SNLG *Regions* 15

Dementia
Diagnosis and Treatment

GUIDELINE

Regional Health Council

REGIONE TOSCANA

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Presentation

Tuscany is engaged in an ongoing project, supported by the Regional Health Council, for the elaboration and dissemination of guidelines, with the objective of reducing the variability in clinical behavior and providing health professional and the general public with information and updates.

Guidelines are not only a mere support to clinical practice or decision making for Tuscan health professionals; they are also a valuable tool allowing an active participation to the continuous process of quality improvement. Health professionals are, in fact, directly involved in the elaboration of documents or in their definition, sharing observations or proposing integrations.

Multidisciplinarity is the basis and the guarantee of quality of the systematic elaboration process of guidelines and diagnostic-therapeutic paths – instruments for Clinical Governance in the Tuscan Health System (SST) –, due to the experience and knowledge of the involved health professionals.

Validity, reproducibility, and flexibility are the characteristics of all the published and in-process documents.

The new objective of Tuscany is the implementation of guidelines, as guidelines are a valuable tool for transferring evidence-based recommendations into clinical practice, thus affecting clinical behavior, and strengthening a changing system.

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Conflicts of interest

All the writers of this guideline, chosen for their expertise, have compiled a statement on possible conflicts of interest occurred in the job processing. Each has fully performed the work as part of their work for the Tuscan Health System (SST).

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Guide to levels of evidence and grade of recommendations
(following the National Guidelines System - SNLG)

Level of evidence

I Evidences from randomized controlled clinical trials and/or systematic reviews of randomized trials.

II Evidences from one single adequately designed randomized trial.

III Evidences from non-randomized cohort studies with concurrent or historical control or their metanalysis.

IV Evidences from non-controlled retrospective case-control studies.

V Evidences from non-controlled case-series studies.

VI Evidences from experts' opinions or opinions from panels as indicated in guidelines or consensus conferences, or based on opinions from members of the work group responsible for this guideline.

Strength of recommendations

A Carrying out the specified procedure or diagnostic test is strongly recommended. The recommendation is supported by good-quality evidences, even if not necessarily type I or II.

B It would be inappropriate to always recommend the specified procedure or intervention, considered the still existing doubts, but it should anyway carefully considered.

C Significant uncertainties exist against recommending to carry out the specified procedure or intervention.

D The specified procedure is not recommended.

E The specified procedure is strongly not recommended.

Scientific information at the basis of recommendations

The most recent and accredited guidelines, and all available consensus statements expressed by the main scientific societies specialized in neurological pathologies have been consulted:

- Dementia Study Group of the Italian Neurological Society;
- Scottish Intercollegiate Guideline Network (SIGN) 86: Management of patients with dementia, February 2006;
- Royal College of Physicians;
- Royal Australian College of General Practitioners;
- U.S. Preventive Services Task Force (USPSTF);
- Work group on Guideline for Alzheimer's Disease Management, 2008;
- European Federation of the Neurological Societies (EFNS);
- National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines;
- Dementia and Neurodegenerative Diseases Research Network (DeNDRoN) Primary Care Study Group;
- Database of Abstracts of Reviews of Effects (DARE);
- Cochrane Database of Systematic Reviews;
- National Institute of Neurological Disorders and Stroke.

Italian and international cohort studies and randomized trials have also been consulted, gathered through search strategies on Medline.

Summary

As senile population is increasing, dementia is the chronic-degenerative pathology whose incidence is expected to rise most in the next decades (+57% in 2030, +130% in 2050). Dementia is a condition currently incurable. The current estimate of the average expense per year for formal and informal cures for each patient (respectively 44% and 56%) is 21,000 euros, and a constant rise is expected.

The present guideline summarizes the most reliable indications from scientific literature on assessment tests, and pharmacological and non-pharmacological treatments, to the benefit of general practitioners and health professionals involved in the diagnostic-therapeutic process.

The suspect of a cognitive and behavioral impairment is usually raised by the general practitioner, on the basis of anamnestic data, information provided by relatives, and psychometric assessments (structured interview and Mini-Cognitive Test) to exclude differential diagnosis or co morbidity of depression and delirium; the use of the Geriatric Depression Scale – Short form (GDS-SF) is suggested to exclude depression, and the DSM-IV-TR criteria are indicated to exclude delirium.

Dementia can be suspected in subjects presenting a clinical profile characterized by deficits in memory, one or more cognitive alterations (aphasia, apraxia, agnosia, impairment in executive functions), and impairment of personal and social autonomy (former DSM-IV criteria).

General practitioners should then search for possible iatrogenic factors causing dementia.

Possible pathological conditions causing cognitive disorders should be assessed through routine blood tests and brain imaging (CT or MR). Functional brain imaging (SPECT and PET) should not be routinely used to assess for dementia.

General practitioners should refer to specialist services dedicated to the treatment of dementia for diagnostic confirmation, differential diagnosis, treatment plans and impairment control.

There is currently no therapy able to cure dementia, except for rare potentially reversible forms (normal pressure hydrocephalus, vitamin deficit, infections, primary brain cancer, etc.). Both pharmacological and non-pharmacological treatments aim at delaying disease progression and improving symptoms.

Benefits from a treatment with cholinesterase inhibitors should be considered for the management of main symptoms (cognitive decline and loss of function). Available data support the effectiveness of cholinesterase inhibitors in Alzheimer's disease, dementia with Lewy bodies and dementia in association with Parkinson's disease. Benefits from starting a treatment with memantine should be considered in patients with moderate-severe Alzheimer's disease.

No evidence is available supporting the use of natural remedies, such as Gynko Biloba and Salvia Officinalis. Expected benefits and potential adverse effects of pharmacological treatments should be discussed with patients and caregivers.

Associated symptoms (psychomotor agitation, aggressiveness, depression, allucinations) are currently treated with the following classes of drugs:

- antidepressant agents (preferably selective serotonin reuptake inhibitors (SSRI), in particular trazodone);

- antipsychotic agents;
- mood stabilizers;
- benzodiazepines.

The use of antipsychotic drugs can cause severe adverse effects. It should therefore be reserved to situations in which the safety of patients and caregivers is at risk, and should be limited in time. The associations of antipsychotic drugs should be avoided. No evidence is currently available supporting the effectiveness of mood stabilizers (for example carbamazepine and gabapentin) and of benzodiazepines in dementia.
The possibility of starting a non-pharmacological treatment should be considered:

- cognitive stimulation;
- orientation to reality;
- short psychotherapy.

