psychotropic (15.8%), analgesic agents (12.8%) and anticoagulants (9.9%) (Table 3). Based on the Beers criteria for inappropriate drugs in the elderly (9), only two are extensively used in France: propoxyphene and meprobamate. During the

study, 8 ADEs were caused by propoxyphene (4%) and 11 by meprobamate (5%). At the date of the study, these drugs were not considered to be inappropriate in France. 6 ADEs were caused by tricyclic antidepressants (3%). Drugs associated with ADEs are presented in table 4.

**Table 3**

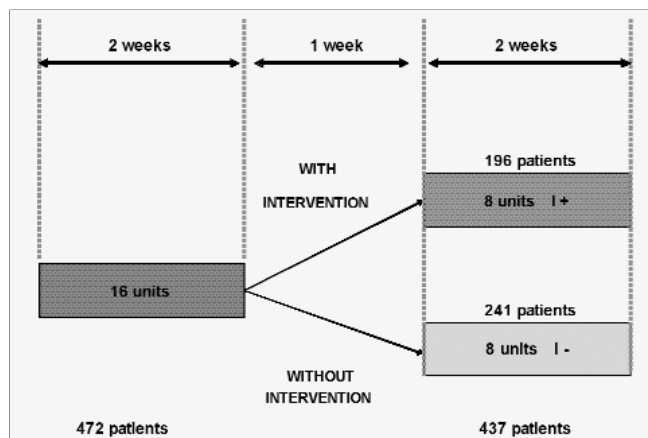
Imputable Adverse Drugs Events

Drug Class	Period 1		Period 2		Total N (%)
	Intervention units	Control units	Intervention units	Control units	
Analgesics	11	17	4	8	40 (12.8%)
Antipsychotics	14	9	3	12	38 (12%)
Antihypertensive	12	4	8	9	33 (10%)
Diuretics	4	9	5	13	31 (9.8%)
Anticoagulants	4	9	5	2	20 (6.4%)
Antidepressants	3	4	2	3	12 (3.8%)
LMWH	3	2	3	3	11 (3.5%)
Antibiotics	2	5	0	3	10 (3.2%)
Diabetes	2	4	1	0	7 (2.2%)
others	24	28	23	38	113 (36.3%)
Total	79	91	54	91	315

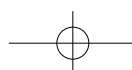
Among the 223 ADEs, 62 (28%) were preventable. The other drugs involved in ADEs were adapted to the clinical context and were considered non-preventable risk factors. In preventable ADEs, the main errors were: excess dose (n = 16, 26%), therapeutic duplication (n = 13, 21%), under dose (n = 8, 13%), inappropriate drug (n = 8, 13%), drug-drug interaction (n = 4, 6%), prior similar adverse drug reaction (n = 2, 3%) and miscellaneous (n = 11, 18%).

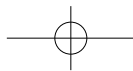
**Figure 1**

The protocol



After the specific educational intervention program, there were fewer ADEs in the intervention group (n = 38, 22%) than in the control group (n = 63, 36%; p = 0.004)(table 2).





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**Table 4**  
Drugs and ADEs

Drugs	Events
Analgesics	Constipation, sleepiness
Antipsychotics	Sleepiness, falls
Antihypertensive	Falls, hypotension
Diuretics	Biologic anomaly, falls
Anticoagulants	Biologic anomaly, hemorrhagic
Antidepressants	Sleepiness, falls
LMWH	Hemorrhagic
Antibiotics	Diarrhea
Diabetes	Biologic anomaly

**Table 5**  
Key recommendations for preventing adverse drug events (ADEs) in the elderly (adapted from 26).

<b>P</b> - Program for monitored drug events
<b>R</b> - Recognise that a clinical sign or symptom could be an ADE
<b>E</b> - Evaluate co-morbidities, frailty, cognitive function and modify treatment in accordance with any change in clinical condition
<b>V</b> - Verify that the number of different drugs prescribed is as low as possible
<b>E</b> - Evaluate renal function (Cockcroft-Gault formula) and adapt the treatment schedule accordingly
<b>N</b> - Nurse and physician training to assess ADEs
<b>T</b> - Treatment adapted to the patient's life expectancy

### Discussion

Although several educational strategies have been used to improve doctors' clinical practice, significant effects are rarely reported (10). In our prospective study, the frequency of ADEs was approximately 29.5%. After a specific educational intervention program ADEs were reduced by 14% in the intervention group (I+) compared to the control group (I-). In practice, the most effective strategies require more resources and repeated interventions; this is probably one of the limits of our study and why the effects were moderate.

