CME Background
Articles are selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME articles on a variety of topics throughout each volume. Activities are planned using a process that links identified needs with desired results.

To obtain credit, read the article, correctly answer the questions in the Posttest, and complete the Evaluation. A $5 processing fee will apply.

CME Objective
After studying this article, you should be able to:

- Prescribe antipsychotics with extreme caution in elderly patients, especially those taking cardiovascular or other psychotropic medications

Accreditation Statement
The CME Institute of Physicians Postgraduate Press, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
The CME Institute of Physicians Postgraduate Press, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note: The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 1 hour of Category I credit for completing this program.

Date of Original Release/Review
This educational activity is eligible for *AMA PRA Category 1 Credit*™ through January 31, 2019. The latest review of this material was December 2016.

Financial Disclosure
All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Alan J. Gelenberg, MD, Editor in Chief, has been a consultant for Zynx Health, has been a stock shareholder of Healthcare Technology Systems, and has been owner and editor of the *Biological Therapies in Psychiatry* newsletter. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

Antipsychotic Drug Interactions and Mortality Among Nursing Home Residents With Cognitive Impairment

Rosa Liperoti, MD, PhD, MPH[a,*]; Federica Sganga, MD[a]; Francesco Landi, MD, PhD[a]; Eva Topinkova, MD, PhD[b]; Michael D. Denkinger, MD[c]; Henriëtte G. van der Roest, PhD[d]; Andrea D. Foebel, PhD[e]; Harriet Finne-Soveri, MD, PhD[f]; Roberto Bernabei, MD[a]; and Graziano Onder, MD, PhD[a]

ABSTRACT

Objective: Among elderly individuals with dementia, the use of antipsychotics has been associated with serious adverse events including ischemic stroke and death. Multiple medications can interact with antipsychotics and increase the risk of such adverse events. The purpose of this retrospective, longitudinal cohort study was to estimate the prevalence of potential antipsychotic drug interactions and their effect on increasing the risk of death among cognitively impaired elderly individuals treated with antipsychotics.

Methods: We conducted a retrospective longitudinal cohort study in 59 nursing homes of 7 European Union countries and Israel. The study was conducted during the years 2009 to 2011. Participants were cognitively impaired individuals aged 65 years or older residing in the participating nursing homes and being treated with antipsychotics (N = 604). Risk of death associated with potential antipsychotic drug interactions was the main outcome. The inter–Resident Assessment Instrument for Long Term Care Facilities (interRAI LTCF) was used to assess participants. Follow-up time was 12 months.

Results: The prevalence of potential antipsychotic drug interactions was 46.0%. Antipsychotic drug interactions were associated with higher mortality (incidence rate of 0.26 per person-year in the antipsychotic drug–interaction group versus 0.17 per person year in the no antipsychotic drug–interaction group). After adjusting for potential confounders, risk of death was higher in the group of residents with potential antipsychotic drug interactions relative to those unexposed to such interactions (hazard ratio = 1.71; 95% CI, 1.15–2.54).

Conclusions: Part of the observed excess risk of death associated with the use of antipsychotic medications in elderly individuals with cognitive impairment may be attributable to antipsychotic drug interactions. Antipsychotics should be used with extreme caution especially among those individuals receiving concomitant cardiovascular or psychotropic medications.

J Clin Psychiatry 2017;78(1):e76–e82
https://doi.org/10.4088/JCP.15m10303

[a]Department of Geriatrics, Neuroscience and Orthopedics, Agostino Gemelli University Hospital, Università Cattolica del Sacro Cuore, Rome, Italy
[b]Department of Geriatrics, First Faculty of Medicine, Charles University, Prague, Czech Republic
[c]AGAPLESION Bethesda Clinic, Competence Centre of Geriatrics, University of Ulm, Ulm, Germany
[d]EMGO Institute for Health and Care Research, Department of General Practice and Elderly Care Medicine, VU University Medical Centre, Amsterdam, The Netherlands
[e]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[f]Ageing and Services Unit, National Institutes of Health and Welfare (THL), Helsinki, Finland
**Corresponding author:* Rosa Liperoti, MD, PhD, MPH, Department of Geriatrics, Neuroscience and Orthopedics, Agostino Gemelli University Hospital, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168, Rome, Italy (rossella.liperoti@rm.unicatt.it).

