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Contemporary Management of Alzheimer's Disease

Lon S. Schneider, MD

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Contemporary Management of Alzheimer's Disease

Lon S. Schneider, MD

Dr. Schneider is professor of Psychiatry, Neurology, and Gerontology at the University of Southern California.

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Table of Contents

The purpose of this pocket guide is to provide convenient, tabular information on the diagnosis and treatment of Alzheimer's disease (AD) and other dementias of late-life in one place. We aspired to provide such essential clinical information as diagnostic criteria, tests, guides, and important clinical pharmacological data to physicians for ready referencing.

This pocket guide is divided into several sections:

1. Necessary background facts on AD
2. Diagnostic aids and criteria for dementia diagnoses
3. Medications used by people with AD and/or other dementias

There are also sections called "Micro-Guides." Micro-Guides are comprehensive tables that are provided to be practical and brief, covering areas such as the molecular pathology of AD, brain imaging, neuropsychological assessment, and rating scales.

For pharmacological treatment, basic drug information on marketed drugs and supplements is provided regardless of whether the drug is approved for AD. All approved cholinesterase inhibitors are listed. For example, not all antipsychotics or antidepressants are listed, because some such drugs are seldomly used with the elderly; some others that should be avoided are also omitted. Yet some drugs that should be avoided are listed because they are commonly used among younger adults, and, unfortunately, still prescribed to older patients. Cautionary comments are sometimes included in these listings.

This pocket guide does not address the evidence base for the efficacy of the medications listed. Assessing efficacy and effectiveness is complex, especially with medications that are used off-label and with which there may be few controlled clinical trials. Such evidence can be found in reports and textbooks dedicated to the subject. It is hoped that this pocket guide might prove a useful clinical companion and reference.

Caveats: Except for the cholinesterase inhibitors, the discussions and tables of medications for people with dementia nearly always involve off label use, ie, uses not approved or reported in the prescribing information. For example, antidepressants and antipsychotics are indicated in the Food and Drug Administration (FDA)-approved prescribing information for major depression and the psychosis of schizophrenia, and not for depressive symptoms or the delusions or hallucinations occurring within the context of dementia. In these instances the medications and doses listed are for reference only and should not be considered recommendations or assertions toward their appropriateness, efficacy, or safety in patients with dementia.

Unapproved/Investigational Uses: This booklet may contain information about experimental and clinical uses of drugs that are not within product labeling currently approved by the FDA or currently approved by the FDA for use in the United States.

Readers are requested to consult the product package labeling for any drug mentioned in this work before use.

A Epidemiology, Etiology, Neuropathology of AD

1 Prevalence and Incidence of AD by Age[1]

Age	Prevalence (%)	Incidence (%)
60-64	<0.5	0.1
65-69	<1.0	0.2
70-74	<2.0	0.4
75-79	4.3	0.7
80-84	8.5	1.4
85-89	16.0	2.9
90-95	28.5	6.0

Comment: The incidence and prevalence roughly doubles every 5 years. The median age of patients with AD is approximately 82 years of age, and 43% of patients are between 75 and 85 years of age. Overall rates of dementia are higher.

2 Genetics and Risk Factors of AD[1]

Autosomal Dominant Mutations

- Represents 5% of all cases
- Age of onset is 50 to 60 years of age (or earlier)
- PS-1 Chromosome 14
- PS-2 Chromosome 1
- β-APP Chromosome 21
- The PS-1 mutations account for greater than 50% of early onset familial AD cases

Susceptibility Polymorphism

- Apolipoprotein E Chromosome 19
- Risk factor
- 3 Allele types: ∈2, ∈3, ∈4
- ∈4—>greater risk of late onset AD
- ∈2—>protective

Comment: Although Apolipoprotein E genotyping is available, it is not useful for diagnosis.

Risk Factors

- Age
- Family History
- Gender
- Head trauma
- Lower educational level
- Genetic risk factors (see above)
- Down syndrome (Trisomy 21)

NOTE: Other mutations and polymorphisms have yet to be described.
PS=presenilin, β-APP=β-amyloid precursor protein.

3 Neuropathology and Pathogenesis of AD[2]

Key neuropathological features include neuronal and synaptic loss, the appearance of neuritic plaques, and NFTs.

Aß 1-42 and neuritic plaques (synaptic loss)

- Plaques are composed of small poorly-soluble proteins derived from a much larger β-APP encoded on chromosome 21.
- β-APP is normally found in neuronal membrane. Aß1-42 is the product of abnormal β-APP cleavage by a beta-secretase and a gamma-secretase. PS-1 is probably the gamma-secretase. The deposition of Aß1-42 is hypothesized to accelerate neurofibrillary degeneration. Both β-secretase and γ-secretase inhibitors are in Phase I pharmacological trials. Muscarinic agonists and cholinesterase inhibitors may also decrease the production of Aß1-42, but this has yet to be proven.

NFT and neuronal loss

- Abnormally-phosphorylated tau proteins
- Tau is necessary for the assembly and function of microtubules (the molecular-transport system within neurons)

Progression of pathology

The first neurons susceptible to neurofibrillary degeneration are the phylogenetically oldest:

- The limbic areas (ie, amygdala and hippocampus) which are critical for memory and learning.
- Later the heteromodal association areas (ie, temporal-parietal regions important for language and visual spatial function, as well as prefrontal lobe, necessary for abstract reasoning) are affected.
- The primary motor and sensory areas involved in movement, vision, hearing, and somatosensory perception are relatively spared.
- The symptom profile of AD roughly corresponds to this regionally selective distribution of NFT.

Aβ 1-42=beta amyloid; β-APP=beta-amyloid precursor protein; PS-1=Presenilin 1; NFT=neurofibrillary tangles.

4 Mild, Moderate, and Severe Characteristics of AD

Severity	Symptoms	Brain Region Involved
Early		
Mild cognitive impairment, mild dementia (1–3 years)	Clear impairments of memory and learning Depressed or anxious mood may be manifested Impairment in financial judgment and ability	Limbic-diencephalic memory system
Middle		
Moderate and severe dementia (3–6 years)	Aphasia (loss of language ability): word-finding problems Visual spatial impairment "Dysexecutive" syndrome: poor judgment, insight, and planning Impairment of ADL: trouble with dressing, hygiene, and toileting	Multi-modal association areas
	Behavioral changes: agitation, wandering, delusions and hallucinations	Paralimbic areas
Late		
Profound and terminal dementia (7–10 years)	Global cognitive decline Unable to recognize family Unable to make needs known	Widespread and severe involvement of neocortical brain regions

ADL=activities of daily living

Micro-Guide # 1

American Academy of Neurology Quality Standards Subcommittee Comments on the Diagnosis of Dementia[3]

American Academy of Neurology Subcommittee on Quality Standards offers the following comments on diagnosis:

- The following clinical criteria for AD are reliable: *DSM-IIIR* definition of DAT, NINCDS-ADRDA, and *DSM-IV* diagnostic criteria.
- Vascular dementia, DLB and FTD should be excluded when diagnosing AD, but the current diagnostic criteria for those diseases are imperfect.
- Structural neuroimaging (ie, CT or MRI) is appropriate to detect lesions that may result in cognitive impairment.
- The CSF-14-3-3 protein is useful when CJD is suspected and recent stroke or viral encephalitis can be excluded.
- Evidence supports the following tests in the routine evaluation of the demented patient:
  - Complete blood cell count
  - Vitamin B_{12} levels
  - Depression screening
  - Glucose-blood urea nitrogen/creatinine
  - Serum electrolytes
  - Thyroid function tests
  - Liver function tests
- Evidence indicates the following tests should not be included in the routine evaluation of demented patients:
  - Screening for syphilis (unless patient has a specific risk factor)
  - Linear or volumetric MRI or CT measurement strategies
  - Single photon emission computed tomography
  - Genetic testing for DLB or CJD
  - Apolipoprotein E genotyping for AD
  - Electroencephalogram
  - Lumbar puncture (unless presence of metastatic cancer, suspicion of CNS infection, reactive serum syphilis serology, hydrocephalus, <55 years of age, rapidly progressive or unusual dementia, immunosupression, or suspicion of CNS vasculitis)
- There is not enough evidence to support or refute the use of the following tests:
  - Positron emission tomography
  - Genetic markers for AD not listed above
  - CSF or other biomarkers for AD
  - Tau mutations in patients with FTD
  - AD gene mutations in patients with FTD

DSM-IIIR=Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, text revision; DAT=dementia of Alzheimer's type; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association; *DSM-IV=Diagnostic and Statistical Manual of Mental Disorders*, 4th ed; DLB=dementia with Lewy Bodies; FTD=frontotemporal dementia; CT=computed tomography; MRI=magnetic resonance imaging; CSF=cerebrospinal fluid; CJD=Creutzfeldt-Jakob disease; CNS=central nervous system.

5 *DSM-IV-TR* Criteria for Dementia of the Alzheimer's Type[4]

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:
      (a) Aphasia – language disturbance
      (b) Apraxia – impaired ability to carry out motor activities despite intact motor function
      (c) Agnosia – failure to recognize or identify objects despite intact sensory function
      (d) Disturbance in executive function – 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 course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   (1) Other CNS conditions that cause progressive deficits in memory and cognition – eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor
   (2) Systemic conditions that are known to cause dementia – eg, hypothyrodism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV-infection
   (3) Substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium
F. The disturbance is not better accounted for another Axis I disorder – eg, major depressive disorder, schizophrenia.

Code based on presence or absence of a clinically significant behavioral disturbance:
Without Behavioral Disturbance: If the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
With Behavioral Disturbance: If the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (eg, wandering, agitation).

Specify subtype:
With Early Onset: If onset is at age 65 years or younger
With Late Onset: If onset is after age 65 years
Coding note: Also code 331.0 AD on Axis III. Indicate other prominent clinical features related to the AD on Axis I (eg, 293.83 Mood Disorder Due to AD, With Depressive Features, and 310.1 Personality Change Due to AD, Aggressive Type).

DSM-IV-TR=*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text review; CNS=central nervous system; HIV=human immunodeficiency virus.

6 National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association Criteria for AD[5]

NINCDS-ADRDA Criteria for Probable AD

I. The criteria for the clinical diagnosis of PROBABLE AD include:
   - Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests.
   - Deficits in two or more areas of cognition.
   - Progressive worsening of memory and other cognitive functions.
   - No disturbance of consciousness.
   - Onset between ages 40 and 90, most often after 65 years of age.
   - Absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition.

