SNLG *Regioni* 15

Dementia
Diagnosis and Treatment

GUIDELINE
Regional Health Council

REGIONE TOSCANA

Publication date: 2015
Update: 2019

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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.
The following authors have declared a conflict of interest:
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Presentation

The need to support physicians' behaviors through guidelines and best practices in diagnostic and therapeutic interventions is based on several reasons, including the heterogeneity in clinical practice, the crisis of reliability in medical profession and health services in general, the strong need of improving the quality of healthcare, and the rationalization of available resources for health expenses, in a context of constantly increasing expenses.

However, guidelines would actually be able to improve healthcare quality (in a balanced integration between the imperative of efficacy and the need of professional autonomy), only if used as a tool for clinical governance, appropriately contextualized in the different healthcare backgrounds, and aimed at assessing, through adequate strategies, the quality of the services provided by the structures.

The elaboration, update, and implementation of guidelines thus become the key points of the commitment of Tuscany in the process of improving the efficiency in using the scarce resources, without affecting the professional quality of healthcare.

Regional Health and Welfare Minister
Stefania Saccardi

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 on which recommendations are based

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);
- Workgroup 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.

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Epidemiology

Dementia is a clinical condition related to aging, affecting 1% to 5% of people over 65 years. It is usually diagnosed in a clinical advanced stage, and is associated to a 3.3- to 11.7-years (more frequently 7-10 years) survival time from diagnosis.
Current incidence and prevalence of dementia are reported in Table 1.
The 2010 World Alzheimer Report estimated that if the incidence of the disease and the aging trend of population remained unchanged, the absolute number of people with dementia should double within 2030. However, the estimate should probably be adjusted based on the demographic trend and the incidence rates.
As for demographics, the United Nations' World Population Ageing (Prince 2013) indicates that all countries are uniformly experiencing a decrease of the proportion of newborns, and a concurring increase in the elder population. Subjects older than 60 years increased, in world population, from 9.2% in 1990 to 11.7% in 2013, and are expected to further increase to over 20% by 2050. The transition to the rectangular shape of the age pyramids in both highly developed and less developed countries in the years 1970, 2013 and (estimated) 2050, do confirm the current demographic transition, thus the relative increase of elder subjects. However, demographic projections have been actually proven to have a margin of error, mainly attributable to mortality and net migration rates forecasts unconfirmed by real data. This makes the estimate of the future absolute size of the age classes, and consequently of the number of cases of dementia, less reliable.
To estimate the expected incidence a recessive trend should be taken into account that appears to be affecting western countries in the last decades. Less developed areas in the world, where WHO forecasts are reported to underestimate real data, seem not to share this trend.
The UK Cognitive Function and Ageing Study (CFAS), carried out over 20 years in 3 densely populated areas of the United Kingdoms, reported a 2-points decrease in the incidence, in the analysed areas, referred by the authors to a better control of the cardiovascular risk factors and to people sharing a higher level of cultural knowledge (Matthews 2013).
The Rotterdam study followed 2 cohorts of patients, enrolled respectively in 1990 and 2000, and reported a lower incidence, probably due to preventive interventions, in the most recently enrolled cohort (Hofman 2015).

Table 1. Incidence and prevalence of dementia, according to gender

Age	Incidence %		Prevalence %	
	Males	Females	Males	Females
60 - 64	0.2	0.2	0.4	0.4
65 - 69	0.2	0.3	1.6	1.0
70 - 74	0.6	0.5	2.9	3.1
75 - 79	1.4	1.8	5.6	6.0
80 - 84	2.8	3.4	11	12.6
85 - 89	3.9	5.4	12.8	20.2
90+	4	8.2	22.1	30.8

Researchers from the Karolinska Instituten reached the same conclusions after carrying out a study in some selected areas of Stockholm (Qiu 2013).
In the USA, a closer control of potential risk factors produced an almost 50% decrease in acute cardiovascular events, including stroke and consequently vascular dementia, during the last 20 years.
A population analysis concluded that controlling diabetes could prevent 3% of incident cases of Alzheimer's dementia, 5% of them could be prevented controlling hypertension, and 13% could be prevented by promoting physical activity. Moreover, atrial fibrillation resulted significantly correlated with dementia, and, though evidence is still missing, a timely and effective anticoagulant therapy is thought to limit the incidence of the latter.
Based on the previously stated assumptions, prevalence forecasts proposed for the subsequent decades in the first version of this guideline cannot be confirmed, also considering that therapeutic intervention has yet proven to be effective. Health care plans for subjects with dementia can currently only be limited, for these reasons, to short-term plans.

Planning health care

Dementia is particularly relevant among other chronic conditions due not only to the progressive decline of cognitive functions, but also to the frequency of severe behavioral disorders.
This aspect of the disease unbalances the whole environment in which the subject lives, it prevents or makes much more difficult to carry out normal family activities, determining a strong demand for institutionalization. Every type of support, either private, by hiring a professional caregiver, or the institutionalization in a nursing home, is affected by the progressive increase of dementias.
An early referral to proper care, a high personalization, and a constant review of the therapeutic plan can allow to contain behavioral disorders, promoting patient care in a familiar environment supported by health care services tailored to the level of disability of each patient.
A progressive condition with such strong social consequences, lasting an average of 8-10 years, until end-of-life care, must be considered as needing constant tutoring.
A general project of care should necessarily start from the strictly clinical aspects, such as the diagnosis and the pharmacological and non-pharmacological treatments.
Specific services are concurrently needed, dedicated to the different stages of the disease, family issues, and settings of care.
In summary, a system should be designed that, taking into account the environmental and social situation of each single patient, provides:

- early diagnosis and referral to proper care;
- non-pharmacological and pharmacological therapy;
- education of patients and, mainly, of their caregivers;
- commitment to a territorial team with specific competences;
- specialist health and social competences aimed at providing support in the monitoring and management of breakdowns or crises;
- availability of health and social structures dedicated to temporary residential care;
- residential and semi-residential structures built based on specific architectonic and organizational indications.

The clinical governance of this condition, therefore, requires a systematic approach, merging knowledge from both general medicine and specialist services for the treatment of dementias.
This guideline is focused on the timely diagnosis, and pharmacological and non-pharmacological treatment of dementia. It is targeted to the general practitioners (who can first identify the clinical signs of cognitive decline, and who remain the main responsible for the health of their patients throughout the care path), and to the services that gather all the clinical, psychological, and nurse and social specialists dedicated to the treatment of dementia.

Primary and secondary prevention of dementia: the new European standards

Both WHO in 2012 and the G8 dementia summit in 2013, due to the lack of an effective disease-modifying treatment, identified prevention as a key element to confront the dementia epidemic.
Available evidence identify seven potentially modifiable risk factors associated to dementia:

- diabetes;
- adult hypertension;
- adult obesity;
- smoking;
- depression;
- low educational level;
- physical inactivity.