Clinical Points

- Antipsychotic medications have been associated with an increased risk of death in elderly individuals with dementia. Mechanisms underlying such adverse effects are still unclear.
- Part of the excess risk of death associated with the use of antipsychotic medications may be attributable to antipsychotic drug interactions.
- Antipsychotics should be used with extreme caution especially among elderly individuals receiving cardiovascular or psychotropic medications.

Antipsychotic medications are approved for the treatment of schizophrenia and psychotic disorders. Although regulatory agencies worldwide have issued recommendations not to use antipsychotics in the elderly population without these two indications, these drugs are frequently prescribed off-label for the treatment of behavioral and psychological symptoms of dementia.[1–3]

Numerous side effects ranging from cardiovascular events, extrapyramidal symptoms, falls, sedation, and metabolic and hematologic disturbances are known to occur during antipsychotic treatment.[4,5] In particular, among older adults with dementia, antipsychotics have been shown to be potentially associated with serious adverse events including ischemic stroke, fractures, arrhythmias, venous thromboembolism, and pneumonia, leading ultimately to increased mortality rate.[6–11]

Elderly patients, including those with dementia, are a heterogeneous group of subjects with very different individual clinical profiles. In such populations, genetic, clinical, and environmental factors may interact with each other and modify the effect of antipsychotics, thus influencing response to treatment and onset of adverse events.[12] In this context, multiple medications used to treat comorbidities in residents with dementia can interact with antipsychotics and increase the risk of adverse drug reactions.

Nursing home residents represent a category of frail, elderly individuals who often present with some degree of cognitive impairment and are usually given 7 to 8 different medications during the day.[13,14] Polypharmacy coupled with the age-related changes in pharmacodynamics and pharmacokinetics makes this population particularly susceptible to developing adverse events related to drug interactions.

A review[15] of observational studies conducted between 2000 and 2010 has identified 16 studies reporting an increased risk of hospitalization for elderly patients due to drug interactions. The drugs commonly involved in the interactions included cardiovascular agents (angiotensin-converting enzyme inhibitors, diuretics, angiotensin receptor blockers, calcium channel blockers, digoxin), antibiotics (sulfamethoxazole/trimethoprim, macrolide antibiotics, ciprofloxacin), psychotropics (benzodiazepines, zolpidem, phenytoin, lithium), sulfonylureas, theophylline, warfarin, and nonsteroidal antiinflammatory drugs. In addition, a single study[16] reported increased mortality for breast cancer in women treated with paroxetine and tamoxifen.

Numerous possible pharmacodynamic and pharmacokinetic interactions have been described for antipsychotic medications[17]; nonetheless, data on the negative outcomes possibly associated with such interactions are lacking.

The purpose of this study is to estimate the prevalence of potential drug interactions involving antipsychotic medications and their effect on increasing the risk of death in a population of elderly nursing home residents treated with antipsychotics in 7 European Union (EU) countries and Israel.

METHODS

Data Source

We conducted a retrospective, longitudinal cohort study among elderly nursing home residents with cognitive impairment. The participants were a selected subset of the SHELTER—Services and Health for Elderly in Long TERm care—study population. The SHELTER study was funded by the 7th Framework Programme of the EU.[18] The study population consisted of 4,156 nursing home residents in 59 facilities of 7 EU countries (Czech Republic, England, Finland, France, Germany, Italy, The Netherlands) and 1 non-EU country (Israel) participating in the SHELTER study. The SHELTER study was primarily aimed at validating the inter–Resident Assessment Instrument for Long Term Care Facilities (interRAI LTCF), a comprehensive standardized instrument, as a tool to assess the care needs and provision of care to residents of nursing homes in Europe.

Methodology of the SHELTER study is described in detail elsewhere.[18,19] The study was conducted during the years 2009 to 2011. Briefly, older adults residing in participating nursing homes at the beginning of the study and those admitted in the 3-month enrolment period following the initiation of the study were assessed using the interRAI LTCF (baseline assessment) and reassessed at 6 and 12 months (follow-up assessments) if still residing in the facility. If no longer in the facility, reason (death, hospitalization, discharged to home or to another institution) and date of death or discharge were recorded. The only exclusion criteria were age less than 65 years and unwillingness to participate to the study.