II. Other clinical features consistent with the diagnosis of PROBABLE AD, after exclusion of causes of dementia other than AD, include:
   - Plateaus in the course of progression of the illness;
   - Associated symptoms depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
   - Seizures in advanced disease; and
   - CT normal for age

III. Clinical diagnosis of POSSIBLE AD:

   - May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presences of variations in the onset, in the presentation, or in the clinical course;
   - May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not consdiered to be *the* cause of the dementia; and
   - Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; CT=computed tomography.

7 AIREN Criteria for Vascular Dementia[6]

Vascular dementia occurs most often in patients with a history of hypertension, diabetes, coronary artery disease or any of the other diseases that place an individual at risk for vascular disease. A diagnosis of vascular dementia requires the presence of documented cardiovascular disease, a documented dementia syndrome and a definitive temporal relationship between the two. Can present with a high degree of variability, depending on the location of the lesions.

NINDS-AIREN Criteria for Probable Vascular Dementia

I. The criteria for the clinical diagnosis of PROBABLE vascular dementia include all of the following:
   1. Dementia defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control or praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone. Exclusion criteria: cases with disturbances of consciousness, delirium, psychosis, severe aphasia or major sensimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
   2. CVD, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopsia, dysarthria, etc., consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including:
      - Multiple large-vessel strokes
      - Or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, PCA or ACA territories)
      - Mild cortical involvement
      - As well as multiple basal ganglia and white matter lacunes (>1)
      - Or extensive periventricular white matter lesions
      - Or combinations thereof
   3. A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following:
      - Onset of dementia within 3 months following a recognized stroke
      - Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits

7 AIREN Criteria for Vascular Dementia[6] (continued)

II. Clinical features consistent with the diagnosis of PROBABLE vascular dementia include the following:
   1. Early presence of a gait disturbance (small-step gait or marche a petits-pas, magnetic, apraxic-ataxic or Parkinsonian gait)
   2. History of unsteadiness and frequent, unprovoked falls
   3. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
   4. Personality and mood changes, abulia, depression, emotional incontinence, other subcortical deficits including psychomotor retardation and abnormal executive function

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include:
   1. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging
   2. Absence of focal neurological signs, other than cognitive disturbance
   3. Absence of cerebrovascular lesions on brain CT or MRI

IV. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathological features, for subcategories or defined conditions such as:
   - Cortical vascular dementia
   - Subcortical vascular dementia
   - Binswanger's disease
   - Thalamic dementia

AIREN=Association Internationale Pourla Recherche et l'Enseignement en Neurpsciences; NINDS-AIREN=National Institue of Neurological Disorders and Stroke Association Internationale Pourla Recherche et l'Enseignement en Neurpsciences; CVD=cerebrovascular disease; CT=computed tomography; MRI=magnetic resonance imaging; PCA=posterios cerebral artery; ACA=anterior cerebral artery.

8 *DSM-IV-TR* Diagnostic Criteria for Vascular Dementia[7]

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:
      (a) Aphasia (language disturbance)
      (b) Apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) Agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) Disturbance in executive functioning (ie, 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. Focal neurological signs and symptoms (eg, exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory/imaging evidence indicative of cerebrovascular disease (eg, multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.
D. The deficits do not occur exclusively during the course of a delirium.

Code based on presence or absence of a clinically significant behavioral disturbance:
With Delirium: If delirium is superimposed on the dementia
With Delusions: If delusions are the predominant feature
With Depressed Mood: If depressed mood (including presentations that meet full symptom criteria for a major depressive episode) is the predominant feature. A separate diagnosis of mood disorder due to a general medical condition is not given.
Uncomplicated: If none of the above predominates in the current clinical presentation.

Specify if (can be applied to any of the above subtypes):
With Behavioral Disturbance: If there is clinically significant behavioral disturbance (eg, wandering)
Coding note: Also code cerebrovascular condition on Axis III.

DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision.

9 ADDTC California Criteria for Ischemic Vascular Dementia[8]

Probable IVD
A. The criteria for the clinical diagnosis of PROBABLE IVD include all of the following:
   1. Dementia
   2. Evidence of two or more ischemic strokes by history, neurological signs, and/or neuroimaging studies (CT or T1-weighted MRI) or occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia
   3. Evidence of at least one infarct outside the cerebellum by CT or T1-weighted MRI.
B. The diagnosis of PROBABLE IVD is supported by:
   1. Evidence of multiple infarcts in brain regions known to affect cognition
   2. A history of multiple transient ischemic attacks
   3. History of vascular risk factors (eg, hypertension, heart disease, diabetes mellitus)
   4. Elevated Hachinski Ischemia Scale (original or modified version)
C. Clinical features that are thought to be associated with IVD, but await further research, include:
   1. Relatively early appearance of gait disturbance and urinary incontinence
   2. Periventricular and deep white matter changes on T2-weighted MRI that are excessive for age
   3. Focal changes in electrophysiologic studies (eg, EEG, evoked potentials) or physiologic neuroimaging studies (eg, SPECT, PET, NMR spectroscopy).
D. Other clinical features that do not constitute strong evidence either for or against a diagnosis of PROBABLE IVD include:
   1. Periods of slowly progressive symptoms
   2. Illusions, psychosis, hallucinations, delusions
   3. Seizures
E. Clinical features that cast doubt on a diagnosis of PROBABLE IVD include:
   1. Transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies
   2. Absence of central neurologic symptoms/signs, other than cognitive disturbance.

9 ADDTC California Criteria for Ischemic Vascular Dementia[8] (continued)

Possible IVD

A clinical diagnosis of POSSIBLE IVD may be made when there is:

1. Dementia, and one or more of the following:

2a. History or evidence of a single stroke (but not multiple) without a clearly documented temporal relationship to the onset of dementia; *OR*

2b. Binswanger's syndrome (without multiple strokes) that includes all of the following;

- i. Early-onset urinary incontinence not explained by urologic disease, *or* gait disturbance, eg, parkinsonnian, magnetic, apraxic, or "senile" gait, that is not explained by peripheral cause
- ii. Vascular risk factors
- iii. Extensive white matter changes on neuroimaging

ADDTC=Alzheimer's Disease Diagnostic and Treatment Centers; IVD=ischemic vascular dementia; CT=computed tomography; MRI=magnetic resonance imaging; EEG=electroencephalogram; SPECT=single photon emission computed tomography; PET=positron emission tomography; NMR=nuclear magnetic resonance.

10 Consensus Criteria for Dementia with Lewy Bodies[10]

1. The central feature is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for possible DLB:
   a. Fluctuating cognition with pronounced variations in attention and alertness
   b. Recurrent visual hallucinations that are typically well formed and detailed
   c. Spontaneous motor features of Parkinsonism
3. Features supportive of the diagnosis are:
   a. Repeated falls
   b. Syncope
   c. Transient loss of consciousness
   d. Neuroleptic sensitivity
   e. Systematized delusions
   f. Hallucinations of other modalities
4. A diagnosis of DLB is less likely in the presence of:
   a. Stroke disease, evident as focal neurologic signs or on brain imaging
   b. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture.

DLB=dementia with Lewy Bodies.

11 Frontotemporal Lobe Dementia: Consensus on Clinical Diagnostic Criteria[11]

I. Core Diagnostic Features

1. Insidious onset and gradual progression
2. Early decline in social interpersonal conduct
3. Early impairment in regulation of personal conduct
4. Early emotional blunting
5. Early loss of insight

II. Supportive Diagnostic Features

Behavioral disorder

1. Decline in personal hygiene and grooming
2. Mental rigidity and inflexibility
3. Distractibility and impersistence
4. Hyperorality and dietary changes
5. Perseverative and stereotyped behavior
6. Utilization behavior

Speech and language

1. Altered speech output
   - A. Aspontaneity and economy of speech
   - B. Press of speech
2. Stereotype of speech
3. Echolalia
4. Perseveration
5. Mutism

Physical signs

1. Primitive reflexes
2. Incontinence
3. Akinesia, rigidity, and tremor
4. Low and labile blood pressure

Investigations

1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
2. EEG: normal on conventional EEG despite clinically evident dementia
3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

III. Supportive Features

1. Onset before 65 years of age: positive family history of similar disorder in first-degree relative bulbar palsy, muscular weakness and wasting, fasciculations (associated motor neuron disease present in a minority of patients)

11 Frontotemporal Lobe Dementia: A Consensus on Clinical Diagnostic Criteria[11] (continued)

IV. Diagnostic Exclusion Features

Historical and Clinical

1. Abrupt onset with ictal events
2. Head trauma related to onset
3. Early, severe amnesia
4. Spatial disorientation
5. Logoclonic, festinant speech with loss of train of thought
6. Myoclonus
7. Corticospinal weakness
8. Cerebellar ataxia
9. Choreoathetosis

Investigations

1. Brain imaging: predominant post-central structural or functional deficit; multifocal lesions on CT or MRI
2. Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as MS, syphilis, AIDS, and herpes simplex encephalitis

V. Relative Diagnostic Exclusion Features

1. Typical history of chronic alcoholism
2. Sustained hypertension
3. History of vascular disease (eg, angina, claudication)

EEG=electroencephalogam; CT=computed tomography; MRI=magnetic resonance imaging; MS=multiple sclerosis; AIDS=acquired immunodeficiency syndrome.

12 Criteria for Creutzfeldt-Jakob Disease[12]

Must have both:

- Rapidly progressive dementia
- Periodic sharp spikes on EEG, or 14-3-3 protein in the CSF

Must have at least 2 of the following:

- Myoclonus
- Visual and/or cerebellar symptoms
- Pyramidal and/or extrapyramidal signs
- Akinetic mutism

EEG=electroenchephalogram; CSF=cerebrospinal fluid.

13 Criteria for Delirium[13]

A. Disturbance of consciousness, such as reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
B. 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.
C. The disturbance develops over a short period of time, usually hours to days, and tends to fluctuate during the course of the day.
D. 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.

Coding note: If delirium is superimposed on a preexisting vascular dementia, indicate the delirium by coding 290.41 Vascular Dementia, With Delirium.
Coding note: Include the name of the general medical condition on axis I, eg, 293.0 Delirium Due to Hepatic Encephalopathy; also code the general medical condition on axis III (see Appendix G for codes).