Some recent studies showed the effectiveness of the behavioral approach on cognitive symptoms and on symptoms associated with dementia, using a combination of cognitive stimulations. These interventions are very heterogeneous and there is currently no conclusive evidence supporting their use.

Introduction

Dementia is a pathological condition characterized by the interaction of cognitive disorders, psychiatric disorders, and behavioral disorders, together with other comorbidities and often in precarious balance.
It is a complex disease, as it is age-related: the high variability of symptoms can cause diagnostic delays and consequent delay in starting behavioral and pharmacological interventions that could slow disease progression and improve symptoms.
The epidemiological data reported in the following table refer to the entire population divided in age classes, and accounts for the reason why dementia can be considered an impending pandemy:

PERCENTAGE OF CASES OF DEMENTIA PER AGE	
Age class	**Percentage of dementia**
60-64	0.60%
65-69	1.60%
70-74	3.50%
75-79	7.40%
80-84	15.70%
85-89	26.20%
90-94	41.00%
>95	46.30%

The expenses related to dementia are very high. The recent European guidelines for Alzheimer's disease estimate an expense of 21,000 euros/year for the assistance of a patient with dementia. The whole expense in Europe is around 141 billion euros per year, of which 56% is for informal treatments. The following table reports the number of over 60, divided per age, estimated by ISTAT for Italy for the years 2010, 2030 and 2050 and, beside, the number of expected cases of dementia if the level of scientific knowledge remained the same.
The extension of the issue is related to the phenomenon of demographic transition, that is with the transition from a population with a high birth and death rates, to a population with both these rates constantly decreasing. Italy is one of the countries most advanced in this demographic transition, with a balance of population near to negative: as a consequence, the absolute number of elder people, then also of people with dementia, is bound to increase in the next decades, maybe even more than in other countries. The extension of this pathology, with its direct and indirect costs, is bound to put a significant strain on the measures for the country social benefit.

FUTURE ITALIAN POPULATION AND DEMENTIA						
Age classes	**Pop. 2010**	**Dem. 2010**	**Pop. 2030**	**Dem. 2030**	**Pop. 2050**	**Dem. 2050**
60-64	3,684,382	22,106	4,823,143	28,939	3,642,751	21,857
65-69	3,155,739	50,492	4,373,703	69,979	3,782,652	60,522
70-74	3,023,563	105,825	3,602,723	126,095	4,073,641	142,577
75-79	2,524,699	186,828	3,012,315	222,911	4,157,191	307,632
80-84	1,889,263	296,614	2,558,545	401,692	3,659,133	574,484
85-89	1,157,855	303,358	1,602,491	419,853	2,601,176	681,508
90-94	324,912	133,214	911,073	373,540	1,373,270	563,041
>95	140,155	64,892	380,223	176,043	707,677	327,654
All	15,900,568	1,163,329	21,264,216	1,819,052	23,997,491	2,679,276
Gen. Pop.	60,224,114		62,128,993		61,716,517	

The relevance of dementia, among other chronic conditions, is due not only to the progressive decline of cognitive functions, but particularly to the frequency of severe behavioral disorders. This aspect of the disease affects the whole life of the patient, precludes or makes normal familiar activities difficult, and determines a strong demand for institutionalization. Every kind of support, from private caregivers to care centers, is affected by the increase of incidence of dementia.

An early assistance, and a strong personalization and constant revision of intervention plans can allow to control behavioral disorders, improve the quality of assistance and therefore allow patients to stay in his/her familiar environment, with the support of assistance services appropriate to his/her level of disability. This means that a disease with a strong social impact, lasting 8 to 10 years, with a progression leading to a difficulty in the end-of-life care, requires constant monitoring.

A general project for the management of dementia should necessarily start from strictly clinical aspects, such as diagnosis, and pharmacological and non-pharmacological treatments. At the same time, specific services dedicated to the different phases of the disease, to familiar issues, and to place of care, are necessary. In short, a system should be elaborated that, taking into account the social and environmental situation of each single patient, can guarantee:

- early diagnosis and assistance;
- non-pharmacological and pharmacological therapy;
- patient and, mainly, caregiver education;
- reliance on a territorial team with specific competence;
- specialist social and heath competence aimed at providing assistance in monitoring and management of decompensation phase;
- availability of social-health structures dedicated to temporary residential care;
- residential structures built following specific architectonic and organizational indications.

Clinical governance of dementia requires a systematic approach, merging general medicine knowledge and specialist service knowledge for the treatment of dementia.

The present guideline, focused on early diagnosis and pharmacological and non-pharmacological treatment of dementia, is dedicated to general practitioners (who can first identify clinical signs of cognitive decay and who remains the only responsible of patient's health throughout the care path) and to the services where clinical, psychological, nurse and social specialists in the treatment of dementia are centered.

Part one

General indications for diagnosis

Dementia is a clinical syndrome characterized by deficits in cognitive functions (such as memory, language, praxis, gnosia) and executive functions, and frequently by psychological and behavioral disorders.
Mild Cognitive Impairment has recently been identified (Petersen 1999). This is a condition characterized by a mild cognitive deficit. It does not appear as a frame of dementia, but can evolve in dementia in 5 to 10% of patients each year, versus 1% of general population of the same age (Mitchell 2009).
Early diagnosis of dementia is not frequent, due to the high variability of symptoms (Bradford 2009). A systematic review by the US Preventive Services Task Force (USPTF) concluded that signs of cognitive decay can be reliably assessed with an interview and a brief test (Boustani 2003).
Early diagnosis allows the elaboration and testing of interventions, even pharmacological interventions, when brain damage is still not severe, and therefore irreversible (Dubois 2007).
The issue of treatable dementias is relevant. Some of them are potentially reversible if identified and treated as early as possible (Kabasakalian 2009). Early diagnosis of dementia allows a better management of some crucial psychological and practical implications of the disease, affecting also the equilibrium of the familiar and social context in which the patient is involved (Ashford 2007).

Recommendation 1

I/A The general practitioner knows the cognitive-behavioral profile of his/her patients and can identify the clinical signs of cognitive decay at their onset, taking also into account the observations of relatives.