A system has been elaborated on the basis of this evidence and the Finnish study CAIDE (Cardiovascular Risk Factors, Aging and Dementia) that estimates in adults the risk of developing dementia in advanced age (Kivipelto 2013). Other scales have been subsequently developed. The main objective of their use is to identify preventive intervention targeted to those subjects who are most at risk to develop dementia, and to provide accessible information on risk factors to general population.
No definite conclusions can be currently drawn on these experiences, but based on positive results obtained for some chronic conditions, further controlled studies are necessary to verify the actual effectiveness of interventions aimed at modifying risk factors, assuming a possible decrease of the prevalence of dementia, mainly if associated to the strengthening of protective factors (such as physical activity and education).
Several epidemiological studies, in fact, suggest that a high educational level, a high occupational complexity, and the engagement in cognitively and physically challenging activities are associated to a decreased risk of dementia, underlying the protective role of the cognitive reserve.
The project MIND-AD, started in 2015, has the objective of identifying a possible prevention and strategies for dementia tailored on subjects at different levels of risk.
The project is based on experiences and data from five in-progress European intervention studies on AD, LiPIDiDiet (Therapeutic & Preventive Impact of Nutritional Lipids on Neuronal and Cognitive Performance in Ageing, Alzheimer's Disease and Vascular Dementia) (Germany, Finland, Netherlands, Sweden), Hatice (Healthy Ageing Through Internet Counselling in the Elderly) - Healthy Ageing Through Internet Counselling in the Elderly (Finland, France, Netherlands, Sweden), and the already cited FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) (Finland), MAPT (MultiDomain Alzheimer Preventive Trial) (France) and PreDIVA (Prevention of dementia by intensive vascular care) (Netherlands).
All of these studies are testing the effects of multi-modal interventions in healthy, cognitively normal, elder subjects, to prompt them to change lifestyle habits through physical activity programmes (including exercises to improve postural balance), nutritional education, cognitive training, and social activities.

One of the great issues, among the still debated questions, is whether there is a critical time span to carry out these interventions, and if these risk and/or protective factors may have a different weight at different ages.

Diagnosis

Early diagnosis

The diagnosis of a non-overt dementia syndrome is rarely certain. The risk of under-diagnosis is relevant both in a primary care setting (Connolly 2011), and in hospitals (Douzenis 2010) and residential structures (Lithgow 2012).
A risk of over-diagnosis, on the other hand, can exist, in particular in presence of a depressive syndrome concurrent to a minor brain injury (Garcia 1981). This risk is now particularly relevant being the screening for cognitive decline part of the current health policies, with dedicated funds and incentives (Le Couteur 2013). This is what in 2012 some representatives of primary care physicians also highlighted to the British government in an open letter in which they also suggest to reallocate the large amounts of funds from the screening of dementia to health interventions with a better benefit-cost ratio.
A systematic review from the US Preventive Services Task Force (USPSTF) concluded that the signs of cognitive decline (Boustani 2003) can be reliably detected through an interview and a short test.
A timely diagnosis allows to design and test interventions, even pharmacological treatments, before the neuronal damage gets too advanced, thus irreversible (Dubois 2007).
The issue of treatable dementias is relevant. Some of them are potentially reversible if identified and treated as soon as possible (Kabasakalian 2009). A timely diagnosis of dementia allows a better management of some crucial psychological and practical implications of this condition, also affecting the balance of the social and family environment surrounding the patient (Ashford 2007).

Recommendation 1

General practitioners know the cognitive/behavioural profile of their patients, and can identify the onset of clinical signs of cognitive decline, relying also on reports from relatives and family members.

Strength of recommendation A, level of evidence I

Some clinical conditions can often progress to dementia, such as Mild Cognitive Impairment (MCI), a common condition in elder population. The prevalence of MCI varies from 10% to 20% in subjects older than 65 years (Petersen 2011, Plassmann 2008).
An individual reporting a subjective cognitive decline confirmed by an external observer, that does not affect his/her normal activities and autonomy in instrumental daily activities, can receive diagnosis of MCI. The neuropsychological assessment identifies a impairment in 1 or more cognitive domains, such as memory, executive functions, attention, language, or visuospatial abilities (Albert 2011).
MCI is considered a transition from normal aging to dementia: the conversion rate is almost 10% per year (Petersen 2011, Mitchell 2009, Plassmann 2008). However, in a relevant number of subjects, an estimated 30% of cases, MCI is reversible (Manly 2008).

The prevalence of MCI increases with age and is higher in males than in females. Further risk factors are a low educational level, cardiovascular conditions such as diabetes and hypertension, being apoE4 genotype carrier, a deficit of vitamin D, respiratory sleep disorders (Yaffe 2011).
All subjects with suspected MCI should undergo an accurate clinical and pharmacological assessment, and an objective examination aimed at assessing cognitive functions and functional status, with the objective of discriminating between normal aging, dementia, and potentially reversible forms of MCI (depression, drug-induced MCI, thyroid disorders, and deficit of vitamin 12 and folates) (Mc Carten 2013, Holsinger 2007).
An accurate neuropsychological characterization is crucial for a precise definition of the prognosis of MCI (Mitchell 2009). Recent data suggest that a reduced gait speed with concurrent mild cognitive deficit (the so called Motoric Cognitive Risk Syndrome) identifies a subgroup of subjects at particularly increased risk of dementia (Verghese 2014).
Relying on cerebrospinal fluid biomarkers and morphological neuroimaging can support the identification of subjects at risk of dementia, even if their use is to be restricted to selected cases in a specialist setting.
The use of neuroimaging for the diagnosis of MCI is not recommended (Albert 2011), even though some studies showed that the presence of an hippocampal atrophy in the T1-weighted sequences (Ferreira 2015), or of a metabolic pattern typical of Alzheimer's disease with fludeoxyglucose (18F) PET (Perani 2014) are predictive of conversion to dementia. Recent data showed that PET used along with amyloid tracers has high sensitivity, but limited specificity, mainly in elder subjects, in predicting the conversion from MCI to dementia (Zhang 2014, Jansen 2015).
The reduction of Abeta42 peptide associated to an increase of phospho-tau levels proved to be accurate, mainly in subjects younger than 70 years, in predicting the conversion to Alzheimer's disease (Ferreira 2014).

Recommendation 2

General practitioners have a determinant role in promoting preventive interventions aimed at delaying or preventing the conversion from MCI to dementia by reducing cardiovascular risk factors, promoting a more physically, mentally and socially active lifestyle, and starting preventive strategies for physical conditions.

Strength of recommendation A, level of evidence I

Depression and cognitive deficit

Data from literature show that 67% of patients with early-stage dementia have concurrent depression at different stages of severity, and that most of them have a history of depression (Rosness 2010).
A prospective study enrolling more than 22,000 patients with depressive symptoms, including bipolar symptoms, showed that each acute episode causes a 13% increase in the risk of developing dementia during the following years (EBMH 2005).

Depression can have, on the other hand, particularly in elder subjects, cognitive deficits as its early symptoms, that can revert after antidepressant treatments.
The intertwining of symptoms can make difficult the differential diagnosis, which can become clearer by monitoring patients in time (Steffens 2007).
A metanalysis of the database of Abstracts of Reviews of Effects (DARE 2009) verified that general practitioners are able to correctly exclude the presence of a depressive syndrome in the majority of unaffected patients, mainly if using the 15-items Geriatric Depression Scale (Sheikh 1986).

Recommendation 3

General practitioners, in case of cognitive-behavioral anomalies, should assess the presence of depressive symptoms, possibly using psychometric tools and other professional competences. The use of the 5-items Geriatric Depression Scale is suggested.