14 Proposed Criteria for Psychosis of AD[14]

A. Characteristic symptoms
Presence of one (or more) of the following symptoms:
1. Visual or auditory hallucinations
2. Delusions

B. Primary diagnosis
All the criteria for dementia of the Alzheimer's type are met.*

C. Chronology of the onset of symptoms of psychosis versus onset of symptoms of dementia
There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia.

D. Duration and Severity
The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer. Symptoms are severe enough to cause some disruption in patients' and/or others' functioning.

E. Exclusion of schizophrenia and related psychotic disorders
Criteria for schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features have never been met.

F. Relationship to delirium
The disturbance does not occur exclusively during the course of a delirium.

G. Exclusion of other causes of psychotic symptoms
The disturbance is not better accounted for by another general medical condition or direct physiological effects of a substance (eg, a drug of abuse, a medication)

Associated Features (specify if associated):
With agitation: When there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression
With negative symptoms: When prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present
With depression: When prominent depressive symptoms, such as depressive mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present.

* Note: For other dementias, such as vascular dementia, Criterion B will need to be modified appropriately.

15 Proposed Criteria for Depression of AD[15]

NIMH Provisional Diagnostic Criteria for Depression of AD

A. Three (or more) of the following symptoms have been present during the same 2 week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or decreased positive affect or pleasure:
   (1) Clinically significant depressed mood (eg, depressed, sad, hopeless, discouraged, and tearful)
   (2) Decreased positive affect or pleasure in response to social contacts and usual activities
   (3) Social isolation or withdrawal
   (4) Disruption in appetite
   (5) Disruption in sleep
   (6) Psychomotor changes (eg, agitation or retardation)
   (7) Irritability
   (8) Fatigue or loss of energy
   (9) Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
   (10) Recurrent thoughts of death, suicidal ideation, plan or attempt

Note: Do not include symptoms that, in your judgment, are clearly due to a medical condition other than AD, or a direct result of non-mood related dementia symptoms (eg, loss of weight due to difficulties with food intake).

B. All *DSM-IV-TR* criteria are met for dementia of the Alzheimer's type.
C. The symptoms cause clinically significant distress or disruption in functioning.
D. The symptoms do not occur exclusively during the course of a delirium.
E. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, medication).
F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of AD, anxiety disorders, or substance-related disorder.

Specify if:
Co-occurring Onset: if onset antedates or co-occurs with the AD diagnosis
Post AD Onset: if onset occurs after AD diagnosis

Specify if:
With delusions
With hallucinations
With other significant behavioral signs or symptoms
With past history of mood disorder

NIMH=National Institute of Mental Health; *DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision.

16 The Ten Warning Signs of AD[16]

The Alzheimer's Association has developed a list of warning signs that include common symptoms of AD. Individuals who exhibit several of these symptoms should see a physician for a complete examination.

1. **Memory loss that affects job skills**. It is normal to occasionally forget an assignment, deadline, or colleague's name, but frequent forgetfulness or unexplainable confusion at home or in the workplace may signal that something is wrong.
2. **Difficulty performing familiar tasks**. Busy people get distracted from time to time. For example, you might leave something on the stove too long or not remember to serve part of a meal. People with Alzheimer's might prepare a meal and not only forget to serve it but also forget they made it.
3. **Problems with language**. Everyone has trouble finding the right word sometimes, but a person with AD may forget simple words or substitute inappropriate words, making his or her sentences difficult to understand.
4. **Disorientation to time and place**. It is normal to momentarily forget the day of the week or what you need from the store. But people with AD can become lost on their own street, not knowing where they are, how they got there, or how to get back home.
5. **Poor or decreased judgment**. Choosing not to bring a sweater or coat along on a chilly night is a common mistake. A person with Alzheimer's, however, may dress inappropriately in more noticeable ways, wearing a bathrobe to the store or several blouses on a hot day.
6. **Problems with abstract thinking**. Balancing a checkbook can be challenging for many people, but for someone with AD, recognizing numbers or performing basic calculation may be impossible.
7. **Misplacing things**. Everyone temporarily misplaces a wallet or keys from time to time. A person with AD may put these and other items in inappropriate places – such as an iron in the freezer or a wristwatch in the sugar bowl – and then not recall how they got there.
8. **Changes in mood or behavior**. Everyone experiences a broad range of emotions – it is part of being human. People with AD tend to exhibit more rapid mood swings for no apparent reason.
9. **Changes in personality**. People's personalities may change somewhat as they age. But a person with AD can change dramatically, either suddenly or over a period of time. Someone who is generally easygoing may become angry, suspicious, or fearful.
10. **Loss of initiative**. It is normal to tire of housework, business activities, or social obligations, but most people retain or eventually regain their interest. The person with AD may remain uninterested and uninvolved in many or all of his usual pursuits.

Micro-Guide # 2

Rating Instruments for Evaluation of Efficacy in AD Clinical Trials

Rating Scale	Symptoms/Domains Assessed	Information Source	Scale/Interpretation/Comment
Primary Outcomes			
Alzheimer's Disease Assessment Scale (Cognitive Subscale)	Battery of brief individual performance-based tests; assesses word recall, naming, response to commands, constructional and ideational praxis, orientation, word recognition, spoken language ability and comprehension, word-finding, recall of test instructions **(35, 36)AU:?**	Patient	0–70 points 0=no errors (normal, 0–10) 70=severe impairment Most commonly used in trails to assess the efficacy of drugs
Clinician's Interview-Based Impression of Change-Plus	7-point rating scale used to assess change in three areas (cognition, daily function, and behavior). **(37)AU:?** Note: The "Plus" represents information from the caregiver.	Patient and caregiver interviews	1–7 points 1, 2, 3=minimal, moderate, or marked improvement 4=no change 5, 6, 7=minimal, moderate, or marked deterioration Used in clincal trials as a "global" clincal assessment
Secondary Measures			
Mini-Mental State Examination	Staging of disease severity; cognition	Patient	1–30 points (the lower the score, the greater the deterioration)
Global Deterioration Scale (GDS); Clinical Dementia Rating (CDR)	Overall staging of disease severity; cognition, memory, self-care, activities of daily living (ADL)	Patient and caregiver interviews	For the GDS: 1–7 points (1=no decline, 7=severe decline) For the CDR: 0-3 points (0=normal, 3=severe) Also useful clinically
AD Cooperative Study – Activities of Daily Living Disability Assessment Dementia Interview for Deterioration in Daily Living Activities in Dementia Progressive Deterioration Scale		Caregivers are interviewed	Various scaling is used. to assess ADLs of patients.
Neuropsychiatric Inventory (NPI) Behavioral Pathology in AD Rating Scale (BEHAVE-AD)	Behavior rating scales addressing the following	The NPI is a structured interview with a caregiver rating both severity and frequency of 10–12 behaviors. The BEHAVE-AD is a 25-item scale assessing individual symptoms in several domains.	NPI, total rating scores are from 0 to 120 or 144 (depending on whether there are 10 or 12 items). Individual scales can be assessed. BEHAVE-AD is from 0–75 on the 25 items, plus an overall severity score from 0–3.

17 Mini-Mental State Examination

The Mini-Mental State Examination is a screening instrument that is the most widely used and briefest mental status test and the familiarity of many physicians with the scoring system enhances communication. The scores are used to help screen for cognitive impairment, as a clinical index of severity and change, and to regulate the use of cholinesterase inhibitors.

Interpretations: Normal or only mild cognitive impairment >26, mild dementia 20-26, moderate dementia 10–20, severe dementia <10.
Education adjustments: <8 years of education >17 might be normal, >16 years of education >27 might be normal.

Orientation
1. What is today's date?
2. What is the year?
3. What is the month?
4. What day is today?
5. Can you also tell me what season it is?
6. Can you also tell me the name of the hospital?
7. What floor are we on?
8. What town or city are we in?
9. What country are we in?
10. What state are we in?

Immediate Recall
Ask the subject if you may test his/her memory. Then say: "ball," "flag," "tree." Ask him/her to repeat them. This first repetition determines his/her score.
If the subject could not repeat all 3 words in the first trial then the investigator should now keep saying "ball," "flag," "tree" until the subject can repeat all 3, up to 6 trials. If he/she does not eventually learn all 3, recall cannot be meaningfully tested.

Attention and Calculation
Ask the subject to begin with 100 and count backwards by 7. Stop after 5 subtractions. Score the total number of correct answers. Spell W-O-R-L-D backwards.

Delayed Recall
Ask the subject to recall the 3 words you previously asked him/her to remember.

Language
Object naming: Watch, pencil
Repetition: "No ifs, ands, or buts"
Three-stage command: "Take the paper in your right hand, fold it in half and put it on the floor"
Reading: Close eyes
Writing: Writes a sentence with a subject and a verb and is sensible
Copying: Intersecting pentagons

18 Hachinski Ischemic Scale[17]

Features	Point Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of presence of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2

19 Clinical Dementia Rating Scale Interview[18]

Impairment	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully orientated	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment and Problem Solving	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

20 Global Deterioration Scale[19]

Stage	Example of Deficits
1. No cognitive decline either by subjective complaint or a clinical interview	None
2. Very mild cognitive decline	Subjective complaints of memory loss only – eg, forgetting where one has placed familiar objects. No objective evidence of loss in clinical interview
3. Mild cognitive decline	Decreased performance in demanding employment and social settings. Objective evidence of impairment only obtained in intensive interview
4. Moderate cognitive decline	Decreased knowledge of current events. Decreased ability to perform complex tasks. Decreased ability to market, handle finances
5. Moderately severe cognitive decline	Unable to recall a major aspect of current life. May have difficulty with choice of clothing; can no longer survive without some assistance
6. Severe cognitive decline	Largely unaware of recent life events. Increasing difficulties with dressing and bathing. Eventually develop problems with toileting. Emotional changes, such as agitated behavior, may emerge.
7. Very severe cognitive decline	All verbal abilities are lost. Incontinence is present, progressive loss of basic psychomotor skills

21 Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory[20]

This hierarchic ADL scale was developed by the ADCS and is commonly used in clinical trials. By interviewing an informant it assesses the following ADLs:

1. Finding belongings at home
2. Selecting clothes for the day
3. Dressing
4. Cleaning a room
5. Balancing checkbook/credit card statement
6. Writing things down
7. Cleaning a load of laundry (clothes)
8. Keeping appointments or meetings
9. Using a telephone
10. Preparing a meal or snack
11. Traveling beyond home
12. Talking about current events
13. Reading
14. Watching television
15. Shopping
16. Left alone
17. Using a household appliance
18. Participating in a pastime or hobby
19. Driving a car
20. Taking medications regularly
21. Carrying through complex activities
22. Initiating complex activities
23. Time to complete complex activities
24. Extenuating circumstances

ADL=activities of daily living; ADCS=Alzheimer's Disease Cooperative Study.

