The Black Book of Alzheimer’s Disease, Part 2

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INTRODUCTION

This educational review is the second of a two-part adaptation of an ultra-quick reference guide useful in the diagnosis and treatment of Alzheimer’s disease and other dementias (The Black Book of Alzheimer’s Disease. J.L. Cummings, MD, 2008, publication pending). The classification of dementia, the expansion of diagnostic approaches to include more mild syndromes such as mild cognitive impairment (MCI), and the rapid evolution of new therapies make it difficult to remain informed about all critical progress relevant to Alzheimer’s disease and related conditions. These two articles provide information needed to manage patients using contemporary advances in diagnosis and management. They will be updated annually in the form of a Black Book to ensure that the information remains current.

This educational review is not intended as a comprehensive reference. It provides critical information only. The first part provided references and Websites where more information can be found on each topic presented. This second part emphasizes criteria-based diagnosis and optimizing pharmacotherapy. The set of diagnostic criteria provided in this educational review is among the most comprehensive available. However, the presentations and discussions have been kept deliberately short, as the purpose is not to serve as a comprehensive review but to provide information critical to patient care embedded in enough context to make management decisions coherent and logical.

Alzheimer’s disease research is forging ahead rapidly toward new therapies and the possibility of disease-modifying interventions. The context of these therapies is provided in the pathophysiology section of the text and the forward-looking therapies are introduced in the antidementia therapy section.
CLINICAL FEATURES AND DIAGNOSTIC CRITERIA FOR DEMENTIAS AND RELATED SYNDROMES

Differential Diagnosis of Cognitive Impairment

The differential diagnosis of cognitive impairment include depression, delirium, MCI, and a variety of common and uncommon dementia syndromes (Figures 1–3). Distinctive mental status, neuropsychiatric, neurologic, and imaging manifestations assist in differential diagnosis. Data are collected to determine if patients meet diagnostic criteria for specific neurologic disorders. Research diagnostic criteria are provided here to assist the clinician in diagnosis and differential diagnosis.

Mild Cognitive Impairment

MCI refers to patients who have cognitive impairment greater than age- and education-matched healthy elderly but do not meet diagnostic criteria for Alzheimer’s disease or any dementia. The patient or family member is aware of cognitive decline, the patient does not have impaired activities of daily living, and the patient does not meet criteria for dementia. Most patients with MCI progress to a dementia syndrome within 3 years; however, some remain

FIGURE 1
DIFFERENTIAL DIAGNOSIS OF THE DEMENTIA SYNDROME

- Memory Complaint
- ADL Impairment?
- Consider, Depression, Delirium
- Dementia
- Laboratory Evaluation
- Metabolic Encephalopathy
- Focal Neurologic Deficits and Abnormal MRI
- Vascular Dementia*
- Parkinsonism
- PDD, DLB†
- Disinhibition, Aphasia
- Frontotemporal Dementia‡
- Episodic Memory Deficit
- Alzheimer’s Disease
- Atypical Features
- Rare Dementia Syndrome

* Other disorders producing focal neurologic signs can be considered such as subdural hematomas and brain tumors
† Uncommon disorders producing parkinsonism and dementia such as progressive supranuclear palsy can also be identified here
‡ This category includes frontal temporal dementia, primary progressive aphasia, and semantic dementia

ADL=activities of daily living; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; PDD=Parkinson’s disease dementia; DLB=dementia with Lewy bodies.


FIGURE 2
CLINICAL SYNDROMES CORRESPONDING TO INCREASINGLY SEVERE ALZHEIMER’S DISEASE

- No clinical symptoms
- MCI (of the AD Type)
- Dementia (of the AD Type)

MCI=mild cognitive impairment; AD=Alzheimer’s disease.


FIGURE 3
RECOMMENDATIONS FOR THE GENERAL CRITERIA FOR MCI

- Cognitive complaint
- Not normal for age
- Not demented
- Cognitive decline
- Essentially normal functional activities
- MCI
- Impairment in memory?
- Yes
- No
- Only memory impairment?
- Yes
- No
- More than one domain impaired?
- Yes
- No
- Anamnetic MCI
- Multidomain MCI Amnestic
- Multidomain MCI Non-amnestic
- Single nonmemory MCI

MCI=mild cognitive impairment.

with MCI for long periods of time and some recover. The amnestic form of MCI (disproportionate memory impairment) is often the prodrome of dementia of the Alzheimer type. Patients with amnestic MCI progress to diagnosable dementia of the Alzheimer type at a rate of 12% to 15% annually. Nonamnestic forms of MCI may presage Alzheimer type dementia or other types of dementia. Alzheimer’s disease progresses from an asymptomatic phase to MCI to Alzheimer type dementia as the burden of pathology increases (Figure 4).

Dementia Syndromes

Dementia syndromes comprise memory impairment, decline in at least one other cognitive domain, deterioration from a higher level of function, and sufficient cognitive impairment to interfere with activities of daily living. The disorder cannot be present exclusively during a delirium.

Specific diagnostic criteria assist in identifying individual types of dementia syndromes (Figures 5 and 6; Tables 1-27). Dementia of the Alzheimer type, vascular dementia, frontotemporal dementia, prion disorders (eg, Creutzfeldt-Jakob disease), and dementia with various types of parkinsonism are the major diagnostic categories to be identified.

FIGURE 5
CLASSIFICATION OF THE FTLD*

*With or without progranulin or valosin-containing protein gene mutation

FTLD=frontotemporal lobar degeneration; R=repeat; MAPT=microtubule-associated protein tau gene; TDP=TAR deoxyribonucleic acid-binding protein; NF=neurofilament; IN=alpha-internexin; CBD=corticobasal degeneration; PSP=progressive supranuclear palsy; ADR=argyrophilic grain disease; MSTD=sporadic multisystem tauopathy with dementia; NFT=neurofibrillary tangle; OPCA=olivoponto-cerebellar atrophy; DLDH=dementia lacking distinctive histopathology; U=ubiquitin; MND=motor neuron disease; NFID=neuronal intermediate filament inclusion disease; BIBD=basophilic inclusion body disease; CHMP2B=charged multivesicular body protein 2B gene.


FIGURE 6
DIFFERENTIAL DIAGNOSIS OF DEMENTIA WITH PARKINSONISM

DA=dopamine; REM=rapid eye movement; OPCA=olivoponto-cerebellar atrophy; MSA=multiple system atrophy; FTD=frontotemporal dementia.