A sensible percentage of patients in the preclinical phase of dementia shows symptoms of depression (Chen 2008, Panza 2009). Recent data from the literature report that 67% of all patients with dementia suffer also from a certain grade of depression and that most of them have a history of depression (Rosness 2010).
A prospective study of more than 22,000 patients with depression and bipolar disorders documented that each acute episode causes a 13% increase of the risk of developing dementia in subsequent years (EBMH 2005).
On the other hand, depression can manifest, especially in elder patients, even in an early stage, with cognitive deficits, that can improve with an antidepressant treatment.
The overlap of symptoms can make the differential diagnosis difficult, but monitoring the patient in time can clarify the diagnosis (Steffens 2007).
A metanalysis from the Database of Abstracts of Reviews of Effects (DARE 2009) verified that

general practitioners are able to correctly exclude the presence of depression in the large majority of non-affected patients, and especially if they use the Geriatric Depression Scale with 15 items (Sheikh 1986).

Recommendation 2

III/A The general practitioner should assess the presence of symptoms of depression in case of cognitive-behavioral alterations, adopting, if it is the case, psychometric tools and other professional competences. The use of the Geriatric Depression Scale with 15 items is suggested.

GERIATRIC DEPRESSION SCALE SHORT FORM, (GDS-SF)		
	Yes	**No**
1. Are you basically satisfied with your life?	0	1
2. Have you dropped many of your activities and interests?	1	0
3. Do you feel that your life is empty?	1	0
4. Do you often get bored?	1	0
5. Are you in good spirits most of the time?	0	1
6. Are you afraid that something bad is going to happen to you?	1	0
7. Do you feel happy most of the time?	0	1
8. Do you often feel helpless?	1	0
9. Do you prefer to stay at home, rather than going out and doing things?	1	0
10. Do you feel that you have more problems with memory than most?	1	0
11. Do you think it is wonderful to be alive now?	0	1
12. Do you feel worthless the way you are now?	1	0
13. Do you feel full of energy?	0	1
14. Do you feel that your situation is hopeless?	1	0
15. Do you think that most people are better off than you are?	1	0
Score 0-5 = normal; Score >5 = depression		

Dementia should be distinguished from **delirium**, even if both can coexist (SIGN 2006). Delirium is an age-related condition affecting more than 30% of elder population with an acute or chronic decompensated pathology (RDP 2006). It is a confusional state developing in a lapse of time variable from hours to days (even if in some subjects the onset can be sudden), and fluctuating during the day. Up to 60% of patients over 75, in care structures, can present delirium in any moment. Up to 80% of patients with terminal diseases develops delirium near to death.

Delirium is generally a direct consequence of a systemic disease or of the administration or interruption of drugs. In particular it should be suspected in presence of infections, recent surgery, traumatic injuries, metabolic decompensation, acute hallucinatory state, interruption or starting of pharmacological treatments (RACGP 2003).
The differential diagnosis with dementia is of fundamental importance, as delirium is treatable and potentially reversible.

Recommendation 3

III/A Delirium can be suspected in subjects presenting a clinical/behavioral profile similar to the one described by the DSM-IV-TR diagnostic criteria.

Diagnostic criteria of delirium due to a general medical condition
(From the Diagnostic and Statistical Manual of Mental Disorders, IV Edition, Text Revision, 2000)

- Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
- A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
- There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

The diagnostic criteria included in the Diagnostic and Statistical Manual of Mental Disorder – IV edition (DSM-IV, 1994) are proven to have a high level of accuracy and an 80% sensitivity (Lim 1999, Knopman 2001).

Recommendation 4

I/A Dementia can be suspected in subjects presenting a clinical profile similar to the one described by the DSM-IV criteria for the definition of dementia.

Diagnostic criteria for Dementia from the DSM-IV, 1994 (multiple etiologies)

A The development of multiple cognitive deficits manifested by both

1) memory impairment (impaired ability to learn new information or to recall previously learned information)

2) one (or more) of the following cognitive disturbances:

- aphasia (language disturbance)
- apraxia (impaired ability to carry out motor activities despite intact motor function)
- agnosia (failure to recognize or identify objects despite intact sensory function)
- disturbance in executive functioning (planning, organizing, sequencing, abstracting).

B The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C The deficits do not occur exclusively during the course of a Delirium.

Scientific evidence exist (PSTF 2003) supporting the usefulness of an early clinical assessment and a specific interview, at primary care level, each time signs of cognitive decay or reports of them from relatives are present.
General Practitioners can use simple psychometric tools (Holsinger 2007) to reach early diagnosis, and therefore the adoption of potentially useful therapeutic interventions and assistance (Löppönen 2003).
Evidence from the literature supports also the accuracy of an initial structured interview carried out by nurses in detecting cognitive deficits that can suggest dementia (Page 2008).

Recommendation 5

I/A The general practitioner raises the diagnostic hypothesis of dementia through the anamnesis, a general examination, an assessment of possible iatrogenic causes and a structured interview, carried out within a multi-professional team.

Questionnaire for the person who best knows the patient				
1	Do you find it difficult to remember recent conversations, events and dates?	☐ yes	☐ no	MULTIPROFESSIONAL TEAM
2	Do you find it difficult to remember the current day or date?	☐ yes	☐ no	
3	Do you often leave objects in inappropriate places?	☐ yes	☐ no	
4	Are you more repetitive in talking?	☐ yes	☐ no	
5	Do you find it difficult to follow complex thoughts or tasks requiring numerous actions?	☐ yes	☐ no	
6	Are you unable to answer simple issues at home or at work?	☐ yes	☐ no	
7	Are you uncommonly not regardful or social rules of behavior?	☐ yes	☐ no	
8	Do you find it difficult to orientate while you are driving?	☐ yes	☐ no	
9	Do you tend to get lost even in familiar places?	☐ yes	☐ no	
10	Are you passive, not adequately reacting to different situations and do you appear indifferent and distant?	☐ yes	☐ no	
11	Do you misinterpret hearing and visual stimuli?	☐ yes	☐ no	
12	Are you more irritable and suspicious than usual?	☐ yes	☐ no	
13	Do you find it more difficult to find words expressing what you mean ("on the tip of your tongue") and to follow conversations?	☐ yes	☐ no	