Study researchers responsible for data collection were trained following a previously validated procedure.[18] Study researchers were ordinary clinical staff, external research staff, or a mixture of both. All data were processed anonymously.

Ethical approval for the study was obtained in all countries according to local regulations. Residents were invited to take part in the study and were free to decline participation. Informed consent was obtained with assurance of data confidentiality.

Antipsychotic Drug Interactions

Data about any drugs residents received in the 3 days prior to the assessment were collected from physician order sheets and drug administration records. Drug information included nonproprietary and proprietary name, Anatomic Therapeutic and Chemical code of the WHO Collaborating Centre for Drug Statistics Methodology,[20] formulation, dosage, frequency (number of times per day, week, or month the drug was taken), and route of administration.

For the purpose of the present study, we considered all drug interactions involving antipsychotics that have been described in previous literature. According to the classification proposed by Bleakley,[21] interactions were classified based on potential adverse effects into the following categories: pharmacodynamic interactions causing QT prolongation, increased risk of neutropenia or agranulocytosis, increased sedation, increased risk of anticholinergic side effects, decreased blood pressure or falls, increased risk of seizures, increased weight gain or metabolic changes, and pharmacokinetic interactions involving the induction or inhibition of cytochrome P450 1A2, 2D6, and 3A4.[17,21–23] Participants were defined as potentially exposed to antipsychotic drug interactions if at least 1 of the described interactions was documented for that person at the baseline assessment.

Mortality

Residents were followed during their stay in nursing homes and all deaths were recorded. Time-to-death was calculated from the date of the baseline assessment to the date of death. The maximum length of follow-up was 12 months. Participants were censored at the time of their death, at discharge from nursing home, or at the end of the follow-up period (12 months).

Potential Confounders

Residents' sociodemographic characteristics, indicators of functional and cognitive status, comorbid conditions, and concurrent drug use were assessed. The demographic variables included age and sex. The Cognitive Performance Scale[24] (CPS) was used to assess cognitive status. The CPS combines information on memory impairment, level of consciousness, and executive function, with scores ranging from 0 (intact) to 6 (very severe impairment). To evaluate functional status, the 7-point Minimum Data Set (MDS) Activities of Daily Living (ADL) Hierarchy scale[25] was used. The ADL Hierarchy scale groups ADLs according to the stage of the disablement process in which they occur. The ADL Hierarchy scale ranges from 0 (no impairment) to 6 (total dependence). ADL disability was categorized as follows: assistance required (ADL Hierarchy scale score 2 to 4) and dependence (ADL Hierarchy scale score ≥ 5). The MDS Depression Rating Scale[26] was used to assess the presence of depressive symptoms, and a score ≥ 3 indicates a probable diagnosis of depression. Presence of pain in the 3 days prior to assessment was also assessed based on nurse reports and review of medical records. Clinical diagnoses were recorded by study physicians gathering information from the patient, the general practitioner, physical examination, careful review of clinical documentation, and previous medical history.

Study Sample

From the initial sample of 4,156 residents participating in the SHELTER study, those receiving antipsychotic drugs were selected (n = 1,064). To improve homogeneity of the sample with respect to level of cognition and cardiovascular risk profile, residents with schizophrenia (n = 88), those cognitively intact (defined as CPS score of 0 or 1, n = 149), and those with very severe cognitive impairment or in comatose state (defined as CPS score of 6, n = 141) were excluded. Finally, those residents with missing data at follow-up (n = 82) were also excluded. The final analytic sample consisted of 604 residents.

Analytic Approach

Baseline characteristics of participants according to presence of potential antipsychotic drug interactions were compared using analysis-of-variance analyses for normally distributed variables, nonparametric Mann-Whitney *U* test for skewed variables, and χ^2 analyses for dichotomous variables.