Strength of recommendation A, level of evidence III

Table 2. Geriatric Depression Scale Short Form (GDS-FS)

		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			

Delirium

Dementia should be distinguished from *delirium*, though it can coexist with it (SIGN 2006). Up to 60% of institutionalized subjects in nursing homes aged >75 years can show symptoms of *delirium* at any moment.
Delirium is an age-related condition affecting more than 30% of elder subjects with unstable acute or chronic conditions (RCP 2006). *Delirium* is a confused state whose onset can vary from within hours or days (though some subjects can have a sudden onset of symptoms), and has fluctuating symptoms during the day.
Delirium is generally directly subsequent to a systemic medical condition or the administration or discontinuation of a drug. It should be suspected particularly in case of infectious diseases, recent surgery, trauma, metabolic disorders, acute hallucinatory syndromes, or initiation of drug therapies (RACGP 2003).
Differential diagnosis is crucial, as *delirium*, unlike dementia, is a treatable and potentially reversible condition.
Box 1 shows the definition of *delirium* according to DSM-V criteria.

Box 1. Definition of *delirium* (Diagnostic and statistical manual of mental disorders, 5th edition - DSM-V)

"A disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)", that "develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day", associated to at least an "additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)".
"The disturbances [...] are not better explained by a pre-existing, established or evolving neurocognitive disorder".
"There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiology".

Recommendation 4

***Delirium* can be suspected in subjects with a clinical/behavioral profile similar to the one described in the DSM-V diagnostic criteria.**

Strength of recommendation A, level of evidence III

The criteria for the diagnosis of dementia according to the National Institute on Aging and Alzheimer's Association workgroup 2011 are the following:
- interfere with the ability to function at work or at usual activities;
- represent a decline from previous levels of functioning and performing;
- are not explained by *delirium* or major psychiatric disorder;

- are detected and diagnosed through history-taking and confirmed by objective assessment;
- involve a minimum of two of the following domains:
  - memory
  - reasoning and handling of complex tasks
  - visuospatial abilities
  - language
  - personality and behavior (agitation, apathy, obsessive or socially inappropriate behaviors).

Caratteristiche del danno cognitivo sono:

- gradual onset over months to years;
- progressive worsening;
- initial and most prominent cognitive deficit in one of the following categories:
  - amnestic presentation (typical): impairment in learning and recall of recently learned information
  - nonamnestic presentations: language presentation (most prominent deficits in word-finding), visuospatial presentation (object agnosia, impaired face recognition, simultanagnosia, and alexia), or executive dysfunction (most prominent deficits affecting reasoning, judgment, and problem solving);
- no evidence of core features of other types of dementias (i.e. substantial concomitant cerebrovascular disease).

Recommendation 5

Dementia can be suspected in subjects with a clinical profile similar to the one described in the criteria for the diagnosis of dementia defined by the National Institute on Aging and Alzheimer's Association workgroup, 2011.

Strength of recommendation A, level of evidence I

Scientific evidence (PSTF 2003) support the utility of a timely assessment, within a primary care setting, and a targeted interview in case of early symptoms of cognitive decline, or in case such symptoms are reported by a relative. For this purpose, general practitioners can use simple psychometric tools (Holsinger 2007) with the objective of reaching an early suspected diagnosis, to subsequently define potentially useful therapeutic and supportive interventions (Löppönen 2003).

Evidence also showed that an initial structured interview carried out by professional nurses can accurately identify cognitive deficits suggestive of dementia (Page 2008).

Recommendation 6

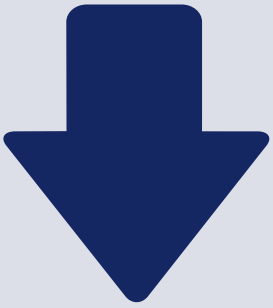
General practitioners diagnoses a suspected dementia based on clinical history, clinical assessment, potential causal, iatrogenic factors, and a structured interview.

Strength of recommendation A, level of evidence I

Figure 1. Diagnostic interview for dementia

Questionnaire for the person who has a better knowledge of the patient				
1	Difficulties in recalling recent conversations, events and appointments?	❒ Yes	❒ NO	MULTIPROFESSIONAL TEAM
2	Difficulties in remembering the day of the week or the date?	❒ Yes	❒ NO	
3	Often puts away objects in inappropriate places?	❒ Yes	❒ NO	
4	Repetitive talking?	❒ Yes	❒ NO	
5	Difficulties in following complex thoughts or carrying out tasks requiring several actions?	❒ Yes	❒ NO	
6	Unable to face simple problems at home or at work?	❒ Yes	❒ NO	
7	Unusually disrespectful of social or behavioral rules?	❒ Yes	❒ NO	
8	Difficulties in orientating while driving?	❒ Yes	❒ NO	
9	Tends to get lost even in familiar places?	❒ Yes	❒ NO	
10	Passive, does not adequately react to different situations, and appears indifferent and detached?	❒ Yes	❒ NO	
11	Interprets in a wrong way auditory and visual stimuli?	❒ Yes	❒ NO	
12	More irritable and suspicious than usual?	❒ Yes	❒ NO	
13	Growing difficulties in finding the adequate words to describe what he/she means ("on the tip of the tongue") and to carry out conversations?	❒ Yes	❒ NO	