If at least one of the answers is YES

Initial cognitive assessment

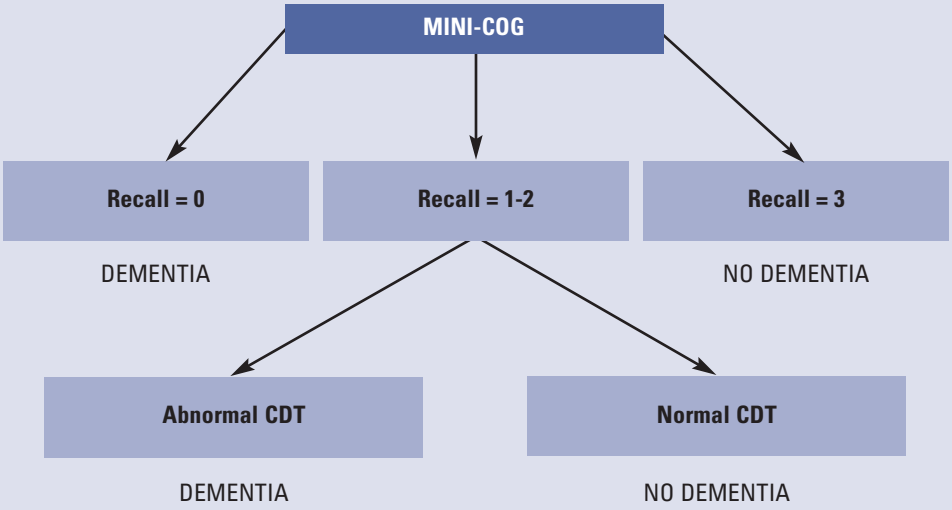
Musicco et al. 2004.

The administration of the **Mini-Cog Test** is suggested for the initial cognitive assessment (Borson 2000). This instrument allows the verification of long-term and short-term memory, visual and spatial representation, attention and executive functions.
The test lasts 3 minutes and consists in learning three words, drawing a clock and memorizing the three words.

Mini-Cog Test

1. First, the patient is asked to repeat three unrelated words, as in the Mini-Mental State Examination (MMSE).
2. Then the person is administered the clock drawing test, requiring:
   - to drow a clock
   - complete it with numbers
   - put the hands to ten past eleven

   (the test is considered correct if all numbers are in correct sequence and position and if the hands indicate the required hour).
3. Finally, the person is asked to recall the three words: suspect of dementia is raised on the basis of the following scoring algorithm:



Several pathological situations can determine dementia (ART 2010). Among the forms with onset after 60 years, 60% is related to Alzheimer's disease, 15-20% is determined by cerebrovascular diseases (vascular dementia), or by dementia with Lewy bodies. The most frequent forms with early onset are of the fronto-temporal type, followed by Alzheimer's disease. Less common forms of dementia appear along with Parkinson's disease, multiple sclerosis and AIDS; less often Huntington disease, Korsakoff syndrome and Kreutzfeld-Jakob disease.

The following table (Moo 2009) indicates the various pathological conditions that can cause dementia, part of which are potentially reversible.

DIFFERENTIAL DIAGNOSIS OF THE VARIOUS FORM OF DEMENTIA
(in bold the potentially reversible conditions)

Type	Common	Unusual	Rare
degenerative	Alzheimer's disease	- dementia with Lewy bodies - frontotemporal dementia - Parkinson's disease - Huntington's disease - corticobasal degeneration - progressive supranuclear palsy - argyrophilic grain disease - SLA	**Wilson's disease**
cerbrovascular	**diffuse small vessel disease**	- amyloid angiopathy - **multiple emboli** - diffuse hypoxic/ischemic injury	- **cerebral vasculitis** - Binswanger's disease - CADASIL*
neoplastic	**metastatic disease**	- **primary CNS tumor** - post-XRT	**paraneoplastic syndrome**
traumatic	**chronic subdural hematoma**	diffuse axonal injury	boxers' dementia
toxic/nutritional	- **alcohol abuse** - **medications**	- **thiamine deficiency (Wernicke-Korsakoff)** - **B12 deficiency** - **niacin deficiency (Pellagra)** - **vitamin E deficiency**	- anoxia/carbon monoxide poisoning - **heavy metal poisoning (Pb, Hg, As)**
metabolic/endocrine	- uremia/dialysis dementia - chronic hepatic encephalopathy	- **hypo/hyperthyroid** - **Cushing's syndrome** - **Addison's syndrome** - **hyperparathyroid**	
infectious/inflammatory		- HSV - **Lyme's disease (*borrelia*)** - **HIV (primary and associated to Toxoplasmosis Cryptococcosis, PML)** - **TB/Fungal Meningitis**	
demyelinating	multiple sclerosis		- leukodystrophy (adult onset) - electrical injury
psychiatric	**depression**	post-ECT	
from prions		Creutzfeldt-Jacob disease	Gerstmann-Sträussler-Scheinker disease
epileptic		refractory epilepsy	**epileptic status**
hydrocephalus		- **communicating/non-communicating** - **normal pressure hydrocephalus**	
other		- **sleep apnea** - **chronic hypercapnea/hypoxemia** - **chronic sleep deprivation**	

* CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Epidemiological data on the relative prevalence of the different forms of dementia is still controversial in literature, and there are very few studies on vascular dementia if compared to the ones on Alzheimer's disease (Rocca 2004); moreover, vascular dementia is not an homogeneous entity, and it is often associated to Alzheimer's disease.

Recommendation 6

VI/A General practitioners should assess all pathological conditions that could cause cognitive disorders.

Hypothesizing a dementia, especially in the eldest class of age, implies the necessity of assessing the relationship between the cognitive-behavioral situation and the coexistence of chronic conditions (co-morbidities) (CWG 2008). Co-morbidities can rapidly worsen patients' cognitive and functional status (Doraiswamy 2001), and can also make more difficult the identification of the pathology that is prevalent in determining the disability (Verbrugge 1989).
Assessing the environmental situation of subject with suspect cognitive disorders is also useful: some studies show that social isolation can lead to cognitive disorders (House 1988, Fratiglioni 2000).

Recommendation 7

VI/A In raising the diagnostic hypothesis of dementia, general practitioners should assess the presence of co-morbidities and identify risk factors due to social isolation.