TABLE 1

DIAGNOSTIC CRITERIA FOR DEMENTIA3

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 (i.e., planning, organizing, sequenc-
      ing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment
   in social or occupational functioning and represent a significant decline from
   a previous level of functioning
C. The deficits do not occur exclusively during the course of a delirium
D. The disturbance is not better accounted for by another Axis I disorder (e.g., major
   depressive disorder, schizophrenia)

*DSM-IV code 294.1x.


TABLE 2

DIAGNOSTIC CRITERIA FOR DELIRIUM3

A. Disturbance of consciousness (i.e., reduced clarity of awareness or the envirom-
   nment) with reduced ability to focus, sustain, or shift attention
B. A change in cognition (such as memory deficit, disorientation, language dis-
   turbance) 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 find-
   ings that the disturbance is caused by the direct physiologic consequences of
   a general medical condition.

*DSM-IV code 293.0.


TABLE 3

DIAGNOSTIC CRITERIA FOR ALZHEIMER’S DISEASE

Core Diagnostic Criteria
A. Presence of an early and significant episodic memory impairment that
   includes the following features:
1. Gradual and progressive change in memory function reported by patients
   or informants >6 months
2. Objective evidence of significantly impaired episodic memory on testing:
   this generally consists of recall deficit that does not improve significantly
   or does not normalize with cueing or recognition testing after effective
   encoding of information that has been previously controlled
3. Episodic memory impairment that can be isolated or associated with
   other cognitive changes at the onset of AD or as AD advances
Supportive features
B. Presence of medial temporal lobe atrophy
   • Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI
     with qualitative ratings using visual scoring (referenced to well-characte-
     rized population with age norms) or quantitative volumetry of regions of inter-
     est (referenced to well characterized population with age norms)
C. Abnormal cerebrospinal fluid biomarker
   • Low amyloid β1-42 concentrations, increased total tau concentrations, or
     increased phospho-tau concentrations, or combinations of the three
   • Other well-validated markers to be discovered in the future
D. Specific patterning on functional neuroimaging with PET
   • Reduced glucose metabolism in bilateral temporal parietal regions
   • Other well-validated ligands, including those that foreseeably will emerge
     such as Pittsburg compound B or FDDNP
E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria
History
• Sudden onset
• Early occurrence of the following symptoms: gait disturbances, seizures,
   behavioral changes
Clinical features
• Focal neurologic features including hemiparesis, sensory loss, visual field
   deficits
• Early extrapyramidal signs
Other medical disorders severe enough to account for memory and related
   symptoms
• Non-AD dementia
• Major depressive disorder
• Cerebrovascular disease
• Toxic and metabolic abnormalities, all of which may require specific inves-
   tigations
• MRI FLAIR or T2 signal abnormalities in the medial temporal lobe
   consistent with infectious or vascular insults

Criteria for definite AD
AD is considered definite if the following are present:
• Both clinical and histopathologic (brain biopsy or autopsy) evidence of the
   disease, as required by the NIA-Reagan criteria for the post-mortem diag-
   nosis of AD; criteria must both be present

AD=Alzheimer’s disease; MRI=magnetic resonance imaging; PET=positron emission tomogra-
phy; FDDNP=2-(1-(6-[(2-[18]F)fluoroethyl](methyl)amino)-2-naphthyl)ethylidene)malononitrile;
FLAIR=fluid attenuation inversion recovery; NIA=National Institute on Aging.

TABLE 4
NINCDS-ADRDA CRITERIA FOR DEFINITE, PROBABLE, AND POSSIBLE ALZHEIMER’S DISEASE

Definite Alzheimer’s disease
• Clinical criteria for probable Alzheimer’s disease
• Histopathologic evidence of Alzheimer’s disease (autopsy or biopsy)

Probable Alzheimer’s disease
• Dementia established by clinical examination and documented by mental status questionnaire
• Dementia confirmed by neuropsychologic testing
• Deficits in ≥2 areas of cognition
• Progressive worsening of memory and other cognitive functions
• No disturbance of consciousness
• Onset between 40 and 90 years of age
• Absence of systemic disorders or other brain diseases capable of producing a dementia syndrome

Possible Alzheimer’s disease
• Presence of systemic disorder or other brain disease capable of producing dementia but not thought to be the cause of the dementia
• Gradually progressive decline in a single intellectual function in the absence of any other identifiable cause (eg, memory loss or aphasia)

Unlikely Alzheimer’s disease
• Sudden onset
• Focal neurologic signs
• Seizures or gait disturbance early in the course of illness

NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer’s Disease and Related Disorders Association.


TABLE 5
STAGES OF ALZHEIMER’S DISEASE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Memory</th>
<th>Language</th>
<th>V-S Skills</th>
<th>Executive Function</th>
<th>ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>Amnesia</td>
<td>Normal</td>
<td>Normal</td>
<td>Minimally affected</td>
<td>No impairment</td>
</tr>
<tr>
<td>Mild</td>
<td>Amnesia</td>
<td>Decreased verbal fluency</td>
<td>Mildly abnormal</td>
<td>Mildly abnormal</td>
<td>IADL affected</td>
</tr>
<tr>
<td>Moderate</td>
<td>Amnesia plus remote memory impairment</td>
<td>Anomia; decreased comp.</td>
<td>Moderately abnormal</td>
<td>Moderately abnormal</td>
<td>ADL affected</td>
</tr>
<tr>
<td>Severe</td>
<td>Absent</td>
<td>Aphasia</td>
<td>Severely abnormal</td>
<td>Untestable</td>
<td>Totally dependent</td>
</tr>
</tbody>
</table>

V-S=visuospatial; ADL=activities of daily living; IADL=instrumental activities of daily living; MCI=mild cognitive impairment.


TABLE 6
CATEGORIES OF VASCULAR COGNITIVE DISORDER

VCI: The term is equivalent to CI-ND and to vascular MCI.
VaD: Dementia is defined as executive control deficit producing loss of function for instrumental ADL.
Mixed AD+CVD: Pre-existing AD worsened by stroke (equivalent to pre-stroke dementia).
VCI=vascular cognitive impairment; CI-ND=cognitive impairment, no dementia; MCI=mild cognitive impairment; VaD=vascular dementia; ADL=Alzheimer’s disease with Lewy bodies; CVD=cerebrovascular disease.


TABLE 7
DIAGNOSTIC CRITERIA FOR PSYCHOSIS OF ALZHEIMER’S DISEASE

A. Characteristic symptoms: Presence of ≥1 of the following symptoms:
1. Visual or auditory hallucinations
2. Delusions

B. Primary diagnosis: All the criteria for dementia of the Alzheimer 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. 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 physiologic 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 depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death are present

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

TABLE 8
PROVISIONAL DIAGNOSTIC CRITERIA FOR DEPRESSION OF ALZHEIMER’S DISEASE

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 1) depressed mood or 2) decreased positive affect or pleasure

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

1. Clinically significant depressed mood (eg, depressed, sad, hopeless, discouraged, 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

B. Criteria are met for dementia of the Alzheimer 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 physiologic effects of a substance (eg, a drug of abuse or 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 Alzheimer’s disease, anxiety disorders, or substance-related disorder.


