Sperimentazione di percorsi assistenziali integrati per la prevenzione delle complicanze della malattia di Alzheimer sulla base del modello ampliato del Chronic Care Model nell’ASP di Catanzaro

La diffusione delle malattie croniche e le risposte dei sistemi sanitari: la situazione internazionale, italiana e calabrese

Il paziente con Alzheimer: dalla comorbidità alla politerapia

Pietro Gareri, MD, PhD

20 Ottobre 2012
Late-Life Dementias: Does This Unyielding Global Challenge Require a Broader View?

Thomas J. Montine, MD, PhD\(^1\) and Eric B. Larson, MD, MPH\(^2\)

- If the pace of increase in life expectancy in developed countries over the past two centuries continues through the 21\(^{st}\) century, most babies born since 2000 in France, Germany, Italy, the UK, the USA, Canada, Japan, and other countries with long life expectancies will celebrate their 100th birthdays.
- Prevalence rates for dementia are estimated to double every 5 years after age 65.
- Rates of dementia in community studies increase from 30\% for persons aged 85 through 89 years to 50\% for persons aged 90 through 94 years to 74\% for those 95 years or older.
- Given the burden of dementia on patients, families, and caregivers, the high rates in late life, and the clear demographic trends, it is imperative for research to find solutions that prevent, delay, slow, and treat Alzheimer disease and related dementias.
Prevalence of Chronic Diseases and Multimorbidity Among the Elderly Population in Sweden

Alessandra Marengoni, MD, PhD; Bengt Winblad, MD, PhD; Anita Karp, PhD; and Laura Fratiglioni, MD, PhD

We explored the role of age, gender, and socioeconomic status in the occurrence of chronic diseases and multimorbidity in 1099 elderly participants in the Kungsholmen Project. Cardiovascular and mental diseases were the most common chronic disorders. Of the participants, 55% had multimorbidity. Advanced age, female gender, and lower education were independently associated with a more than 50% increased risk for multimorbidity. Multimorbidity is the most common clinical picture of the elderly and may be increased by unhealthy behaviors linked to education. (Am J Public Health. 2008;98:1198–1200. doi:10.2105/AJPH.2007.121137)

To compare the medical comorbidity of older patients with and without dementia in primary care.

Cross-sectional study.

Three thousand thirteen patients aged 65 and older attending seven primary care centers in Indianapolis, Indiana.

An expert panel diagnosed dementia using International Classification of Diseases, 10th Revision, criteria. Comorbidity was assessed using 10 physician-diagnosed chronic comorbid conditions and the Chronic Disease Score (CDS).

Patients with dementia attending primary care have on average 2.4 chronic conditions and receive 5.1 medications. Approximately 50% of dementia patients in this setting are exposed to at least one anticholinergic medication, and 20% are prescribed at least one psychotropic medication. After adjusting for patients' age, race, and sex, patients with and without dementia have a similar level of comorbidity (mean number of chronic medical conditions, 2.4 vs 2.3, P=.66; average CDS, 5.8 vs 6.2, P=.83).
Table 3. Comorbidity Profile of Older Adults with and without Dementia Attending Primary Care Clinics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Dementia</th>
<th>Dementia</th>
<th>P-value</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic comorbid conditions, mean ± SD*</td>
<td>2.3 ± 1.4</td>
<td>2.4 ± 1.4</td>
<td>.37†</td>
<td>.66</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>73.5</td>
<td>82.2</td>
<td>.04†</td>
<td>.06</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>34.9</td>
<td>39.3</td>
<td>.36‡</td>
<td>.19</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>20.5</td>
<td>20.6</td>
<td>1.00‡</td>
<td>.97</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>9.4</td>
<td>10.3</td>
<td>.74‡</td>
<td>.89</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>14.6</td>
<td>14.0</td>
<td>1.00‡</td>
<td>.47</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, %</td>
<td>16.7</td>
<td>12.2</td>
<td>.24‡</td>
<td>.33</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>12.0</td>
<td>8.4</td>
<td>.36‡</td>
<td>.17</td>
</tr>
<tr>
<td>Osteoarthritis, %</td>
<td>36.5</td>
<td>41.1</td>
<td>.36‡</td>
<td>.65</td>
</tr>
<tr>
<td>Liver failure, %</td>
<td>0.8</td>
<td>0.0</td>
<td>1.00‡</td>
<td>.98</td>
</tr>
<tr>
<td>Renal failure, %</td>
<td>8.3</td>
<td>11.2</td>
<td>.28‡</td>
<td>.77</td>
</tr>
</tbody>
</table>

Medication-based comorbidity
- Chronic disease score, mean ± SD          | 6.2 ± 4.7   | 5.8 ± 4.0| .39†    | .83              |
- Number of medications, mean ± SD          | 6.1 ± 5.0   | 5.1 ± 3.8| .05†    | .24              |
- Receiving definite ACH, %                  | 25.7        | 21.5     | .37‡    | .68              |
- Receiving possible ACH, %                  | 46.5        | 40.2     | .24‡    | .27              |
- Receiving any ACH, %                       | 55.4        | 49.5     | .24‡    | .37              |
- Receiving anxiolytics, %                   | 7.2         | 6.5      | 1.00‡   | .82              |
- Receiving antidepressants, %               | 19.7        | 11.2     | .03‡    | .17              |
- Receiving antipsychotics, %                | 2.3         | 3.7      | .31‡    | .26              |
- Receiving any psychotropic, %              | 24.9        | 19.6     | .25‡    | .73              |

