Significance of the Study

- Pharmacotherapy in older patients with a limited life expectancy should avoid unnecessary polypharmacy and focus on symptom control. This study showed a small reduction in the use of commonly prescribed preventive medications. Medications could be reviewed to optimize polypharmacy.

Keywords

Elderly · End of life · Limited life expectancy · Polypharmacy · Symptomatic medications

Abstract

Objective: Older people approaching the end of life are at a high risk for adverse drug reactions. Approaching the end of life should change the therapeutic aims, triggering a reduction in the number of drugs. The main aim of this study is to describe the preventive and symptomatic drug treatments prescribed to patients discharged with a limited life expectancy from internal medicine and geriatric wards. The secondary aim was to describe the potentially severe drug-drug interactions (DDI). Materials and Methods: We analyzed Registry of Polytherapies Societa Italiana di Medicina Interna (REPOSI), a network of internal medicine and geriatric wards, to describe the drug therapy of patients discharged with a limited life expectancy. Results: The study sample comprised 55 patients discharged with a limited life expectancy. Patients with at least 1 preventive medication that could be considered for deprescription at the end of life were significantly fewer from admission to discharge ($n = 30$; 54.5% vs. $n = 21$; 38.2%; $p = 0.02$). Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, lipid-lowering drugs, and clonidine were the most frequent potentially avoidable medications prescribed at discharge, followed by xanthine oxidase inhibitors and drugs to prevent fractures. Thirty-seven (67.3%) patients were also exposed to at least 1 potentially severe DDI at discharge. Conclusion: Hospital discharge is associated with a small reduction in the use of commonly prescribed preventive medications in patients discharged with a limited life expectancy. Cardiovascular drugs are the most frequent po-
tentially avoidable preventive medications. A consensus framework or shared criteria for potentially inappropriate medication in elderly patients with limited life expectancy could be useful to further improve drug prescription.

© 2019 The Author(s)
Published by S. Karger AG, Basel

Introduction

The end of life is the preterminal phase of a person’s decline towards death and normally involves accumulating health problems over a period of weeks to months, with failing homeostasis that is irreversible and inexorably leads to death [1]. Older people approaching the end of life are at a high risk for adverse drug reactions resulting from polypharmacy, declining organ function, comorbidity, malnutrition, cachexia, and changes in body composition [2]. As a consequence, approaching the end of life should shift the therapeutic aims, triggering a reduction in the number of drugs, but this is not the usual practice [3–5].

The aim of pharmacotherapy in the rising numbers of end-of-life older people should be to avoid polypharmacy and focus on controlling symptoms rather than prolonging life [1, 2]. Although polypharmacy is very common among older end-of-life patients, with their need to relieve symptoms, disease-related problems, and quality of life [6–8], it may also be a major risk factor for inappropriate prescribing and potentially severe drug–drug interactions (DDI) [2, 9, 10]. In this circumstance, drugs for the prevention of secondary diseases are of no value if the time to therapeutic benefit exceeds the probable life expectancy and should be discouraged. However, the few studies that have examined drug therapy in patients at the end of life have found that about half of them continued to take ineffective and unnecessary medication for the prevention or treatment of chronic diseases [11], although the potential for harm can be expected to outweigh any benefit in view of the limited life expectancy [6, 12]. Statins, antihypertensives and bisphosphonates are frequently used in patients with a terminal disease and advanced disability, although the real benefits are unknown because their safety and efficacy have been demonstrated for a young general population but evidence supporting their utility at the end of life is limited [12–14].

No study has examined the prescription of internal and geriatric hospital specialists to patients with a limited life expectancy. The main aim of this study was to describe the preventive and symptomatic drug treatments prescribed to patients discharged with a limited life expectancy from internal medicine and geriatric wards. The secondary aim was to describe the potentially severe DDI.