If the subject answered YES to at least one of the previous questions



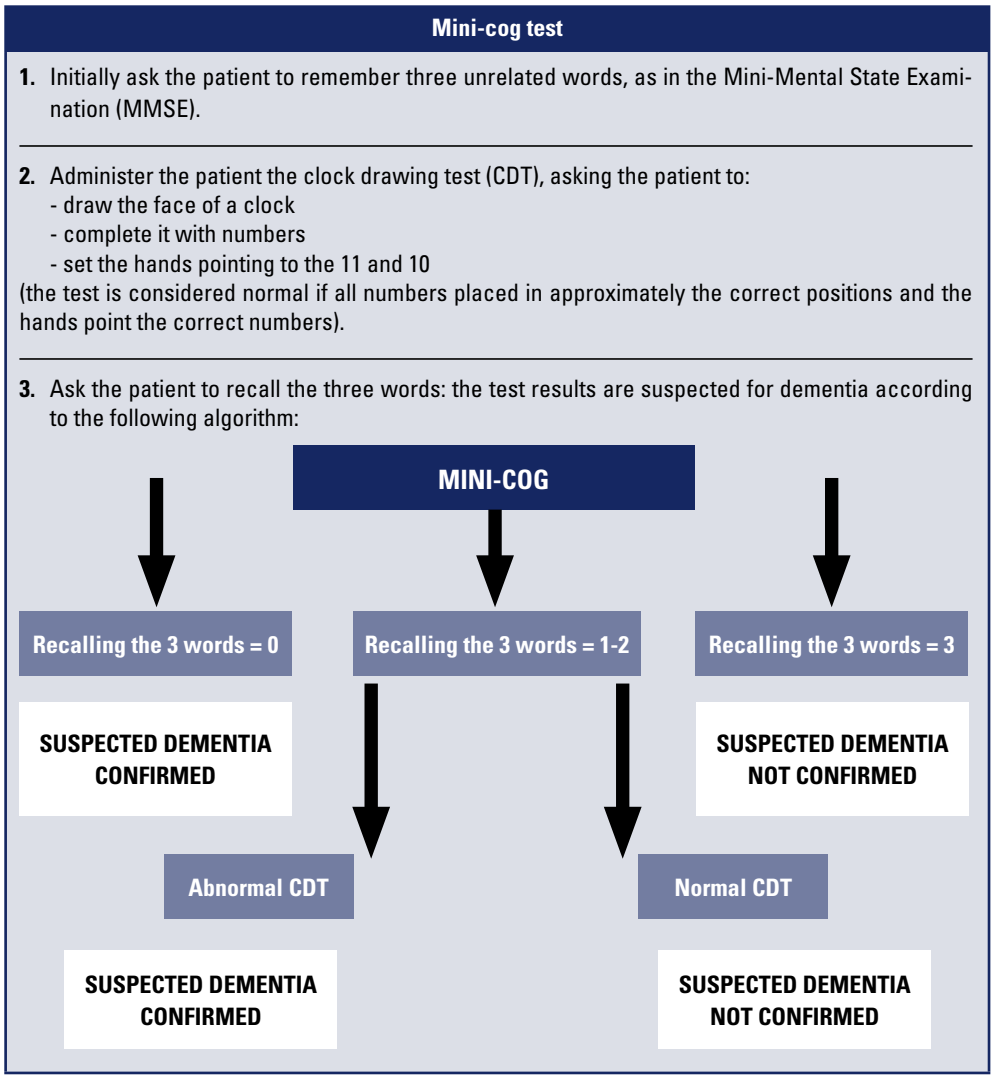
Initial cognitive assessment

Musicco et al. 2004

Administering the Mini-Cog Test is useful for the initial assessment, that allows to assess both long-term and short-term memory, visual and spatial representation abilities, attention, and executive functions.

The test lasts few minutes and requires the patient to memorize three words, draw the face of a clock, and recall the three previously memorized words.

Figure 2. Algorithm of Mini-Cog score



Causes of dementia

Several pathological conditions can cause dementia (ART 2010).
Almost 60% of the types of dementia with onset after 60 years is related to Alzheimer's disease, while 15-20% is due to cerebrovascular conditions (vascular dementia) or Lewy's bodies disease. The most frequent early-onset dementias are of the frontotemporal type, followed by Alzheimer's disease. Table 3 shows the early symptoms of non-Alzheimer dementias, while Table 4 shows the 10 early symptoms of Alzheimer's disease.

Table 3. Early symptoms of non-Alzheimer's dementia (BMJ 2015)

Frontotemporal dementias	- more frequent in younger subjects (50-60 years) - the most common aspect is a behavioral modification with changes in personality; characteristic traits are impulsiveness e disinhibition, memory remains usually intact
Vascular dementias*	- high number of signs and symptoms attributable to the damaged area and the severity of the damage. Symptom onset can be sudden or more insidious (small vessel disease). Memory loss can be present, but less severe than in Alzheimer's disease. Language disorders can be concomitant to visuospatial deficits and deficits in other cognitive functions. Changes in mood and apathy are common.
Dementias with Lewy's bodies	- The key trait are complex visual hallucinations: during the early phase hallucinations appear concurrently to physical stress (i.e. infections) or during the night, and can be associated to subtle perceptive symptoms (delusions). - Parkinsonism (tremor, bradykinesia, instability) can be present: tremor can be slight, but subjects with Lewy's bodies have slow movements, tend to easily fall. Fluctuations in cognitive abilities can be present, almost indistinguishable from *delirium*. Autonomic disorders can be present (orthostatic hypotension). Sleep disorders with rapid eye movement and agitation, can also be present, even long before the onset of dementia.
Parkinson's disease dementia	- 80% of subjects with Parkinson's disease develop dementia. Symptoms are similar to dementia with Lewy's bodies.
Posterior cortical atrophy	- Is a less common type of Alzheimer's disease that affects subjects aged 50-60 years. Symptoms throughout the disease include - visual agnosia (inability to recognise faces, objects), apraxia, acalculia, alexia. Memory usually remains intact.
Less common types of dementia	- alcoholic dementia - Creutzfeldt-Jakob disease - HIV-related cognitive impairment - Huntington's chorea - corticobasal syndrome - progressive supranuclear palsy - multiple sclerosis - Type C Niemann Pick's disease - Normal pressure hydrocephalus**

* vascular dementia can coexist with Alzheimer's disease, and this syndrome is called mixed dementia.

** Normal pressure hydrocephalus (NPH) is a type of dementia with a 0.2% prevalence in population aged 70-79 years (5.9% in people aged over 80 years). NPH is due to an abnormal accumulation of cerebrospinal fluid (CSF) in the ventricles and cavities of the brain, and is characterized by an unstable CSF pressure. It mainly affects elder males and can be reversible if adequately treated.

Epidemiological data on the relative prevalence of the different types of dementia are still debated, and few studies are available on vascular dementia compared to Alzheimer's dementia (Rocca 2004). Further issues are raised by vascular dementia being a heterogeneous entity, often associated to Alzheimer's disease.
The European guideline on the diagnosis and management of dementia and related disorders was published in 2012 (Sorbi 2012).

Table 4. Ten early symptoms of Alzheimer's disease (Alzheimer Association, 2009)

1	Short-term memory loss, to be distinguished from "normal" subjects with rapidly reversible memory losses.
2	Challenges in planning or solving problems, even in common daily activities: significant only if continuous.
3	Difficulty completing familiar daily tasks, such as driving to a familiar location or preparing usual foods.
4	Confusion with time or place (unable to recognize the period of the year, the day of the week or a familiar location).
5	Trouble understanding visual images (including their own reflection in the mirror).
6	Problems with structuring and understanding sentences, trouble recognizing objects.
7	Putting things in unusual places.
8	Decreasing judgment, such as poor judgement when dealing with money.
9	Withdrawal from work and social activities.
10	Changes in mood and personality.

Recommendation 7

General practitioners have also the duty to investigate all clinical conditions that can possibly cause cognitive disorders.

Strength of recommendation A, level of evidence VI

The relationship between cognitive-behavioral status and concomitant chronic conditions (comorbidities) must be assessed when suspecting dementia, mainly in subjects in the oldest age-class (CWG 2008). Comorbidities can cause a rapid worsening of both the cognitive and functional status (Doraiswamy 2001), and make further difficult to establish of the role of the main clinical condition in determining the disability (Verbrugge 1989).
Assessing the environment in which subjects with a suspected cognitive disorder live is also useful:

several studies report that factors related to social isolation can induce cognitive disorders (House 1988, Fratiglioni 2000).
The reorganization of territorial health care should include dementia syndromes among the considered clinical conditions, according to the Chronic Care Model.

Recommendation 8

General practitioners, in case of suspected dementia, should assess comorbidities and identify possible risk factors related to social isolation.

Strength of recommendation A, level of evidence I

Laboratory tests

Routine laboratory tests, though supported by few clinical trials, is widely considered necessary in the initial diagnostic workup for cognitive decline, to identify possible risk factors or concomitant diseases (Waldemar 2007).
Cognitive disorders can, in fact, be associated with several metabolic, infectious or toxic conditions that could be treatable.
In addition to the following screening tests, selected according to the most recent guidelines (Hort 2010), further investigations can be carried out, on an individual basis, such as specific tests for the identification of syphilis, and HIV-related or Borrelia-related infections:

- complete blood count
- electrolyte levels (Na, K, Ca);
- blood glucose levels;
- serum creatinine, azotemia;
- ALT, AST, gamma GT;
- TSH;
- folic acid, vitamin B12.

Recommendation 9

General practitioners, in case of suspected dementia, should offer patients baseline blood tests.

Strength of recommendation B, level of evidence VI

Diagnostic imaging and biomarkers

The use of biomarkers for the diagnosis of Alzheimer's disease can be useful in selected cases, subsequent to an accurate neuropsychological assessment aimed at defining the severity and type of cognitive decline (Padovani 2015).

The use of biomarkers is not recommended in clinical practice in absence of an objective cognitive deficit.