Routine laboratory tests are generally considered necessary, even if scarcely documented by clinical studies (Waldemar 2007), during the initial phase of diagnosing cognitive disorders, to detect possible risk factors of diseases.
Cognitive disorders, in fact, can be associated to different dysmetabolic, infective or toxic conditions that could be treated.
The following exams are selected following the recommendations of the most recent guidelines (Hort 2010); more specific analysis can be added, on individual basis, such as serum syphilis, HIV, or *Borrelia* tests:

- complete blood count
- electrolytes (Na, K, Ca)
- blood sugar
- serum creatine, azotemia
- ALT, AST, gamma GT
- TSH
- folic acid, vitamin B12

Recommendation 8

VI/B General practitioners should prescribe blood tests to patients with suspect dementia.

DSM-IV-TR states that "brain imaging can help in the differential diagnosis of dementia. Computed tomography (CT) or magnetic resonance (MR) can reveal brain atrophy, focal brain lesions, hydrocephalus, or periventricular brain ischemic lesions. Functional imaging, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT) should not be routinely used in assessing dementia". Several guidelines on dementia include similar recommendations (RACGP 2003, Musicco 2004, SIGN 2005, NICE 2006).
Recent studies report that normal pressure hydrocephalus causes between 9 to 15% of dementias (in this case potentially reversible); this incidence is higher than the one reported lately (Marmarou 2007).

Recommendation 9

VI/A General practitioners should prescribe to patients with suspect dementia a brain imaging exam (CT or MR) for a diagnostic definition of dementia.

General practitioners can treat patients in the initial phase of dementia (RAGCO 2003, Iliffe 2009), but should refer them to a specialist in the following cases:

- identify a treatable cause;
- define diagnosis;
- study a possible genetic hypothesis;
- patient's rapid deterioration;
- presence of psychiatric or clinical co morbidities;
- onset at less than 60 years;
- possible work exposure to heavy metals;
- presence of behavioral disorders.

The Centre for Reviews and Dissemination of the York University confirmed (DARE 2009) the conclusions of an economical study (Banerjee 2009) presenting a cost-benefit analysis of the referral to Memory Clinics (Hejl 2002) for patients with dementia. The study demonstrated a significant benefit, in terms of health and expenses, of referring to these Services for diagnosis, treatment and monitoring of dementias.

Recommendation 10

VI/A General practitioners can refer to specialist services for diagnostic confirmation, differential diagnosis, and for the organization of interventions and stabilization of complex situations.

Part two

Treatment

Pharmacological treatment

Dementia is caused by a neurodegenerative damage or by a vascular brain damage, or both. The most common types of dementia are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, fronto-temporal dementia and mixed forms. A rare type of autosomal dominant-transmitted neurodegenerative dementia is Huntigton's Chorea. There are currently no therapies able to cure dementia: all pharmacological treatments aim at delaying disease progression and improve symptoms (Qaseem 2008). According to the practical classification criteria of the SIGN#86 guideline (Scottish Intercollegiate Guidelines Network), 2005, main symptoms can be distinguished in core symptoms (cognitive decline and loss of function) and associate symptoms (psychomotor agitation, aggressiveness, depression, hallucinations, sleep disorders, other aspecific manifestations). The following table summarizes the indications to treatment for the main symptoms:

Core symptoms	**Therapy**
Cognitive decline	donepezil, galantamine, rivastigmine, memantine
Loss of function	donepezil, galantamine, rivastigmine, memantine
Associated symptoms	**Therapy**
Psychomotor agitation	trazodone
Aggressiveness	antipsychotic drugs
Depression	antidepressant drugs
Hallucination	donepezil, antipsychotic drugs
Sleep disorders	no evidence for drug treatment
Aspecific manifestations	donepezil, galantamine, rivastigmine, memantine, antipsychotic drugs
Guideline SIGN#86, modified.	

Core symptoms

Core symptoms are described by the DSM-IV-TR criteria and reported by the table following recommendation 4. The classes of drugs currently used to treat dementia are acetylcholinesterase inhibitors and memantine, whose effectiveness has been proven in some types of dementia. International literature reports also evidence of the effectiveness of some natural agents (in particular *Ginko Biloba*, alkaloids from *Huperzia Serrata, Salvia Officinalis, Curcuma Longa*, and abstracts from *Vinca Minor*) (May 2009).

Acetylcholinesterase inhibitors				
molecule	**product**	**dose**	**tolerability**	**adverse effects**
donepezil	Aricept, Memac	5-10 mg/d	good	cholinergic overstimulation
galantamine	Reminyl Reminyl RP	4-8-12 mg x 2/d 8-16-24 mg/d	good	cholinergic overstimulation
rivastigmine	Exelon Exelon patch	1.5-6 mg x 2/d 4.6-9.5 mg/d	good	cholinergic overstimulation

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors: Alzheimer's disease compromises the cholinergic system, causing a reduction in neurotransmitter acetylcholine. The molecules inhibiting the acetylcholinesterase enzyme can reduce the catabolism of acetylcholine (Birkg 2003): two systematic reviews with metanalysis of randomized controlled trials (Hansen 2008, Birks 2006) report that in mild and moderate Alzheimer's dementia donepezil, galantamine and rivastigmine can cause a statistically significant delay of cognitive functions decline and of the autonomy in daily activities after 6-12 months of treatment. Several guidelines (Hort 2010, APA 2007, Qaseem 2008) underline how this benefit is modest from the clinical point of view and is limited to a subgroup of patients, and therefore recommend to discuss with patients and relatives expected benefits and potential adverse effects.
The number of studies on the use of acetylcholinesterase inhibitors in vascular dementia, characterized by a loss of nervous tissue due to ischemic damage or hemorrhage, is limited: three systematic reviews from the Cochrane Collaboration (Malouf 2009, Craig 2008 a and b) report evidence of a benefit of donepezil on cognitive level and functional autonomy in patients with mild to moderate vascular dementia. A subsequent metanalysis (Kavirajan 2007), however, shows that these benefits are less than those observed for Alzheimer's disease and not very clinically significant.
According to the NINDS (National Institute of Neurological disorders and Stroke), the neuropathological trait that characterizes dementia with Lewy bodies and dementia associated with Parkinson's disease is the presence of the alpha-synucleine protein inside the brain neuronal nuclei. A systematic review from the Cochrane Collaboration (Wild 2008) reports that patients with dementia with Lewy bodies and behavioral disorders or psychological disorders, can benefit from treatment with rivastigmine, if well tolerated. Weak evidence supports the use of galantamine and donezepil (Rowan 2007, Edwards 2007). A review from the Cochrane Collaboration reports the effectiveness of rivastimine in improving cognitive level and autonomy on daily activities in patients with dementia associated with Parkinson's disease (Maidment 2006).
Fronto-temporal dementia is characterized by neuronal loss, gliosis and spongiosis of the superficial layers of the frontal and temporal cortex, with a relative safety of the sub-cortical areas. A systematic review (Huey 2006), that DARE (Database of Abstracts of Reviews of Effects) is currently updating, reported a loss of serotonin and dopamine neurotransmitters, but not acetylcholine neurotransmitters, in patients with fronto-temporal dementia (Raina 2008, DARE 2009). There is no evidence, in fact, supporting the efficacy of acetylcholinesterase inhibitors (Moretti 2004, Mendez 2007, Kertesz 2008).
Mixed dementia is a condition characterized by the coexistence of the neuropathological damage of Alzheimer disease, and vascular lesions. Post-mortem tests demonstrate that the two conditions coexist in 45% of subjects with dementia and that the association is more frequent with the increasing of age (Langa 2004). There are no systematic reviews on the treatment with acetylcholinesterase inhibitors. A randomized trial on the use of galantamine in a sample of subjects with mixed dementia and with vascular dementia shows a modest improvement in cognitive tests, statistically significant only in the subgroup with mixed dementia (Erkinjuntti 2002).
Huntington's Chorea is an hereditary autosomal dominant-transmitted neurodegenerative disease, with complete penetrance, characterized by a progressive cognitive, motor and psychological decline. The age of diagnosis is typically around 40 years. Life expectancy is 15-20 years

