

# Appropriateness of pharmacological treatment in older people with dementia

Eleonora Meloni, Davide Liborio Vetrano, Roberto Bernabei, Graziano Onder

Department of Geriatrics, Neurosciences and Orthopedics, Catholic University of Sacred Heart, Rome, Italy

## ABSTRACT

Dementia is associated with a number of comorbidities often observed in older people, including hypertension, cardiovascular disease, stroke and diabetes. Treating these comorbidities in older adults with dementia results challenging for many reasons. First, older adults with dementia are generally excluded from clinical trials, so application of clinical guidelines for treatment of chronic diseases in this population might lead to polypharmacy and adverse drugs effects. Second, memory, intellectual function, judgment and language are commonly impaired in patients with cognitive deficits, compromising the compliance to complex pharmacological regimens, increasing the risk of adverse drug reactions. Third, cognitive impairment is associated with limited life expectancy and therefore limits the efficacy of pharmacological treatments and questions the appropriateness of treatment. In the present study we examine most relevant concerns related to the treatment of comorbidities in demented patients, referring also to the existing criteria for inappropriate drugs in the elderly. The application of such instruments, along with the comprehensive geriatric assessment of the older adult with cognitive impairment, could result useful to reduce the burden of polypharmacy and inappropriate drug prescriptions.

## Introduction

Dementia is a syndrome characterized by progressive impairment in memory, cognitive functions and behavior, caused by progressive and irreversible damage of cerebral structures and functions. Among the different types of dementia, Alzheimer's disease is

generally considered the most common, accounting for 60% to 80% of all cases. Dementia could be considered a typical and paradigmatic geriatric syndrome, in fact, its prevalence increases exponentially with age, rising from 3% among those 65-74 years to almost 50% among those 85 years or older<sup>1</sup> and this condition is associated with negative health outcomes including impaired physical function, institutionalization and hospital admission, leading to increased resources consumption and health care costs. The global population aging makes dementia an emergent disease worldwide: it was estimated that 35.6 million people were living with dementia in 2010 and the number of cases was estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050.<sup>2</sup> This outbreak of dementia has deep economic, political and social consequences. The total estimated worldwide costs of dementia were US\$ 604 billion in 2010, equal to costs of cancer, heart disease, and stroke combined.<sup>3</sup> Incalculable are, instead, the *social costs* of a person with dementia, for his or her family and caregivers, often shaping the life of all relatives.

Correspondence: Eleonora Meloni, Department of Geriatrics, Neurosciences and Orthopedics, Catholic University of Sacred Heart, L.go Francesco Vito 1, 00135 Rome, Italy.  
Tel.: +39.06.30154341 - Fax: +39.06.3051911.  
E-mail: meloni.eleonora@hotmail.it

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## Treatment of comorbidities in dementia

The management of patients with dementia is often challenging, in particular in the advanced stages of disease, when the presence of cognitive deficits is further complicated by comorbidities, geriatric syndromes (delirium, falls, malnutrition, etc.) and functional deficits. Dementia is a condition with a long clinical history so that people with this condition are likely to

suffer from a number of other diseases typical of age, such as diabetes, cardiovascular diseases, osteoporosis, *etc.*, resulting in the concomitant use of a high number of drugs (polypharmacy). According to guidelines, physicians should treat, on average, every disease with three drugs, and in adults aged 80 or older with an average of 3.3 diseases, this would result in an average of 10 drugs per person.<sup>4</sup> Nevertheless, geriatric patients, and those with dementia in particular, are usually excluded by the major clinical trials, so findings of these studies cannot be generalized to people with dementia and recommendations of clinical guidelines are not applicable to this population. Indeed, systematic treatment of comorbidities based on clinical guidelines in complex older adults with dementia might lead to an elevated rate of iatrogenic illnesses or adverse drug reactions (ADRs), both because of disease-drug interactions and drug-drug interactions.

Table 1 summarizes factors most commonly limited the benefits of prescribed drugs in dementia.<sup>5</sup> The cognitive impairment occurring during late stages of the disease, limits the ability of the patient to speak and to express thoughts or problems and so his capacity to explain symptoms or problems related to an ADR. At the same time, it is difficult to understand the benefits received by symptomatic drugs, with the risk of overdose or keeping on unnecessary therapies (*i.e.*, analgesics). Finally, in patients with dementia correct interpretation of symptoms is often difficult and this might lead to inappropriate drug use. For example in a patient with dementia pain, constipation or fecal impaction may present as psychomotor agitation. This can be mistaken for behavioral disorder and cause the prescription of antipsychotic drugs, increasing polypharmacy and risk of adverse events. In addition, misinterpretation of side effects of drugs might lead to a *prescribing cascade*. This phenomenon happens when a new symptom is not caused by a new disease, but the manifestation of an ADR. This can lead to the prescription of a new drug and, in a dangerous circle, to polypharmacy, inappropriate polypharmacy and increased number of iatrogenic illnesses.