22 Dependence Scale[21]

A. Does the patient need reminders or advice to manage chores, go shopping, cook, play games, or handle money?
B. Does the patient need help to remember important things such as appointments, recent events, or names of family or friends?
C. Does the patient need frequent (at least once a month) help finding misplaced objects, keeping appointments, or maintaining health or safety (locking doors, taking medication)?
D. Does the patient need household chores done for them?
E. Does the patient need to be watched or kept company when awake?
F. Does the patient need to be escorted when outside?
G. Does the patient need to be accompanied when bathing or eating?
H. Does the patient have to be dressed, washed, and groomed?
I. Does the patient have to be taken to the toilet regularly to avoid incontinence?
J. Does the patient have to be fed?
K. Does the patient need to be turned, moved, or transferred?
L. Does the patient wear a diaper or a catheter?
M. Does the patient need to be tube fed?

Note: Items A and B are coded: no=0; occasionally=1 (at least once a month); frequently=2 (at least once a week). Items C–M are coded: no=0; yes=1.

Derivation of Dependence Level

Level 0 (0 to all items)	0
Level 1 (Either A, B or C=1)	1
Level 2 (2 of A, B or C=1 or A or B=2 or D=1)	2
Level 3 (E, F or G=1)	3
Level 4 (H, I or J =1)	4
Level 5 (K, L or M=1)	5

23 Functional Activities Questionnaire[22]

The functional activities questionnaire (FAQ) is a simple, straightforward clinical instrument. Adding the scores together gives the total FAQ score. Scores range from 0 to 30. Scores of 9 or below are normal. Scores of 10 and above indicate reduced functional ability.

Caregivers score each area as follows:

Category	Score
Fully dependent on others	3
Some assistance needed	2
Finds it difficult but manages alone	1
No difficulty	0
Unfamiliar activity could not manage	1
Unfamiliar activity could manage	0

- Dealing with financial matters, paying bills, writing checks
- Keeping records of taxes, business affairs
- Shopping for everyday necessities: groceries, clothes, etc
- Hobbies or playing games
- Making tea, turning the kettle on and off
- Cooking a balanced meal
- Perception of current events
- Level of attention and understanding: books, television
- Memory: remembering appointments and medications
- Getting about: driving or taking public transport

Micro-Guide # 3

Neuropsychological Assessments for Dementia

Major Area	Tests	Comments
Attention	Letter Cancellation Digit Span Continuous Performance Task	Attention must be adequate for performance of other tasks.
Language	Boston Diagnostic Aphasia Western Aphasia Battery Boston Naming Test Reitan Aphasia Screening Controlled Word Association Test	Testing involves naming, fluency, examination, comprehension, repetition, vocabulary, reading, writing. Naming difficulty is age-related and common in dementia.
Memory	Wechsler Memory Scale, Logical Memory I and II New York University Paragraph Recall Rey Auditory Verbal Learning Test Selective Reminding Test California Verbal Learning Test Delayed Recognition Span Test Randt Memory Test Fuld Object Memory Test ADAS-cog	Must distinguish between immediate and delayed memory.
Visuospatial Abilities	Benton Visual Retention Test Block Design Subtest of the WAIS-R	Involves figure copying
Executive Function	Similarities subtest of WAIS-R Proverbs Test Trailmaking Test (A and B) Wisconsin Card Sort Test Stroop Letter number selection	Tests of concept formation, abstraction, set shifting, and maintenance. Affected in depression, most dementia, and especially in frontotemporal lobe dementia
Dementia Batteries	Mattis Dementia Rating Scale CERAD Battery ADAS-cog	Potentially clinically useful because they assess a broad range of abilities, and are scaled so that dementia patients are more likely able to complete them without excessive stress

ADAS-cog=Alzheimer's Disease Assessment Scale (Cognitive Subscale);
WAIS-R=Wechsler Adult Intelligence Scale-Revised;
CERAD=Consortium to Establish a Registry for Alzheimer's Disease.

24 Contents of the AD Assessment Scale – Cognitive Subscale[23,24]

The Alzhemier's Disease Assessment Scale (Cognitive Subscale; ADAS-cog) is the standard primary measure of cognitive outcome in clinical trials of antidementia medications. Typically, the drug-placebo difference in these trials is between 2 and 4 points after 6 months. The difference is largely due to cognitive deterioration in the placebo group. The average annual deterioration on the ADAS-cog in patients enrolled in trials is approximately 5 points. These considerations are useful in determining clinical significance of change on the ADAS-cog.

Description: Contains items assessing several cognitive domains impaired in AD including memory, language, praxis and orientation. It was designed specifically as an outcome measure in clinical trials. It consists of 11 items; scores on the test range from 0 for a patient who makes no errors to 70 for a patient who is profoundly demented. The battery itself and its scoring is heavily weighted toward immediate and delayed memory

Time to Administer: 20–45 minutes, depending on the patient's level of functioning.

Test Items:

Word recall task	10-item, 3-trial list learning task
Naming fingers and objects	Subject names each finger, simple items (flower, bed, whistle, pencil), moderate items (rattle, mask, scissors, comb), difficult items (harmonica, stethoscope, wallet, tongs).
Commands	Patient performs 5 basic tasks. For example, "put the pencil on top of the card, then put it back."
Constructional praxis	Patient copies a circle, two overlapping rectangles, rhombus, and cube.
Ideational praxis	Patient is asked to fold a letter, put it in an envelope, seal it, address it, and identify location to place a postage stamp.
Orientation	Patient is asked to provide name, date, day, month, season, year, location, and time of day.
Word recognition	Subject is shown 12 words, and then has to recognize those words from a set of 12 distractor words. 3 trials are performed.
Spoken language ability	5-point rating of patient's clarity of speech, without considering word finding.
Comprehension	5-point rating of patient's ability to comprehend speech, assessed via conversation.
Word finding difficulty	5-point rating of patient's word finding, assessed via conversation.
Remembering test instructions	Frequency that patient needs re-instruction during word recognition.

25 California Guidelines for AD Management[25]

About the Guideline

This document was developed by the California Workgroup on Guidelines for AD Management through a collaborative effort of healthcare providers, consumers, academicians, professional and volunteer organizations, and purchasers of health care. A companion document is available which explains each of the areas of the guideline in greater detail. To receive a copy of the guideline and related information, visit the Alzheimer's Association of Los Angeles web site at www.alzla.org.

Purpose of the Guideline

This clinical practice guideline represents core care recommendations for AD management that are clear, measurable, practical and based on scientific evidence, as available. The California Workgroup has provided its expert opinion when research evidence has been unavailable or when research results were inconsistent. The intended audience of this guideline is primary care practitioners, including physicians, nurse practitioners, physician assistants, social workers, and other professionals providing primary care to AD patients and their families.

Assessment

1. Conduct and document an assessment of:
   - Daily functions, including feeding, bathing, dressing, mobility, toileting, continence, and ability to manage finances and medications
   - Cognitive status using a reliable and valid instrument (eg, Mini-Mental State Examination)
   - Other medical conditions
   - Behavioral problems, psychotic symptoms, or depression
2. Reassessment should occur every 6 months or more frequently, if indicated.
3. Identify the primary caregiver and assess the adequacy of family and other support systems.
4. Assess the patient's decision-making capacity and whether a surrogate has been identified
5. Assess the patient's and family's culture, values, primary language, and decision-making process.

25 California Guidelines for AD Management[25] (continued)

Treatment

Develop and implement an ongoing treatment plan with defined goals. Include:

- Use of cholinesterase inhibitors, if clinically indicated, to treat cognitive decline
- Referral to appropriate structured activities such as exercise, recreation and adult day care services
- Appropriate treatment of medical conditions

Treat behavioral problems and mood disorders using:

- Non-pharmacologic approaches, such as environmental modification, task simplification, appropriate activities, etc.
- Referral to social service agencies or support organizations, including the Alzheimer's Association's Safe Return Program for people who wander
- Medications, if clinically indicated

Patient and Caregiver Education and Support

Discuss the diagnosis and progression of AD with the patient and family in a manner consistent with their values, preferences and the patient's abilities.

Refer to support organizations for educational materials on community resources, support groups, legal and financial issues, respite care, future care needs and options. A list of resources is included on page 74.

Discuss the patient's need to make advance directives and to identify surrogates for medical and legal decision-making.

Reporting Requirements in California

Abuse: Monitor for evidence of and report all instances of abuse to Adult Protective Services or police department, as required by law.
Driving: Report the diagnosis of AD in accordance with California law (Sections 2500 and 2572 of Title 17, California Code of Regulations).

26 Approach to Psychosis Symptoms in Dementia

Characterize the behavioral syndrome

Delirium
Psychosis (delirium and hallucinations)
Depression

Characterize symptoms to be treated

Excessive suspiciousness
Delusions
Manifest or apparent hallucinations
Aggression and agitation
Frightened
Bizarre ideation/verbalization

Medical evaluation to identify possible medical disorder

Intercurrent medical problems?
Concurrent medication?
If delusions/ hallucinations due to medical disorder or medica tion, treat and monitor target symptoms (however, psychosis may not improve)

Evaluate psychiatrically, differential diagnosis

If psychiatric disorder, treat and monitor target symptoms

Current and past medication

Assess for contributing factors

Concurrent medical illness, medication use
Precipitating stress

Safety evaluation prior to prescribing

whole blood count, cardiac evaluation, hepatic screen

Empirical trials of symptomatic pharmacotherapy

Start low, but adjust dosage, dosage individualization
Assess target symptoms
Increase dose until benefit or toxicity
If effective, continue for weeks to months, taper and reevaluate
If ineffective, taper and reevaluate; consider second medication

Maintenance treatment at efficacious dose

Nonpharmacologic management of psychosis

Ensure sensory input
Enhance and regulate environment
Ensure appropriate environmental cues
Optimize psychosocial milieu:
maintain special interests, routines, social contacts, familiar objects, maintain religious identity, support, reassurance
Educate/support caregivers simple, clear communication, distraction, redirection

Micro-Guide # 4

Structural and Functional Brain Imaging[33]

Imaging Technique	Description	Typical Findings/Uses
CT Scanning	X-ray procedure, contrast agent usually not needed; scan time is a few minutes, finer temporal resolution than MRI	Findings: Normal for age; mild to moderate generalized atrophy; no space occupying lesions. Uses: Extent of atrophy, white-matter changes; infarction, tumor, subdural hemorrhage
MRI	Non-invasive; detects molecular activation from radio frequency waves; scan time is long, about 40 minutes. More sensitive to small lesions and less specific for clinically important lesions.	Normal for age: Mild to moderate generalized atrophy; small vessel changes; periventricular hyperintensities, leucoencephalopathy; no evidence of infarctions
MRI and CT morphometrics (research techniques)	Careful computer-assisted measurements of whole brain volumes, or regions of interest such as hippocampal volumes	Uses: Determination of ventricular size, medial temporal lobe size, decreased hippocampal volumes in AD, and further decrease with disease progression. Experimental procedure, no clinical use.
SPECT	Visualizes regional cerebral blood flow reflecting metabolic activity	Typical findings with AD: Biparietal hypometabolism
PET	Can assess metabolic activity such as glucose utilization, blood flow, receptor binding, neurotransmitter function.	Typical findings with AD: Biparietal hypometabolism. Uses: A research tool
Magnetic Resonance Spectroscopy	**AU: BLANK. DOES ANYTHING GO HERE?**	NAA, MI

CT=Computed Tomography; MRI=magnetic resonance imaging; SPECT=Single Photon Emission Computed Tomography; PET=Positron Emission Tomography; NAA=N-acetyl aspartate; MI=myo-inositol.