since diagnosis. There is no evidence supporting the effectiveness of acetylcholinesterase inhibitors in the treatment of this disease. Tetrabenazine, causing the depletion of monoamine in the central nervous system, has a positive effect on motor symptoms, but not on cognitive symptoms (Mestre 2009).

Memantine

A systematic review from the Cochrane Collaboration (McShane 2010) documented a good tolerability and a modest, but clinically relevant, positive effect of memantine on the cognitive level and functional autonomy of subjects with moderate-severe Alzheimer's dementia, but not in subjects with vascular dementia. There is no evidence of its effectiveness in fronto-temporal dementia (Diehl-Schmid 2008) and in Huntington's Chorea. A double-blind randomized controlled clinical trial on the association of donepezil and memantine, documented that this association improves significantly cognitive symptoms and autonomy in daily living in patients with moderate-severe Alzehimer's disease versus treatment with donepezil alone (Evidence-Based Mental Care 2004, Tariot 2004). Memantine is a molecule that acts on the glutamatergic system, blocking the NMDA (N-methyl D-aspartate)-glutamate, reducing the excitotoxic effect of glutamate, the main excitatory neurotransmitter of the central nervous system (Sucher 1996).
Memantine (commercial name Ebixa, in 10-20 mg tablets) is prescribed at a dose of 5 to 20 mg. It is usually well tolerated. Reported adverse effects are: instability, headache, stypsis and sleepiness.
A systematic review by May, 2009, on natural remedies did not report significant conclusions, even if it acknowledges some modest effects on cognitive functions. A further assessment carried out by DARE (2009) judged unreliable these effects.

Recommendation 11

I/A Starting a therapy with acetylcholinesterase inhibitors, whose effectiveness on core symptoms is proven, should be considered at moment of diagnosis of mild and moderate Alzheimer's disease. Expected benefits and potential adverse effects of the treatment should be discussed with patients and caregivers. Evidence of effectiveness of acetylcholinesterase inhibitors is available also in dementia with Lewy bodies and in dementia associated with Parkinson's disease. The option of starting a therapy with memantine should be considered in patients with moderate-severe Alzheimer's disease to treat core symptoms. No evidence is available on natural remedies.

Associated symptoms

These are several different, heterogeneous and mutable symptoms (Lawlor 2002). Motor agitation, verbal agitation, aggressiveness, depression, delirium, hallucinations, wandering, and sleep disorders, are among the most frequent (IPA 2002). Symptoms of depression affect 20-32%, of patients with dementia of any type, those of psychosis 12-24%, those of aggressiveness 27%, and those of anxiety 20% (Lyketsos 2000).
Associated symptoms can be primary or secondary to environmental situations (environment modification, hospitalization, changing of caregivers, acute pathological events, etc) (Finkel

1996). A recent study on emotional variations in patients with sever bilateral lesions of the hippocampus and subsequent loss of recent memory, demonstrated a longer persistence of emotion then in control subjects, even in absence of the memory of the event (Feinstein 2010).
The classes of drugs currently used to treat associated symptoms are antidepressant agents, antipsychotic agents, and mood stabilizers.

Antidepressant drugs

Antidepressant drugs are classified on the basis of their mechanism of action, as in the following table. The tricyclic class is the one used for the longest period. Tricyclic antidepressant drugs block norepinephrine and serotonin reuptake. A Cochrane review (Mottram 2006) on the use of antidepressant drugs in elder population showed less compliance to tricyclic agents (due to adverse effects) than to selective serotonin reuptake inhibitors (SSRI), that increase synaptic levels of serotonin; the first molecule of this class to be approved for therapeutic use has been fluoxetine. Drugs able to increase norepinephrine reuptake (SNRI) have been recently introduced, and the first one is venlafaxine.
Research on the effectiveness of antidepressant drugs for the treatment of associated symptoms is still scarce (SIGN 2005) and no conclusive evidence from the literature is available supporting the effectiveness of antidepressant drugs in patients with dementia. A Cochrane review (Bains 2008), recently updated, on the use of antidepressant drugs amitriptiline, amoxapine, citalopram, dotiepine, doxepine, fluoxetine, imipramine, lofepramine, mirtazapine, nefalazone, nortriptiline,