Table 2. Demographic Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Dementia (n = 2,906)</th>
<th>Dementia (n = 107)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± standard deviation</td>
<td>71.1 ± 5.6</td>
<td>75.6 ± 6.2</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Female, %</td>
<td>70.6</td>
<td>62.6</td>
<td>.09†</td>
</tr>
<tr>
<td>African American, %</td>
<td>59.7</td>
<td>69.2</td>
<td>.06†</td>
</tr>
</tbody>
</table>

CONCLUSION: Multiple medical comorbid conditions are common in older adults with and without dementia in primary care. Despite their cholinergic deficit, a substantial proportion of patients with dementia are exposed to anticholinergic medications. Models of care that incorporate this medical complexity are needed to improve the treatment of dementia in primary care. J Am Geriatr Soc 54:104–109, 2006.
Co-Morbidity and Dementia

• Poor control of or acute exacerbation of conditions such as congestive heart failure, coronary artery disease, or chronic obstructive pulmonary disease may adversely affect the cognitive function of patients with dementia.

• Thus, attention to and aggressive treatment of co-morbidity is an important part of the care plan.

• As the dementia progresses, treatment goals vary, depending on patient-family values, quality of life, and symptoms and burden of proposed interventions.

• In the late stages of dementia, a more purely palliative or hospice care plan may call for treatment of other medical conditions only if they are producing symptoms.
Co-Morbidity and Dementia

• Abrupt changes in clinical status for patients with dementia usually signal an intercurrent illness, which is often treatable (e.g., urinary tract infection, pneumonia, malnutrition, constipation). Appropriate steps should be taken to identify and treat the underlying problem.

• Pain, dyspnea, agitation, depression, and other symptoms should be treated. Sometimes this can best be accomplished by treating the underlying condition (e.g., treating congestive heart failure or chronic obstructive pulmonary disease to relieve dyspnea). At other times, symptomatic measures may be more appropriate (e.g., morphine for dyspnea).
L’importanza della VMD

• CIRS

• ADL, IADL, Barthel Index

• MMSE

• GDS

• **MNA** (perdita di peso di più del 10% del peso corporeo ideale in 6 mesi; livelli di albuminemia < 2.5 g/dl)

STRUMENTI DI VALUTAZIONE

• CIRS o indice cumulativo di comorbilità
• GIC o indice geriatrico di comorbilità

• Valutazione del “burden of illness” (carico che le malattie comportano, in termini di costi economici e/o emotivi per la famiglia e la società)
• Gravità funzionale (impatto della malattia sulla capacità individuale di svolgere un’attività adeguata alla propria età)
• Gravità fisiopatologica e morfologica (tests di laboratorio, referti anatomici)
Comorbidity in AD patients tend to accelerate cognitive and functional decline.
MALATTIE CHE AGGRAVANO IL DISTURBO COGNITIVO

- Diabete
- BPCO
- Scompenso cardiaco
- Ipertensione

Mecocci et al., 2002
Undiagnosed diseases in patients with dementia – a potential target group for intervention.

Löppönen MK et al., Dement Geriatr Cog Disord, 2004

Percentuale dei soggetti con patologie non diagnosticate suddivisi in base alla severità della demenza
Treatment of obstructive sleep apnea syndrome (OSAS) with continuous positive airway pressure (CPAP) may delay cognitive decline in older adults with Alzheimer’s disease and related dementias (AD).

In this study, the investigators contacted all participants who had completed a 6-week randomized controlled trial (RCT) of the use of CPAP in persons with mild to moderate dementia and OSAS after approximately 1 year had elapsed.

The authors reported that sustained CPAP use in patients with AD resulted in moderate to large effect sizes on cognitive measures, depressive symptoms, daytime sleepiness, and patient and caregiver subjective sleep quality.
Impact of geriatric comorbidity and polypharmacy on cholinesterase inhibitors prescribing in dementia

Falk Hoffmann1*, Hendrik van den Bussche2, Birgitt Wiese3, Gerhard Schön4, Daniela Koller1, Marion Eisele2, Gerd Glaeske1, Martin Scherer2 and Hanna Kaduszkiewicz2

We suggest that a lack of contacts to specialists and geriatric morbidity patterns reduce the chance for patients with incident dementia of being prescribed a ChEI. It seems that not age as such but the occurrence of care dependency and geriatric comorbidities influences prescriptions.
Management of Demented Patients in Emergency Department

Lavinia Valeriani

Table 1: The diseases that most often drive the elderly to apply for an urgent evaluation.

Medical emergency
- Cardiovascular diseases (angina, heart failure, arrhythmias, syncope)
- Respiratory (acute exacerbation of chronic bronchitis, bronchial asthma, pneumonia)
- Cancer (cancer of the lung, breast, large bowel)
- Neurological diseases (acute cerebrovascular disease, altered state of consciousness)

Chirurgical emergency
- Trauma and fractures

Clinical emergency
- Dehydration, urinary tract infections, intestinal sub-ileus, delirium, behavioral disturbances and subsequent guidance of therapeutic prescription
- Acute respiratory failure from respiratory infection, acute myocardial infarction, sepsis

Clinical problems related to an incorrect home management
- Oversedation from psychopharmacological treatment, side effects from medications (iatrogenic hypotension, hypoglycemia jatrogena)

Table 2: Principal pathologies associated with patients with dementia.