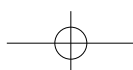
In a retrospective study (11), 110 (10.8%) of 1014 patients experienced an ADE. About half of these events were judged preventable with ordinary standards of care. 30 to 50% of ADEs could be prevented if physicians took into account certain risk factors, e.g. physiological changes in renal function, interfering disease, drug-drug interactions (DDIs), inappropriate number or dose of drugs or inappropriate prescriptions. In the study by Doucet et al (7), 40.2% of the ADEs were considered preventable. In our study, only 28% of ADEs were considered preventable. This is the same percentage found by Gurwitz et al (12) in older ambulatory patients. In a French prospective study (13) in an acute medical geriatric unit, only 79 of 1131 (5.9%) ADEs from inappropriate drug use were directly attributable to the inappropriateness of the drugs themselves.

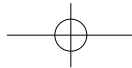
Beers criteria (9) are difficult to use in France because certain drugs on the list are extensively used in the elderly with no side effects (e.g. dextropropoxyphene or meprobamate).

Even in the United-States, Beers found a high prevalence of propoxyphene use (6.6% in 1999) in the community-dwelling elderly Medicare population (14). Piccoro et al (15) reported that 16% of nursing home residents in Kentucky were being prescribed propoxyphene. However, in a large Canadian study (16), less than 1% of patients in nursing homes were dispensed propoxyphene. A review of the literature to evaluate the efficacy and safety of dextropropoxyphene compared with other opioids in the elderly showed that they had similar efficacy and safety (17). On the other hand, many medications on the Beers list were not or were rarely prescribed in the French elderly population: phenylbutazone, pentazocine, trimethobenzamide, amitriptyline, methyl dopa, reserpine, cyclandelate, isoxsuprine, orphenidrate, dipyrindamole... In practice, drug use review tools are based on North American and Canadian drug formulas and may not be appropriate for use in European countries because of differences in national drug formulas and prescriptive behaviors (18). A specific French consensus list was proposed in 2007 (19). In the French list, dextropropoxyphene and digoxin were not included as inappropriate medications. For meprobamate, only gastrointestinal indications were considered inappropriate.

Polypharmacy is a well-known risk factor for ADEs. Nguyen et al (20) found a positive correlation between the use of  $\geq 9$  different scheduled medications and ADEs in 335 geriatric nursing home residents (OR 2.33; 95% CI, 1.54-3.52;  $P < 0.001$ ). Polypharmacy correlates strongly with the incidence of ADEs, and older people – especially hospital inpatients – are prescribed more drugs than younger patients. In addition, the drugs most commonly involved in adverse drug reactions are taken more often by the elderly than by other patients. In our study, the mean number of drugs was  $9.4 \pm 4.24$  drugs per patient, which is very high. In the study by Laroche et al, the mean number of drugs taken was  $7.3 \pm 3.0$  in patients with ADEs and  $6.0 \pm 3.0$  in those without ADEs (13). In our study, 5 drug classes (analgesics, antipsychotics, antihypertensives, diuretics and anticoagulants) were responsible for 51% of ADEs. Anticoagulants (warfarin), insulin and diuretics (furosemide) are high-risk medications frequently involved in ADEs in assisted living (21) or nursing homes (22) and resulting in an emergency department visit (23).

Computer-assisted prescriptions could help decrease ADEs (24): indications of potential interactions between drugs, time-limited prescriptions with automatic stops, adapting the patient's dose in chronic insufficiencies, easier to report incidents... This type of program has now been set up in geriatric units in this study, and a new evaluation of ADEs will be necessary to evaluate the impact of the computer-assisted prescription. These results suggest that an educational intervention program could result in a decrease in the number of ADEs. Adequate training for medical and nursing staff and regular analysis of ADEs is necessary and should be included during initial and continuing education professional training programs. National French recommendations to avoid ADEs in





the elderly have been accessible on Internet since 2005 (25).

### Limitations

There was some difficulty making sure that the entire staff was aware of the study to guarantee good compliance and thorough data collection. Another bias was possible under-reporting due to work pressure.

Thus, events that were not reported were not included in the results. As a result the reported rates are probably underestimated.

### Conclusion

Our study identifies the need for adequate training of the nursing and medical staff to minimize the risk of ADEs. This type of intervention is more effective but requires more resources. As a result of this study a set of prescription rules were drafted (table 5). Education programs could reduce the prevalence of ADEs by 14% and encourage physicians to change outdated prescription habits. For this type of program to be a success information must be circulated. However, effective strategies for changing prescription patterns should probably include reinforcement information sessions.

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