TABLE 9
PROPOSED PROVISIONAL DIAGNOSTIC CRITERIA FOR SLEEP/WAKE CYCLE DISTURBANCES IN PATIENTS

The following proposed provisional criteria are based on the best current understanding of sleep/wake cycle disturbances in the AD patient. They are designed to correct the limitations of prior criteria.

1. The patient has a complaint (either expressed by the patient or observed by the caregiver) of insomnia and/or excessive daytime sleepiness. The insomnia may be associated with confusional behavior.

2. Polysomnographic, actigraphic, or structured sleep log observation (completed by the patient or caregiver) demonstrates disturbances of sleep/wake cycle characterized as having at least 2 of the 4 following characteristics:
   a. Increased wake after sleep onset characterized by number and/or length of wake episodes occurring often or long enough to affect the function or well being of either the patient or the caregiver.
   b. Decreased total sleep time with a reduction of 25% of the patient’s total nocturnal sleep relative to their premorbid nocturnal sleep pattern or, when this is not known, a pattern of sleeping <6 hours during a period from 9PM–6AM.
   c. Poor daytime wake continuity with an increase in the number and/or duration of naps during the day relative to the patient’s premorbid daytime wakefulness and napping pattern
   d. Desynchronization of sleep/wake rhythm as reflected by altered diurnal patterns of sleep, that is, day-night sleep ratio.

3. The sleep disorder is associated with a diagnosis of AD. The sleep disturbance was not present before the onset of dementia, and the nature and degree of the sleep disturbance can be expected to change with the stage of the disease.

4. Differential diagnosis:
   a. Other medical disorders, specifically delirium, depression, chronic pain, and medication use, may be present but do not account for the primary symptoms.
   b. Other sleep disorders (eg, periodic limb movement disorder, restless legs syndrome, obstructive sleep apnea syndrome) may be present but do not account for the primary symptoms. If there is a suspicion or objective documentation of a sleep disorder that does not account for the primary symptoms, it should be treated first.
   c. The sleep disturbance cannot be characterized as a parasomnia. Parasomnias may include behavioral manifestations of epileptiform activity or suspension of REM sleep atonia characteristic of REM behavior disorder. REM behavior disorder consists of dream-enactment behaviors, often accompanied by REM-specific motor activity and dream recall of frightening and/or dramatic events. REM behavior disorder may be present in an idiopathic form or may co-occur in Parkinson’s disease, Lewy body dementia, or AD/Parkinson’s disease overlap, if presumed nigrostriatal pathology exists. If symptoms and signs compatible with such diagnoses exist in a given patient, PSG would be indicated to establish this differential. If PSG is not possible because the patient cannot tolerate it, a video recording to differentiate REM behavior disorder may be substituted.

REM=rapid eye movement; AD=Alzheimer’s disease; PSG=polysomnograph.

### TABLE 10
**CRITERIA FOR POSTERIOR CORTICAL ATROPHY**

*Diagnostic criteria*:
- Insidious onset and gradual progression
- Presentation with visual complaints but intact primary visual function
- Evidence of a predominant complex visual disorder, such as: Visuospatial and constructional deficits; Balint’s syndrome; Gerstmann’s syndrome; Prosopagnosia; and Visual agnosia
- Proportionately less impairment on tests of memory and verbal fluency
- Relatively preserved insight with or without depression

*Most cases have Alzheimer’s disease; the syndrome also can be produced by dementia with Lewy bodies, corticobasal degeneration, or Creutzfeldt-Jakob disease*.  


### TABLE 11
**THE CLINICAL DIAGNOSTIC FEATURES OF FRONTOTEMPORAL DEMENTIA**

Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spacial skills, praxis, and memory are intact or relatively well preserved.

**Core diagnostic features**
- Insidious onset and gradual progression
- Early decline in social interpersonal conduct
- Early impairment in regulation of personal conduct
- Early emotional blunting
- Early loss of insight

**Supportive diagnostic features**
- Behavioral disorder
  - Decline in personal hygiene and grooming
  - Mental rigidity and inflexibility
  - Distractibility and imper sistence
  - Hyperorality and dietary changes
  - Perseverative and stereotyped behavior
  - Utilization behavior
- Speech and language
  - Altered speech output
  - Aspontaneity and economy of speech
  - Press of speech
  - Stereotypy of speech
  - Echolalia
  - Perseveration
  - Mutism
- Physical signs
  - Primitive reflexes
  - Incontinence
  - Akinesia, rigidity, and tremor
  - Low and labile blood pressure
- Investigations
  - Neuropsychology: significant impairment on frontal lobe tests in the absence of a severe amnesia, aphasia, or per consequuos spatial disorder
  - Electroencephalography: normal to conventional electroencephalograph despite clinically evident dementia
  - Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality
- Clinical features
  - Onset at <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)


### TABLE 12
**THE CLINICAL DIAGNOSTIC FEATURES OF PROGRESSIVE NONFLUENT APHASIA**

Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.

**Core diagnostic features**
- Insidious onset and gradual progression
- Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, or anomia

**Supportive diagnostic features**
- Speech and language
  - Stuttering or oral apraxia
  - Impaired repetition
  - Alexia, agraphia
  - Early preservation of word meaning
  - Late mutism
- Behavior
  - Early preservation of social skills
  - Late behavioral changes similar to FTD
- Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor
- Investigations
  - Neuropsychology: nonfluent aphasia in the absence of severe amnesia or perceptuospatial disorder
  - Electroencephalography: normal or minor asymmetrical abnormality predominantly affecting dominant (usually left) hemisphere
- Clinical features
  - Onset at <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)

FTD=frontotemporal dementia.

Table 13

The Clinical Diagnostic Features of Progressive Semantic Dementia

Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well preserved.