For mild to moderate dementia:
- Tumours, diabetes, gastrointestinal disease

For severe dementia:
- Pneumonia and other infectious diseases, stroke, malnutrition, hip fractures, bed sores
**Table 3: Clinical assessment of patients with dementia.**

| Anamnesis: medical history collected or at least confirmed by the principal caregiver or a person who knows the history |
| Risk of underestimation of the symptom in older cognitively compromised |
| Objective examination: patient visit in order to capture significant clinical signs |
| Useful indicator of an underlying organic disease not reported or underestimated by the patient and the family |
| Pharmacological anamnesis: drug history of the patient |
| Many drugs may cause side effects, especially when administered by not clinical prepared persons |
| Vital signs: for better understanding of the patient’s general condition |
| Determination of blood pressure, heart rate, oxygen saturation (blood gas, or), body temperature, and glycemia |
Key points

• 12% of patients who are admitted to medical ward from the emergency department suffer from severe dementia, so it is possible to envisage a double rate if we include patients with dementia in mild to moderate impairment.

• It is necessary that the staff of the DEA is prepared (and not just on the field) to the assessment and planning of the elderly patient with dementia: how to recognize cognitive, sensory deficits, to identify the patient’s functional status and social resources at home are fundamental factors that drive both the diagnostic orientation and treatment choices (hospital care versus at home care).

• The low level of experience, and the lack of specific training in geriatric medicine for acute care and in relation to the elderly and their families, are factors contributing to increased stress for staff.
Comorbidità dei pz con demenza severa visitati negli ultimi 15 mesi

<table>
<thead>
<tr>
<th>Comorbilità</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipertensione Arteriosa</td>
<td>26,7</td>
</tr>
<tr>
<td>Cardiopatia</td>
<td>15,4</td>
</tr>
<tr>
<td>S. Immobilizzazione</td>
<td>16,9</td>
</tr>
<tr>
<td>Pregresso ictus cerebrale</td>
<td>9,8</td>
</tr>
<tr>
<td>Diabete Mellito, LaD</td>
<td>7,1</td>
</tr>
<tr>
<td>BPCO, depressioni</td>
<td>5,6</td>
</tr>
<tr>
<td>Neoplasie, fratture anca, conv...</td>
<td>4,2</td>
</tr>
<tr>
<td>IRC, MRGE, vasculopatie peri...</td>
<td>2,8</td>
</tr>
</tbody>
</table>

DEMENTIA ALZHEIMER

Associazioni molto frequenti nell’anziano demente

DEPRESSIONE
MORBO DI PARKINSON

Cause più frequenti di demenza potenzialmente reversibile

DEPRESSIONE
EFFETTI COLLATERALI DI FARMACI

Il trattamento delle condizioni “sottostanti” può determinare un miglioramento della maggior parte dei sintomi manifestati dal paziente
Recettori 5HT2

Piastrina

Depressione: ridotta 5HT

Up-regulation compensatoria 5HT2

Recettori 5HT2

Fibrinogeno: aumento aggregazione

Aumento adesione su parete vasale

Aumentato rilascio di fattori aggreganti (PF4 e β-TG)
### Table 1
Signs and symptoms indicating a sleep disorder

<table>
<thead>
<tr>
<th>Nighttime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apneic episodes</td>
</tr>
<tr>
<td>Frequent awakenings</td>
</tr>
<tr>
<td>Noticeable snoring</td>
</tr>
<tr>
<td>Wandering</td>
</tr>
<tr>
<td>Falls</td>
</tr>
<tr>
<td>Talking while asleep</td>
</tr>
<tr>
<td>Frequent leg movement during sleep or when lying in bed awake</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daytime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation, hostility, combativeness</td>
</tr>
<tr>
<td>Excessive daytime sleepiness and/or napping</td>
</tr>
<tr>
<td>Falls</td>
</tr>
<tr>
<td>Reduced cognitive function: problems in concentration, attention, and memory</td>
</tr>
<tr>
<td>Loss of physical function</td>
</tr>
<tr>
<td>Falling asleep early in the evening</td>
</tr>
<tr>
<td>Reduced participation in activities</td>
</tr>
<tr>
<td>Complaints by roommate or caregiver</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System stimulants</td>
<td>Modafinil, Caffeine</td>
<td>Sleep onset difficulties</td>
</tr>
<tr>
<td>Stimulating antidepressants</td>
<td>Protriptyline, bupropion, selective serotonin reuptake inhibitors, venlafaxine, monoamine oxidase inhibitors</td>
<td>Reduced REM sleep, short total sleep time</td>
</tr>
<tr>
<td>Lithium</td>
<td>Lithium</td>
<td>Daytime sleepiness</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Beta-blockers, alpha blockers</td>
<td>Insomnia, nightmares, vivid dreams, daytime fatigue</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Theophylline, albuterol</td>
<td>Sleep onset difficulties, increase in awakenings during night</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone, dexamethasone</td>
<td>Daytime fatigue, sleep onset difficulties, and increase in awakenings during night</td>
</tr>
<tr>
<td>Decongestants</td>
<td>Pseudoephedrine, phenylephrine</td>
<td>Sleep onset difficulties</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>diphenhydramine</td>
<td>Daytime sleepiness (older varieties)</td>
</tr>
<tr>
<td>Histamine Type 2 receptor antagonists</td>
<td>Cimetidine, ranitidine, famotidine, and nizatidine</td>
<td>Insomnia and somnolence</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Nonsteroidal Anti-inflammatory Drugs Opioids</td>
<td>Decreased sleep efficiency, Sedation, decrease REM and SWS</td>
</tr>
<tr>
<td>Antiparkinsonian Drugs</td>
<td>Levodopa/carbidopa (high doses), Dopamine agonists</td>
<td>Insomnia, daytime sleepiness</td>
</tr>
<tr>
<td>Antipsychotic Drugs</td>
<td>Clozapine, Olanzapine, Quetiapine</td>
<td>Sedation</td>
</tr>
</tbody>
</table>