Materials and Methods

Data Collection

The Registry of Polytherapies Societa Italiana di Medicina Interna (REPOSI) is a collaborative, independent initiative of the Italian Society of Internal Medicine (SIMI), the Istituto di Ricerche Farmacologiche Mario Negri IRCCS, and the IRCCS Ca’ Granda Maggiore Policlinico Hospital Foundation. The registry was set up in 2008 by a network of internal medicine and geriatric wards in order to collect information on elderly hospital in-patients with multimorbidities receiving multiple drugs. The first run of data collection was between January and December 2008, and the second, third, and fourth runs as well as ongoing runs took place between January and December 2010, 2012, 2014, and 2016, respectively. To ensure an unselected population of elderly patients admitted to internal medicine and geriatric wards, the first 5 patients admitted to the wards participating in this study during 4-week periods 3 months apart were consecutively recruited if they were 65 years old or older. Participation was voluntary and all patients gave signed informed consent. Data collection complied fully with Italian law on personal data protection and this study was approved by the ethics committees of each ward participating in REPOSI.

The attending physicians completed a standardized web-based case report form, recording sociodemographic details and the diagnosis and drug treatment at admission, during the hospital stay, and at discharge. From the second REPOSI runs we collected the following additional information for a short-term follow-up in order to improve the quality of the data: main laboratory parameters, comorbidity according to the Cumulative Illness Rating Scale (CIRS), basic activities of daily living, cognitive impairment, depression, and clinical events during the hospital stay. Patients were followed for 3 months after discharge via a telephone interview in order to collect information on new diagnoses, hospital readmissions, drug regimens, adverse events, basic activities of daily living, and mortality.

To describe the drug therapy of patients discharged with a limited life expectancy, we considered eligible for analysis all patients discharged in “critical condition,” defined as a high risk of short-term mortality (at 3 months) on the basis of the clinical evaluation. Analysis of each patient’s drug therapy at admission reflects drugs prescribed by general practitioners for patients who lived at home, or physicians in nursing homes for those in an institution; drug therapy at discharge referred to prescriptions by hospital internists or geriatricians. Patients transferred to palliative care wards, though potentially terminally ill, were excluded because the drug therapy at discharge was not collected.

Classification of Drug Therapies

The drugs prescribed at admission and discharge were divided into the following 3 main classes according to their preventive or symptomatic effects: (1) potentially avoidable preventive medications, i.e., drugs that usually have no place in the end-of-life patient because the time to benefit is clearly shorter than the life expec-
Drugs that need a case-by-case evaluation because they could have a role in end-of-life patients but their real effectiveness is questionable due to the short life expectancy; and (c) potentially appropriate treatments, i.e., drugs that provide symptomatic relief or that should be tapered slowly over several weeks or months in order to avoid withdrawal symptoms, such as psychotropic drugs or proton pump inhibitors [15]. A geriatrician and a clinical pharmacist separately analyzed drug prescriptions and resolved any discordances with a final round.

### Statistical Analysis
The patients’ sociodemographic characteristics were compared using univariate analysis by χ² tests for categorical variables and t tests or matched pair t tests for continuous variables. The McNemar test was used to compare drug treatments at admission and discharge. p < 0.05 were considered statistically significant. Analyses were done using JMP Pro 12 (SAS Institute Inc., Cary, USA).

### Results
The sample comprised 55 end-of-life patients recruited among the patients discharged by the internal medicine and geriatric wards of REPOSI. Follow-up data were available for 30 of those discharged in critical conditions; 27 (90%) died between discharge and the 3-month follow-up, confirming their limited life expectancy. The main sociodemographic characteristics and diagnoses are reported in Table 1. Patients had high rates of comorbidity and most of them suffered from cardiovascular diseases. About 72% had a caregiver and most had cognitive impairment consistent with a diagnosis of dementia. Half of the patients had been admitted in the previous 6 months and were bedridden at discharge with pressure sores.

The mean number of drugs remained the same from admission to discharge (mean ± SD: 5.5 ± 3.6 and 5.5 ± 3.4; p = 0.97). Table 2 lists the drugs that we considered as potentially avoidable preventive medications in end-of-life patients, those of uncertain appropriateness, and those that were potentially appropriate. There were significantly fewer patients with at least 1 preventive medication that could be considered for deprescription at the end of life from admission to discharge (p = 0.02). Angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, lipid-lowering drugs, and clonidine were the most frequent potentially avoidable cardiovascular medications prescribed at discharge, followed by xanthine oxidase inhibitors and drugs to prevent fractures. Drugs for peptic ulcer and gastroesophageal reflux disease, analgesics, psychotropic drugs, and systemic corticosteroids were the potentially appropriate symptomatic medications maintained at discharge.