Another issue factor limiting the benefits of drugs prescribed for the treatment of comorbidities in patients with dementia is poor adherence. Adherence to long-term therapies is a relevant factor limiting the benefits of drug therapy. An older patient with dementia takes an average of 7-8 drugs and he/she is often at higher risk of drug errors and poor adherence because of cognitive problems. Adherence rate of patients with cognitive impairment, ranging from 42% to 97%, is another factor limiting the benefits of drug therapy. It depends on the occurrence of adverse drug reaction, the presence and competence of the caregiver and the complexity of the regimen.<sup>6</sup> In addition, adherence might be limited in patients with advanced dementia by feeding problems which make the oral administration of several medications difficult.

Another aspect that makes questionable the use of a particular drug in older people affected by dementia is the reduced life expectancy, which might impact on the risk-benefit ratio of a therapy. In a study conducted on 126 patients with dementia, the average life span from the onset of the disease was 9 years, whereas the average survival of a patient at the end stage of the disease was less than a year.<sup>7</sup> Therefore, drugs that have effective benefits only after years should be reconsidered in function of life expectancy. With the progression of the disease, approaches or treatment of *prevention* should be replaced by palliative cares and drugs to prolong life should be replaced by drugs that improve the quality of life and reduces symptoms and discomfort. For example, in a study by Onder *et al.* polypharmacy was associated with increased mortality among residents with limited life expectancy (identified by ADEPT score  $\geq 13.5$ ) but not among those without limited life expectancy (ADEPT score  $< 13.5$ ). Furthermore, no differences were found regarding the use of medications between the two groups.<sup>7</sup> These findings underline the need to assess life expectancy in older adults to improve the prescribing process and to simplify drug regimens among those with limited life expectancy.

Finally, anticholinergic properties of prescribed drugs might worsen cognitive function in dementia.

**Table 1. Issues related to treatment of comorbidities in patients with dementia.**

Problem	Consequences
Cognitive impairment and difficulty to speak	Impaired ability to make decisions Increased burden on the caregiver Reduced adherence to therapy Difficulties in reporting adverse events Difficulty titrating medicines based on symptoms reported by the patient
Reduced life expectancy	Reduction of the potential benefits
Exclusion from clinical trial of elder patients with dementia	Uncertainty about effects of therapy
Anticholinergic burden	Negative cognitive effects from anticholinergic effects of non-dementia drugs

Adapted from Brauner *et al.*, 2000.<sup>5</sup>

Some drugs, routinely used for common condition such as asthma, urinary incontinence and various psychiatric disorders, have an intrinsic well known anticholinergic activity. It has been demonstrated that these drugs have effects on central nervous system, especially in older patients due to the decrease in cholinergic neurons and receptors, the reduction in hepatic and renal metabolism and excretion and the larger blood-brain permeability.<sup>8</sup> They can be cause of both acute delirium and chronic effects on cognition that are more frequent in patients with cognitive impairment. The anticholinergic cognitive burden scale is an instrument to calculate the potential anticholinergic burden of a therapy; grading with a score the anticholinergic impact of a drug. In the study of Carriere and coll., conducted on 6912 subjects evaluated for cognitive performance, clinical diagnosis of dementia and anticholinergic use, at baseline and after 2 and 4 years of follow up, patients reporting continuous anticholinergic therapies showed greater decline in global cognitive function and a higher risk of incident dementia than patients not using anticholinergic drugs.<sup>9</sup> Physicians should carefully consider prescription of anticholinergic drugs in elderly people especially in the oldest with cognitive impairment where their use is also associated with impaired physical performance and functional status.<sup>10</sup>

conducted and aimed at defining inappropriate drug use, its consequences and how to reduce its prevalence. Indeed, inappropriate drug use is associated with increased risk of adverse drug events, functional decline, cognitive impairment, falls, hospitalization and death.<sup>11</sup> In the past decades, several implicit and explicit criteria have been published from several groups, in order to define appropriateness of drug prescription, as the Beers, the STOPP, the Holmes and the CRIME criteria. These criteria include specific recommendations for patients with dementia (Table 2).

The Beers criteria provide an instrument to identify drugs for which the risk in older adults outweighs potential benefits. Since 1991, Beers and colleagues have produced a list of medications for identifying the inappropriate drug use, which was recently revised and updated in 2012 by the American Geriatrics Society.<sup>12</sup> Potentially inappropriate medications are divided into three groups: medications to avoid in older adults regardless of disease or conditions, medications considered potentially inappropriate when used in older adults with certain diseases or syndrome and medications to be used with caution in older adults. The second group includes drugs inappropriate in people with dementia, such as drugs with adverse central nervous system effects including drugs with anticholinergic properties and benzodiazepines and those associated with increased risk of stroke and mortality in this population including antipsychotics.