Core diagnostic features
- Insidious onset and gradual progression
- Language disorder characterized by
  - Progressive, fluent empty spontaneous speech
  - Loss of word meaning, manifest by impaired naming and comprehension
  - Semantic phaphasia and/or
- Perceptual disorder characterized by
  - Prosopagnosia: impaired recognition of object identity or familiar faces and/or
  - Associative agnosia: impaired recognition of object identity
- Preserved perceptual matching and drawing reproduction
- Preserved single-word repetition
- Preserved ability to read aloud and write to dictation orthographically regular words

Supportive diagnostic features
- Speech and language
  - Press of speech
  - Idiosyncratic word usage
  - Absence of phonemic paraphasia
  - Surface dyslexia and dysgraphia
  - Preserved calculation
- Behavior
  - Loss of sympathy and empathy
  - Narrowed preoccupations
  - Parsimony
- Physical signs: absent or late primitive reflexes, akinesia, rigidity, and tremor
- Investigations
  - Neuropsychology: Profound semantic loss, manifest in failure of word comprehension and naming and/or face and object recognition. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memorizing
  - Electroencephalography: normal
  - Brain imaging (structural and/or functional); predominant anterior temporal abnormality (symmetric or asymmetric)
- Clinical features
  - Onset at <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)


Table 14

United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

Inclusion Criteria
- Bradykinesia: Slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions
- And at least one of the following: muscular rigidity; 4–6 Hz rest tremor; or postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Exclusion Criteria
- History of repeated strokes with stepwise progression of Parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Supportive Criteria (three or more required for diagnosis of definite PD)
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70% to 100%) to levodopa
- Severe levodopa response for 5 years

CT=computerized tomography; PD=Parkinson's disease.

TABLE 15

CRITERIA FOR THE DIAGNOSIS OF PROBABLE AND POSSIBLE PD-D

Probable PD-D
A. Core features: both must be present
B. Associated clinical features:
   • Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuospatial functions, and impaired free recall memory which usually improves with cueing)
   • The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PD-D; lack of behavioral symptoms, however, does not exclude the diagnosis
C. None of the group III features present
D. None of the group IV features present

Possible PD-D
A. Core features: both must be present
B. Associated clinical features:
   • Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve cueing or in recognition tasks) with preserved attention
   • Behavioral symptoms may or may not be present
OR
C. One or more of the group III features present
D. None of the group IV features present


TABLE 16

DEFINITIONS OF IMPULSE CONTROL AND REPETITIVE BEHAVIORS IN PARKINSON’S DISEASE: COMPULSIVE SHOPPING

A. Maladaptive preoccupation with buying or shopping that is manifested as impulses or behaviors that:
   1. Are experienced as irresistible, intrusive, and/or senseless
   2. Result in frequent buying of more than can be afforded, items that are not needed, or longer periods of time than intended
B. Cause marked distress, are time consuming, significantly interfere with social or occupational functioning, or result in financial problems
C. The behavior does not occur exclusively during periods of hypomania or mania


TABLE 17

DEFINITIONS OF IMPULSE CONTROL AND REPETITIVE BEHAVIORS IN PARKINSON’S DISEASE: COMPULSIVE MEDICATION USE (HEDONISTIC HOMEOSTATIC DYSREGULATION)

A. Clinical diagnosis of levodopa-responsive Parkinson’s disease
B. Need for increasing dopamine replacement therapy in excess of that required for motor signs and symptoms
C. Pathologic use despite severe behavioral disturbances and drug-induced dyskinesias
D. Social or occupational impairment
E. Development of a dopaminergic withdrawal state with dose reduction


TABLE 18

DEFINITIONS OF IMPULSE CONTROL AND REPETITIVE BEHAVIORS IN PARKINSON’S DISEASE: HYPERSEXUALITY

A. The sexual thoughts or behaviors are excessive or an atypical change from baseline marked by >1 of the following:
   1. Maladaptive preoccupation with sexual thoughts
   2. Inappropriately or excessively requesting sex from spouse or partner
   3. Habitual promiscuity
   4. Compulsive masterbation
   5. Calls to telephone sex lines or viewing of pornography
   6. Paraphilias
B. The behavior must have persisted for at least 1 month
C. The behavior causes ≥1 of the following:
   1. Marked distress
   2. Attempts to control thoughts and behavior that are unsuccessful or result in marked anxiety or distress
   3. Becomes time consuming
   4. Significant interference with social or occupational functioning
D. The behavior does not occur exclusively during periods of hypomania
E. If all criteria except C are fulfilled, the disorder is subnormal

TABLE 19
DEFINITIONS OF IMPULSE CONTROL AND REPETITIVE BEHAVIORS IN PARKINSON’S DISEASE: COMPULSIVE EATING AND PUNDING

Compulsive eating: binge eating
A. Recurrent binge eating characterized by eating large amounts in a discrete period, along with a loss of control
B. ≥3 of the following:
   1. Rapid eating
   2. Feeling uncomfortably full
   3. Eating large amounts when not hungry
   4. Eating alone because of embarrassment over amounts
   5. Feeling disgusted or guilty
C. Marked distress
D. Occurs 2 days a week for 6 months
E. Does not occur with compensatory behaviors during anorexia or bulimia nervosa
Uncontrollable consumption of larger amount of food than normal in excess of that necessary to alleviate hunger

Punding
An intense fascination with complex, excessive, repetitive, non-goal-oriented behaviors. The behaviors include less complex acts, such as shuffling papers, reordering bricks, or sorting handbags, or more complex acts, such as hobbyism (gardening, painting), writing, or excessive computer use.

TABLE 20
PROPOSED RESEARCH CRITERIA FOR CBD

Lang and colleagues
Inclusion criteria: Rigidity plus one cortical sign (apraxia, cortical sensory loss, alien limb) or asymmetric rigidity, dystonia, and focal reflex myoclonus

Core features (two core features are sufficient for a diagnosis of probable DLB):
1. Central feature (essential for a diagnosis):
   - Dementia defined as 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
2. Core features (two core features are sufficient for a diagnosis of probable DLB):
   - Fluctuating cognition with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous features of parkinsonism
3. Suggestive features (if ≥1 of these is present in the presence of ≥1 key features, a diagnosis of probable DLB can be made. In the absence of any core features, ≥1 suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone):
   - REM sleep behavior disorder
   - Severe neuroleptic sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated SPECT or PET imaging
4. Supportive features (commonly present but not proven to have diagnostic specificity):
   - Repeated falls and syncope
   - Transient, unexplained loss of consciousness
   - Severe autonomic dysfunction (eg, orthostatic hypension, urinary incontinence)
   - Hallucinations in other modalities
   - Systematized delusions
   - Depression
   - Relative preservation of medial temporal lobe structures on CT/MRI scan
   - Generalized low uptake on SPECT/CT perfusion scan with reduced occipital activity
   - Abnormal (low uptake) MIBG myocardial scintigraphy
   - Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is less likely:
   - In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
   - In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
   - If parkinsonism only appears for the first time at a stage of severe dementia

6. Temporal sequence of symptoms: DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson’s disease dementia should be used to describe dementia that occurs in the context of well-established Parkinson’s disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and Parkinson’s disease dementia, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinico-pathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or α-synucleinopathy.