Patients exposed to at least 1 potentially severe DDI slightly increased between admission (31; 56.4%) and discharge (37; 67.3%; p = 0.18); drugs that concomitantly increased the risk of QT prolongation and torsades de pointes, followed by those that increased the risk of bleeding, were the most frequent potentially severe DDI (Table 3).

### Discussion
Identification of the end of life should bring about a significant reduction in the number of daily drugs, but this was not observed in the present study. Hospital discharge was associated with only a small, though significant, reduction in the use of preventive medications that are commonly prescribed. However, these results could be further optimized through more targeted deprescription efforts.

### Table 1. Main characteristics and diagnosis of the 55 patients discharged in critical condition

| Characteristic                      | Value                        |
|-------------------------------------|------------------------------|
| Age, years                          | 80.8±83                      |
| Female sex, %                       | 43.6                         |
| Caregiver                           | 38 (71.7)                    |
| Hospital admission in the previous 6 months | 27 (49.1)                    |
| BMI                                 | 23.6±3.7                     |
| Underweight                         | 4 (9.7)                      |
| Normal                              | 25 (61.0)                    |
| Overweight                          | 12 (29.3)                    |
| Bedridden                           | 20 (40.8)                    |
| Pressure sores                      | 24 (66.7)                    |
| Systolic blood pressure             | 116.2±22.1                   |
| Diastolic blood pressure            | 67.1±12.4                    |
| Short Blessed Test                  | 15.6±8.6                     |
| Barthel index                       | 54.7±34.4                    |
| Geriatric depression scale          | 1.8±1.1                      |
| Cumulative illness rating scale     |                              |
| Severity index                      | 1.9±0.4                      |
| Comorbidity index                   | 3.9±2.1                      |
| Main diagnosis                      |                              |
| Hypertension                        | 41 (74.6)                    |
| Heart failure                       | 15 (27.3)                    |
| Chronic renal failure               | 13 (23.6)                    |
| Atrial fibrillation                 | 14 (25.4)                    |
| Cancer                              | 23 (41.8)                    |
| Diabetes                            | 13 (23.6)                    |
| Ischemic heart disease              | 14 (25.4)                    |
| Chronic bronchitis                  | 13 (23.6)                    |
| Anemia                              | 11 (20.0)                    |
| Dementia                            | 13 (23.6)                    |
| Cachexia                            | 1 (0.2)                      |

Values are presented as means ± SD or numbers (%) unless otherwise stated.
improved since in fact about 40% of patients were discharged with avoidable medications. Cardiovascular drugs were the potentially avoidable preventive medications most frequently prescribed at admission that were partially reduced at discharge. Most cardiovascular drugs usually have no place in end-of-life patients because the time to benefit is clearly shorter than the life expectancy [2]; when prescribed to prevent diabetic nephropathy or reduce mortality from heart failure angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers (excluding diltiazem or verapamil) are of little value when a patient’s life expectancy is severely curtailed as a result of other irreversible disorders. Similarly, lipid-lowering drugs are almost always inappropriate at the end of life. There were definite reductions in the prescription of oral antidiabetics and xanthine oxidase inhibitors at discharge. Stopping these drugs is generally appropriate because the goals for managing diabetes change at the end of life since it is no longer important to prevent the long-term effects of hyperglycemia. Similarly, treating asymptomatic hyperuricemia to prevent gout is clearly inappropriate [16] in the end-of-life patient.

Among the preventive medications of uncertain appropriateness, the use of low-molecular-weight heparin increased at discharge while the proportion of patients treated with antiplatelet drugs decreased; these drugs could be useful in preventing thrombotic events, although they increase the risk of bleeding in older and frailer pa-