Sources: (Ancoli-Israel, Ayalon, & Salzman, 2008; Salzman, 2008; Neubauer, 2008; Ancoli-Israel & Ayalon, 2009; Mintzer & Burns, 2000)
SINDROMI EXTRAPIRAMIDALI

SEGNI MOTORI DI TIPO EXTRAPIRAMIDALE MOLTO DIFFUSI NELLA DEMENZA

QUESTI MALATI PRESENTANO

* DETERIORAMENTO CLINICO PIU’ VELOCE

* SONO PIU’ ISTITUZIONALIZZATI

* SOPRAVVIVONO DI MENO

(Stem et al., 1994)
Segni extrapiramidali

Nella demenza compaiono dopo il disturbo cognitivo

Nel Parkinson seguito da demenza sono presenti fin dall’inizio
Delirium

• Demenza tra i principali fattori di rischio negli anziani

• Riguarda dal 22% all’89% degli anziani dementi ospedalizzati

• Aggrava quadro cognitivo e funzionale

• Bisogna riconoscerlo e trattarlo precocemente

Fick et al., 2002
ANTICHOLINERGIC DRUG-INDUCED DELIRIUM IN AN ELDERLY ALZHEIMER'S DEMENTIA PATIENT

P. GARERI\textsuperscript{a,b}, P. DE FAZIO\textsuperscript{c}, A. COTRONEO\textsuperscript{d}, R. LACAVA\textsuperscript{b}, L. GALLELLI\textsuperscript{a}, S. DE FAZIO\textsuperscript{a} and G. DE SARRO\textsuperscript{a•}
Valproate-induced delirium in a demented patient.
P. Gareri, R. Lacava, A. Cotroneo, N.M. Marigliano, A. Castagna, D.S. Costantino, G. Ruotolo, G. De Sarro
MALATTIE CONCOMITANTI NELLA DEMENZA

Fattore di rischio per decadimento cognitivo (associazione tra deficit di vit. B1, B12, PP, folati, magnesio e demenza)

Vitamine del gruppo B

Coinvolte nei processi metabolici che regolano la disponibilità di unità monocarboniose (sintesi DNA, mielina, DA, NA, 5-HT)

La loro carenza può danneggiare le strutture cerebrali indirettamente attraverso l’incremento dei livelli circolanti di omocisteina, aminoacido coinvolto nel metabolismo delle unità monocarboniose
DEMENTIA IN FASE TERMINALE

- Grave malnutrizione (spesso severa ipoalbuminemia, < 2.4 g/dl)
- Cadute
- Sindrome da immobilizzazione

RUOLO DELLA PREVENZIONE
(RICONOSCIMENTO DELLE CAUSE ED ATTUAZIONE DELLE DOVUTE CONTROMISURE)
Conseguenze della perdita di peso nell’ AD

• Compromissione del sistema immunitario = aumento del rischio di infezioni

• Perdita di massa muscolare = atrofia muscolare, declino funzionale, cadute e fratture

• Atrofia cutanea = rischio di ulcere

• Aumentato rischio di istituzionalizzazione
Il problema della malnutrizione

Feeding Tubes in Patients with Severe Dementia

INA LI, M.D., Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

April 15, 2002 / Volume 65, Number 8

www.aafp.org/afp

American Family Physician

Tube feeding does not prevent weight loss or improve nutritional markers such as hemoglobin, hematocrit, albumin, and cholesterol levels.

Data do not support the use of tube feeding in the prevention of pressure sores.

Giving patients small amounts of food, or using mouth swabs, sips of water, ice chips and lubrication of the lips, may be sufficient to alleviate hunger and thirst.
**TABLE 1**
Potential Complications Related to Percutaneous Endoscopic Gastrostomy Tubes

<table>
<thead>
<tr>
<th>Category</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Local pain, Suture breakage, Cellulitis of the abdominal, Abscess of the abdominal, Stomal inflammation, Skin excoriation, Bleeding from the site, Closure or stenosis of stom, Hematoma</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Erosion of bumper into abdomen, Tube leakage, Tube blockage, Tube migration or loose fix, Tube malfunction, Fractured tube, Kinked tube</td>
</tr>
<tr>
<td>Pleuropulmonary</td>
<td>Erosion of tube into pleura, Aspiration pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Flatulence, Nausea, Vomiting, Diarrhea, Ileus, Gastroesophageal reflux, Bowel obstruction (requiring jejunostomy), Intra-abdominal leak, Intra-abdominal peritonitis, Intra-abdominal bleeding, Gastric mucosal erosion, Gastric perforation, Upper gastrointestinal bleed, Necrotizing fasciitis</td>
</tr>
<tr>
<td>Other</td>
<td>Anorexia, Fluid overload, Increased skin moisture, Agitation, self-stimulation, Use of restraints, Metabolic disturbances, Loss of social aspects of feeding, Altered cosmnes, Fever, Sepsis</td>
</tr>
</tbody>
</table>