DLB = dementia with Lewy bodies; REM = rapid eye movement; SPECT = single photon emission computed tomography; PET = positron emission tomography; CT = computerized tomography; MRI = magnetic resonance imaging; MIBG = metaiodobenzylguanidine; EEG = electroencephalogram; LB = Lewy bodies.


TABLE 21
REVISED CRITERIA FOR THE CLINICAL DIAGNOSIS OF DEMENTIA WITH LEWY BODIES

1. Central feature (essential for a diagnosis):
   - Dementia defined as 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
2. Core features (two core features are sufficient for a diagnosis of probable DLB):
   - Fluctuating cognition with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous features of parkinsonism
3. Suggestive features (if ≥1 of these is present in the presence of ≥1 key features, a diagnosis of probable DLB can be made. In the absence of any core features, ≥1 suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone):
   - REM sleep behavior disorder
   - Severe neuroleptic sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated SPECT or PET imaging
4. Supportive features (commonly present but not proven to have diagnostic specificity):
   - Repeated falls and syncope
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   - Severe autonomic dysfunction (eg, orthostatic hypension, urinary incontinence)
   - Hallucinations in other modalities
   - Systematized delusions
   - Depression
   - Relative preservation of medial temporal lobe structures on CT/MRI scan
   - Generalized low uptake on SPECT/CT perfusion scan with reduced occipital activity
   - Abnormal (low uptake) MIBG myocardial scintigraphy
   - Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is less likely:
   - In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
   - In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
   - If parkinsonism only appears for the first time at a stage of severe dementia

6. Temporal sequence of symptoms: DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson’s disease dementia should be used to describe dementia that occurs in the context of well-established Parkinson’s disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and Parkinson’s disease dementia, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinico-pathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or α-synucleinopathy.

DLB = dementia with Lewy bodies; REM = rapid eye movement; SPECT = single photon emission computed tomography; PET = positron emission tomography; CT = computerized tomography; MRI = magnetic resonance imaging; MIBG = metaiodobenzylguanidine; EEG = electroencephalogram; LB = Lewy bodies.

TABLE 22
NINDS-SPSP CLINICAL CRITERIA FOR DIAGNOSIS OF PSP

**Inclusion Criteria**
For possible and probable:
- Gradually progressive disorder with age of onset ≥40 years
- Either verticle or supranuclear palsy or both slowing of vertical saccades and postural instability with falls <1 year of disease onset

**Possible**
- Vertical supranuclear palsy and prominent instability with falls within first year of disease onset*

**Probable**
- All criteria for possible or probable PSP are met and histopathologic confirmation at autopsy

**Exclusion Criteria**
- Recent history of encephalitis
- Alien limb syndrome, cortical sensory deficits
- Focal frontal or temporoparietal atrophy
- Hallucinations or delusions unrelated to dopaminergic therapy
- Cortical dementia of Alzheimer type
- Prominant early cerebellar symptoms
- Unexplained dysautonomia
- Evidence of other diseases that could explain the clinical features

**Supportive Criteria**
- Symmetric akinesia or rigidity, proximal more than distal
- Abnormal neck posture, especially retrocollis
- Poor or absent response of parkinsonism to levodopa
- Early dysphagia and dysarthria
- Early onset of cognitive impairment including >2 of apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs

*Later defined as falls or the tendency to fall (patients able to stabilize themselves)


TABLE 23
DIAGNOSTIC CATEGORIES OF MSA

**I. Possible MSA**
One criterion plus two features from separate other domains. When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence only one additional feature is required)

**II. Probable MSA**
Criterion for autonomic failure/urinary dysfunction plus poor levodopa responsive parkinsonism or cerebellar dysfunction

**III. Definite MSA**
Pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways

MSA=multiple system atrophy.


TABLE 24
CLINICAL DOMAINS, FEATURES, AND CRITERIA USED IN THE DIAGNOSIS OF MULTIPLE SYSTEM ATROPHY

A feature (A) is a characteristic of the disease and a criterion (B) is a defining feature or composite of features for required diagnosis

**I. Autonomic and urinary dysfunction**
A. Autonomic and urinary features
1. Orthostatic hypotension (by 20 mmHg systolic or 10 mmHg diastolic)
2. Urinary incontinence or incomplete bladder emptying

B. Criterion for autonomic failure or urinary dysfunction in MSA. Orthostatic fall in blood pressure (by 30 mmHg systolic or 15 mmHg diastolic) or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men) or both

**II. Parkinsonism**
A. Parkinsonian features
1. Bradykinesia (slowness of voluntary movement with progressive reduction in speed and amplitude during repetitive actions)
2. Rigidity
3. Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
4. Tremor (postural, resting, or both)

B. Criterion for parkinsonism in MSA: bradykinesia plus at least one of items 2–4

**III. Cerebellar dysfunction**
A. Cerebellar features
1. Gait ataxia (wide-based stance with steps of irregular length and direction)
2. Ataxic dysarthria
3. Limb ataxia
4. Sustained gaze-evoked nystagmus

B. Criterion for cerebellar dysfunction in MSA: gait ataxia plus at least one of items 2–4

**IV. Corticospinal tract dysfunction**
A. Corticospinal tract features: extensor plantar responses with hyperreflexia
B. Corticospinal tract dysfunction in MSA: no corticospinal tract features are used in defining the diagnosis of MSA

MSA=multiple system atrophy.

TABLE 25  
CREUTZFELDT-JAKOB DISEASE CRITERIA STUDIED

European Criteria

Definite
• Neuropathologic confirmation and/or immunocytochemically confirmed PrPsc, positive Western blot, and/or scrapie associated fibrils

Probable
• Progressive dementia, typical EEG, at least two of the four clinical features listed

Possible
• Progressive dementia at least two of the four clinical features listed, no EEG or atypical EEG, duration <2 years

Clinical features
• Myoclonus
• Visual or cerebellar signs
• Pyramidal or extrapyramidal signs
• Akinetic mutism

PrPsc=pathogenic isoform of the prion protein; EEG=electroencephalogram.


TABLE 26  
HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

HIV-associated minor cognitive/motor disorder
• Poor short-term memory and concentration, behavioral problems, or personality changes
• Psychiatric symptoms of depression and anxiety. Behavioral changes also include apathy, lethargy, loss of sexual drive, diminished emotional responsiveness, delusions, or hallucinations
• Early motor symptoms may include an unsteady gait, leg weakness, clumsiness, slowing of fine motor movements, and tremor. In some patients, smooth pursuit eye movements or saccadic movements may be impaired.