| Patients | Potentially avoidable preventive medications | Potentially appropriate drugs |
|---|---|---|
| | admission | discharge | admission | discharge |
| Cardiovascular drugs | | | | |
| Omega-3 | 1 | 1 | High-ceiling diuretic | 21 | 19 |
| Statins | 5 | 3 | β-Blockers | 15 | 10 |
| Clonidine | 3 | 3 | Diltiazem | 1 | 1 |
| ACE inhibitors or ARB | 15 | 9 | Potassium-sparing diuretics | 9 | 5 |
| Calcium channel blockers | 10 | 4 | Long-acting nitrates | 7 | 7 |
| Hematological agents | Iron | – | Cardiac therapy | 9 | 8 |
| | Follic acid | – | Analgesics | 11 | 17 |
| Antidiabetic agents | Oral antidiabetic | 4 | 0 | Gastrointestinal drugs |
| | | | | Drug for peptic ulcer and GERD | 35 | 36 |
| | | | | Laxatives | 3 | 4 |
| | | | | Prokinetics | 2 | 3 |
| Psychotropic drugs | Antidepressants | 7 | 5 | | |
| | Hypnotic sedatives | 5 | 3 | | |
| | Antipsychotics | 4 | 5 | Other |
| | Antidiabetic agents | Insulin | 10 | 11 |
| | Low-molecular-weight heparin | 12 | 20 | Systemic corticosteroids | 10 | 20 |
| | Erythropoietin-stimulating agents | 2 | 4 | Antiasthmatics | 11 | 8 |
| | Antiplatelets | 18 | 7 | Antibiotics | 8 | 16 |
| | Oral anticoagulants | 4 | 4 | Alpha antagonists for BPH | 5 | 4 |
| | | | | Testosterone 5α-reductase inhibitors | 2 | 2 |
| | | | | Antipeptic | 9 | 7 |
| | | | | Antifungals | 1 | 4 |
| | | | | Antiparkinson | 3 | 1 |
| | | | | Thyroid therapy | 6 | 5 |
| | | | | Values are presented as numbers (%) or numbers. ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor antagonist; BPH, benign prostatic hypertrophy; GERD, gastroesophageal reflux disease. a To relieve itching caused by partial biliary obstruction. b Including nitroglycerin and isosorbide. c Including trazodone, venlafaxine, and duloxetine; p = 0.02.
patients who often fall. It is hard to assess the appropriateness of these medications and a case-by-case evaluation is needed, although anticoagulants and antiplatelets were frequently involved in potentially severe DDI at discharge, increasing the risk of adverse drug events. Because deprescribing must consider not only the risks of individual drugs but also the cumulative risk of DDI [17], the higher percentage of patients exposed to potentially severe DDI emphasizes the need for closer evaluation of drugs prescribed to end-of-life patients.

Our findings suggest that the review of drug medications, optimizing polypharmacy and deprescribing could be further improved in older adults discharged with a very limited life expectancy (e.g., less than 3 months). A consensus framework, or shared criteria with deprescribing guidelines for potentially inappropriate medication, could be useful in rationalizing drug therapy. Careful consideration of a patient’s life expectancy, the time to benefit of treatments, goals of care, and treatment targets for each drug (including those used for a long time before the end-of-life period) is important for recommending any rational framework for decision making [2, 5, 18].

There may be several reasons for physicians not considering the discontinuation of futile medications in patients with a limited life expectancy. Scant awareness, as well the reactions of patients or their relatives, seems to be an important factor [19]. Unexpectedly, patients may be more willing to stop unnecessary medications than their physicians believe, as observed in a study of older patients with multiple chronic morbidities who were favorable to discontinue medication in 90% of cases [20].

Emphasizing the positive aspects of stopping medicines, such as reducing the burden of taking pills, rather than insisting on the uselessness of continuation, may be a helpful approach [21] that physicians could emphasize in conversations with patients and relatives.

The strength of this study is that this it analyzes how the hospital transition can be associated with changes in preventive and symptomatic medications by internal medicine and geriatric specialists for patients with a limited life expectancy.

This study has some limitations. First, REPOSI was not specifically designed to collect information about patients with a limited life expectancy and only those able to give written informed consent were enrolled, thus excluding those who were too frail to give consent. The sample of patients is very small, because we focused on patients in ‘critical conditions’, so we could assess the use of preventive or symptomatic drugs in patients with a limited life expectancy according to the clinical evaluation.

### Conclusion

Hospital discharge is associated with a small reduction in the use of commonly prescribed preventive medications in patients discharged with a limited life expectancy. Cardiovascular drugs are the most frequent potentially avoidable preventive medications. A consensus framework or shared criteria for potentially inappropriate medication in elderly patients with a limited life expectancy could help improve drug prescription.
Acknowledgement

REPOSI is a network of Italian internal medicine hospital wards which, voluntarily and with no financial support, agreed to participate in the collection of data for this study over the 4 index weeks (see the Appendix for a list of investigators and coauthors of the REPOSI Study Group). The authors are grateful to J.D. Baggott for editorial assistance.