Class		Active principle
non-selective	tricylcic	- amitriptiline - imipramine - clormipramine
	I MAO	- fenezine - tranilcypromine - isocarbazide - selegiline
selective reuptake inhibitors	serotonine (SSRI)	- fluvoxamine - fluoxetine - paroxetine - citalopram - escitalopram - sertraline
	serotonine and norepinephrine (SNRI)	- duloxetine - venlafaxine
	norepinephrine and dopamine (NDRI)	- bupropione
	noradrenaline (NARI)	- reboxetine
receptor blockers	serotonine and serotonine reuptake inhibitors	- trazodone - nefazodone
	noradrenergic and serotonergic (NASSA)	- mirtazapina

paroxetine, roboxetine, sertraline and sulpiride in subjects with dementia and depression, reported weak effects for every investigated drug. However, the review did not consider new antidepressant drugs, and few studies investigated serotoninergic drugs.
A recent RCT (Rosenberg 2010) reported no significant effects of serotoninerginc drugs for the treatment of depression in patients with Alzheimer's disease. A review (Best Evidence Summaries of Topics in Mental Healthcare 2007) of 4 systematic reviews, including 7 randomized trials, on the use of antidepressant drugs in patients with dementia and agitation, reported no significant differences between trazodone, citalopram, sertraline, flluoxetine, and placebo.
A non-systematic review (Mendez 2009) concluded that serotoninergic drugs can have some efficacy in improving impulsive behavior in fronto-temporal dementia, even if they are not approved for this use. An RCT (Sultzer 2002) reported some efficacy of trazodone and citalopram in controlling agitation. Two subsequent reviews on trazodone and citalopram concluded that it was not sufficient to recommend its use (Hermann 2007, Martinon-Torres 2008).
A Cochrane review is currently in course on the use of antidepressant drugs for the treatment of agitation and psychosis in dementia (Dallas 2010).
DARE carried out in 2005 a critical assessment of a systematic review published on JAMA (Sink 2005) on the pharmacological treatment of neuropsychiatric symptoms in dementia. The review included 25 RCTs and 4 metanalysis, and investigated typical antipsychotic drugs (haloperidol, tioridazine, tiotixene, chlorpromazine, trifluoperazine, acetofenazine, perfenazine), atypical antipsychotic drugs (risperidone and olanzapine), antidepressant drugs (fluoxetine, trazodone, citalopram and sertraline), mood stabilizers (carbamazepine, divalproate, valproate), acetylcholinesterase inhibitors (rivastigmine, donepezil, galantamine, metrofinate, taurine, velnacrine, fisostigmine), and memantine, concluding that risperidone and olanzapine resulted having more evidence of effectiveness; however, effects were modest, and there was a risk of increasing brain vascular accidents.

Recommendation 12

VI/B The use of antidepressant drugs, preferably SSRI, can be useful in the treatment of patienhts with dementia and depression. Trazodone can be useful in case of agitation.

Antipsychotic drugs

Antipsychotic drugs are divided into various classes, reported in the following table.
These drugs (neuroleptics, major tranquilizers) are used to treat acute and chronic psychosis, delirium, psychomotor agitation, and aggressiveness. They influence the activity of brain neurotransmitters, in particular the dopaminergic system.
The first generation of antipsychotic drugs was released during the fifties: these molecules act on all the receptors of the dopaminergic system, causing therefore also significant extrapyramidal adverse effects.
The second generation of antipsychotic drugs (the atypical ones) is in use sine the seventies, and is characterized by the selectivity on some dopamine and serotonin receptors, thus limiting extrapyramidal adverse effects.

Class	Active principle
fenotiazine	clorpromazine dixirazine flufenazine flufenazine decanoate levomepromazine perfenazine perfenazine enantate promazine propericiazine tioridazine trifluoperazine zuclopentixolo
butirrofenons	haloperidol haloperidol decanoate bromperidol dipiperone droperidol
benzamides	amisulpride levosulpride sulpiride sultopride tiapride
atypical	risperidone olanzapina quetiapina clozapina

A 2004 Consensus Conference carried out by the 48 main US experts on the use of psychopharmacological drugs on elder population (Alexopoulos 2004) reported the following conclusions on their use in the treatment of behavioral disorders in patients with dementia:

- one atypical antipsychotic drug alone (risperidone, olanzapine, or quetiapine) should be used in demented patients with delirium;
- treatment should not last more than 3-6 weeks at the minimum effective dose;
- the association of clozapine and olanzapine with typical neuroleptic drugs should be avoided in case of comorbidity with diabetes or dyslipidemia;
- the first choice treatment for patients with parkinsonism is quetiapine;
- use of clozapine, ziprasidone and typical neuroleptic drugs is not suggested in patients with chronic cardiac insufficiency;
- typical antipsychotic drugs should not be associated with fuoxetine and paroxetine.

Extrapyramidal adverse effects	Manifestations	Treatment
parkinsonism	bradykinesia, rigidity, tremor, facies amimica, camptocormia	dopaminergic drugs
acute dystonia	tongue, face, neck and back muscle spasm	farmaci antiparkinsoniani
acatisia	motor restlessness without anxiety	propranololo
late dyscinesia	orofacial dyskinesia, diffuse dystonia, coreoatetosis	unsatisfying
perioral tremor	thin lip tremor	antiparkinsonian drugs
malign neuroleptic syndrome	catatonia, stupor, high fever, muscular dystonia, unstable PA, kidney failure, hyperCPKmia	dantrolene

Several data from the literature suggest an association between the use of typical and atypical antipsychotic drugs and the increased risk of sudden cardiac death (Baldessarini 2009). A meta-analysis published in 2005 on JAMA (Shneider 2005), underlined an increase on death due to acute cerebro-vascular events in subjects with dementia taking atypical neuroleptic drugs. A 2006 Cochrane review (Ballard 2006) confirmed the increase of death, and stated that the use of risperidone and olanzapine should be limited to at-risk, or extremely suffering patients or caregivers, and should be limited in time, even though it underlined their efficacy in controlling delirium and aggressiveness in subjects with dementia. Subsequent studies (Schneeweiss 2007, Kales 2007, Douglas 2008) reconfirmed the higher mortality of subjects treated with antipsychotic agents versus untreated subjects, while underlining that the use of neuroleptic drugs in patients with dementia causes a higher frequency of fatal events if compared with atipical antipsychotic drugs (Wang 2005, Gill 2007, Liperoti 2009). The DART-AD study (Ballard 2009) highlights the difference in probability of long-term survival between treated (with any neuroleptic drug) and untreated subjects: 70% vs 77% at 1 year, 46% vs 71% at 2 years, 30% vs 59% at 3 years. A 2009 critical assessment (DH 2009) commissioned by the Deprartment of Health, on the use of antipsychotic drugs in subjects with dementia, recommended to limit as much as possible their prescription, limiting pharmacological treatment only to at-risk patients or caregivers, recommending non pharmacological treatment as the treatment of choice.