HIV-associated dementia complex
• Cognitive deterioration progressing to and akinetic mutic state
• Quadripareisis
• Myoclonus

HIV=human immunodeficiency virus.


TABLE 27  
BOSTON CRITERIA FOR DIAGNOSIS OF CEREBRAL AMYLOID ANGIOPATHY-RELATED HEMORRHAGE

1. Definite CAA
   Full postmortem examination demonstrating:
   • Lobar, cortical, or corticosubcortical hemorrhage
   • Severe CAA with vasculopathy
   • Absence of other diagnostic lesion

2. Probable CAA with supporting pathology
   Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:
   • Lobar, cortical, or corticosubcortical hemorrhage
   • Some degree of CAA in specimen
   • Absence of other diagnostic lesion

3. Probable CAA
   Clinical data and MRI or CT demonstrating:
   • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
   • Age 55 ≥ years
   • Absence of other cause of hemorrhage

4. Possible CAA
   Clinical data and MRI or CT demonstrating:
   • Single lobar, cortical, or corticosubcortical hemorrhage
   • Age 55 ≥ years
   • Absence of other cause of hemorrhage

* Criteria established by the Boston Cerebral Amyloid Angiopathy Group: Steven M. Greenberg, MD, PhD; Daniel S. Kanter, MD; Carlos S. Kase, MD; and Michael S. Pessin, MD.

† Other causes of intracerebral hemorrhage: excessive warfarin (INR>3.0); antecedent head trauma or ischemic stroke, CNS tumor, vascular malformation, or vasculitis; and blood dyscrasia or coagulopathy. (INR>3.0 or other nonspecific laboratory abnormalities permitted for diagnosis of possible CAA).

CAA=cerebral amyloid angiopathy; MRI=magnetic resonance imaging; CT=computerized tomography; INR=international normalized ratio; CNS=central nervous system.

ANTIDEMENTIA THERAPIES

Current Treatment Approaches

Currently available antidementia therapies include cholinesterase inhibitors and the (NMDA) receptor antagonist, memantine. Tables 29–34 provide comprehensive prescribing and side-effect monitoring information.

Emerging Therapies

Alzheimer's disease research has identified plausible targets for new symptomatic and disease-modifying treatment. Some of these agents are in advanced stages of clinical testing. The steps of the amyloid cascade comprise one set of pharmacologic targets, and neuroprotective approaches comprise an alternate treatment strategy (Figures 7–10; Tables 28–35).

FIGURE 7
THERAPEUTIC APPROACH TO DEMENTIA OF THE ALZHEIMER TYPE

- Dementia of the Alzheimer Type
- Exclude Delirium and Other Causes of Cognitive Impairment
- Cholinesterase Inhibitor (Mild to Moderate Dementia)
  Memantine (Moderate to Severe Dementia)
- Combination Therapy (Cholinesterase Inhibitor and Memantine) if Begun on Monotherapy


FIGURE 8
THERAPEUTIC APPROACH TO PDD

- Parkinson’s Disease
- PDD Criteria
- Optimize Therapy
- Eliminate Therapies Compromising Cog Anticholinergic

PDD=Parkinson’s disease dementia; PD=Parkinson’s disease.

FIGURE 9
THERAPEUTIC APPROACH TO DLB*

- Parkinson’s Disease
- PDD Criteria
- Optimize Therapy
- Eliminate Therapies Compromising Cog Anticholinergic

*Use antipsychotics with caution, some patients have extreme reactions.
DLB=dementia with Lewy bodies; PDD=Parkinson’s disease dementia; PD=Parkinson’s disease.
FIGURE 10
THERAPEUTIC APPROACH TO VASCULAR DEMENTIA


TABLE 28
NONPHARMACOLOGIC APPROACHES TO DEMENTIA

- Assess the patient for comorbid conditions that may be aggravating the dementia (eg, delirium, pain, thirst, hunger)
- Educate the caregiver about the symptoms, why they occur, and how best to respond
- Identify precipitants of behavioral outbursts (eg, bothersome roommates in a nursing home, noise of grandchildren at home)
- Observe the patient to identify any calming influences (eg, pets, music, swimming, walks)
- Avoid confrontation and redirect the patient (eg, to rides in the car, tea, walks, watching television)
- Adapt to the patient’s schedule to the extent possible (eg, bathing, eating, sleeping)
- Provide regular toileting to avoid incontinence in later stage patients
- Avoid evening fluids and stimulants (tea, coffee) to optimize night-time sleep


TABLE 29
BASIC PRINCIPLES FOR USE OF ANTIDEMENTIA TREATMENT

- Make an accurate diagnosis of the dementia syndrome
- Characterize the severity of the dementia (mild, moderate, severe)
- Inform the patient and caregiver of reasonable treatment expectations (small symptomatic improvements and delay in decline are typical responses)
- Optimize the dose of each medication
- Slow the titration of the medication if side effects emerge during the titration period
- Monitor multiple domains for beneficial responses (eg, cognition, behavior, function)
- Monitor side effects (especially gastrointestinal side effects with cholinesterase inhibitors)
- Offer pill (donepezil, galantamine, rivastigmine) or patch (rivastigmine) formulations to determine patient and caregiver preference
- Switch from one cholinesterase inhibitor to another if the patient is intolerant or shows no response to the current treatment
- Emphasize the importance of taking medications regularly
- Continue therapy until the severe phases of dementia are reached
- Monitor for rapid emergence of new cognitive, behavioral, or functional symptoms if the medications are discontinued
- Combine a cholinesterase inhibitor and memantine for optimal therapeutic response