Disclosure Statement

The authors declare no conflict of interests.

Appendix

The investigators and coauthors of the REPOSI Study Group are as follows:

Steering committee: Pier Mannuccio Mannucci (Chair, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy); Alessandro Nobili (Cochair, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy); Mauro Tettamanti, Luca Pasina, and Carlotta Franchi (IRCCS-Istituto di Ricerche Farmacologiche Mario Negri); Salvatore Corrao (ARNAS Cívico, Di Cristina, Benfratelli, DiBiMIS, Università di Palermo, Palermo, Italy); Alessandra Marengoni (Spedali Civili di Brescia, Brescia, Italy); Francesco Salerno (IRCCS Policlinico San Donato Milanese, Milan, Italy), Matteo Cesari (UO Geriatria, Università degli Studi di Milano), Francesco Perticone (President, SIMI); Giuseppe Licata (Medicina Interna e Cardioangiologia, Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Italy); Francesco Violi (Prima Clinica Medica, Policlinico Umberto I, Rome, Italy); and Gino Roberto Corazza, (Clinica Medica I, Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Italy).

Clinical data monitoring and revision: Carlotta Franchi and Laura Cortesi (IRCCS-Istituto di Ricerche Farmacologiche Mario Negri).

Database management and statistics: Mauro Tettamanti, Laura Cortesi, and Ilaria Ardoino (IRCCS-Istituto di Ricerche Farmacologiche Mario Negri).

