



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH



European Network of Centres  
for Pharmacoepidemiology and Pharmacovigilance

# Pharmacovigilance in the Elderly - highlights from informal PhVWP

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Pharmacovigilance Working Party





# Scope of presentation

- Public health impact of ADRs in Elderly
- Current status of regulatory activities and drugs of interest
- Points to Consider
- Way forward





## “Evidence base” for iPhVWP discussion

- Published literature on healthcare impact of adverse drug reactions
- Strengthening pharmacovigilance – patient reporting, signal detection
- Regulatory perspective and data from ES surveys (Dolores Montero)





# Healthcare impact of ADRs

## Review

### Incidence of Adverse Drug Reactions in Hospitalized Patients

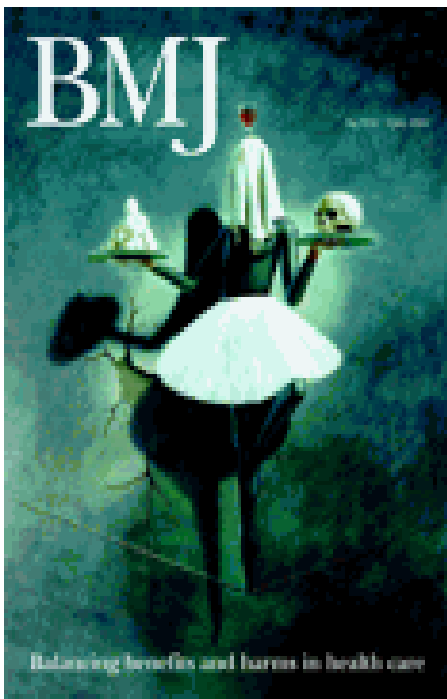
A Meta-analysis of Prospective Studies

Jason Lazarou, MSc; Bruce H. Pomeranz, MD, PhD; Paul N. Corey, PhD

- Overall incidence of serious ADRs - 6.7% hospital admissions
- 4th – 6<sup>th</sup> leading cause of death in USA after heart disease, cancer and stroke



# Healthcare impact of ADRs



6.5% hospital admissions in UK

ADRs were responsible for death of 0.15% and 72% were classified as avoidable

Patients admitted with ADRs were significantly older (median 76 years, interquartile range 65-83) than patients without ADRs (66 years, 46-79)

*Pirmohamed et al 2004 BMJ 329; 15-19*



# Hospitalisation due to NSAIDs complications

Hospitalisations per 1000 person-years

25

20

15

10

5

0

- Male users
- Female users
- Male non-users
- Female non-users

15 20 25 30 35 40 45 50 55 60 65 70 75 80 85+ years

Age

*Pérez-Gutthann et al 1997*



# Direct costs of ADRs in Germany

- Incidence of hospitalization due to at least 'possible' serious outpatient ADRs - 3.25%
- Average treatment costs of a single ADR €2250
- Total costs - €434 million per year for Germany
- Preventable cases 20.1% - potential saving of €87m per year
- Mean age of 1834 patients - 71.0 years (SD14.7)