**Box 1** Review of evidence of tube feeding in patients with advanced dementia (Finucane et al, 1999)

- **Aspiration pneumonia.** No published studies to suggest tube feeding reduces risk
- **Prevention of malnutrition.** Delivering extra nutrients may not provide benefit to those in a catabolic state; additional nutrients might be beneficial in other instances, but effects might be outweighed by the adverse effects of tube feeding
- **Improving survival.** No published studies to suggest tube feeding prolongs survival in people with dementia and dysphagia
- **Prevention of pressure ulcers.** No published studies found to suggest tube feeding improves outcome for pressure sores
- **Risks of other infections.** No evidence that tube feeding reduces the risks of infection; in fact nasogastric feeding may increase the chances of sinus and middle-ear infection and PEG tubes the risk of diarrhoea, cellulitis and abscess
- **Functional status.** No published studies to support claims that tube feeding might improve functional abilities
- **Comfort.** No published studies to support claims that tube feeding might improve comfort

**TABLE 2**
Recommendations for Oral Feeding in Patients with Severe Dementia

- **Rationing pneumonia** for those patients at risk
  - Right (45 degrees) while eating
  - More than one teaspoon
  - Into the mouth
  - Coughs after each swallow
  - Multiple times after each mouthful of food to
  - Improve food intake
  - Flavors, amounts, consistency, and availability of food

- It may be helpful to:
  - Use cream, spices
  - Miniature chocolate bars
  - Units of food
  - E.g., sandwiches, chicken fingers
  - Foods in large quantities (e.g., ice cream)
  - Consistency to suit the individual
  - E.g., should be given one and one half to
  - For the next meal; should never be given with
  - Can promote satiety
  - Edible food (e.g., puddings, milkshakes)
  - Foods (e.g., cereals mixed with eggnog or pudding)
  - Useful to the patient
  - Times because it takes longer for demented
gest, chew, and swallow food
  - To keep their supplements (e.g., liquid
  - And/or candy bars) at the bedside

**Modify environmental factors**
- Capitalize on the midday meal when patients demonstrate
  - Maximal cognitive function
- For those resistive or combative at mealtime, try holding hands
  - Or reassuring touches on the arms, or try cheerful
  - Conversations or singing softly
Figure 1.
Kaplan-Meier estimation of cumulative proportion of nursing home residents who died

Comparison of median survival by diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Median Survival (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>50.57</td>
</tr>
<tr>
<td>No history of pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72.57</td>
</tr>
<tr>
<td>History of pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24.57</td>
</tr>
<tr>
<td>Alzheimer dementia</td>
<td>42.14</td>
</tr>
<tr>
<td>Mixed dementia and other dementias</td>
<td>83.43</td>
</tr>
</tbody>
</table>

<sup>a</sup>Within 6 months prior to enrollment

NIH Public Access
Author Manuscript

Predictors of mortality in nursing home residents with advanced dementia

Kathryn L. Hicks, BA, Betty S. Black, PhD, and Peter Rabins, MD, MPH
Il trattamento delle infezioni nel paziente affetto da demenza

- Le infezioni (polmonite e infezioni delle vie urinarie in particolare) rappresentano una complicanza frequente soprattutto nelle fasi avanzate della demenza.
- Si caratterizzano per una maggiore mortalità rispetto ai soggetti cognitivamente integri.
- La prognosi dei pazienti con demenza avanzata e comorbidità acuta è sfavorevole, anche quando il paziente viene ricoverato in ambiente ospedaliero e ciò sottolinea l’esigenza di una terapia che tenga conto anche della qualità della vita del paziente.
Survival in End-Stage Dementia Following Acute Illness

**Figure.** Kaplan-Meier Survival Curves for Patients With Hip Fracture and Pneumonia

- Patients With Hip Fracture (n = 97)
- Patients With Pneumonia (n = 119)

Morrison RS, Siu LA
JAMA. 2000;284:47-52
I pazienti con demenza in fase avanzata e frattura dell’anca o polmonitì avevano una prognosi sfavorevole.

Data la limitata aspettativa di vita nei pazienti con demenza terminale conseguentemente a queste patologie ed il carico associato al loro trattamento, bisognerebbe prestare maggiore attenzione al miglioramento della qualità di vita in questi pazienti.
Lesione sacrale al IV stadio in fase di iniziale colliquazione

Lesione in sede sacrale al IV stadio in fase necrotica

Lesione sacrale al IV stadio fibro-membranosa con zone di colliquazione

Lesione in sede trocanterica al III stadio detersa e in fase di granulazione - sottominata
Sintomi più comunemente riportati dalle persone affette da demenza nell’ultimo anno di vita

- confusione 83%
- incontinenza urinaria 72%
- dolore 64%
- umore triste 61%
- stipsi 59%
- perdita di appetito 57%

Fig. 1 A three-step hierarchy of drugs for pain relief (based on World Health Organization, 2006).
Fattori di rischio per problemi farmaco-correlati

- Età avanzata
- Demenza
- Farmaci a più elevato rischio
- Basso BMI
- Politerapia
- Numerosi prescrittori
- Condizioni croniche multiple
- Pazienti recentemente ospedalizzati
- Insufficienza renale cronica

Gareri & De Sarro, 2011
<table>
<thead>
<tr>
<th>Psicofarmaci</th>
<th>Barbiturici</th>
<th>Neurolettici  (soprattutto i classici)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benzodiazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oppiacei</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antidepressivi triciclici</td>
<td></td>
</tr>
</tbody>
</table>