NMR

Specific patterns of focal atrophy, mainly affecting the mesial temporal lobe, may be investigated in T1-weighted sequences to support an early clinical diagnosis of Alzheimer's disease, using, when possible, qualitative scales based on the scoring of visual inspection (Ferreira 2015).

FDG (Fludeoxyglucose) PET

FDG PET imaging can be used to confirm diagnosis in subjects meeting diagnostic criteria for MCI and resulting from structural imaging, and clinical and neuropsychological assessment, as having a suspected prodromal phase of a neurodegenerative disease. The presence of a metabolic pattern typical of Alzheimer's disease is predictive of a conversion to Alzheimer's dementia, though available data are insufficient to suggest its routine use in clinical practice, given also its high economical impact (Zhang 2014). This exam can also be used, in case of uncertainties in interpreting clinical features, to support the differential diagnosis between Alzheimer's disease and other types of dementia (Perani 2014).

CSF biomarkers

The identification of reduced CSF levels of ABeta42 associated to increased levels of phospho-tau proved accurate in predicting conversion to dementia in subjects younger than 70 years with MCI (Ferreira 2014).
CSF biomarkers should not be considered a routine test due also to the still existing difficulties is standardizing their dosage (Mattsson 2013), and their evaluation should always be considered as a support to clinical assessment.

Amyloid PET

Amyloid imaging should not be considered a routine practice. This exam showed high sensitivity, but limited specificity in predicting the conversion to Alzheimer's disease in elder subjects with MCI (Jensen 2015). Amyloid PET can be used in subjects with suspected dementia if data on the presence or absence of beta-amyloidosis increase diagnostic certainty and thus modify the treatment. The use of CSF biomarkers and amyloid PET is not recommended in subjects with no cognitive deficit or with clinical features typical of Alzheimer's disease.

DaTSCAN SPECT

DaTSCAN SPECT showed high specificity in identifying degenerative Parkinsonism (Parkinson's disease dementia, dementia with Lewy's bodies, progressive supra-nuclear palsy, multi-system atrophy) in subjects with Parkinson's disease dementia, and in distinguishing them from subjects with drug-induced Parkinsonism, vascular Parkinsonism, normal pressure hydrocephalus, and Alzheimer's disease (Booth 2015).

Recommendation 10

General practitioners should offer to their patients neuroimaging as a support to the definition of a diagnosis dementia.

Strength of recommendation A, level of evidence VI

Recommendation 11

The use of biomarkers is not recommended as a routine exam, but is limited to selected cases in specialist centers.

Strength of recommendation A, level of evidence VI

Referral to specialized centers

Referral to specialized centers, even though patients with early stages of dementia can be effectively treated by general practitioners (Iliffe 2009), may be indicated in the following cases:

- investigating possible treatable causes;
- need to define the diagnosis;
- studying possible genetic hypotheses;
- rapid deterioration of symptoms;
- presence of psychiatric or clinical comorbidities;
- onset of symptoms in subjects younger than 60 years;
- possible occupational exposure to heavy metals;
- concomitant behavioral disorders.

The Centre for Reviews and Dissemination of the University of York confirmed (DARE 2009) the conclusions from an economic evaluation (Banerjee 2009) on the cost/benefit ratio of Memory Clinics (Hejl 2002) for people with dementia. The study reported that relying on these services for the diagnosis, treatment and monitoring of dementias lead to significant economic and health benefits.

Recommendation 12

General practitioners can rely on specialized centers dedicated to dementias to confirm the diagnosis, discriminate among the different types of dementia, defining the treatment plan, and stabilizing complex medical conditions.

Strength of recommendation A, level of evidence VI

Treatment

Pharmacological therapy

No disease-modifying treatment is currently available for dementia: the goal of drug therapies is to slow the progression of the disease and control symptoms (Qaseem 2008). Main symptoms, according to the practical criteria provided by the 2005 SIGN 86 guideline (Scottish Intercollegiate Guidelines Network), can be classified as core (cognitive decline and functional decline), and associated (psycho-motor agitation, aggression, depression, hallucinations, sleep disorders and other non-specific disturbances).
The following table summarizes the main indications for the treatment of the main symptoms.

Table 5. Symptomatic treatment of dementia.

Core symptoms	Therapy
cognitive decline	donepezil, galantamine, rivastigmine, memantine
functional decline	donepezil, galantamine, rivastigmine, memantine
Associated symptoms	**Therapy**
anxiety/agitation	SSRIs, trazodone
aggression	antipsychotics
depression	antidepressants
hallucinations	donepezil, antipsychotics
sleep disturbance	no evidence-based therapies available
non-specific disturbance	donepezil, galantamine, rivastigmine, memantine
from SIGN Guideline 86, modified	

Core symptoms

Core symptoms are those reported among the diagnostic criteria defined by the National Institute on Aging and Alzheimer's Association workgroup (McKhann 2011). Core symptoms are defined as deficits in at least two of the following cognitive-behavioral areas:

- memory;
- reasoning and planning;
- visuospatial abilities;
- language;
- personality and behavior.

(for the full version, see page 18).

Cognitive deficits in Alzheimer's disease can be of the amnesic type (typical) or of the non-amnesic type (aphasia, agnosia, alexia, impaired judgement or reasoning).
Acetylcholinesterase inhibitors and memantine are the main currently available drugs that proved effective in some forms of dementia.
Literature also reports some efficacy of selected natural products:

- *Ginko Biloba*;
- *Huperzia Serrata*;
- *Salvia Officinalis*;
- *Curcuma Longa*;
- extracts of *Vinca Minor.*

(May 2009).

Moreover, the Cochrane collaboration is currently reviewing some nutritional approaches.

Acethylcolinsterase inhibitors

Alzheimer's disease is characterized by a disruption of the cholinergic system, with a reduction of the neurotransmitter acethylcholine. The molecules inhibiting the enzyme acetylcholinesterase can reduce the catabolism of acethylcholine (Birkg 2003): two systematic reviews and meta-analysis of randomized clinical trials (Hansen 2008, Birks 2006) showed that patients with mild to moderate Alzheimer's disease treated with donepezil, galantamine and rivastigmine show a statistically significant reduction in the decline of cognitive functions and autonomy in daily activities after 6-12 months of therapy. Several guidelines (Hort 2010, APA 2007, Qaseem 2008, Sorbi 2012) underline that such benefit is clinically modest, and therefore recommend to discuss with patients and their relatives what benefits can be actually expected and all possible adverse effects.
Few clinical studies are available on the use of acetylcholinesterase inhibitors in patients with vascular dementia, which is characterized by a loss of nervous tissue subsequent to an ischemic or hemorrhagic damage. Three Cochrane systematic reviews (Malouf 2009, Craig 2008 a e b) report that the cognitive level and functional autonomy of patients with mild to moderate vascular dementia can benefit from the treatment with donepezil. A more recent metanalysis (Kavirajan 2007), however, shows that these benefits are lower than those observed in patients with Alzheimer's disease, and of low clinical significance.
Donepezil was also reported in some studies to be effective in controlling the progression of dementia with Lewy's bodies (Graff-Radford 2012, Mori 2012).
The typical neuro-pathological sign of dementia with Lewy's bodies and Parkinson's disease dementia, according to the NINDS National Institute of Neurological Disorders and Stroke), is the presence of the protein alpha-synuclein within the brain neuronal nuclei. Patients with dementia with Lewy's bodies and concomitant behavioural disorders or psychiatric conditions, according to a Cochrane systematic review, can benefit from the treatment with rivastigmine, if well tolerated. Weak evidence supports also the use of galantamine and donepezil.
A Cohrane review shows that rivastigmine is effective in improving cognitive performances and autonomy in daily activities in patients with Parkinson's disease dementia (Maidment 2006).