Indications for structural imaging: Headache, consideration of focal brain lesions, abrupt or rapid cognitive decline, dementia onset earlier than 65 years of age, seizures, gait impairments or motor signs, atypical features of AD

Note on vascular dementia: Typical changes, white matter changes, multiple cortical infarctions, single cortical infarctions, multiple subcortical infarctions, single lacunar infarction. There is no conclusive evidence that neuroimaging is beneficial, either in the diagnosis of AD or as a guide for its treatment. It remains unclear whether neuroimaging studies are warranted in selected patients or in the general population of patients suspected of having AD.

27 Psychotropic Medications Used with Elderly Patients with Dementia

This is merely a listing of medications that have been used in both younger and older individuals and it is for reference only. No recommendations are implied. In some cases there may be a specific cautionary comment but many of the medications listed should not be considered first line choices in the elderly and should be avoided. Dosage ranges in the elderly may vary by indication. Some drugs may be contraindicated or require lower doses. Consult the prescribing information of individual drugs for more detailed information.

Generic	Brand Name	Usage
Alprazolam	Xanax	Anti-anxiety, benzodiazepine
Amitriptyline	Elavil and others	TCA
Amoxapine	Asendin	Antidepressant with antipsychotic properties
Buproprion, Buproprion SR	Zyban	Antidepressant (as Zyban, marketed for cigarette smoking cessation)
Wellbutrin, Wellbutrin SR	**AU:??**	**AU:??**
Buspirone	BuSpar	Anti-anxiety agent also sometimes used to treat aggression or agitation in dementia patients.
Carbamazepine	Tegretol generics	Anticonvulsant used as mood stabilizer, and for aggression and agitation in dementia patients
Chloral hydrate	Noctec, Aquachloral Supprettes	Hypnotic
Chlordiazapoxide	Librium, Libritabs	Anti-anxiety, benzodiazepine
Chlorpromazine	Thorazine	Antipsychotic, phenothiazine
Citalopram	Celexa	SSRI
Clonazepam	Klonopin	Anti-anxiety, anticonvulsant, benzodiazepine
Clorazepate	Tranxene, others	Anti-anxiety, benzodiazepine
Clozapine	Clozaril	First marketed atypical antipsychotic; requires WBC monitoring
Desipramine	Norpramin, Pertofrane	TCA
Diazepam	Valium, Valrelease	Anti-anxiety, anticonvulsant, benzodiazepine
Divalproex sodium	Depakote, Depakene	Enteric-coated formulation of divalproex, valproic acid
Donepezil	Aricept	Cognitive enhancer, cholinesterase inhibitor
Doxepin	Adapin, Sinequan	TCA
Estazolam	ProSom	Hypnotic, benzodiazepine
Fluoxetine	Prozac, Serafin	Prozac-enteric coated SSRI antidepressant, once per week enteric-coated 90 mg once per week formulation
Fluphenazine	Permitil, Prolixin	Antipsychotic
Flurazepam	Dalmane	Hypnotic, benzodiazepine
Fluvoxamine	Luvox	SSRI, marketed for OCD

27 Psychotropic Medications Used with Elderly Patients with Dementia (continued)

Generic	Brand Name	Usage
Gabapentin	Neurontin	Anticonvulsant
Galantamine	Reminyl	Cognitive enhancer, cholinesterase inhibitor
Ginkgo Biloba	Ginkoba, others	Flavanoides derived from the leaves of the maidenhair or ginkgo biloba tree
Haloperidol	Haldol	Antipsychotic
Huperzine A	Memorall, Huperzine Rx-Brain	Cholinesterase inhibitor extracted from plant product; sold over the counter as a "supplement," variable quality
Imipramine	Janimine, Tofranil	TCA
Lamotrigine	Lamictal	Anticonvulsant
Lithium	Eskalith, Lithane, Lithobid, Lithotabs	Mood-stabilizer used for bipolar disorder, mania
Lorazepam	Ativan	Anti-anxiety, benzodinezepine
Loxapine	Loxitane	Antipsychotic
Maprotiline	Ludiomil	Heterocyclic antidepressant, similar to TCAs
Mesoridazine	Serentil	Antipsychotic (second line medication)
Mirtazapine	Remeron	Newer generation mixed noradrenergic and serotonergic antidepressant
Molindone	Moban	Antipsychotic
Nefazodone	Serzone	Newer generation mixed noradrenergic and serotoninergic antidepressant
Nortriptyline	Aventyl, Pamelor	TCA
Olanzapine	Zyprexa	Atypical antipsychotic
Oxazepam	Serax	Anxiolytic, benzodiazepine
Oxcarbazepine	Trileptal	Anticonvulsant
Paroxetine	Paxil	SSRI
Perphenazine	Trilafon	Antipsychotic
Phenelzine	Nardil	MOAI, antidepressant
Phenytoin	Dilantin	Anticonvulsant
Risperidone	Risperdal	Atypical antipsychotic
Rivastigmine	Exelon	Cognitive enhancer, cholinesterase inhibitor
Selegiline	Eldepryl	Monoamine oxidase type B selective inhibitor marketed for Parkinson's disease
Sertraline	Zoloft	SSRI
Temazepam	Restoril	Hypnotic, benzodiazepine
Thioridazine	Mellaril	Antipsychotic (second line medication)
Thiothixene	Navane	Antipsychotic
Tiagabine	Gabitril	Anticonvulsant
Topiramate	Topamax	Anticonvulsant

27 Psychotropic Medications Used with Elderly Patients with Dementia (continued)

Generic	Brand Name	Usage
Tranylcypromine	Parnate	MOAI, antidepressant
Trazodone	Desyrel, others	Antidepressant, also used to treat agitation or aggression in dementia
Triazolam	Halcion	Hypnotic, benzodiazepine
Trifluoperazine	Stelazine	Antipsychotic
Valproic acid Divalproex	Depkene, Depakote	Anticonvulsant, also used to treat agitation or aggression in dementia
Venlafaxine-SR	Effexor-SR	Antidepressant
Venlafaxine	Effexor	
Zaleplon	Sonata	Hypnotic, benzodiazepine receptor agonist
Ziprasidone	Geodon	Atypical antipsychotic
Zolpidem	Ambien	Hypnotic, benzodiazepine receptor agonist

TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; WBC=whole blood count; OCD=obsessive-compulsive disorder; MAOI=monoamine oxidase inhibitor.

28 Dosages of Marketed Cholinesterase Inhibitors

Drug	How Supplied	Initial Dosage	Maintenance Dosage	Comments
Tacrine (Cognex)	10, 20, 30, 40 mg capsules	10 mg QID	30 or 40 mg QID, 120–160 mg/day are efficacious doses.	Reversible direct hepatotoxicity in about 33% of all patients, requiring initial biweekly transaminase monitoring and dose titration. Not commonly used
Donepezil (Aricept)[26]	5, 10 mg tablets	5 mg QD	5–10 mg QID	10 mg is most optimal dose; 5 mg shows borderline efficacy; higher doses not tested
Rivastigmine (Exelon)[27]	1.5, 3, 4.5, 6 mg capsules; liquid concentrate (x mg /mL)	1.5 mg BID	3, 4.5, or 6 mg BID	Available as a liquid concentrate. Doses of 4.5 mg BID may be most optimal. May be taken with food.
Galantamine (Reminyl)[28]	4, 8, 12 mg capsules	4 mg BID	8 or 12 mg BID	8 mg BID is the modal optimal dose; doses of 12 mg BID are effective as well

Initial dosages should be maintained for at least 2 weeks and preferably 4–6 weeks before increasing. Adverse events may occur with dosage titration.

The FDA approved indication for these drugs is: “indicated for the treatment of mild to moderate dementia of the Alzheimer’s type.”

29 Pharmacodynamics and Pharmacokinetics of Marketed Cholinesterase Inhibitors[3]

Drug	Tacrine (Cognex)	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine(Reminyl)
Pharmacodynamics	Noncompetitive, reversible cholinesterase inhibitors, both butryrl and acetyl-cholinesterase inhibitors, also multiple other actions	Noncompetitive, reversible acetyl-cholinesterase inhibitors	Noncompetitive cholinesterase inhibitors, both butryrl and acetyl-cholinesterase inhibitors, may differentially affect different acetylcholinesterase inhibitors	Competitive, reversible cholinesterase inhibitors, modulates nicotine receptors
Absorption	Delayed by food	Not affected by food	Delayed by food	Delayed by food
Bioavalability	17%	100%	40%	90%
Peak Plasma (hours)	1–2	3–4	1.4–2.6	1
Elimination Half-life (hours)	2–4	70	<5	7
Protein Binding (%)	55	96	40	18
Metabolism/ Comments	1A2, nonlinear pharmacokinetics; hepatoxicity requires regular monitoring of serum ALTs	2D6, 3A4. Nonlinear pharmacokinetics at 10 mg/day	Hydrolysis by esterases and excreted in urine (nonhepatic). Duration of cholinesterase inhibition longer than plasma half-life. Nonlinear pharmacokinetics	2D6, 3A4

Note: Pharmacodynamic effects of some cholinesterase inhibitors are longer than their elimination half-lives. Drugs that inhibit or induce the cytochrome enzymes above might be expected to increase or decrease blood levels.