Investigators

Italian Hospitals

Domenico Prisco, Elena Silvestri, Caterina Cenci, and Giacomo Emmi (Medicina Interna Interdisciplinare, Azienda Ospedaliero Universitaria Careggi Firenze); Gianni Biolo, Michelina Zanetti, Martina Guadagni, and Michele Zacca (Clinica Medica Generale e Terapia Medica, Azienda Sanitaria Universitaria Integrata di Trieste); Massimo Vanoli, Giulia Grignani, and Edoardo Alessandro Pulixi (Medicina Interna, Azienda Ospedaliera della Provincia di Lecco, Ospedale di Merate, Lecco); Mauro Bernardi, Silvia Li Bassi, Luca Santi, and Giacomò Zacerbelli (Semeiologia Medica Bernardi, Azienda Ospedaliero Policlinico Sant’Orsola-Malpighi, Bologna); Elmo Mannarino, Grazianna Lupattelli, Vanessa Bianconi, and Francesco Paciluo (Medicina Interna, Azienda Ospedaliera Santa Maria della Misericordia, Perugia); Ranuccio Nuti, Roberto Valenti, Martina Ruvio, Silvia Cappelli, and Alberto Palazzuoli (Medicina Interna I, Azienda Ospedaliero Università Senese, Siena); Olivierio Olivieri, Domenico Girelli, and Thomas Matteazzi (Medicina Generale a indirizzo Immuno-Ematologico e Emocoagulativo, Azienda Ospedaliera Universitaria Integrata di Verona, Verona); Mario Barbagallo, Ligia Dominguez, Floriana Cocita, Vincenza Beneduce, and Lidia Planes (Unità Operativa di Geriatria e Lungodegenza, Azienda Ospedaliero Universitaria Policlinico P. Giaccone di Palermo); Marco Zoli, Ilaria Lazzari, and Mattia Brono (Unità Operativa di Medicina Interna, Azienda Ospedaliero Universitaria Policlinico Sant’Orsola-Malpighi; Franco Laghi Pasini and Pier Leopoldo Capeccich (Unità Operativa Complessa Medicina 2, Azienda Ospedaliero Università Senese); Giuseppe Palaciano, Maria Ester Modeo, and Carla Di Gennaro (Medicina Interna Ospedaliero L. D’Agostino, Medicina Interna Universitaria A. Murri, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari); Maria Domenica Cappellini, Diletta Maira, Valerie Di Stefano, Giovanna Fabio, Sonia Seghezzi, and Marta Markcilia (Unità Operativa Medicina Interna 1A, Fondazione IRCCS Cà Grand Ospedale Maggiore Policlinico); Matteo Cesari, Paolo Dionigi Rossi, Sarah Damanti, Marta Clerici, and Federica Conti (Geriatria, Fondazione IRCCS Cà Grand Ospedale Maggiore Policlinico); Gino Roberto Corazza, Emanuela Miceli, Marco Vincenzo Lenti, Martina Pisati, and Costanza Caccia Dominioni (Clinica Medica I, Reparto 11, IRCCS Policlinico San Matteo di Pavia); Giovanni Murielado, Alessio Marra, and Federico Cattaneo (IRCS Azienda Ospedaliero Universitaria San Martino-IST di Genova, Genoa); Maria Beatrice Lucchi and Davide Ghelli (Divisione Medicina, Ospedale Bassini di Cinisello Balsamo, Milano); Luigi Anastasio, Lucia Sofia, and Maria Carbone (Medicina Interna, Ospedale Civile Jozzolo di Vibo Valentia, Vibo Valentia); Francesco Cipollone, Maria Teresa Guagnano, Ermanno Angelucci, and Emanuele Valerian (Clinica Medica, Ospedale Clinicoizzato SS. Annunziata, Chieti); Gerardo Mancuso, Daniela Calipari, and Mosè Bartone (Unidad Operativa Complessa Medicina Interna, Ospedale Giovanni Paolo II Lamezia Terme, Catanzaro); Giuseppe Delitala and Maria Berria (Clinica Medica, Azienda Ospedaliero-Universitaria di Sassari); Maurizio Muscaritoli, Alessio Molfino, and Enrico Petrilillo (Medicina Interna e Nutrizione Clinica, Policlinico Umberto I, Sapienza Università di Roma); Giuseppe Zuccalà and Gabriella D’Aurizio (Unità Operativa Complessa Medicina d’Urgenza e Pronto Soccorso, Policlinico Universitario A. Gemelli, Rome); Giuseppe Romanelli, Alessandra Marengoni, and Alberto Zucchelli (Geritaria, Spedali Civili di Brescia); Antonio Picardi, Umberto Vespasiani Gentilucci, Paolo Gallo, and Chiara Dell’Ungo (Medicina Clinica-Epatologica, Università Campus Biomedico, Rome); Giorgio Annoni, Maurizio Corsi, Giuseppe Bellelli, Sara Zazzetta, Paolo Mazzola, Hajnalka Szabo, and Alessandra Bonfanti (Unità Operativa di Geriatría, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza); Franco Arturi, Elena Succurro, and Mariangela Rubino (Unità Operativa di Medicina Interna, Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza).
Spanish Hospitals
Nieves Ramirez Duque (Hospital Universitario Virgen del Rocío, Sevilla); Alberto Muela Molinero (Hospital de León); Pedro Abad Requejo, Vanessa Lopez Pelaye, and Lara Tamargo (Hospital del Oriente de Asturias, Arriondas); Xavier Corbella Viros and Francesc Formiga (Hospital Universitario de Bellvitge); Jesús Diez Manglano, Esperanza Bejarano Tello, Esther Del Corral Behamonte, and Maria Sevil Puras (Hospital Royo Villanova, Zaragoza); Manuel Romero (Hospital Infanta Elena Huelva); Blanca Pinilla Llorente, Cristina Lopez Gonzalez-Cobos, and M. Victoria Villalba García (Hospital Gregorio Marañon, Madrid); Saez Lopez and Juan Bosco (Hospital Universitario de Puerto Real, Cadiz); Susana Sanz Baena, Marta Arroyo Gallego (Hospital Del Henares De Coslada, Madrid); Concepcion Gonzalez Becerra, Antonio Fernandez Moyano, Mercedes Gomez Hernandez, and Manuel Poyato Borrego (Hospital San Juan De Dios Del Aljarafe, Sevilla); Raquel Pacheco Cuadros, Florencia Perez Rojas, Beatriz Garcia Olid, and Sara Carrascosa Garcia (Hospital Virgen De La Torre De Madrid); Alfonso Gonzalez-Cruz Cervellera, Marta Peinado Martinez, and Sara Carrascosa Garcia (Hospital General Universitario De Valencia); Alberto Ruiz Cantero, Antonio Albarracin Arriaga, Montserrat Godoy Guerrero, and Miguel Angel Baron Ramos (Hospital De La Serrania De Ronda); Machin Jose Manuel (Hospital Universitario De Guadalajara); Ignacio Novo Veleiro, Lucia Alvela Suarez (Hospital Universitario De Santiago De Compostela); Alfonso Lopez, David Rubal Bran, and Iria Iñiguez Vazquez (Hospital Lucus Augusti De Lugo); and Monica Rios Prego (Hospital Universitario De Pontevedra).