TABLE 30
CHOLINESTERASE INHIBITORS*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Aricept (Aricet in some countries)</td>
<td>Exelon and Exelon patch</td>
<td>Razadyne and Razadyne ER</td>
</tr>
<tr>
<td>Indication(s)</td>
<td>Mild to moderate and severe AD</td>
<td>Mild to moderate AD; Parkinson’s disease dementia</td>
<td>Mild to moderate AD</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>70</td>
<td>1.5 (brain half-life is 8)</td>
<td>7</td>
</tr>
<tr>
<td>Administration Schedule</td>
<td>QD</td>
<td>BID for capsules; QD for the patch</td>
<td>BID for the non-ER form; QD for the ER form</td>
</tr>
<tr>
<td>Metabolism by hepatic CYP enzymes</td>
<td>2D6, 3A4</td>
<td>No</td>
<td>2D6, 3A4</td>
</tr>
<tr>
<td>Protein binding</td>
<td>96%</td>
<td>40%</td>
<td>18%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>40%</td>
<td>90%</td>
</tr>
<tr>
<td>Time to peak serum level</td>
<td>3–4 hours</td>
<td>1 hour</td>
<td>1 hour (2.5 hours with food); 4.5 hours for ER form</td>
</tr>
<tr>
<td>Absorption delayed by food</td>
<td>No</td>
<td>No</td>
<td>Yes (1 hour to 2.5 hours)</td>
</tr>
<tr>
<td>Titration</td>
<td>Begin with 5 mg and advance to 10 mg after 1 month</td>
<td>Oral form: 1.5 mg BID for 4 weeks; 3 mg BID for 4 weeks; 4.5 mg BID for 4 weeks; advance to 6 mg BID if tolerated Patch form: begin the 5 cm² patch for 1 month then advance to 10 cm² patch</td>
<td>Non-ER form: begin 4 mg BID, advance to 8 mg BID after 1 month, and to 12 mg BID after 1 additional month ER form: begin at 8 mg QD, advance after 1 month to 16 mg QD and after 1 additional month to 24 mg QD</td>
</tr>
</tbody>
</table>

*Tacrine (Cognex) is now rarely used because of associated liver enzyme elevations and is not included in this chart.

ER=extended release; AD=Alzheimer’s disease; CYP=cytochrome P450.


TABLE 31
MEMANTINE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Namenda (Ebixa or Axura in some countries)</td>
</tr>
<tr>
<td>Indications</td>
<td>Moderate to severe AD (US) up to MMSE scores of 20 in Europe and Asia</td>
</tr>
<tr>
<td>Half-life</td>
<td>60–80 hours</td>
</tr>
<tr>
<td>Protein binding</td>
<td>50%</td>
</tr>
<tr>
<td>Metabolism by hepatic CYP enzymes</td>
<td>No</td>
</tr>
<tr>
<td>Absorption delayed by food</td>
<td>No</td>
</tr>
<tr>
<td>Time to peak serum level</td>
<td>3–7 hours</td>
</tr>
<tr>
<td>Adjustment in hepatic or renal disease</td>
<td>Decrease dose by 50% in patients with renal failure</td>
</tr>
<tr>
<td>Titration</td>
<td>5 QD for 1 week; 5 BID for 1 week; 10 mg in AM and 5 mg in PM for 1 week; 10 mg BID thereafter</td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease; US=United States; MMSE=Mini-Mental Status Examination; CYP=cytochrome P450.


TABLE 32
PHARMACOTHERAPY OF COGNITION IN NON-ALZHEIMER DEMENTIAS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>Donepezil delayed progression from MCI to AD for the first 18 months of a 3-year study; no medications are approved by the FDA for treatment of MCI</td>
</tr>
<tr>
<td>Parkinson’s disease dementia</td>
<td>Rivastigmine produced improvement in cognition, function and behavior; it is approved by the FDA for treatment in this setting</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Cholinesterase inhibitors have been assessed in double-blind trials and found useful; not approved by FDA</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Memantine has been assessed and has been shown to have benefit; not approved by FDA</td>
</tr>
<tr>
<td>MCI=mild cognitive impairment; AD=Alzheimer’s disease; FDA=Food and Drug Administration.</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 33
SIDE EFFECTS MOST COMMONLY REPORTED WITH CHOLINESTERASE INHIBITORS*

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Placebo (%)</th>
<th>Donepezil (%)</th>
<th>Placebo (%)</th>
<th>Rivastigmine Patch (%)</th>
<th>Placebo (%)</th>
<th>Galantamine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Pain, various locations</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident</td>
<td>6</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GI system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>9</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (upper)</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>&lt;1</td>
<td>3</td>
<td></td>
<td></td>
<td>5</td>
<td>7</td>
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<tr>
<td>Somnolence</td>
<td>&lt;1</td>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
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<tr>
<td>Abnormal dreams</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CNS disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Vertigo</td>
<td></td>
<td></td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Metabolic disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decrease</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td><strong>Urinary system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent urination</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Cardiovascular disorders</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Bradycardia</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hemic disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td></td>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Observed in at least 2% of patients receiving active treatment and occurring at a greater rate than in placebo-treated patients; taken from Food and Drug Administration-approved product labeling.

**TABLE 34**

**AMYLOID-BASED THERAPEUTICS**

<table>
<thead>
<tr>
<th>Target</th>
<th>Approaches</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-secretase</td>
<td>Inhibitors</td>
<td>Inhibit the first step in the generation of the amyloid peptide</td>
</tr>
<tr>
<td>γ-secretase</td>
<td>Inhibitors and modulators</td>
<td>Inhibit the second and final step in the generation of the amyloid peptide</td>
</tr>
<tr>
<td>α-secretase</td>
<td>Enhancers</td>
<td>Statins and muscarinic (M₁) agonists may increase the “benign” metabolism of amyloid precursor protein and decrease amyloid production</td>
</tr>
<tr>
<td>Monomers and oligomers</td>
<td>Immunotherapy</td>
<td>Bind these peptides prior to aggregation</td>
</tr>
<tr>
<td></td>
<td>Metal protein attenuating agents</td>
<td>Prevent transport of amyloid into the brain (to create “sink” with flow from brain)</td>
</tr>
<tr>
<td>Aggregation</td>
<td>Antithrillization agents</td>
<td>Prevent this step that is essential to neurotoxicity</td>
</tr>
<tr>
<td>Neurotic plaques</td>
<td>Immunotherapy</td>
<td>Reduce plaque burden</td>
</tr>
<tr>
<td></td>
<td>PPAR-γ agonists</td>
<td>Reduce hyperglycemia and increase availability to insulin degrading enzyme to metabolize amyloid</td>
</tr>
</tbody>
</table>

RAGE=receptor for advanced glycation end products; PPAR=peroxisome proliferator-activated receptor.