ALT=??

30 Adverse Effects of Cholinesterase Inhibitors[39]

Adverse event estimates vary widely among the cholinesterase inhibitors causing relative adverse event rates among drugs to be difficult to estimate. Cholinergic side effects generally occur early and are related to initiating or increasing medication. Medications should be restarted at lowest doses after temporarily stopping. They tend to be mild and self-limited. It is impossible to assess relative adverse events without appropriate drug comparisons.

Summary of adverse event data in placebo-controlled, randomized clinical trials. The method of obtaining adverse events and their reporting vary among trials.

Drug	Adverse Events
Tacrine	Nausea, vomiting, diarrhea, dyspepsia, myalgia, anorexia, dizziness, confusion, insomnia, rare agranulocytosis. Approximately 50% of patients will develop direct, reversible hepatotoxicity manifested by elevated transaminases. Drug interactions may include increased cholinergic effects with bethanacol and increased plasma tacrine levels with cimetidine or fluvoxamine. This may occur by inhibition of P450 1A2 **(45).** The association of tacrine with haloperidol may increase parkinsonism **(46, 47)** and tacrine increases theophylline concentration. **AU: 45, 46, & 47**
Donepezil	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia, dizziness, abdominal pain, myasthenia, rhinitis, weight loss, anxiety, syncope (2% vs 1%).
Rivastigmine	Nausea, vomiting, anorexia, dizziness, abdominal pain, diarrhea, malaise, fatigue, asthenia, headache, sweating, weight loss, somnolence, syncope (3% vs 2%). Rarely: severe vomiting with esophageal rupture.
Galantamine	Nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain, dizziness, tremor, syncope.

30 Adverse Effects of Cholinesterase Inhibitors[39] (continued)

General precautions with cholinesterase inhibitors:

By increasing central and peripheral cholinergic stimulation cholinesterase inhibitors may:

- Increase gastric acid secretion, increasing the risk for gastrointestinal bleeding especially in patients with ulcer disease or those taking antiinflammatories
- Vagal effects on the heart may cause bradycardia, especially in patients with sick sinus or other supraventricular conduction delay, leading to syncope, falls, and possible injury
- May exacerbate obstructive pulmonary disease
- Cause urinary outflow obstruction
- May increase risk for seizures
- May prolong the effects of succinylcholine-type muscle relaxants

31 Frequently Discussed and Commonly Used Potential Alternative Treatments for AD That May Be Disease Modifying

Substance/ Dosage Range	Dosage*	Potential Mechanism	Comments
Vitamin E, alpha-tocopherol	1,000 IU BID used in clinical trial	Antioxidant	In one clinical trial, delayed the loss of ADL, nursing home placement or death, similar in effect to selegiline. Some experts prescribe vitamin E to AD patients. **(Sano et al 1996) (AU: FULL REFERENCE?)**
Selegiline or l-deprenyl (Eldepryl and others)	5 mg BID	Antioxicant, neuroprotective	Selective irreversible MAO-B inhibitor marketed for Parkinson's disease. In some clinical trials showed symptomatic effects, and in one other delayed the loss of ADL, nursing home placement or death, similar in effect to vitamin E. **(Sano et al 1996)**
Aspirin	81–162 mg/day	Platelet aggregation inhibitor	Could be useful in preventing aspects of vascular dementia. However, there is little evidence for this. Main use is for established cardioprotective effects.
Ginkgo biloba, (Ginkoba and others, EGb 761)	120–240 mg/day	Presumed active ingredients: Ginkgo-flavonoids and terpenoids are antioxidant, free-radical scavengers.	EGb 761 is the pharmacologically standardized extract of 22%–27% flavonoids and 5%–7% terpenoids from the leaves of the ginkgo biloba (maidenhair tree). Adverse events are mild GI symptoms, headache, and allergy, no different from placebo in trials. It also inhibits platelet activating factor and may interfere with clotting, and some cases of severe bleeding were reported in German surveillance studies**. (Le Bars et al 1998) AU: FULL REF?**
Nonsteroidal antiinflammatories (NSAIDs; naproxen, ibuprofen, celecoxib, rolecoxib, others)	Unknown, possibly usual antiinflammatory doses	Antiinflammatory effects may alter progression of dementia	Case-control trials suggest a protective effect with older NSAIDs. Trials with celecoxib and rolecoxib in AD patients have been negative. Other trials with rolecoxib and naproxen are under way. GI adverse events are common, including bleeding. Cannot be recommended for treatment of AD.
Estrogen replacement (ERT), conjugated equine estrogens (eg, Premarin), estradiol.	0.62–1.25 mg/day of conjugated	Estrogens have protean metabolic effects. May be trophic to cholinergic neurons, neuroprotective.	Causes uterine hyperplasia, cancer. Must be given with a progestin to women with uteri. Caution advised. No clinical evidence of efficacy in trials with patients with AD. Epidemiological studies suggest that ERT taken in midlife is protective against AD. Use of ERT for AD cannot be recommended. (**Mulnard et al 2000, Henderson et al 2000, Schneider and Finch, 1999). (AU: FULL REFERENCES?)**
Huperzine A, (Biomedisyn) (derived from Chinese herb Huperzia serrata)	Doses used in studies are 50–200 g BID.	Cholinesterase inhibitor	Available as a nutriceutical from various manufacturers, quality uncertain and variable. Adverse events similar to cholinesterase inhibitors: eg, dizziness nausea and vomiting. No controlled clinical trials outside China.
Mixed B vitamins (B12, B6, folate)	Doses are various and unknown	May reduce levels of homocysteine	Unproven; clinical trials are under way. Many elderly patients may benefit generally and nonspecifically from vitamin supplementation, because of age-related changes in absorption and utilization **(Smith et al 199x). (AU: FULL REF?)**

* Dosages reported in the literature are used.

ADL=activities of daily living; MAO-B=monoamine oxidase B; GI=gastrointestinal.

F Pharmacologic Treatment of Behavioral Symptoms

The main behavioral syndromes **AU: OF WHAT?** are depression, psychosis, agitation/aggression without psychosis, and sleep disorders. Often clinicians, staff, and caregivers notice only "agitation." It is useful to try to identify the predominant symptomatology (eg, depression or delusions) prior to considering treatment. A search for possible antecedents to the behaviors should be made; environmental and behavioral interventions should be considered along with pharmacological interventions. Wandering can be particularly difficult to treat.

32 Potential Therapies for Agitation in Dementia

The following drugs have been variously advocated to treat a range of agitated behaviors observed in patients with dementia. The anticonvulsants have been subjected to small scale clinical trials in both outpatients and nursing home patients, and many of the antipsychotics to larger trials. Not all trials were positive.

Antipsychotics (low dose)
- High-potency conventional antipsychotics (eg, haloperidol or perphenazine)
- Atypical antipsychotics (eg, clozapine, risperidone, olanzapine, quetiapine)

Anticonvulsants
- Carbamazepine
- Sodium valproate (divalproex)

Anxiolytics (limited data available)
- Short-acting benzodiazepines (eg, lorazepam, oxazepam)
- Buspirone

Beta-blockers (limited data available)
- eg, propranolol, pindolol

Serotoninergic antidepressant agents
- eg, citalopram, sertraline, trazodone

33 Antipsychotic Adverse Effects
Adverse Events Associated with Conventional Antipsychotics in Dementia

Extrapyramidal effects
- Neuroleptic-induced parkinsonian signs: Bradykinesia, decreased postural reflexes, rigidity, masked faces, tremor, drooling, gait disturbance
- Acute dystonic reaction
- Akathisia
- Tardive dyskinesia

Other neurological effects
- Catatonia, neuroleptic malignant syndrome, seizures, hypo- or hyperthermia

Anticholinergic effects
- Peripheral: dry mouth, constipation, urinary retention, blurry vision, glaucoma
- Central: confusion, delirium, impaired memory, (visual hallucinations, irritability, agitation)

Cardiovascular
- Orthostatic hypotension, tachycardia, conduction delays

Sedation

Falls/fractures

Miscellaneous
- Agranulocytosis (uncommon) but associated with phenothiazines
- Weight gain
- Rashes and dermatological
- Retinal pigmentation (eg, thioridazine)
- SIADH

SIADH=syndrome of inappropriate antidiuretic hormone secretion.

34 Antipsychotics

Antipsychotic	How Supplied	Geriatric Dosage Range	Comments
Conventional Antipsychotics			
Haloperidol (Haldol, others)	Tablets: 0.5, 1, 2, 5, 10, 20 mg Concentrate: 2 mg/mL Injection: 5 mg/mL	Starting: 0.5 mg/day Maintenance: 1–3 mg/day	2–3 mg/day is efficacious but associated with acute adverse effects. 1 mg/day tends not to be efficacious but is still associated with TD after only several months in the elderly. High incidence of EPS, low rate of anticholinergic, sedative, or orthostatic effects.
Perphenazine (Trilifon, others)	Tablets: 2, 4, 8, 16 mg Injection: 5 mg/mL	4–24 mg/day	Conventional antipsychotic.
Thioridazine (Mellaril, others)	Tablets: 10, 15, 25, 50, 100, 150, 200 mg Oral Solution: 30, 100 mg/mL	Starting: 10–25 mg/day Maintenance: 25–100 mg/day	Associated with prolonged QT intervals, arrhythmia and death. No longer can be recommended for treating elderly patients.
Atypical Antipsychotics			
Risperidone (Risperdal)	Tablets: 0.25, 0.5, 1, 2, 3, 4 mg Oral Solution: 1 mg/mL	Starting: 0.5 mg/day Maintenance: 1–3 mg/day	In nursing home patients 1–2 mg/day appears efficacious with 2 mg associated with greater side effects. 3 mg/day may be needed for late onset psychoses.
Olanzapine (Zyprexa, Zyprexa Zydis)	Tablets: 2.5, 5, 7.5, 10 mg Rapidly dissolvable tablet: 5 mg Intramuscular: **AU: DOSAGE?**	Starting: 2.5 mg/day Maintenance: 5–15 mg/day	In nursing home patients 5–10 mg/day orally appears efficacious. 10–15 mg/day associated with greater side effects.
Quetiapine (Seroquel)	Tablets: 25, 100, 200, 300 mg	Starting: 25–50 mg/day Maintenance: 50–400 mg/day	Data from open case series suggests a wide dosage range and need to individualize treatment.
Clozapine (Clozaril and others)	Tablets: 25, 100 mg	Starting: 12.5–25 mg/day Maintenance: 12.5–100 mg/day	Substantially increased risk of agranulocytosis with age. Requires WBC monitoring biweekly.
Ziprasidone (Geodon)	Capsules: 20, 40, 60, 80 mg Intramuscular: Geriatric dosage range unknown. Adult range for schizophrenia: **AU: Dosage?**	Starting: 20 mg/day Maintenance: 20–80 mg BID	No available experience with elderly dementia patients. Higher doses associated with prolonged QT intervals rarely. EKG, serum magnesium, and potassium should be checked prior to treatment. 5–20 mg reported effective for tics in children. Main adverse events in young adults: sedation, hypotension.