*Rottenkolber 2011, Pharmacoepi & Drug Safety; 20: 626–634*

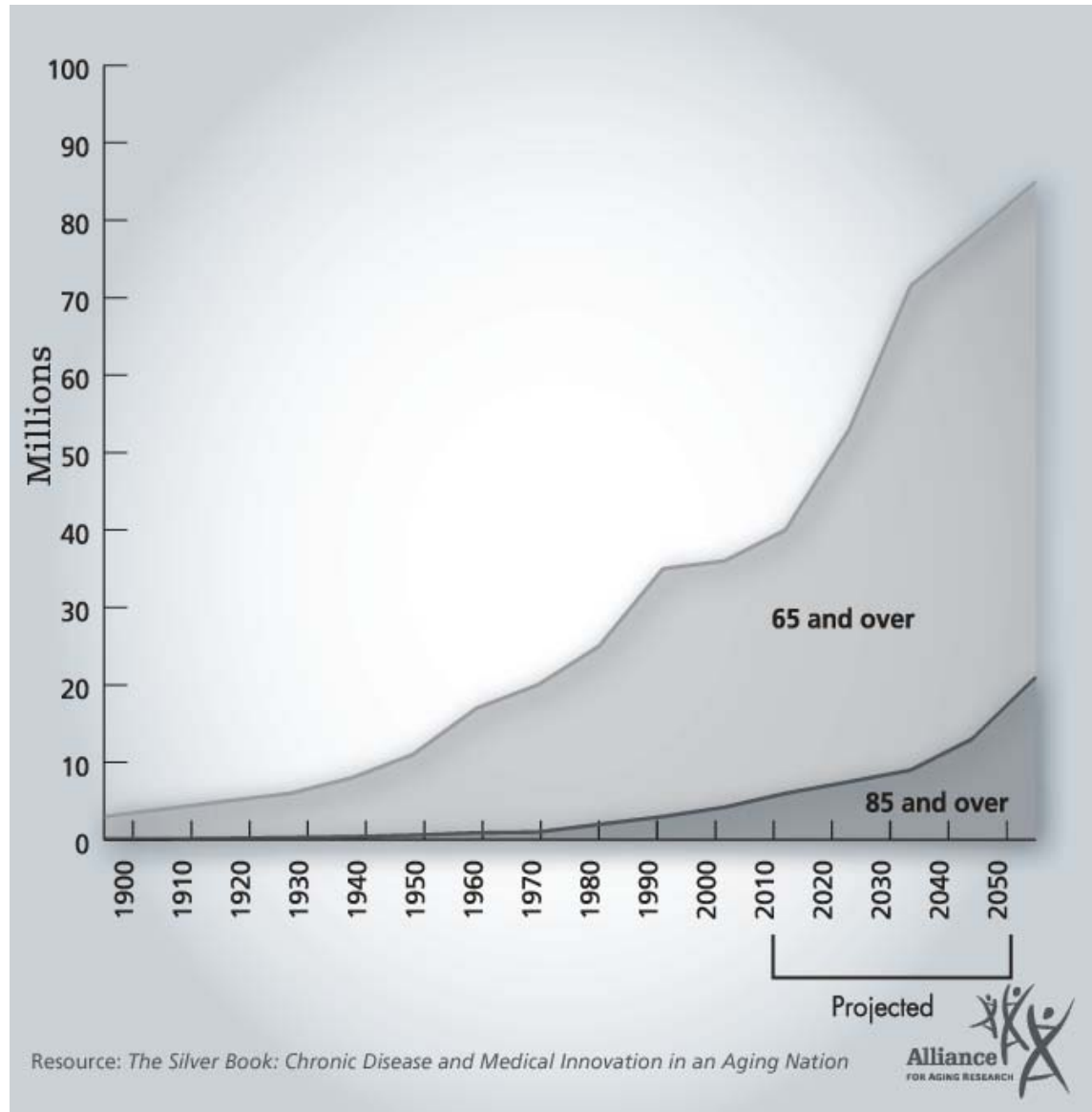


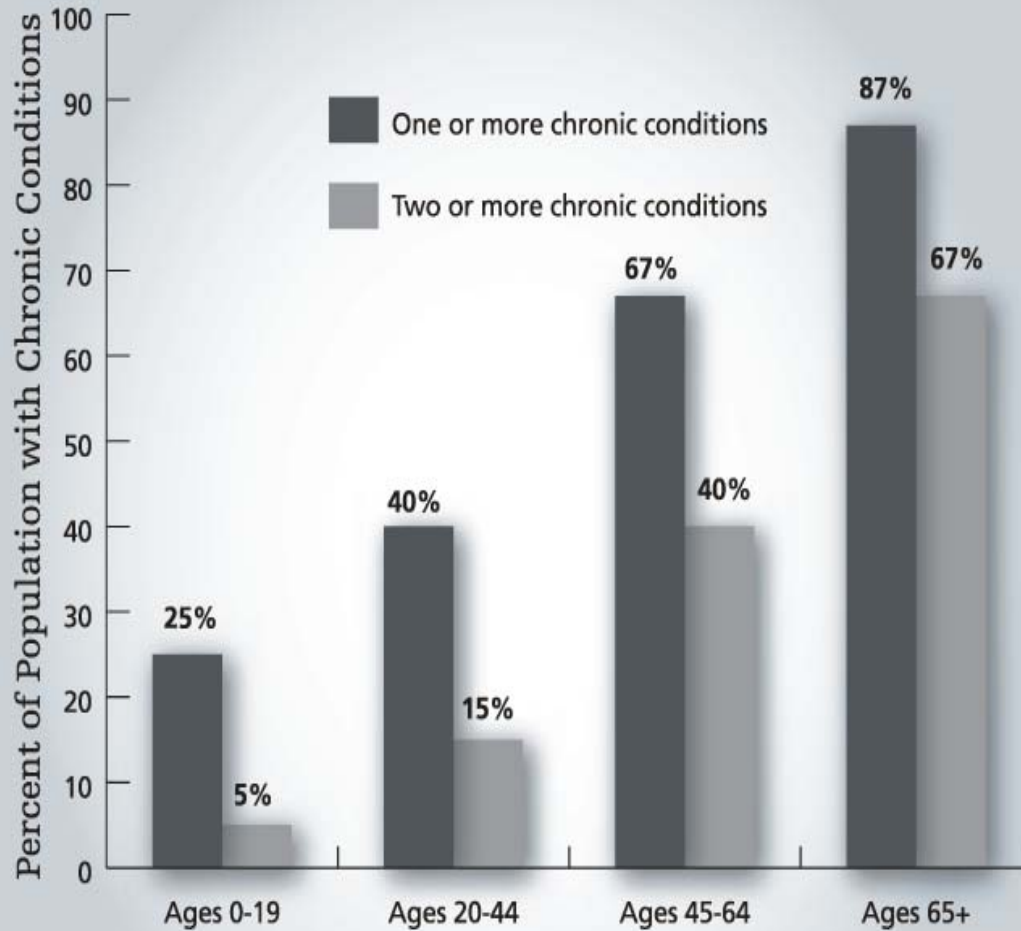
# Opportunities to improve PhVig for elderly in New European legislation