Cox proportional hazards regression models were fit to evaluate the effect of antipsychotic drug interactions on time-to-death, adjusting for potential confounders. To exclude departure from proportionality assumption, the log-log survival function was examined. Analyses were adjusted for age, sex, country, severity of cognitive impairment, and variables associated with potential antipsychotic drug interactions at the univariate analysis with $P \leq .10$ (number of drugs, ischemic heart disease, heart failure, and total number of diseases). The impact of antipsychotic drug interactions on survival was also tested comparing the survival curves obtained with the Kaplan-Meier method. All analyses were conducted using PASW Statistics for Windows, Version 18.0 (SPSS Inc, Chicago, Illinois, released 2009).

RESULTS

Mean ± SD age of the 604 residents was 82.9 ± 8.8 years, and 433 (71.7%) were women. Of the total sample, antipsychotic drug interactions were observed in 278 residents (46.0%). Among these, 248 residents (89%) presented 1 interaction and 30 residents (11%) presented 2 or more interactions.

Characteristics of the study sample according to presence of potential antipsychotic drug interactions are summarized in Table 1. Compared to the remaining sample, residents in the antipsychotic drug–interaction group were more frequently women, received a higher number of drugs, and presented a higher number of coexisting diseases. In particular, prevalence of ischemic heart disease and heart failure was highest in the antipsychotic drug–interaction group.

Table 1. Characteristics of the Sample According to Presence of Potential Antipsychotic Drug Interactions (N = 604)[a]

Characteristic	No Interactions (n = 326)	Interactions (n = 278)	*P*
Demographics			
Age, mean ± SD y	82.9 ± 9.1	82.9 ± 8.3	.960
Women	222 (68.1)	211 (75.9)	.034
Functional status			
ADL disability[b]			.939
Assistance required	215 (66.0)	181 (65.1)	
Dependent	97 (29.8)	86 (30.9)	
Cognitive status[c]			.760
Mild/moderate impairment	206 (63.2)	179 (64.4)	
Severe impairment	120 (36.8)	99 (35.6)	
Depression[d]	129 (39.6)	108 (38.8)	.449
Pain	96 (29.4)	90 (32.4)	.452
Number of drugs, mean ± SD	6.9 ± 3.4	8.3 ± 3.0	< .01
Comorbidity			
COPD	22 (6.7)	25 (9.0)	.305
Ischemic heart disease	89 (27.3)	100 (36.0)	.022
Heart failure	39 (12.0)	51 (18.3)	.028
Stroke	57 (17.5)	49 (17.6)	.964
Diabetes	73 (22.4)	75 (27.0)	.192
Cancer	26 (8.0)	28 (10.1)	.368
Number of diseases, mean ± SD	2.3 ± 1.3	2.7 ± 1.5	.002

[a]All values are n (%) unless otherwise noted.
[b]Assistance required is defined by ADL Hierarchical scale score of 2 to 4, and dependent by ADL Hierarchical scale score of 5 to 6.
[c]Mild/moderate cognitive impairment is defined by Cognitive Performance Scale (CPS) score of 2 to 4, severe impairment by CPS score of 5.
[d]Depression Rating Scale score ≥ 3.
Abbreviations: ADL = activities of daily living; COPD = chronic obstructive pulmonary disease.

Table 2. Most Common Interactions Involving Antipsychotic Drugs (N = 604)

Potential Adverse Effect Caused by Interactions Between Antipsychotic and Other Drugs	n (%)	Interactions	n (%)
Decreased blood pressure and falls	210 (34.8)	Risperidone + diuretics	50 (8.3)
		Risperidone + beta-blockers	45 (7.5)
		Tiapride + diuretics	37 (6.1)
		Tiapride + ACE inhibitors	32 (5.3)
		Tiapride + beta-blockers	29 (4.8)
		Olanzapine + diuretics	12 (2.0)
		Olanzapine + calcium antagonists	9 (1.5)
QT prolongation	44 (7.3)	Tiapride + citalopram/escitalopram	20 (3.3)
		Haloperidol + citalopram/escitalopram	14 (2.3)
		Melperone + citalopram/escitalopram	11 (1.8)
		Olanzapine + citalopram/escitalopram	6 (1.0)
Sedation	43 (7.1)	Quetiapine + benzodiazepines	39 (6.5)
		Quetiapine + opioids	7 (1.2)
		Clozapine + benzodiazepines	4 (0.7)
Inhibition of cytochrome P450	9 (1.5)	Olanzapine + paroxetine	2 (0.3)
		Olanzapine + sertraline	2 (0.3)
		Chlorpromazine + sertraline	2 (0.3)
		Haloperidol + sertraline	2 (0.3)
Anticholinergic effects	2 (0.3)	Melperone + anticholinergic drugs	1 (0.2)
		Melperone + TCA	1 (0.2)
		Olanzapine + TCA	1 (0.2)
		Olanzapine + anticholinergic drugs	1 (0.2)
Seizures	1 (0.2)	Chlorpromazine + TCA	1 (0.2)
Agranulocytosis	1 (0.2)	Thioridazine + carbamazepine	1 (0.2)