TD=tardive dyskinesia; EPS=extrapyramidal symptoms; WBC=whole blood count; EKG=electrocardiogram.

35 Adverse Events Associated with Atypical Antipsychotics

The differences in dosages between younger schizophrenic patients and elderly dementia patients are great. Side effects in younger patients do not necessarily apply to older, especially in their frequency, distribution, and severity.

Drug	Mixed Aged Adults	Comments and Usage in Elderly Dementia Patients
Clozapine	Drowsiness, sedation, dizziness, vertigo, headache, tremor, dry mouth, constipation, nausea, fever, weight gain, orthostatic hypotension, tachycardia. Rarely: agranulocytosis	Agranulocytosis rate increases with age. Requires biweekly WBC counts.
Olanzapine	**AU: BLANK?**	Somnolence, pain, abnormal gait are main adverse events.
Quetiapine	Somnolence, dizziness, orthostatic hypotension, d ry mouth, elevated cholesterol and triglycerides.	Cataracts may occur after prolonged use. Wide dosage ranges have been used.
Risperidone	**AU: BLANK?**	Somnolence, peripheral edema, extra-pyramidal signs
Ziprasidone	Somnolence, nausea, constipation, dizziness or orthostatic hypotension, restlessness, tremor, diarrhea, rash (5%), sedation, very modest or no weight gain, occasional EPS (see prescribing information for additional precautions)	Should not be used with other drugs that prolong cardiac conduction (eg, quinidine, pimozide, TCAs). Serum potassium and magnesium should be normal; diuretics should be used with caution. Contraindicated with recent myocardial infarction, heart failure, bradycardia.

WBC=??; EPS=extrapyramidal symptoms; TCA=tricyclic antidepressant

36 Anticonvulsants

The main use of these drugs in patients with dementia is for the treatment of aggression. In this context they are used as an alternative to antipsychotics or in addition to them. In general, the treatment of clearly defined delusions should be with antipsychotic medication, but aggression or agitation in the absence of psychosis might be treated with divalproex or carbamazepine, the only anticonvulsants thus far tested in controlled trials, or with antipsychotics.

Anticonvulsant	How Supplied	Geriatric Dosage Range	Comments
Carbamazepine (Tegretol, others)	Capsules: 200, 300 mg Chewable Tablets: 100 mg Tablets: 200 mg XR-Tabs: 100, 200, 400 mg Suspension: 100 mg/5 mL (tablespoon)	200–600 mg/day	Adverse events: dizziness, drowsiness, ataxia, weight gain. A major inducer of CYP 3A4; interacts with a range of medications, generally lowering plasma levels; rarely associated with agranulocytosis.
Divalproex (Depakote, Depakote-ER, Depakene)	Depakote Sprinkle Capsules: 125 mg Depakote Tablets: 125, 250, 500 mg Depakote ER: 500 mg Depakene Capsules: 250 mg Depakene Syrup: 250 mg/5 mL	750–1,250 mg/day in divided doses BID (blood levels: 13–100 uG/mL)	Adverse events: sedation, nausea, diarrhea, tremor, ataxia, transient elevation of transaminases, weight gain, rash, thrombocytopenia. Rare reactions: hemorrhagic pancreatitis, agranulocytosis.
Lamotrigine (Lamictal)	Tablets: 25, 100, 150, 200 mg Chewable Dispersible Tablets: 2, 5, 25 mg	**AU: BLANK**	**AU: BLANK**
Gabapentin (Neurotin)	Capsules: 100, 300, 400 mg Tablets: 600, 800 mg	**AU: BLANK**	**AU: BLANK**

NOTE: Other anticonvulsants occasionally used to treat behavioral problems in the elderly include lamotrigine, gabapentin, topiramate, tiagabine, and oxcarbazepine.

37 Drugs Used as Hypnotics for Patients with AD

The prevalence of sleep abnormalities may range from 20% to40% in AD patients and has been strongly associated with wandering, daytime agitation, and sundowning. Sleep/wake cycles among AD patients deteriorate over time and are replaced by arrhythmic polyphasic patterns of sleep. Nocturnal sleep is fragmented and associated with markedly increased in daytime sleep **(Rebok et al 1991, Reynolds et al, 1988). AU: FULL REFS?** Non-pharmacological treatments, such as bright light therapy, have been studied but their role is not clear. **(Satlin et al 1992, Lovell et al 1995, Colenda et al 1997) AU: FULL REFS?** Treatment Response: Standard pharmacological treatment with benzodiazepines may have limited or even adverse effects in demented elderly people, including excessive sedation, confusion, impaired cognition, and personality changes. The following table lists hypnotics.

Drug	How Supplied	Daily Adult Dosage (mg/day)	Elderly Dosage (mg/day)	Onset of Action	Time to Peak Plasma Level (hours)	Duration	$t_{1/2}$ (hours)	Metabolic Pathway	PK Parameters/ Active Metabolites
Benzodiazepines									
Estazolam (ProSom)	Tablets: 1, 2 mg	0.5–2.0	**AU: BLANK**	Rapid or intermediate	0.5–6.0	Intermediate	10–24	Oxidation	None
Flurazepam (Dalmane)	Capsules: 15, 30 mg	15–30	15	Rapid	1	Long	40–100	Oxidation, N-dealkylation	Yes
Quazepam (Doral)	**AU: BLANK**	7.5–15	7.5	Rapid	2	Long	40	Oxidation	Yes
Temazepam (Restoril)	Capsules: 7.5, 15, 30 mg	7.5–30	7.5–15	Intermediate	2–3	Intermediate	3.5–18.4	Conjugation	None
Triazolam (Halcion)	Tablets: 0.125, 0.25 mg	0.25–0.5	0.125–0.25	Intermediate	0.5–1.5	Short	1.5–5.5	Oxidation	None
Oxazepam* (Serax, others)	Capsules: 10, 15, 30 mg	30	15–30	Intermediate to slow	**AU: BLANK**	Short	**AU: BLANK**	Conjugation	None
Lorazepam* (Atavan, others)	Tablets: 0.5, 1.0, 2.0 mg	1.0–2.0	0.5–1.0	Intermediate	**AU: BLANK**	Intermediate	**AU: BLANK**	Conjugation	None
Benzodiazepine Agonists									
Zaleplon (Sonata)	Capsules: 5, 10 mg	10	5–10	Rapid	1	Short	1	Oxidation	None
Zolpidem (Ambien)	Tablets: 5, 10 mg	10	5–10	Rapid	1.6	Short	2.6, 1.4–4.5	Oxidation, hydroxylation	None
Other Medications Used as Hypnotics									
Chloral hydrate (Noctec, Aquachloral Supprettes, others)	Syrup: 500 mg/5 mL	500–2,000	250–1,000	Intermediate	0.5–12*	Intermediate	8–11	Oxidation, reduction	Yes
Trazodone (Desyrel, others)*	Tablets: 50, 100 mg	25–50	25–50	Intermediate	**AU: BLANK**	Short	**AU: BLANK**	**AU: BLANK**	None
Diphenhydramine (Benadryl, Unisom, others)*	Capsules/ tablets: 25, 50 mg, Liquid: 12.5 mg/5 ml	25–50	25–50	**AU: BLANK**	**AU: BLANK**	**AU: BLANK**	**AU: BLANK**	**AU: BLANK**	**AU: BLANK**

* Not FDA indicated hypnotics, but used for this purpose regardless. Diphenhydramine is an antihistaminic, anticholinergic.

38 Anti-Anxiety Medications[47]

Anxiety includes GAD, phobias, PD, OCD, and PTSD. Anxiety that occurs in the context of dementia should be distinguished from agitation, psychomotor agitation, depression, or aggression. Excessive concern or complaints about physical symptoms may represent anxiety or depression. Potential medical causes of anxiety should be considered.

Anxiety often co-exists with depression. Social phobias such as fear of eating in public may be more common in the elderly. Dementia patients may express more anxiety earlier in the course of their illnesses. There are few if any efficacy studies for these drugs in older adults, and especially those with dementia.

Medication	How Supplied	Geriatric Dosage	Onset of Action (hour)	Duration of Action	Adverse Events	Comments
Benzodiazepines						
Oxazepam (Serax, others)	Capsules: 10, 15, 30 mg	Starting dose: 10–15 mg Maintenance: 10–15 mg TID	1	Short	**AU: BLANK**	No active metabolite, conjugated and excreted. Used to reduce agitiation and restlessness, and as a hypnotic
Lorazepam (Ativan, others)	Tablets: 0.5, 1.0, 2.0 mg	Starting: 0.5 mg Maintenance: 0.5–1.0 mg BID	**AU: BLANK**	8–12 hours	**AU: BLANK**	**AU: BLANK**
Alprazolam (Xanax, others)	**AU: BLANK**	Starting: 0.25 mg Maintenance: 0.25–1.0 mg bid	**AU: BLANK**	12 hours	**AU: BLANK**	Delayed clearance in the elderly. Used for treatment of panic disorder in younger patients.
Chlordiazepoxide (Librium, others)	**AU: NOTHING UNDER CHLORDIAZEPOXIDE, DOES ANYTHING GO HERE?**					
Diazepam (Valium, others)	**AU: BLANK**	1–2 mg/day or in divided doses	**AU: BLANK**	Long	**AU: BLANK**	**AU: BLANK**
Clonazepam (Klonipin, others)	**AU: BLANK**	0.25–1 mg/day or in divided doses	**AU: BLANK**	Long	Ve ry sedating	Clearance is prolonged. Used for treatment of PD and OCD in younger patients
Other Medications						
Buspirone (BuSpar)	**AU: NOTHING UNDER BUSPIRONE**					
Hydroxyzine (Vistaril, others)	**AU: NOTHING UNDER HYDROXYZINE**					

GAD=generalized anxiety disorder; PD=panic disorder; OCD=obssessive-compulsive disorder; PTSD=posttraumatic stress disorder.