Similarly, the STOPP (screening tool of older persons' potentially inappropriate prescriptions), is constituted by 68 recommendations on drugs to avoid, arranged according to physiological system target.<sup>13</sup>

## Appropriateness of prescribing

The appropriateness of prescribing is a central issue in geriatric medicine. Many studies have been

**Table 2. Inappropriate drugs in older patients with dementia according to available criteria.**

### 2012 Beers criteria

Anticholinergics (antihistamines: loratadine, chlorpheniramine; antidepressants: amitriptyline, paroxetine; bladder antimuscarinics: oxybutynin, tolterodine; antiparkinson agents: bethanechol, trihexyphenidyl; antipsychotics: chlorpromazine, olanzapine; antispasmodics: atropine products, scopolamine; skeletal muscle relaxants: cyclobenzaprine), benzodiazepines, H<sub>2</sub>-receptor antagonists, zolpidem, antipsychotics (chronic and as-needed use)

### STOPP criteria

Tricyclic antidepressants, long-acting benzodiazepines, neuroleptics as long-term hypnotics  
Bladder antimuscarinic drugs, long-term opiates (unless indicated for palliative care or moderate/severe chronic pain)

### CRIME criteria (not recommended in cognitive impairment or dementia)

Intensive glycemic control or use of insulin  
Statins in advanced dementia  
Anticoagulants and drugs with a narrow therapeutic index (including warfarin and digoxin) if any of the following characteristics are present: unable to manage medications or living alone  
Use of more than three antihypertensive drugs or a tight blood pressure control (<140/90 mmHg)

### Holmes criteria (advanced dementia)

#### Rarely appropriate

α-blockers, antiandrogens, appetite stimulants, digoxin, bisphosphonates, bladder relaxants, clonidine, mineralcorticoids, tamsulosin, antiarrhythmics, heparin and low molecular-weight heparins, antispasmodics, hydralazine, warfarin

#### Never appropriate

Lipid-lowering medications, N-methyl-D-aspartate receptor antagonists (memantina), cytotoxic chemotherapy, antiplatelet agents (excluding aspirin), antiestrogens, hormone antagonists, leukotriene receptor antagonists, sex hormones, immunomodulators, acetylcholinesterase inhibitors

Tricyclic antidepressant and long-term opiates (unless indicated for palliative care) due to their risk of worsening cognitive-impairment are considered as potentially inappropriate based on the STOPP criteria in patients with dementia.

Treating multimorbidity in elders with dementia is a challenge for prescribing physicians. As mentioned, the use of drugs to treat non-dementia illnesses in older adults with severe cognitive impairment might be questionable and may lead to serious adverse effects, even when clearly beneficial drugs recommended by clinical guidelines are prescribed. These concerns represent barriers to pharmacological treatment of complex patients with severe cognitive impairment and should be carefully evaluated by prescribing physicians when treating older persons with this condition.

For this reason Holmes and colleagues have developed a set of criteria to identify inappropriate drug treatment, which can be stopped or should not be started in patients with advanced dementia. The Holmes criteria were drawn by a consensus panel of experts, part of the palliative excellence in Alzheimer care efforts (PEACE) program, with the purpose to decrease polypharmacy in the elderly and to reduce the use of medications that are of minimal benefit or high risk to the patients. Inappropriate prescribing in dementia was classified into four categories: never appropriate, rarely appropriate, sometimes appropriate or always appropriate.<sup>14</sup> Applying such criteria in a sample of severe cognitively impaired nursing home residents, Colloca and coll. found that about 44% of patients had been taking a drug considered to be inappropriate or rarely appropriate. These drugs were lipid-lowering agents, antiplatelet agents (excluding acetylsalicylic acid), acetyl-cholinesterase-inhibitors and antispasmodics.<sup>15</sup> Even in this study, the presence of a geriatrician in the facility was associated with a lower prevalence of inappropriate prescription.

More recently the CRIME research group provided recommendations to guide pharmacological prescription in older complex patients, translating the recommendations of clinical guidelines to patients with a limited life expectancy, functional and cognitive impairment, and geriatric syndromes. These recommendations identified areas of prescribing where drugs recommended by clinical guidelines for treatment of chronic diseases might not be considered appropriate in complex older adults.<sup>16</sup>

## Conclusions

In conclusion, older adults with cognitive impairment represent a group at high risk of adverse drug reactions, due to the elevated prevalence of polypharmacy, and the related risk of inappropriate pre-

scription. Today no definitive data are available to guide the physician during the prescribing process and, consequentially, no specific guidelines, regarding multimorbid elders with cognitive impairment, have been issued. For this reason, a great deal of attention should be paid to the pharmacological management of such patients. The application of the above mentioned tools, along with a holistic evaluation of the older adult with cognitive impairment, represent two effective and reliable instruments potentially able to reduce the occurrence of drug-related side effects. In this sense, further and stronger evidences are necessary from dedicated studies.

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