Table 6. Acetylcholinesterase inhibitors

Molecule	Dose	Tolerability	Adverse effects
donepezil	5-10 mg/d	good	cholinergic hyperstimulation
galantamine	4-8-12 mg x 2/d 8-16-24 mg/d	good	cholinergic hyperstimulation
rivastigmine percutaneous Exelon	1.5-6 mg x 2/d 4.6-9.5 mg/d 13.3/24h	good	cholinergic hyperstimulation

Memantine

Memantine is administered in doses ranging from 5 to 20 mg. It is well tolerated, and reported adverse effects are: instability, migraine, constipation, and somnolence.
A Cochrane systematic review (McShane 2010) reported that memantine resulted well tolerated and showed a moderate, but clinically relevant, effect on cognitive functions and functional autonomy in patients with moderate to severe Alzheimer's dementia, but not in patients with vascular dementia. No evidence is available on the effectiveness of memantine in patients with frontotemporal dementia (Diehl-Schmid 2008) and Huntington's chorea. A double-blind randomized clinical trial on the concomitant administration of donepezil and memantine showed that the combined treatment had a significant effect on the cognitive function and autonomy in daily life of patients with moderate to severe Alzheimer's disease compared to the treatment with donepezil alone (Tariot 2004).
Memantine is a molecule that acts on the glutamatergic system by blocking the NMDA (N-methyl D-aspartate)-glutamate receptors, reducing the excitotoxic effect of glutamate, the main excitatory neurotransmitter in the central nervous system (Sucher 1996).
The Cochrane collaboration is currently reviewing international literature on the use of nutritional supplements, which showed initial positive results in the early stages of Alzheimer's disease.

Biological drugs

Clinical trials are currently testing biological drugs for the pharmacological treatment of dementia. Results from two phase III trial investigating the efficacy of anti-amyloid-beta monoclonal antibodies in patients with mild to moderate Alzheimer's disease have been recently published on the New England Journal of Medicine. Bapineuzumab did not prove effective in improving the clinical outcome of enrolled patients, despite a decrease in CSF levels of phospho tau and in amyloid deposits as reported by PIB-PET imaging in the subgroup of patients who were Apolipoprotein E (APOE) ε4 carriers (Salloway 2014).
Also the trials that investigated the use of solanezumab, another anti-Aβ (β-amyloid protein) monoclonal antibody did not report this drug as effective in improving cognitive or functional outcomes in patients with mild to moderate AD (Doody 2014). Starting an anti-amyloid treatment after the clinical onset of dementia appears to be late and ineffective in modifying the

clinical course of the disease. Amyloid starts to deposit in the brain of subjects who will develop Alzheimer's disease several years before the onset of symptoms, therefore further studies are needed investigating the effectiveness of anti-Aβ monoclonal antibodies in patients with mild AD or in asymptomatic subjects with positive biomarkers indicating the presence of amyloid deposits. Multi-center studies are currently are currently being carried out to investigate the effectiveness of anti-Aβ monoclonal antibodies in familiar forms of Alzheimer's disease.

Non-invasive brain stimulation techniques

The development of non-invasive brain stimulation techniques raised a growing interest in their use a potential therapeutic tool for cognitive rehabilitation. In particular, transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are both approaches producing functional changes in brain cortex that are able to induce an even prolonged modulation of neuronal excitability. The safety and low costs of these techniques, and their being easy to use and able to induce significant changes in neuronal excitability, make them particularly suitable to be implemented in clinical practice, even on a large scale. However, further studies are needed on this topic, as the neural mechanism responsible for cognitive improvement is largely unknown (Eliasova 2014).

Recommendation 13

The possibility of starting a therapy with acetylcholinesterase inhibitors should be considered at the time of initial diagnosis of Alzheimer's disease, as they have proven effective in the treatment of core symptoms of AD. Patients and their caregivers should be informed of what benefit can be actually expected and of potential adverse effects. Acetylcholinesterase inhibitors proved effective also in the treatment of dementia with Lewy's bodies and in Parkinson's disease dementia. The option of starting a therapy with memantine should be considered in patients with moderate to severe Alzheimer's disease to treat core symptoms. There is no evidence supporting the use of natural and nutritional remedies.

Strength of recommendation A, level of evidence I

Associated symptoms

More than 90% of patients with dementia shows behavioral symptoms (Lyketsos 2011). These type of disorders have been defined, as from 1996, as psycho-behavioral disorders in dementia (often referred to as BPSD, that is the acronym for Behavioral and Psychological Symptoms of Dementia), including symptoms with widely different etiology, manifestation and treatment (Finkel 1996).
The onset of BPSDs is widely proven to significantly increase the burden of care (Gonzales-Salvator 1999), as it has a strong impact on the quality of life of both patients and their caregivers

(Pearson 1989, Gonzales-Salvator 2000), worsens patients' cognitive performance and autonomy (O' Brien 2001), and increases the risk of institutionalization (Steele 1990).
The onset of BPSDs can be at any stage of the disease and symptoms, in each patient, can vary in time or be stable and persist for several years. The assessment of BPSD is crucial, as each subtype of dementia is characterized by a different behavioral profile, even in the early stages of the disease. Subjects with amnesic MCI, for example, who have a higher probability to progress to non-Alzheimer's dementia, showed a higher frequency of hallucinations and sleep disorders (Rozzini 2008).
Available literature supports two main approaches to assess BPSD in dementia: an approach, that could be defined as symptomatic, aimed at identifying individual symptoms; and a syndromic approach, grouping individual symptoms in clusters of related symptoms.
The latter is most widely used approach in current clinical practice. It identifies 4 main syndromic groups::

- affective symptoms: depression, anxiety, irritability, emotional lability;
- psychotic symptoms: delirium, hallucinations and misidentification;
- behavior disorders: sleep, eating, sexuality;
- specific behaviors: wandering, agitation/aggression, anxiety, persistent vocalization, engaging in aimless activities, persevering, apathy, disinhibition.

These syndromic groups, having some overlapping areas, should be considered as having mainly an operational meaning, allowing to choose the most appropriate medication on the basis of the cluster of symptoms most affects the management of the patient.
Moreover, specific non-pharmacological interventions are proposed to manage behavior symptoms, but for most of these treatments statistically significant evidence is still lacking.
As for pharmacological treatments, a wide clinical consensus supports the use of antidepressants for the treatment of affective disorders, and of antipsychotics for the treatment of the psychotic cluster, aggression and insomnia with psycho-motor agitation, while does indicate the use of anti-epileptic drugs only in selected cases (Mossello 2014).
Antidepressants, anti-psychotics and mood stabilizers are the drug classes currently used to treat associated symptoms.