Abbreviation: ACE = angiotensin-converting enzyme inhibitors, TCA = tricyclic antidepressant.

Table 2 presents most common interactions and their potential adverse effects. Interactions causing decreased blood pressure and falls were the most common (n = 210; 34.8% of study sample), followed by those causing QT prolongation (n = 44; 7.3%), sedation (n = 43; 7.1%), and inhibition of cytochrome P450 (n = 9; 1.5%). Most patients with a potential antipsychotic drug interaction at the baseline assessment were still taking interacting drugs at the 6-month assessment (64.5%) and at the 12-month assessment (61.1%).

Overall, 108 residents (17.9%) died during the 12-month follow-up period. The median follow-up time was 11.4 months in both groups. As shown in Table 3, antipsychotic drug interactions were associated with higher mortality: 59/278 (incidence rate [IR] = 0.26 per person-year) in the antipsychotic drug–interaction group and 49/326 residents in the no antipsychotic drug–interaction group (IR = 0.17 per person year) died during follow-up. After adjusting for potential confounders (including age, sex, country, severity of cognitive impairment, number of drugs, number of diseases, ischemic heart disease, and heart failure), risk of death was higher in the group of residents with potential antipsychotic drug interactions relative to those unexposed to such interactions (hazard ratio [HR] = 1.71; 95% CI, 1.15–2.54). The observed excess risk of death was found to increase with the number of interactions (1 interaction: HR = 1.68 [95% CI, 1.15–2.53]; ≥ 2 interactions: HR = 1.96 [95% CI, 0.90–4.25]).

Figure 1 shows the survival curves according to potential antipsychotic drug interactions. A significant increase in mortality among residents potentially exposed to antipsychotic drug interactions was observed as compared with the unexposed residents (*P* = .02).

DISCUSSION

The present study documented that nearly half of the nursing home residents with cognitive impairment treated with antipsychotics were also prescribed at least 1 drug potentially interacting with these agents. According to our findings, among elderly individuals with cognitive impairment in long-term care, those potentially exposed to antipsychotic drug interactions had a nearly 70% increased risk of death compared to those receiving antipsychotics without potentially interacting concomitant medications.

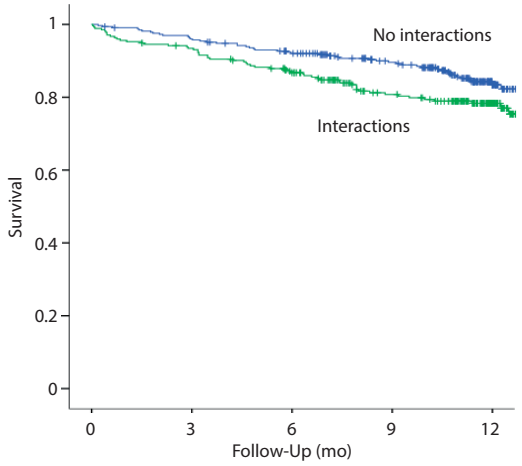
To our knowledge, the current study is the first study investigating the risk of death associated with antipsychotic drug interaction in a cognitively impaired elderly population.