**La gestione della politerapia**

- Corticosteroidi
- Anticolinergici
- Antiipertensivi
- Digitalici

Farmaci somministrati in combinazione (vedi interazioni possibili a livello dei citocromi)
# Drugs Metabolized by Known P450's 2000

**Georgetown University Medical Center**

<table>
<thead>
<tr>
<th>1A2</th>
<th>2C19</th>
<th>2C9</th>
<th>2D6</th>
<th>2E1</th>
<th>3A</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>Amitriptyline</td>
<td>Celecoxib</td>
<td>Amtriptyline</td>
<td>Acetaminophen</td>
<td>Alprazolam</td>
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<tr>
<td>Cyclobenzaprine</td>
<td>Citalopram</td>
<td>Clomipramine</td>
<td>Clozapine</td>
<td>Chlorzoxazone</td>
<td>Astemizole</td>
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<tr>
<td>Fluvoxamine</td>
<td>Clomipramine</td>
<td>Clofedoxib</td>
<td>Codeine</td>
<td>Dapsone</td>
<td>Buspirone</td>
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<td>Haloperidol</td>
<td>Diazepam</td>
<td>Fluibiprofen</td>
<td>Desipramine</td>
<td>Ethanol</td>
<td>Calcium Channel Blockers</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Imipramine</td>
<td>Ibuprofen</td>
<td>Dextromethorphan</td>
<td>Enfurane</td>
<td>Carbamazepine</td>
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<tr>
<td>Mexiletine</td>
<td>Lansoprazole</td>
<td>Losartan</td>
<td>Imipramine</td>
<td>Halothane</td>
<td>Cisapride</td>
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<tr>
<td>Olanzapine</td>
<td>Nelfinavir</td>
<td>Naproxen</td>
<td>Metoprolol</td>
<td>Isoflurane</td>
<td>Cyclosporine</td>
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<tr>
<td>Pentazocine</td>
<td>Omeprazole</td>
<td>Phenytoin</td>
<td>Nortriptyline</td>
<td>HIV Protease Inhibitors</td>
<td>Lovastatin</td>
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<tr>
<td>Propranolol</td>
<td>Phenytoin</td>
<td>Piroxicam</td>
<td>Oxycodone</td>
<td>Simvastatin</td>
<td>NOT pravastatin</td>
</tr>
<tr>
<td>Tacrine</td>
<td>Tolesemide</td>
<td>Tolbutamide</td>
<td>Paroxetine</td>
<td>Midazolam</td>
<td>Pimozide</td>
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<tr>
<td>Theophylline</td>
<td>Warfarin</td>
<td>Venlafaxine</td>
<td>Propranolol</td>
<td>Pimozide</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Propranolol</td>
<td>Triazolam</td>
<td>Triazolam</td>
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</tbody>
</table>

## Inhibitors

<table>
<thead>
<tr>
<th>Cimetidine</th>
<th>Ciprofloxacin</th>
<th>Erythromycin</th>
<th>Fluvoxamine</th>
<th>Ofloxacin</th>
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</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Felbamate</td>
<td>Fluoxetine</td>
<td>Fluvoxamine</td>
<td>Ketocozaole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoxetine</td>
<td></td>
<td>Lansoprazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvoxamine</td>
<td></td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketocozaole</td>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lansoprazole</td>
<td></td>
<td>Ticlopidine</td>
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</table>

## Inducers

<table>
<thead>
<tr>
<th>Carbamazepine</th>
<th>Carbamazepine</th>
<th>Phenobarbital</th>
<th>Chronic Ethanol</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Norethandron</td>
<td>Rifampin</td>
<td>Isoniazid</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Rifampin</td>
<td>Secobarbital</td>
<td>Tobacco</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>

Absent in 15-30 % of Asians
Absent in ~1% of Caucasians
Absent in 7% of Caucasians

**www.drug-interactions.com**
<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
<th>Mechanism of action</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-drug, PK</td>
<td>Ciprofloxacin+calcium and antacid</td>
<td>Decrease in absorption of ciprofloxacin</td>
<td>Treatment failure(^\text{24})</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin+olanzapine</td>
<td>Ciprofloxacin inhibits CYP1A2 leading to an increase in (C_p) of olanzapine</td>
<td>Rigidity, falls</td>
</tr>
<tr>
<td>Drug-drug, PD</td>
<td>Ciprofloxacin+glibenamide</td>
<td>Synergy (hypoglycaemic effect)</td>
<td>Profound hypoglycaemia(^\text{7})</td>
</tr>
<tr>
<td></td>
<td>Anticholinergic drug+donepezil</td>
<td>Antagonism</td>
<td>Decreased effect of donepezil</td>
</tr>
<tr>
<td>Drug-nutritional status</td>
<td>Low albumin+phenytoin</td>
<td>Increase in free phenytoin concentration</td>
<td>Confusion, somnolence, ataxia(^\text{28})</td>
</tr>
<tr>
<td>Drug-herbal product</td>
<td>Gingko+aspirin</td>
<td>Decrease in platelet function and adhesion</td>
<td>Increased risk of bleeding(^\text{29})</td>
</tr>
<tr>
<td>Drug-alcohol</td>
<td>Alcohol+chronic use of bromazepam</td>
<td>Synergy</td>
<td>Increased risk of falls</td>
</tr>
<tr>
<td>Drug-disease or drug-patient</td>
<td>Metoclopromide for gastric dysmotility in a patient with Parkinson’s disease</td>
<td>Increase in dopamine receptor blockade</td>
<td>Worsening Parkinson’s disease(^\text{30})</td>
</tr>
</tbody>
</table>