Antidepressants

A Cochrane review (Mottram 2006) on the use of antidepressants in elder subjects showed a lower compliance in subjects receiving tricyclics (due to adverse effects) compared to subjects receiving selective serotonin reuptake inhibitors (SSRI), which act increasing the levels of serotonin at a synaptic level. Fluoxetine was the first molecule of this last class to be approved for therapeutic use, while venlafaxin was the first approved molecule of the new drugs increasing also norepinephrine reuptake.
No conclusive evidence is available on the efficacy of antidepressants in dementia.
A Cochrane review (Bains 2008) reported small effects for all considered drugs, but it included no studies on new antidepressants and few studies investigating SSRIs.
A recent randomized controlled trial (Rosenberg 2010) showed no significant effects of the treatment with SSRIs on depressive symptoms in patients with Alzheimer's disease. A review of 4 systematic reviews on the use of antidepressants for the treatment of agitation in dementia

including a total of 7 randomized clinical studies (Best Evidence Summaries of Topics in Mental Healthcare 2007), reported no significant differences among trazodone, sertraline, fluoxetine, and placebo.
A wide clinical consensus supports the use of trazodone and SSRIs in specific conditions such as anxiety and irritation (Mossello 2014).
SSRIs, despite not being approved for this indication, may have some efficacy in controlling impulsive behaviors in frontotemporal dementia, (Mendez 2009).

Table 7. Antidepressant drugs

Class		Active principle
non-selective	tricyclics	- amitryptiline - imipramine - clomipramine
	I MAO	- phenelzine - tranylcypromine - isocarboxazid - selegiline
selective reuptake inhibitors	serotonin (SSRI)	- fluvoxamine - fluoxetine - paroxetine - citalopram - escitalopram - sertraline
	serotonin and norepinephrine (SNRI)	- duloxetine - venlafaxine
	norepinephrine and dopamine (NDRI)	- bupropion
	noradrenaline (NARI)	- reboxetine
receptor blockers	serotonin and serotonin reuptake inhibitors	- trazodone - nefazodone
	noradrenergic and specific serotonergic (NASSA)	- mirtazapine

Recommendation 14

Antidepressant drugs, preferably SSRI, can be useful in the treatment of patients with dementia with depressive symptoms. Trazodone can be useful in case of agitation.

Strength of recommendation B, level of evidence VI

Antipsychotics

A 2004 consensus conference of 48 of the main US experts on the use of psychoactive drugs in elder people draw the following conclusions on the management of behavior disorders in patients with dementia:

- only one atypical anti-psychotic drug should be used in patients with dementia and delirium (risperidone, olanzapine, quetiapine);
- treatment should not last more than 3-6 weeks at the minimum effective dose;
- clozapine and olanzapine should not be used in association with typical neuroleptic drugs in case of concomitant diabetes or dyslipidemia;
- quetiapine should be the first choice in the treatment of patients with Parkinsonism;
- clozapine, ziprasidone and typical neuroleptics should not be used in patients with heart failure;
- typical neuroleptics should not be used in association with fluoxetine and paroxetine.

Data from several studies reported an increased risk of sudden cardiac death in subjects treated with typical anti-psychotic drugs (Baldessarini 2009).
A metanalysis published by JAMA in 2005 (Schneider 2005) reported an increased risk of death due to acute cerebrovascular events in subjects with dementia treated with atypical neuroleptic drugs. Subsequent studies confirmed the association. The use of typical neuroleptic drugs should be restricted to specific conditions determining an increased risk or extreme sufferings for patients or their caregivers, and should be limited in time.

Recommendation 15

Anti-psychotics have a limited effect in treating psychosis and aggression in patients with dementia. Due to the potentially severe adverse effects, their use should be limited to specific condition determining an increased risk or extreme sufferings for patients or their caregivers and should be limited in time. The combined use of different anti-psychotic drugs should be avoided.

Strength of recommendation A, level of evidence II

Mood stabilizers

Mood stabilizers are a an heterogeneous group of drugs (lithium salts and some anti-epileptic drugs) that proved in some cases to be useful in containing behaviors such as agitation, aggression, impulsiveness, disinhibition, and maniacal symptoms in patients with dementia. Data on the effectiveness of mood stabilizers in dementia are mainly from observational studies.
Limited evidence suggest that lamotrigine could somewhat well tolerated and effective in the treatment of agitation in patients with dementia (Sajatovic 2007).

Recommendation 16

Evidence is insufficient to support the use of the so-called mood stabilizers in the treatment of behavior disorders in subjects with dementia.

Strength of recommendation A, level of evidence V

Benzodiazepines

Nel 2009 la Società italiana di farmacologia ha sconsigliato "l'uso a lungo termine delle benzodiazepine e di farmaci affini nelle persone anziane, a causa del rischio di assuefazione, dell'impossibilità di sospensione, di mascheramento della depressione e della comparsa o dell'aggravamento di disturbi mnesici".

Recommendation 17

Evidence in insufficient to support the use of benzodiazepines in patients with dementia.

Strength of recommendation A, level of evidence V

Recommendation 18

The pharmacological treatment of behavior symptoms in patients with dementia, in summary, requires:
- **avoiding excessive sedation;**
- **informing relatives on the treatment;**
- **obtaining consent;**
- **starting with low doses of a single medication;**
- **preferring a drug with low anticholinergic activity;**
- **escalating the dose until reaching the effective dose;**
- **maintaining non-pharmacological intervention.**

(NICE, July 2014)

Strength of recommendation A, level of evidence V

Recommendation 19

Physicians, in case their patients prove to have impaired decision-making ability, should suggest to caregivers (relatives or closest ones) to provide for legal guardianship (ward or guardian) in the exclusive interest of patients themselves.

Strength of recommendation B, level of evidence VI

Non-pharmacological treatments

LNon-pharmacological treatments (NPTs) are an evidence-based standardized technical approach of proven effectiveness, aimed at preventing disability, in association with pharmacological treatments, in patients with dementia. The multi-dimensional assessment, along with personal history, is the foundation on which the therapeutic plan is built, the starting point of a continuum care among all the professionals that take care of patients' management in each phase and setting. The pharmacological approach alone, that is, apart from a more global project of care tailored to the stage of the disease, is often associated to a feeling of therapeutic impotence: medications alone, in fact, are not able to create a therapeutic alliance between physician and caregiver which is crucial to establish what psychology defines "helping alliance" within which both the helped and the helper receive gratification and are reinforced in their behavior.
NPTs are characterized by the active involvement of the assisted subject, and are based on a preliminary assessment of the residual potential. This assessment is aimed at supporting and activating, through a tailored project of care, the mental functions that are still not completely deteriorated to maintain the highest possible autonomy and slow the progression of disability.
The assessment turns from a simple measuring and descriptive tool, to an instrument that can identify objectives of care shared among all the subjects involved in management the patient. These objectives will be different for each patient, but will also differ for the same patient at different stages of the disease.
This is the transition from an attitude of custody to an attitude of care: formal and informal caregivers become the "care" themselves through the professionalization of the act.
The targets of NPTs can include: cognition, neuro-sensory functions, affectivity, language, sleep, nutrition, motor functions, personal autonomy, interpersonal relationships. Different levels of severity can be identified in dementia, the main steps from autonomy to complete functional dependence:

- MCI;
- behavior disorders;
- severe deficit in BADL (basic activities of daily living);
- vegetative state.

Cognitive, behavioral and environmental interventions will thus have a different role in each phase of the disease.
The interventions for cognitive rehabilitation include several techniques, such as:

- Memory training, mnemotechniques: effective for mnesic deficits;
- Reality Orientation Therapy (ROT);
- 3R (merging ROT, Reminiscence and Remotivation);
- Validation Therapy: focuses also on patients' affective implications and cognitive deficits, and on more relational aspects.