- Direct patient reporting
- Additional monitoring of certain medicines
- Signal detection using Eudravigilance
- Risk management plans
- Information in patient leaflets







Resource: *The Silver Book: Chronic Disease and Medical Innovation in an Aging Nation*





# Special aspects of elderly population

**Co-morbidities** leading to polypharmacy and relevant drug interactions

- 35% of patients above 65 with 3 or more concomitant illnesses
- Integrated review often lacking, dealing to duplication and “cascade” of drugs

**Functional status** eg calcium antagonists in patients with chronic constipation

**Cognitive status** especially relevant in frail patients



# Special aspects of drugs in the elderly

## Pharmacokinetics

- Higher distribution of lipid soluble drugs
- Decreased hepatic metabolism capacity
- Progressive deterioration of renal function not reflected by serum creatinine

## Pharmacodynamics

- Decreased circulatory response (postural control, thermoregulation, cognitive function)



# Atypical ADRs in the elderly



Examples – risperidone and mild subclinical extrapyramidal effects eg aspiration pneumonia (not overt EPS)

ADRs which resemble disease under treatment – eg acyclovir and lethargy, convulsions



# Current regulatory situation

- Are the elderly accurately represented in clinical trials?
- Does the marketing authorisation / SPC provide helpful information for prescribing in the elderly?
- What about risk management plans?



# Clinical Trials authorised by AEMPS 1993- 2009

Elderly population included in 30% of clinical trials

The percentage has increased over time

14% of trials in 1993

50% of trials in 2009)





## Current regulatory status – ES review

Specific information in marketing authorisation on the 100 drugs most consumed by the elderly:

- 52% specific PK information
- 6% specific PD information
- 81% specific posology
- 46% specific warnings
- 16% specific interactions
- 15% specific information on ADRs