\(C_p=\text{plasma concentration. CYP=cytochrome P450. PD=pharmacodynamic. PK=pharmacokinetic.}\)

**Table:** Examples of different types of drug interactions in elderly patients.
CASE REPORTS

Sertraline-Induced Rhabdomyolysis in an Elderly Patient with Dementia and Comorbidities

Pietro Gareri, Cristina Segura-Garcia, Pasquale De Fazio, Salvatore De Fazio, and Giovambattista De Sarro

The Annals of Pharmacotherapy • 2009 July/August, Volume 43
CONCLUSIONS: To prevent the onset of clinical disturbances during venlafaxine treatment, we suggest careful evaluation of concomitant treatment with CYP2D6 or P-glycoprotein inhibitors (eg, propafenone) and, when possible, venlafaxine serum concentration monitoring.
Cholinesterase Inhibitors and Incidence of Bradycardia in Patients with Dementia in the Veterans Affairs New England Healthcare System

Robin K. Hernandez, MPH, Wildon Farwell, MD, MPH, Michael D. Cantor, MD, JD, and Elizabeth V. Lawler, DSc


OBJECTIVES: To quantify the association between cholinesterase inhibitors (ChE-I) and a new diagnosis of bradycardia and to evaluate the clinical significance of bradycardia.

Because bradycardia in an older population is associated with syncope, cardiovascular outcomes, and other arrhythmias, it is important to identify high-risk patients. Most blinded trials of ChE-I have been 6 months in duration, although a few have been shorter, and one was 1 year long. The current large study offers considerably longer follow-up in a real-world setting, with a median length of follow-up of longer than 2 years. It suggests that there is a greater risk of bradycardia in patients treated with ChE-I, particularly those taking 15 or 20 mg/day of donepezil. Patients who appeared to be at the greatest risk of a decrease in heart rate were those with dementia diagnosed as nonspecific or Alzheimer’s disease; those taking beta-blockers; those who had fallen since diagnosis; and those with a history of MI, heart failure, or hypertension. Therefore, higher rates of heart rate monitoring and surveillance may be warranted in patients with dementia taking a ChE-I, particularly those identified as high risk.

Figure 1. Inclusion and exclusion flowchart for patient population.
The goals of this study were, therefore, to examine changes in function in activities of daily living (ADLs) and cognition over time in NH residents taking ChIs while receiving concomitant therapy with a bladder anticholinergic (dual use) and in those taking ChIs without a bladder anticholinergic. It was hypothesized that the bladder anticholinergics oxybutynin and tolterodine would decrease the efficacy of ChIs with respect to cognitive and functional outcomes. Loss of functioning in persons with dementia is

Even though dual use of anticholinergics and ChIs is common, prior studies have not documented the long-term detrimental effects of dual therapy on patients’ functioning. This study revealed that, for NH residents with higher levels of functioning, the rate of functional decline was 50% faster when bladder anticholinergics were used in combination with ChIs than when ChIs were used without anticholinergics. To the authors’ knowledge, this is the first

L’aspetto cognitivo peggiora con gli anticolinergici
Cholinesterase inhibitors and adverse pulmonary events in older people with chronic obstructive pulmonary disease and concomitant dementia: a population-based, cohort study.

Stephenson A, et al

**Background:** Cholinesterase inhibitors (ChEIs) may worsen airflow obstruction because of their pro-cholinergic properties.

**Objective:** To evaluate the risk of serious pulmonary complications in the elderly with concomitant chronic obstructive pulmonary disease (COPD) and dementia who were receiving ChEIs.

**Methods:** Population-based, cohort study over the age of 66 years and had concomitant dementia and COPD.

**Results:** New users of ChEIs were not at significantly higher risk of ER visits or hospitalizations for COPD.
Furthermore, ER visits for any respiratory diagnoses were not increased among new users of ChEIs (RR 1.02; 95% CI 0.87, 1.19) when compared with non-users.

**Conclusions:** In a large cohort of elderly individuals with COPD and dementia, new users of ChEIs had a similar risk for adverse pulmonary outcomes as those who were not receiving ChEIs.

A review comparing the safety and tolerability of memantine with the acetylcholinesterase inhibitors

R. W. Jones

RICE (The Research Institute for the Care of Older People), Royal United Hospital, Bath, UK
Correspondence to: Professor R. W. Jones, E-mail: r.w.jones@bath.ac.uk

Key points

- AD patients are vulnerable to adverse events (AEs) and/or compliance difficulties due to comorbidity and polypharmacy.
- Memantine and acetylcholinesterase inhibitors are the principal agents used in the management of AD.
- Overall, memantine displays a safety and tolerability profile that is favourable and distinct from that of AChEIs.
- Consideration of drug safety and tolerability is important in AD treatment selection, to maximise efficacy and optimise quality of life.

CURRENT CONCEPTS

The Serotonin Syndrome

Edward W. Boyer, M.D., Ph.D., and Michael Shannon, M.D., M.P.H.