The most widely used therapy in patients with cognitive decline is ROT (Reality Orientation Therapy) (Taulbee 1984, Baroni 1991, Zanetti 1995).
ROT is a technique aimed at reorienting patients in relation to their personal history and the environment surrounding them. It can be distinguished in an informal ROT, structured throughout

the whole 24 hours in acts of information assigned to everyone who interacts with patients, and a formal ROT including the issues of orientation in a structured way.
ROT is part of the numerous contextual therapies (Milieu Therapy), that include also Token Economy and multidiscipinary therapy, and resulted effective in improving cognitive abilities, in particular verbal and orientation aspects, in patients with dementia.
A Cochrane review (Spector 2000, 2003, 2007) confirmed these results and showed that the ROT is effective both on cognitive and behavioral symptoms.
Better results can be obtained including the ROT in a multimodal and multidisciplinary stimulation programme (Zanetti 2005).
Memory training and Spaced retrieval therapy are based on the theoretic assumption that, in the early phases of Alzheimer's disease, procedural memory remains intact (Corkin 1984, Hirono 1997), and are aimed at stimulating the procedural motor, sensory and cognitive learning (Josephsson 1993, Ermini-Funfschilling 1995, Zanetti 1997, Hirono 1997).
Reminiscence therapy is supported by the psychodinamic theory and is based on the normal tendency of elder people to recall their past. The therapy is aimed at stimulating autobiographic memory using visual, olfactory and tactile materials.
Token Economy and multidisciplinary therapy are both based on reinforcing positive behaviors and interventions on functional, sensory and environmental factors that can contribute to create excessive disability.
The "validation" therapy is based on the active listening of patients, with the objective of understanding their way of seeing reality, and establishing with them significant emotional contacts, giving a meaning to the world in which patients believe to be. The technique is particularly effective in improving the relationship with patients with severe dementia.
Remotivation therapy is a cognitive-behavioral technique (Janssen e Giberson 1988) aimed at keeping alive the interest for personal and social events of common knowledge. The main objective is to contrast the tendency to isolation in patients with dementia and depression (Koh 1994).
Occupational therapy stimulates residual abilities through activities aimed at obtaining a finished product or at performing one or more tasks of daily life.
Musicotherapy can be used with different objectives: relaxation, cognitive stimulation through sound and rhythm, stimulation of remote memory through listening known songs or music. It is also used to facilitate verbal communication. Published studies investigated its effect on psychiatric and behavioural disorders, cognitive deficits, relational and social competences, depressive symptoms, quality of life, and caregivers. Available data show that music therapy is significantly effective in the treatment of agitation, affective disorders and communication abilities.
The environmental approach aims at contrasting disorientation in space, time and towards people, which is a usually severe cognitive deficit often responsible for behavioral disorders. The environmental approach is crucial in each phase of the disease. Several guidelines are available on how to structure indoor (lights, colours, roof high, furniture) and outdoor spaces. One of the most interesting outdoor spaces is the "Alzheimer's garden" where the choice of plants and the organization of paths have an essential role in sensory stimulation, orientation in time, and in the treatment of wandering.
In general, to be considered a therapeutic tool, environment should ensure physical and psychological safety, compensate for physical, sensory and cognitive disability, and at the same time respect residual abilities to make decisions and privacy.

Normalization is a therapeutic approach based on a in-depth assessment and knowledge of each patient. It aims at restoring a life style, including house environment, habits and interests, as close as possible to the life style patients had before the onset of dementia. Normalizing the environment can encourage the emergence of normal behaviors, minimizing the stress derived from changes.
Multisensory stimulation (Snoezelen) is based on proposing relaxing and pleasant stimuli aimed at different sensory channels (visual, auditory, olfactory, tactile) based on the knowledge of previous pleasant experiences, and can be carried out in different ways (delirium room, snoezelen device). This approach proved effective in the treatment of apathy and agitation in patients hospitalized in specialized units or Alzheimer Units, and in reducing the use of sedatives and restraint.

Treatment of behavioral disorders

The treatment of non-cognitive BPSD (Behavioral and Psycological Symptoms of Dementia) according to behavioral therapy requires the involvement and training of caregivers and several pharmacological and non-pharmacological treatments (Teri 1992). It requires a careful assessment of behavioral disorders, including an identification and definition of symptoms and their severity according to their frequency and intensity, carried out using specific scales. Each symptom should be contextualized, describing the environmental situation (space and persons) in which it appears, focusing the attention on which facts preceded it and its consequences.
The therapeutic alliance between health and social health professionals, and caregivers becomes essential to identify shared objectives of care that are considered significant, to qualify as therapeutic an act that, in disturbed and disturbing behaviors, is often of custody and restraint. Available literature is substantially consistent in reporting that motivation in caregivers is supported by having objectives, and using standardized tools and procedures (Baroni 1991). Non-pharmacological therapies for behavioral disorders require the identification of strategies to contain their severity and make them more manageable. To this purpose, they include interventions aimed at modifying the environment, considering it as structure and people, with the objective of facilitating the adaptive relationship.
The principle at the basis of all therapies referring to psychosocial interventions is mainly to modify the person's behaviors and expectations (relatives, caregivers) and reduce environmental stress. Token Economy and multidisciplinary therapy can be used to this purpose as they both include the gratification and reinforcements of positive behaviors, and interventions of all factors (functional, sensory and environmental) that may contribute to cause excessive disability.
Occupational therapy itself can be fully included in the project of care if the activities are ecological, significant, tailored to the abilities of the subject to which they are proposed. According to Cohen-Mansfield's interpretation that behavioral disorders are the expression of unsatisfied needs, all interventions aimed at making the environment "normal", thus reassuring, for patients, should be privileged.
Non-pharmacological interventions should be tailored to the needs of patients and their caregivers, considering the complexity of dementia. All programs should include aspects of all the mentioned techniques, and the objectives identified at each step should be cognitive, behavioral, functional and social-relational, to create a "positive" system of care, aimed at identifying the health potential of patients, the growth potential of the operators, an the health/growth potential

of the patients' relatives. Caregivers and relatives (when present) are the target and tool for care: family, to become "prosthetic", should be involved in a continuum care with acts of training, information, and should be supported in the caregiver through counselling and coping. Family members and caregivers, however, should also be considered as persons, not only as care providers, and their well-being should also be pursued.
Literature supports their use in a family environment and in an outpatient setting. The use of non-pharmacological therapies in a specialist setting should also be encouraged.
Day care centers (DCC) and Alzheimer's units in nursing homes, temporary services for patients with dementia and severe behavioral disorders are the appropriate setting for the treatment of behavioral breakdowns, as they make possible to establish a therapeutic contract also with family members, that are sharing a high level of stress.
NPTs help creating among patients, health professionals, relatives and caregivers a dynamic system in which everyone are givers and receivers of care, and care will be pursued and transferred in the home management at the time of discharge from the residential service. The English guidelines on dementia (NICE guidelines CG42) indicate that care plans should include rehabilitation activities in activities of daily life (ADL) such as getting dressed, washing, maintaining continence, eating, moving, to maximize the independence of patients, tailoring activities and plans to residual abilities, and trying to recover lost abilities.

Recommendation 20

The first-line treatment of psychological and behavioral symptoms is non-pharmacological.
A non-pharmacological treatment should be considered, at the time of diagnosis, as a possible option to treat cognitive symptoms, even if supporting evidence is still inconclusive.
Patients and their caregivers should be informed on the actual expected benefits, and caregivers should be offered counselling and training and supportive tools. To this end, general practitioners can refer to specialized services dedicated to the management of dementia.

Strength of recommendation A, level of evidence V

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