39 Antidepressants

Comments: Consultants generally prefer using serotonin uptake inhibitors and avoid the strongly anticholinergic TCAs in the elderly in general as well as with dementia patients. There is limited information on treating depression occurring after dementia. Therefore dosage guidance is based mainly on the treatment of depressed non-demented elderly. Nortriptyline is usually the preferred TCA, used after the SSRIs. SSRIs are sometimes used for agitation as well.

Medication	How Supplied	Dosage Range in Elderly for Depression	Hepatic Metabolism	Comments
Serotonin Uptake Blockers				
Fluoxetine (Prozac, Serafin, others) Fluoxetine ER	Capsules: 10, 20, 40 mg Enteric Coated Tablet: 90 mg Pulvule Liquid Oral Solution: 20 mg/5 mL	Starting: 10 mg/day Maintenance: 10–40 mg/day	Strong inhibitor of CYP 2D6, long acting metabolite	The FDA has approved labelling for use in late-life depression. May raise blood levels of other drugs metabolized by 2D6. Enteric coated tablet for once weekly treatment not recommended for elderly. Serafin brand marketed for premenstrual dysphoric disorder. Generic available.
Paroxetine (Paxil)	Tablets: 10, 20, 30, 40 mg Oral Suspension: 10 mg/5 mL	Starting: 10 mg/day Maintenance: 10–30 mg/day	Strong inhibitor of CYP 2D6	**AU: BLANK**
Sertraline (Zoloft)	Tablets: 25, 50, 100 mg Oral Concentrate: 20 mg/mL	Starting: 25–50 mg/day Maintenance: 50–100 mg/day	Weak cytochrome inhibitor	50 mg appears as efficacious as higher doses
Fluvoxamine (Luvox)	Tablets: 25, 50, 100 mg	**AU: BLANK**	Strong inhibitor of P450 1A2 (theophylline and tacrine); inhibitor of P450 3A (calcium antagonists, quinidine)	Indicated for OCD not major depression. Not recommended for elderly.
Citalopram (Celexa)	Tablets: 20, 40 mg Oral Solution: 10 mg/5 Ll	Starting: 20 mg or less Maintenance: 20–40 mg/day	**AU: BLANK**	**AU: BLANK**

TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor;
FDA=Food and Drug Administration; OCD=obsessive-compulsive disorder.

39 Antidepressants (continued)

Medication	How Supplied	Dosage Range in Elderly for Depression	Hepatic Metabolism	Comments
Selected TCAs				
Amitriptyline (Elavil, others)	Tablets: 10, 25, 50, 75, 100, 150 mg Injection: 10 mg/mL	50–100 mg/day	Inhibitor of 2D6	Not recommended for use in elderly
Imipramine (Tofranil, Tofranil PM, others)	Tablets: 10, 25, 50 mg	50–100 mg/day	Inhibitor of 2D6	Not recommended for use in elderly
Desipramine (Norpramin, others)	Tablets: 10, 25, 50, 75, 100, 150 mg	**AU: BLANK**	Inhibitor of 2D6	Cle **(AU: WHAT DOES THIS MEAN?)**
Nortriptyline (Pamelor, Aventyl, others)	Capsules: 10, 25, 50, 75 mg	50–100 mg/day	Inhibitor of 2D6	Less orthostatic hypotension than other TCAs; less strongly anticholinergic than others but still markedly anticholinergic.
Doxepin (Sinequan, others)	Capsules: 10, 25, 50, 75, 100, 150 mg Cream (Zonalon, Prudoxin): 30, 45 g Oral concentrate: 10 mg/mL	50–100 mg/day	Inhibitor of 2D6	Cream available for itching.
Other Classes				
Nefazodone (Serzone)	Tablets: 50, 100, 150, 200, 250 mg	100–300 **(AU:mg?)**	Inhibitor of 3A4	In young adults higher doses are required.
Trazodone (Desyrel, others)	Tablets: 50, 100 mg	Start: 25 mg Mainentenance: 50–300 mg/day in divided doses	**AU: BLANK**	Often used to treat agitation and as a hypnotic for dementia patients
Mirtazepine, mirtazepine orally disintegrating tablets (Remeron, Remeron SolTab)	Tablets: 15, 30, 45 mg Orally disintegrating tablets: 15, 30, 45 mg	15–30 mg QHS	Extensively metabolized through 2D6, 1A2, 3A3/4	Mixed noradrenergic, serotonergic acting through alpha-2 presynaptic antagonism, strong H-1 antagonist, decreased clearance in the elderly.
Bupropion, Bupropion SR (Wellbutrin, Wellbutrin-SR, Zyban)	Wellbutrin Tablets: 75, 100 mg Wellbutrin SR Tablets: 100, 150 mg Zyban Tablets: 100 mg	100–200 mg/day	**AU: BLANK**	Noradrenegic and dopaminergic uptake in very few; seizures may occur at doses >450 mg/day
Venlafaxine and Venlafaxine-SR (Effexor, Effexor-SR)	Effexor Tablets: 25, 37.5, 50, 75, 100 mg Effexor-XR Capsules: 37.5, 75, 150 mg	75–150 mg/day	Weak cytochrome inhibitor	Mixed effects on norepinephrine and serotonin.

TCA=tricyclic antidepressant.

40 Antidepressant Adverse Events

Below are the more typical adverse events of antidepressants, listed within class. Complete prescribing information should be consulted.

Antidepressant Class	Side Effects	Comment
SSRIs	*Most common*: nausea, headache, nervousness or anxiety, insomnia, diarrhea, fatigue, sexual dysfunction, dry mouth, sweating *Less common*: weight gain, orthostatic hypotension, anticholinergic effects, inappropriate ADH secretion, rashes, bradycardia or tachycardia. *Withdrawal effects*: dizziness, nausea, paresthesias, tremor, palpitations, and anxiety. (Withdraw medications gradually).	Generally mild side effects, nonsedating, not fatal in overdose. Interactions with many others drugs. Should not be used with MAOIs, including selegiline. In general, not cognitive impairing.
TCAs	*Most common*: anticholinergic effects, urinary retention, constipation, dry mouth, blurred vision, orthostatic hypotension, weight gain, sedation, increased heart rate. *Less common*: confusion or delirium, falls, increased intra-ocular pressure in patients with narrow-angle glaucoma, quinidine-like effects. *Withdrawal symptoms (with abrupt discontinuation):* sleep disturbance, nightmares, irritability, gastrointestinal symptoms.	TCAs have quinidine effects, prolonging repolarization. Contra-indicated in patients with cardiac arrhythmias or recent myocardial infarction. Nortriptyline is a preferred TCA because of less orthostatic hypotension
Trazodone	*Common*: sedation, orthostatic hypotension, nausea, GI upset. *Less common*: ventricular arrhythmias, edema. *Rare*: priapism	Commonly used to treat agitation and as a hypnotic. Not fatal in overdose
Buproprion	*Common*: rash, agitation, anxiety, insomnia, anorexia, tremor, dry mouth headache, nausea, weight loss *Uncommon*: seizures in high doses, confusion.	Generally well tolerated. Should not be used with MAOIs, or in patients with seizures.
Venlafaxine, Venlafaxine-ER	*Common*: nausea, nervousness, somnolence, dizziness, headache, sweating, anorexia, insomnia. *Less common*: constipation, weight loss, hypertension, inappropriate ADH secretion	BID or TID schedule. Should not be used with MAOIs.
Mirtazepine	*Common*: somnolence (54%), dizziness, increased appetite and weight gain, increased cholesterol, triglycerides. *Uncommonly*: elevated transaminases, agranulocytosis	Decreased clearance in the elderly; may be especially sedating. Should not be used with MAOIs.

SSRIs=selective serotonin reuptake inhibitors; MAOIs=monoamine oxiade inhibitors; TCAs=tricyclic antidepressants; GI=gastrointestinal; ADH=antidiuretic hormone.

Numerous diagnostic and treatment guidelines exist.

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Administration of Aging
330 Independence Ave., SW
Washington, DC 20201
Tel: (202)619-7501
Fax: (202)619-7586
http://www.aoa.dhhs.gov

Alzheimer's Association
919 N. Michigan Ave., Suite 1100
Chicago, IL 60611-1676
Tel: 800-272-3900
Tel: 312-335-8700
Fax: 312-335-1110
http://www.alz.org

Alzheimer's Disease Education and Referral Center
P.O. Box 8250
Silver Spring, MD 20907-8250
Tel: 800-438-4380
Fax: (301)495-3334
http://www.alzheimers.org

Alzheimer's Disease International
45/46 Lower Marsh
London, SE1 7RG
United Kingdom
Tel: +44-20-7620-3011
Fax: +44-20-7401-7351
http://www.alz.co.uk

Alzheimer's Research Forum
www.alzforum.org

The American Academy of Family Physicians
www.familydoctor.org

American Association for Geriatric Psychiatry
7910 Woodmont Ave.
Bethesda, MD 20814-3004
Tel: 301-654-7850
Fax: 301-654-4137
http://www.aapgpa.org

American Association of Retired Persons (AARP)
601 E. St., NW
Washington, DC 20049
Tel: 202-434-2277
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AARP Pharmacy Price Quote Center
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740 15th St., N.W.
Washington, DC 20005-1019
Tel: 202-662-8690
Fax: 202-662-8298
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Family Caregiver Alliance
690 Market St., Suite 600
San Francisco, CA 94104
Tel: 800-445-8106
Tel: 415-434-3388
Fax: 415-434-3508
http://www.caregiver.org

Geriatric Consultant Resources, LLC
2001 Commonwealth Blvd.
Suite 205
Ann Arbor, MI 48105
Tel: 734-663-9281
Fax: 734-663-9262
http://www.gcrweb.com

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Tel: 800-942-4242

International Psychogeriatric Association
550 Frontage Rd., Suite 2820
Northfield, IL 60093
Tel: 847-784-1701
Fax: 847-784-1705
http://www.ipa-online.org

Medicare Hotline
Tel: 800-638-6833

National Family Caregivers Association
10400 Connecticut Ave. #500
Kensington, MD 20895-3944
Tel: 800-896-3650
http://www.nfcacares.org

National Institutes of Health
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BRAIN (Brain Resource and Information Network)
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Tel: 800-352-9424
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Social Security Information
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