Table 3. Potential Antipsychotic Drug Interactions and Mortality

Interaction	Crude IR per Person-Year	Crude HR	Adjusted[a] HR	95% CI
No interactions (n = 326)	0.17	1	1	…
Interactions (n = 278)	0.26	1.49	1.71	1.15–2.54
1 interaction (n = 248)	0.25	1.65	1.68	1.15–2.53
≥ 2 interactions (n = 30)	0.35	1.79	1.96	0.90–4.25

[a]Adjusted for age, sex, country, number of drugs, ischemic heart disease, heart failure, number of diseases.
Abbreviations: CI = confidence interval, HR = hazard ratio, IR = incidence rate.
Symbol: … = not applicable.

Figure 1. Kaplan-Meier Survival Curves According to Presence of Potential Interactions Involving Antipsychotic Drugs[a]



[a]Log-rank = 0.02.

In April 2005, the US Food and Drug Administration (FDA) issued a black-box warning based on the reanalysis of 17 randomized controlled trials that showed a nearly 1.7 times increased risk of all-cause death associated with the use of atypical antipsychotics compared to placebo in elderly individuals with dementia.[27] In June 2008, the warning was extended by the FDA to conventional antipsychotics.[28] Specifically, the most frequent causes of death documented in those trials included cardiovascular events such as sudden death and heart failure and infections such as pneumonia.[27,28] Some of these negative effects might be related to drug interactions often involving antipsychotics. In the current study, we have reported that over 40% of potential adverse effects due to antipsychotic drug interactions were cardiovascular effects including decreased blood pressure and QT prolongation. The concomitant use of antihypertensive medications may contribute to an increased risk of falls and syncope in elderly patients treated with antipsychotics. Similarly, the concomitant treatment with drugs potentially prolonging the QT interval may increase the risk of life-threatening arrhythmias potentially associated with many antipsychotic medications. There is evidence that the excess risk of cardiac arrest, ventricular arrhythmias, and ischemic stroke associated with antipsychotics is highest among those patients with a previous history of cardiac or cerebrovascular disease and being treated with cardiovascular medications.[29,30] Finally, it is believed that the anticholinergic and antihistaminergic action of antipsychotics may contribute to increased risk of swallowing disturbances and aspiration pneumonia.[10] Concomitant medications with potential anticholinergic effects, such as several common antiparkinsonian drugs and antidepressants, may interact with antipsychotics in determining the onset of such adverse effects.

Different mechanisms of antipsychotic drug interactions have been described.[21] Most of the reported antipsychotic drug interactions, including QT prolongation, sedation, decreased blood pressure, and anticholinergic side effects, have a pharmacodynamic mechanism. Among the pharmacokinetic interactions, the most frequently observed are caused by drugs that affect the metabolism of antipsychotics in the liver through the inhibition or induction of the cytochromeP450 family of enzymes. A recent large population-based study[31] has shown that relative to healthy controls of similar age, elderly patients newly prescribed with quetiapine, risperidone, or olanzapine have over 70% increased risk of acute loss of kidney function. As the authors suggest, such adverse influence on renal function may actually be the result of other specific adverse effects related to antipsychotics such as acute urinary retention, rhabdomyolysis, pneumonia, acute myocardial infarction, and ventricular arrhythmias. The sudden loss of renal function may have an impact on the pharmacokinetics of concomitant medications ultimately leading to an increase in the risk of medication adverse effects and drug interactions.

This study has several limitations. No data were available before the baseline assessment of participants, and this made it impossible to assess the time of initiation of antipsychotic treatment. Similarly, it was not possible to ascertain for all participants that they were still taking antipsychotics at the time of death or at the end of follow-up since data were not available. No information was collected regarding the specific cause of death. It would have been of interest to estimate the effect of each single potential interaction on the risk of death. However, we could not provide such information because single-interaction groups resulted too small in size to be analyzed separately. Finally, although the role of numerous potential confounders was taken into account in the analysis, residual confounding is always possible. The study was conducted in a population of elderly nursing home residents with cognitive impairment, and findings can not be generalized to other populations.

Adverse drug reactions are an important medical problem accounting for nearly 10% of in-hospital costs and being associated with increased morbidity and mortality.[32] The continuous assessment of potential drug-drug interactions and the implementation of tools for the identification of inappropriate drugs, such as the Beers criteria[33] and the Screening Tool of Older Person's

Prescriptions (STOPP) criteria,[34] might represent a valuable strategy to reduce the risk of adverse drug reactions. Limited data are available on the impact of such a strategy on clinical and economic outcomes, and future research should focus on deprescribing to avoid drug-drug interactions and reduce the prescription of inappropriate drugs.