Recommendation 13

II/A Antipsychotic drugs have partial efficacy in the treatment of psychosis and aggressiveness associated with dementia. Their use should be limited to at-risk, or extremely suffering patients or caregivers, and should be limited if possible in time, due to the potentially severe adverse effects of these drugs. Associations of antipsychotic drugs should be avoided.

Mood stabilizers

Mood stabilizers are a non-homogeneous group of drugs (lithium salts and some anticonvulsive agents) that sometimes resulted useful in improving behavior disorders, such as agitation, aggressiveness, impulsivity, uninhibition, and maniacal manifestations in patients with dementia. Studies on the effectiveness and risks associated to the use of mood stabilizers in patients with dementia are still scarce and mainly observational:

- lithium salts: clinical trials (CCTR/CENTRAL 2010), based the experimental data of a reduced amyloidogenesis, are currently in course on the treatment of subjects with MCI (Mild Cognitive Impairment);
- carbamazepine: observational studies and some trials report contradictory results. Cochrane started a protocol to produce a systematic review (Tampi 2009);
- gabapentin: a non-systematic review (Kim 2008) concluded that no sufficient data are available supporting the off-label use of gabapentin patients with dementia and behavioral disorders;
- valproate: a Cochrane review (Lonergan 2009) has currently concluded that valproate is not effective in reducing agitation in patients with dementia due to the unacceptable frequency of adverse effects; further studies are needed;
- lamotrigine: a limited number of studies suggests that the drugs is quite well tolerated and can be effective in improving agitation in patients with dementia (Sajatovic 2007);
- topiramate: one study suggests the possibility of it having the same effectiveness of risepridone in improving behavioral disorders in patients with dementia (Mowla 2010).

Recommendation 14

V/A There is currently no evidence supporting the use of mood stabilizers for the treatment of behavioral disorders in patients with dementia.

Benzodiazepines

There are no systematic reviews nor RCTs investigating the use of benzodiazepines for the treatment of associated disorders in dementia, anxiety included.

A recent investigation carried out in Great Britain (Bishara 2009) on pharmacological treatment of behavioral disorders associated with dementia, reported that, while quetiapine is considered the most appropriate drug, benzodiazepines are the most often prescribed.

The Italian Society of Pharmacology in 2009 did not recommend "the long-term use of benzodiazepines and of similar drugs in elder people, due to the risk of addition, inability to interrupt therapy, masking of depression and of onset or worsening of memory disorders".

Recommendation 15

V/A There is no evidence supporting the use of benzodiazepines in patients with dementia.

Non-pharmacological treatments (behavioral)

Experts are beginning to agree that the use of drugs for the treatment of associated symptoms in dementia should be considered a second-line treatment, due to the relative effectiveness of drugs and their severe adverse effects, while considering that the first-line treatment should be non-pharmacological. Specific procedures are being elaborated, in particular for agitation, aggressiveness, mood disorders, psychosis, disinhibition, eating disorders, and verbal repetition, hoping to favor, on the basis on neuronal plasticity, cortical reorganizations, as in the case of sensorial deprivation.

There are several different types of non-pharmacological interventions (Douglas 2004) (see following table), but evidence is still partial, due to the limited number of studies with adequate design and sample size, and to the non-homogeneity of investigated patients and interventions (Ayalon 2006). In particular:

- RCTs provided evidence supporting the effectiveness of cognitive stimulation, ROT included, alone (Spector 2003) or with donepezil (Onder 2007), on cognitive functions. A subsequent pilot RCT showed some benefits of multimedia stimulation versus traditional stimulation, on cognitive function (Tàrraga 2006);
- one RCT showed that occupational therapy is effective in significantly reduce the decline in daily life autonomy in subjects with dementia after 12 weeks of treatment (Graff 2006);
- a systematic review (Robinson 2007), that DARE validated in 2008, concluded that there is insufficient evidence to recommend non-pharmacological interventions to reduce wandering in subjects with dementia;
- one systematic review of RCTs (Ayalon 2006), that DARE validated in 2007, concluded that interventions to support and train caregivers in carrying out behavioral interventions and identifying patients' unsatisfied needs, can be effective in controlling their psychological and behavioral symptoms, in particular agitation;
- two RCTs (Raglio 2002, Guétin 2009) demonstrated the effectiveness of therapeutic use of music for the treatment of non-cognitive symptoms, in particular agitation, wandering, anxiety and depression, even though the Cochrane Collaboration stated the need of further studies on the topic (Vink 2004);
- one systematic review (Kong 2009), that DARE partially validated in 2010 (due to small sample size), concluded that the only effective non-pharmacological treatment is the multi-sensorial approach (Snoezelen). However, a Cochrane systematic review (Chung 2008) concluded that there is insufficient evidence supporting its efficacy for the treatment of dementia;
- three different Cochrane systematic reviews concluded that there is insufficient evidence supporting the effectiveness of validation therapy (Neal 2005), of complementary therapies such as massage and touch (Hansen 2006), and of the Bright-Light Therapy (Forbes 2009);
- two RCTs demonstrated that a personalized approach, based on the observation of patients, and aimed at the identification and improvement of physical and psychological disorders of patients with dementia, reduced agitation in nursing homes (Cohen-Mansfield 2007, Chenoweth 2009);
- one RCT demonstrated that a structured supporting program for caregivers of patients with

dementia can improve patients' psychological status and reduce the risk of long-term institutionalization (Mittelman 2006);

- the group of experts that elaborated the present guideline considers useful the organization of a regional register of experiences.

Treatment of cognitive symptoms and disability	Treatment of psychological and behavioral symptoms	Short psychotherapy
- ROT (Reality Orientation Therapy) - validation therapy - reminiscence therapy - occupational therapy	- musicotherapy - behavioral therapy - Bright Light Therapy - multi-sensorial approach (Snoezelen) - aromatherapy - pet therapy - art therapy	- cognitive-behavioral therapy - interpersonal approach

Recommendation 16

V/A The first line treatment for psychological and behavioral disorders is non-pharmacological, due to the potentially severe adverse effects caused by pharmacological treatments.
The possibility of a non-pharmacological treatment for cognitive disorders should be considered at the diagnosis of dementia, even if evidence from the literature is not conclusive. Expected benefits should be discussed with patients and caregivers, and times and ways for the training and support of caregivers should be planned. General practitioners should refer to specialist services for these activities.

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