## Some current drugs of interest in elderly

Cilostazol – CVS ADRs, interactions

Citalopram/escitalopram – QT prolongation

Tramadol – CNS ADRs

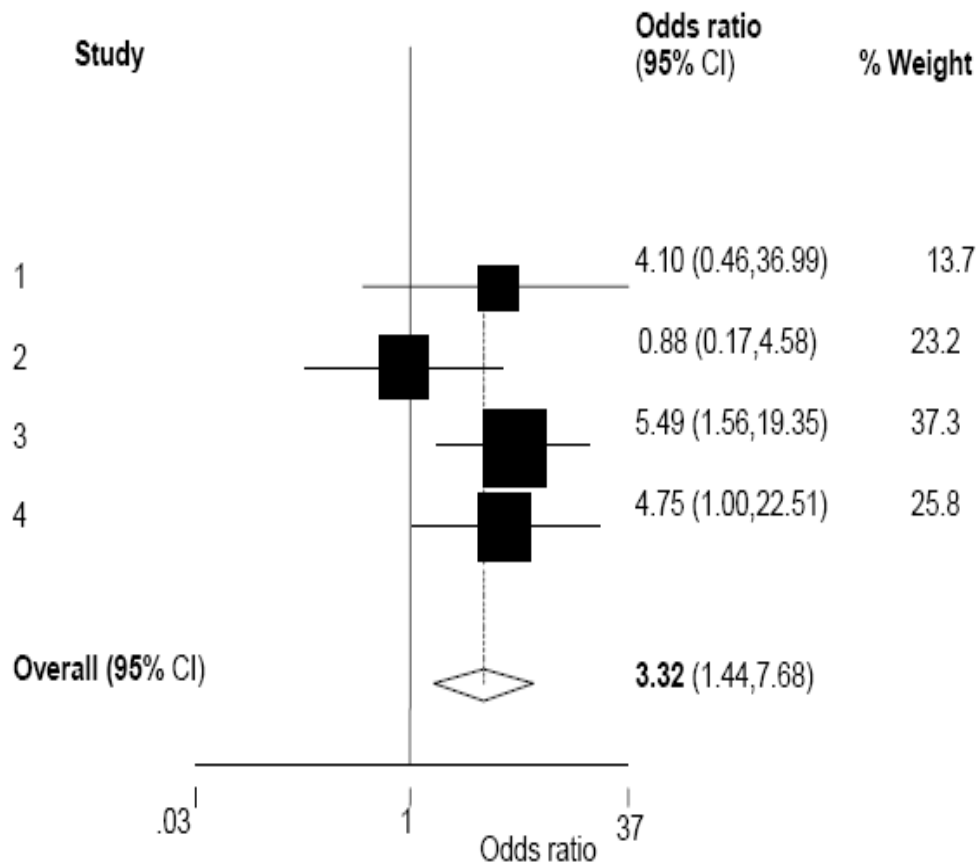
Dronedarone – hepatic, pulmonary ADRs

Dabigatran - haemorrhage

Antipsychotics – increased mortality



# Atypical antipsychotics



Clinical trial data on risperidone and cerebrovascular adverse events

- Meta-analysis in 2004



# Conventional antipsychotics

Epidemiological studies 2007

- Schneeweiss et al
- Gill et al

## RESEARCH

### Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients

Sebastian Schneeweiss, Soko Setoguchi, Alan Brookhart, Colin Dormuth, Philip S. W...

#### ABSTRACT

**Background:** Public health advisories have warned that the use of atypical antipsychotic medications increases the risk of death among elderly patients. We assessed the short-term mortality in a population-based cohort of elderly people in British Columbia who were prescribed conventional and atypical antipsychotic medications.

**Methods:** We used linked health care utilization data of all BC residents to identify a cohort of people aged 65 years and older who began taking antipsychotic medications between January 1996 and December 2004 and were free of cancer. We compared the 180-day all-cause mortality between residents taking conventional antipsychotic medications and those taking atypical antipsychotic medications.

**Results:** Of 37 241 elderly people in the study cohort, 12 882 were prescribed a conventional antipsychotic medication and 24 359 an atypical formulation. Within the first 180 days of use, 1822 patients (14.1%) in the conventional drug group died, compared with 2337 (9.6%) in the atypical drug group (mortality ratio 1.47, 95% confidence interval [CI] 1.39–1.56). Multivariable adjustment resulted in a 180-day mortality ratio of 1.32 (1.23–1.42). In comparison with risperidone, haloperidol was associated with the greatest increase in mortality (mortality ratio 2.14, 95% CI 1.86–2.46) and loxapine the lowest (mortality ratio 0.85, 95% CI 0.78–0.92).

use is outside approved indications.\* It has been rapid shifts away from first-generation agents (e.g., chlorpromazine, haloperidol) to more actively marketed second-generation agents (e.g., clozapine, olanzapine, quetiapine).

In a public health advisory issued on October 1, 2004, the Canadian Council of Ministers of Health warned that, compared with atypical antipsychotic medications, the use of conventional antipsychotic medications increased the risk of death among elderly patients with dementia. The advisory requested that “all manufacturers of first-generation antipsychotic medications, although the Food and Drug Administration (FDA) noted that it is difficult to study in the future.”<sup>2,3</sup>

In the absence of data on the risk of death associated with the use of conventional antipsychotic medications, we examined the possibility that clinicians may switch their elderly patients to atypical antipsychotic medications, particularly since their use has increased so rapidly and recent extrapolations mainly from younger populations suggested that the conventional for theory, pose risks equal to or greater than those associated with the newer, atypical drugs in elderly patients.