References
1 O’Mahony D, O’Connor MN. Pharmacother-apy at the end-of-life. Age Ageing. 2011 Jul; 40(4):419–22.
2 Cruz-Jentoft AJ, Boland B, Rexach L. Drug therapy optimization at the end of life. Drugs Aging. 2012 Jun;29(6):511–21.
3 Blass DM, Black BS, Phillips H, Finucane T, Marrs T, Schmader KE, Barber N, Fried TR, O’Leary J, Towle V, Goldstein MK, Morgan NA, Rowett D, Currow DC. Analysis of drug interactions at the end of life. BMJ Support Palliat Care. 2015 Sep;5(3):281–6.
4 Frechen S, Zoeller A, Volpi, Pietro Bocchi, and Alessandro Vignali (Clinica e Terapia Medica, Azienda Ospedaliera Universitaria di Parma); and Sergio Harari, Chiara Lonati, and Mara Cattaneo (U.O. Medicina Generale, Ospedale San Giuseppe Multimedica Spa)
5 Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul;35(9):745–58.
6 Maddison AR, Fisher J, Johnston G. Preven-
tive medication use among persons with limited life expectancy. Prog Palliat Care. 2011 Jan;19(1):15–21.
7 Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul;35(9):745–58.
8 Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006 Dec;114(25):2788–97.
9 Reid DM, Hosking D, Kendall D, Brandi ML, Wark JD, Marques-Nets JP, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmeno-
pausal women with osteoporosis: 24-month results from FACTS-International. Int J Clin Pract. 2008 Apr;62(4):575–84.
10 Steinman MA, Hanlon JT. Managing medica-
tions in clinically complex elders: “There’s got to be a happy medium”. JAMA. 2010 Oct; 304(14):1592–601.
11 Reid DM, Hosking D, Kendall D, Brandi ML, Wark JD, Marques-Nets JP, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmeno-
pausal women with osteoporosis: 24-month results from FACTS-International. Int J Clin Pract. 2008 Apr;62(4):575–84.
12 Wright JM, Musini VM. First-line drugs for hypertension. Cochrane Database Syst Rev. 2009 Jul;35(9):745–58.
13 Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006 Dec;114(25):2788–97.
14 Reid DM, Hosking D, Kendall D, Brandi ML, Wark JD, Marques-Nets JP, et al. A comparison of the effect of alendronate and risedronate on bone mineral density in postmeno-
pausal women with osteoporosis: 24-month results from FACTS-International. Int J Clin Pract. 2008 Apr;62(4):575–84.
15 A practical guide to stopping medicine in older people. Best Pract J. 2010;27:11–22.
16 Pasina L, Brucato AL, Diade CD, Di Gorato P, Ghidoni S, Tettamanti M, et al.; REPOSI Investigators. Inappropriate prescription of allopurinol and febuxostat and risk of adverse

events in the elderly: results from the REPOSI registry. Eur J Clin Pharmacol. 2014 Dec; 70(12):1495–503.
17 Scott IA, Hiliner SN, Reeve E, Potter K, Le Couteur D, Bigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015 May; 175(5):827–34.
18 Fried TR, O’Leary J, Towele V, Goldstein MK, Trentalange M, Martin DK. Health out-
comes associated with polypharmacy in community-dwelling older adults: a system-
atic review. J Am Geriatr Soc. 2014 Dec;62(12):2261–72.
19 Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007 Jul;370(9582):173–84.
20 Hajjar ER, Cañiero AC, Hanlon JT. Polyphar-
macy in elderly patients. Am J Geriatr Phar-
cmacy. 2007 Dec;5(4):345–51.
21 Morgan NA, Rowett D, Currow DC. Analysis of drug interactions at the end of life. BMJ Support Palliat Care. 2015 Sep;5(3):281–6.
22 Crediblemeds [Internet]. Risk categories for drugs that prolong QT & induce torsades de points (TdP) [cited 2018 Jan 10]. Available from: https://www.crediblemeds.org.