The findings of this study add a piece of knowledge to the ongoing debate on the safety of antipsychotic medications in the elderly population with cognitive impairment. The possibility of antipsychotic drug interaction should be carefully evaluated especially among those patients receiving concomitant cardiovascular or psychotropic medications.

Submitted: August 5, 2015; accepted March 31, 2016.

Drug names: carbamazepine (Tegretol, Epitol, and others), citalopram (Celexa and others), ciprofloxacin (Cipro and others), chlorpromazine (Thorazine and others), clozapine (Clozaril, FazaClo, and others), digoxin (Lanoxin and others), escitalopram (Lexapro and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), phenytoin (Dilantin, Phenytek, and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), sulfamethoxazole/trimethoprim (Bactrim, Septra, and others), tamoxifen (Soltamox and others), theophylline (Aerolate and others), warfarin (Coumadin, Jantoven, and others), zolpidem (Ambien, Edluar, and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, chlorpromazine, clozapine, olanzapine, quetiapine, risperidone, haloperidol, tiapride, and thioridazine are not approved by the US Food and Drug Administration (FDA) for the treatment of behavioral and psychological symptoms of dementia, and melperone is not approved by the FDA.

Author contributions: Rosa Liperoti had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

Financial disclosure: The authors have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This study was funded by the European Union 7th Framework Programme.

Role of the sponsor: The funding organization had no role in the design or conduct of the study; in the collection, management, analysis or interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES

1. Finkel S. Introduction to behavioural and psychological symptoms of dementia (BPSD). *Int J Geriatr Psychiatry*. 2000;15(suppl 1):S2–S4.
2. Madhusoodanan S, Ting MB. Pharmacological management of behavioral symptoms associated with dementia. *World J Psychiatry*. 2014;4(4):72–79.
3. Schulze J, van den Bussche H, Glaeske G, et al. Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. *Eur Neuropsychopharmacol*. 2013;23(9):1034–1042.
4. Alexopoulos GS, Streim J, Carpenter D, et al; Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004;65(suppl 2):5–99, discussion 100–102, quiz 103–104.
5. Gareri P, De Fazio P, Manfredi VG, et al. Use and safety of antipsychotics in behavioral disorders in elderly people with dementia. *J Clin Psychopharmacol*. 2014;34(1):109–123.
6. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. *BMJ*. 2008;337:a1227.
7. Rigler SK, Shireman TI, Cook-Wiens GJ, et al. Fracture risk in nursing home residents initiating antipsychotic medications. *J Am Geriatr Soc*. 2013;61(5):715–722.
8. Wang PS, Schneeweiss S, Setoguchi S, et al. Ventricular arrhythmias and cerebrovascular events in the elderly using conventional and atypical antipsychotic medications. *J Clin Psychopharmacol*. 2007;27(6):707–710.
9. Barbui C, Conti V, Cipriani A. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review and meta-analysis of observational studies. *Drug Saf*. 2014;37(2):79–90.
10. Trifirò G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med*. 2010;152(7):418–425.
11. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934–1943.
12. Fitzgerald SP, Bean NG. An analysis of the interactions between individual comorbidities and their treatments—implications for guidelines and polypharmacy. *J Am Med Dir Assoc*. 2010;11(7):475–484.
13. Furniss L, Craig SK, Burns A. Medication use in nursing homes for elderly people. *Int J Geriatr Psychiatry*. 1998;13(7):433–439.
14. Broderick E. Prescribing patterns for nursing home residents in the US: the reality and the vision. *Drugs Aging*. 1997;11(4):255–260.
15. Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. *Am J Geriatr Pharmacother*. 2011;9(6):364–377.
16. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*. 2010;340:c693.
17. Murray M. Role of CYP pharmacogenetics and drug-drug interactions in the efficacy and safety of atypical and other antipsychotic agents. *J Pharm Pharmacol*. 2006;58(7):871–885.
18. Onder G, Carpenter I, Finne-Soveri H, et al; SHELTER project. Assessment of nursing home residents in Europe: the Services and Health for Elderly in Long TERm care (SHELTER) study. *BMC Health Serv Res*. 2012;12:5.
19. Onder G, Liperoti R, Fialova D, et al; SHELTER Project. Polypharmacy in nursing home in Europe: results from the SHELTER study. *J Gerontol A Biol Sci Med Sci*. 2012;67(6):698–704.
20. WHO Collaborating Centre for Drug Statistics Methodology Web site. http://www.whocc.no/ Accessed September 2, 2014.
21. Bleakley S. Identifying and reducing the risk of antipsychotic drug interactions. *Prog Neurol Psychiatry*. 2012;16:20–24.
22. Hiemke C, Pfuhlmann B. Interactions and monitoring of antipsychotic drugs. *Handbook Exp Pharmacol*. 2012;212(212):241–265.
23. Besag FM, Berry D. Interactions between antiepileptic and antipsychotic drugs. *Drug Saf*. 2006;29(2):95–118.
24. Morris JN, Fries BE, Mehr DR, et al. MDS Cognitive Performance Scale. *J Gerontol*. 1994;49(4):M174–M182.
25. Morris JN, Fries BE, Morris SA. Scaling ADLs within the MDS. *J Gerontol*. 1999;54:M546–M553.
26. Burrows AB, Morris JN, Simon SE, et al. Development of a minimum data set-based depression rating scale for use in nursing homes. *Age Ageing*. 2000;29(2):165–172.
27. Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. US Food and Drug Administration Web site. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafety informationforpatientsandproviders/ucm053171. April 11, 2005. Accessed January 29, 2015.
28. FDA requests boxed warnings on older class of antipsychotic drugs. US Food and Drug Administration Web site. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrug SafetyInformationforPatientsandProviders/ucm124830.htm. June 16, 2008. Accessed January 29, 2015.
29. Liperoti R, Gambassi G, Lapane KL, et al. Conventional and atypical antipsychotics and the risk of hospitalization for ventricular arrhythmias or cardiac arrest. *Arch Intern Med*. 2005;165(6):696–701.
30. Liperoti R, Gambassi G, Lapane KL, et al. Cerebrovascular events among elderly nursing home patients treated with conventional or atypical antipsychotics. *J Clin Psychiatry*. 2005;66(9):1090–1096.
31. Hwang YJ, Dixon SN, Reiss JP, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Ann Intern Med*. 2014;161(4):242–248.
32. Tosato M, Landi F, Martone AM, et al; Investigators of the CRIME Study. Potentially inappropriate drug use among hospitalised older adults: results from the CRIME study. *Age Ageing*. 2014;43(6):767–773.
33. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616–631.
34. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment): consensus validation. *Int J Clin Pharmacol Ther*. 2008;46(2):72–83.

For the CME Posttest, see next page.

POSTTEST

To obtain credit, go to PSYCHIATRIST.COM **(Keyword: January) to take this Posttest and complete the Evaluation.** A nominal processing fee is required.

1. **According to the results of this study, which are the most frequent adverse effects due to antipsychotic drug interactions in nursing home residents with cognitive impairment?**
   a. Anticholinergic effects
   b. Cardiovascular effects
   c. Seizures
   d. Neutropenia and agranulocytocis

2. **Ms A is 85 years old and has dementia associated with depression, wandering, and sleep disturbances. She has the following comorbidities: hypertension, ischemic heart disease, diabetes, and a history of falls. Ms A is being treated with risperidone, diazepam, citalopram, furosemide, metoprolol, aspirin, and insulin. Which of the following potential adverse effects due to antipsychotic drug interactions would you expect from this combination of medications and therefore try to change prescribing?**
   a. Decreased blood pressure, falls
   b. Dry mouth, swallowing disturbances
   c. Weight gain, metabolic disturbances
   d. Acute confusion, worsening of cognitive impairment

3. **According to the results of this study, how much does being exposed to antipsychotic drug interactions increase the risk of death among nursing home residents with cognitive impairment?**
   a. Nearly 50%
   b. Less than 60%
   c. Nearly 70%
   d. Over 80%