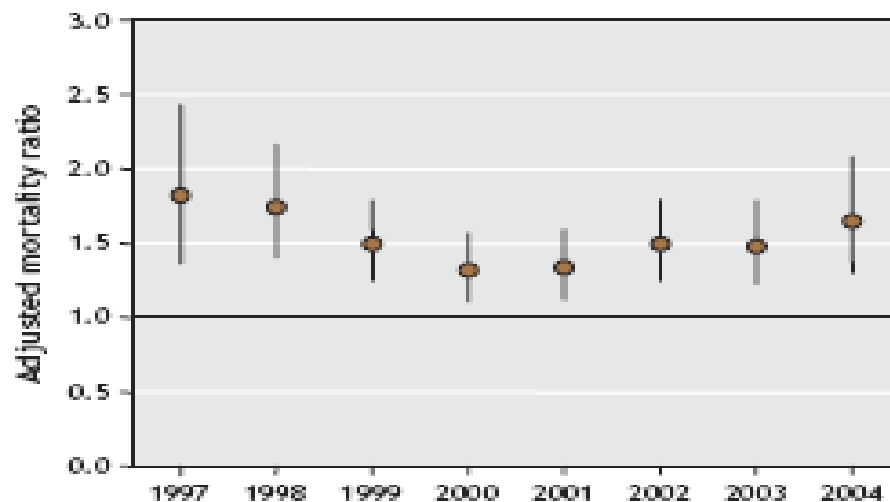


Fig. 2: Yearly adjusted mortality ratios comparing the risk of death between the conventional and atypical antipsychotic drug groups, from 1997 to 2004. Error bars represent 95% confidence intervals.



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9 November 2011  
EMA/838825/2011  
Human Medicines Development and Evaluation

## Informal PhVWP, Warsaw:

# Outcome of discussion on pharmacovigilance in older population: key points for consideration

The PhVWP, at its informal meeting in Warsaw on 6-7<sup>th</sup> October 2011, dedicated a session to pharmacovigilance in the older population, and discussed the key points for consideration outlined below, which could improve the demonstration of an appropriate benefit/risk balance in this population.



# Pharmacovigilance in elderly - Points to consider (1)

## Aspects to be considered at time of marketing authorization:

4. The clinical context of real life drug use in the elderly with regard to functional, cognitive impairment and comorbidities should be considered.
5. If the indication is aimed at covering the elderly population, sufficient and relevant data should be included in the dossier prior to the MA (if considered key to the benefit/risk demonstration in the intended population of use). However, if the older population is only a subset, an "important missing info section on elderly" should be described in the RMP and any additional post-authorisation studies generating such data will be enforceable.



# Pharmacovigilance in elderly - Points to consider (2)

7. RMP: if data are lacking, monitoring should be foreseen for renal impairment, frailty, fractures and aspects not covered in RCTs due to exclusion criteria and excluded comedications.
  - a. Risk minimization measures should be considered when appropriate
  - b. Drug utilization studies could be an appropriate tool to confirm that the age distribution of the real life population corresponds to the CT population, and throw light on compliance with SmPC.
8. PAES trials, requested at time of MA, are particularly useful, especially to provide information on the chronic treatment of frail patients. Use of evolving methodologies for randomized studies in observational databases should be explored. Special measures should be elaborated to minimize discrimination of participation of elderly population (ie. guidelines for assessors).



# Pharmacovigilance in elderly

## - Points to consider (3)

### **Post-authorisation aspects:**

10. Consideration should be given to developing an algorithm for signals of drug interaction in databases (EV, Pharmo, BIFAP, GPRD). Perhaps the EC Innovation Partnership could provide funding.
13. The Survey of Geriatric Needs (Pharmacovigilance) will be conducted. A focus group will meet to identify any points additional to the current draft. In particular, drugs of interest need to be identified for flagging in the PSUR worksharing exercise.
14. ADRs constitute a significant financial burden, often higher than the cost of medication itself, particularly in the elderly. ADR costs are taken into account by some HTA bodies in their assessment.



# Conclusion

- Some regulatory progress in addressing the special issues for drug safety in elderly – probably not enough
- Mismatch between CT population and real life use in elderly means significant knowledge gap
- Special issues of elderly need to be considered in all phases of drug regulation
- Potential to minimise harms in elderly from effective pharmacovigilance





# Way forward



- Maximise opportunity of new pharmacovigilance legislation
- Proposals for FP7 funding in key therapeutic areas
- Engage ENCePP network in strategy to strengthen pharmacovigilance in elderly