Hyperreflexia (greater in lower extremities)

Tremor (greater in lower extremities)

Clonus (greater in lower extremities)

Increased bowel sounds; may have diarrhea

Agitation

Diaphoresis

Mydriasis

Tachycardia

Autonomic instability; often hypertensive
**Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.**

**Drugs associated with the serotonin syndrome**

Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram

Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine

Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid

Anticonvulsants: valproate

Analgesics: meperidine, fentanyl, tramadol, and pentazocine

Antiemetic agents: ondansetron, granisetron, and metoclopramide

Antimigraine drugs: sumatriptan

Bariatric medications: sibutramine

Antibiotics: linezolid (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)

Over-the-counter cough and cold remedies: dextromethorphan

Drugs of abuse: methylenedioxymethamphetamine (MDMA, or “ecstasy”), lysergic acid diethylamide (LSD), 5-methoxydihydroxytryptamine (“foxy methoxy”), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)

Dietary supplements and herbal products: tryptophan, Hypericum perforatum (St. John’s wort), Panax ginseng (ginseng)

Other: lithium

**Drug interactions associated with severe serotonin syndrome**

Zolofit, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron

Phenelzine and meperidine

Tranylcypromine and imipramine

Phenelzine and selective serotonin-reuptake inhibitors

Paroxetine and buspirone

Linezolid and citalopram

Moclobemide and selective serotonin-reuptake inhibitors

Tramadol, venlafaxine, and mirtazapine

Hyperstimulation of postsynaptic serotonin receptor causes serotonin syndrome

Altre possibili interazioni “inutili”

- **TCA + L-DOPA**
  (ridotta biodisponibilità del precursore della DA)

- **TCA** (amitriptilina, clomipramina) + selegilina

- **SSRI + selegilina o con antiparkinsononianì**
  (rischio di sindrome serotoninergica)

- **TCA + anticolinergici**

- **TCA + oppiacei, alcool, ansiolitici, ipnotici, farmaci da banco contro il raffreddore**
  (depressione del SNC)

- **Antidepressivi e antipsicotici**

Interferenze con la clozapina (inibizione enzimatica CYP3A4 e CYP1A2)
Alcuni esempi dell’impatto sui farmaci del polimorfismo genetico del citocromo P450

<table>
<thead>
<tr>
<th>Enzima polimorfo</th>
<th>Clearance diminuita</th>
<th>Reazione avversa</th>
<th>↓ attivazione profarmaco</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Warfarin, Fenitoina, Tolbutamide, FANS</td>
<td>Emorragie, Atassia, Ipoglicemia, Emorragia Cl (?), Clomipramina, desipramina, amitriptilina, imipramina, nortriptilina</td>
<td>Losartan</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Diazepam</td>
<td></td>
<td>Proguanil</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>TCA, Antiaritmici, SSRIs</td>
<td>Cardiotossicità, Aritmie, Nausea</td>
<td>Tramadolo, Codeina</td>
</tr>
</tbody>
</table>
Polimorfismo della G-P

**Substrati:**
- Ciclosporina, Desametasone, Digossina, Diltiazem, Etoposide, Idrossicortisone, Nicardipina, Paclitaxel, Tacrolimus, Verapamil, Vinblastina, Vincristina

**Inibitori:**
**Induttori:**
- SSRI
- Iperico
Strumenti per ridurre il rischio di interazioni

• **Sistemi informatici**
  - analisi computerizzata dell’elenco di farmaci assunti da un paziente
  - Utilizzo di software relativi alle interazioni tra farmaci che offrono un supporto al medico per la prescrizione

• **Lavoro di squadra** (medico, farmacista, infermiere)
  - Tenere presenti tutte le patologie da cui è affetto il pz ed effettuare un’adeguata scelta terapeutica
  - Rivedere continuamente la necessità della somministrazione cronica dei farmaci
  - Avere informazioni sull’uso di alcool
  - Documentare aggiunte o sospensioni di farmaci
  - Quando si aggiunge un nuovo farmaco, effettuare uno screening per le potenziali interazioni
  - Evitare se possibile farmaci con ristretto indice terapeutico
  - Adeguare la dose dei farmaci o l’intervallo tra le dosi
  - Effettuare un periodico monitoraggio dei farmaci ed un follow-up
CONCLUSIONI (1)

La diagnosi e la gestione dei pz dementi con comorbidità è complessa per:

• Le modalità di presentazione della malattia
• L'impatto sul paziente
• Il sistema organizzativo

• La raccolta dei dati anamnestici e l'esame obiettivo richiedono più tempo nel pz demente rispetto al pz anziano cognitivamente integro

• Le caratteristiche e l'entità dei sintomi sono funzione del grado di deterioramento cognitivo e delle comorbidità

• L'utilizzo della diagnostica di laboratorio è di difficile impiego per la difficoltà di gestione del pz e la carenza dei sistemi organizzativi dei servizi

• Le strutture deputate alla cura dei pz sono impreparate alla domanda e tendono ad espellere il più rapidamente possibile il pz dai luoghi di cura
• Il danno iatrogeno da psicofarmaci è molto frequente, particolarmente nell’anziano, che si trova, rispetto al giovane, in condizioni di maggiore vulnerabilità e di ridotte capacità omeostatiche

• Tocca al MMG ed al geriatra mantenere un elevato stato di allerta quando vengono somministrati psicofarmaci, specialmente se associati ad altri farmaci

• Le interazioni farmacologiche vanno costantemente approfondite, al fine di prevenire reazioni avverse, talora molto severe, fino a diventare fatali qualora non vengano prontamente riconosciute

• L’identificazione, il trattamento e la prevenzione delle interazioni farmacologiche possono attuarsi tramite sistemi informatici (software) e tramite un lavoro di squadra (medico-infermiere-farmacista)
“Dying is becoming a small stumble off the long, medically supported high wire act”

Joanne Lynn, 2005