**TABLE 35**

**NEUROPROTECTIVE THERAPIES**

<table>
<thead>
<tr>
<th>Target</th>
<th>Approaches</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau hyperphosphorylation</td>
<td>Kinase inhibitors</td>
<td>Reduced formation of neurofibrillary tangles</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Antioxidants</td>
<td>Reduced oxidative injury to cell membranes</td>
</tr>
<tr>
<td></td>
<td>Homocysteine lowering agents</td>
<td>Homocysteine promotes oxidative injury</td>
</tr>
<tr>
<td>Excitotoxicity</td>
<td>NMDA receptor antagonists</td>
<td>Blocks glutamate-related excitotoxicity and entry of calcium into cells with neurodegeneration</td>
</tr>
<tr>
<td></td>
<td>Ampakines</td>
<td>AMPA receptors may play a role in glutamate-related excitotoxicity</td>
</tr>
<tr>
<td>Inflammation</td>
<td>NSAIDs</td>
<td>Reduced inflammation-related cell injury and death</td>
</tr>
<tr>
<td>NGF</td>
<td>Agents with NGF-like effects</td>
<td>Preserve synapses and neuronal integrity</td>
</tr>
<tr>
<td>Caspase</td>
<td>Caspase inhibitors</td>
<td>Intere the in cell death cascades</td>
</tr>
<tr>
<td>Monoamine oxidase</td>
<td>MAOIs</td>
<td>Reduce free radical generation</td>
</tr>
<tr>
<td>NNR</td>
<td>NNR agonists</td>
<td>Nicotine appears to promote cell survival</td>
</tr>
</tbody>
</table>

NMDA=N-methyl-D-aspartate; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NGF=nerve growth factor; MAOIs=monoamine oxidase inhibitors; NNR=neuronal nicotinic receptor.


**MANAGEMENT OF BEHAVIORAL SYMPTOMS IN DEMENTIA**

Behavioral changes and neuropsychiatric symptoms are among the most disabling manifestations of Alzheimer’s disease and other dementias. Behavioral disturbances are a great source of distress for patients and caregivers, decrease quality of life, may precipitate institutionalization, and increase the cost of care.

**Nonpharmacologic Management**

Nonpharmacologic approaches to management of neuropsychiatric symptoms may obviate the need for pharmacotherapy or may decrease the necessary dose or length of time required for pharmacologic intervention.

**Pharmacologic Management**

There are no medications approved by the FDA specifically for the treatment of behavioral symptoms in patients with dementia. There have been relatively few masked, placebo-controlled trials to provide evidence-based guidance for pharmacotherapy of neuropsychiatric symptoms in dementia (Figures 11 and 12; Tables 36–44; Figures 13–15; Tables 45 and 46).

**FAMILY COUNSELING**

Families provide most of the care to patients with Alzheimer’s disease and other dementias. Even after the patient is resident in a nursing home, families continue to visit often and provide some of the care. Caregiving is associated with increased medical illness, psychological stress, and substance (eg, alcohol, tranquilizers) use. Caregiver burden may lead to caregiver “burnout,” with an inability to continue to provide care. Optimal care of dementia patients requires developing an alliance with the family and referring family members to community resources.

Practical strategies useful in working with families include educating families about the course of Alzheimer’s disease, what to expect over time, and how best to manage the patient and their own response; referring to the Alzheimer Association or other advocacy organizations to identify local resources for patients and families; monitoring the caregiver for “burnout” and recommending respite care or day care as needed; and providing culturally competent care recognizing the cultural individuality of patients and families. PP
FIGURE 11

PSYCHOSIS MANAGEMENT

Psychosis

Pain, delirium, etc

Environmental Provocation

Memantine; ChE-Is

Residual Psychotic Features

Atypical Antipsychotics Neurotics

ChE-Is=cholinesterase inhibitors.


FIGURE 12

AGITATION MANAGEMENT

Agitation

Pain, delirium, etc

Environmental Provocation

Nocturnal

Memantine; ChE-Is

Depressive Features

Psychotic Features

Atypical Antipsychotic Neurotics

Antipsychotics Mood stabilizers

ChE-Is=cholinesterase inhibitors.; NOS=not otherwise specified; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.


TABLE 36

PRINCIPLES OF PHARMACOLOGIC MANAGEMENT OF BEHAVIORAL DISTURBANCES IN DEMENTIA

- Assess the patient for comorbid conditions that may be exaggerating behavioral changes (eg, delirium, pain, thirst, hunger)
- Introduce antidementia agents prior to the use of psychotropics to take advantage of any behavioral responses to antidementia therapy
- Identify specific target symptoms for treatment (agitation in the late afternoon, insomnia, anxiety in social settings)
- Agitation is a nonspecific symptom and may be associated with psychosis, depression, or anxiety; choose pharmacotherapy to reflect this heterogeneity
- Advance any agent to optimal doses (or until side effects emerge) and observe the response before changing medication
- Monitor for side effects (drowsiness, confusion, hypotension, insomnia, etc)
- After 6 months of successful treatment, try to periodically decrease the dose or to gradually eliminate the medication
- Accept symptom reduction (not symptom elimination) as a therapeutic response
- Monitor for drug-drug interactions
- Minimize the use of atypical and conventional antipsychotics; inform patients and caregivers about the increased mortality associated with use of these agents in the elderly.

CYP=cytochrome P450.


TABLE 37

ATYPICAL ANTIPSYCHOTICS FREQUENTLY USED TO TREAT AGITATION AND PSYCHOSIS IN DEMENTIA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-Life</th>
<th>Starting Dose</th>
<th>Range of Usual Treatment</th>
<th>Metabolic Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone (Risperdal)*</td>
<td>20 hrs</td>
<td>0.5 mg/day</td>
<td>1–2 mg/day</td>
<td>CYP 2D6 (major), 3A4 (minor)</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)*</td>
<td>21–54 hrs</td>
<td>5 mg/day</td>
<td>5–15 mg/day</td>
<td>CYP 1A2 (major), 2D6 (minor)</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>6 hrs</td>
<td>25 mg/day</td>
<td>50–100 mg BID</td>
<td>CYP 3A4 (major), 2D6 (minor)</td>
</tr>
<tr>
<td>Aripiprazol (Abilify)*</td>
<td>7.5 hrs</td>
<td>5 mg/day</td>
<td>5–10 mg/day</td>
<td>CYP 2D6 (major), 3A4 (major)</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>12 hrs</td>
<td>12.5 mg</td>
<td>12.5–100 mg</td>
<td>CYP 1A2 (major); minor substrate for 2A6, 2C8, 2C19, 2D6, 3A4</td>
</tr>
</tbody>
</table>

*Intramuscular formulation available

Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration 10 weeks) in these patients revealed a risk of death in the drug-treat patients of between 1.6 and 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was approximately 4.5% compared to a rate of approximately 2.6% in the placebo group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Atypical antipsychotics are not approved for dementia-related psychosis or agitation (from approved product labeling).

CYP=cytochrome P450.

### TABLE 38

**SIDE EFFECTS MOST COMMONLY REPORTED WITH ATYPICAL ANTIPSYCHOTICS**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>Asthenia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, tachycardia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Somnolence, headache, light headedness, dizziness, extrapyramidal symptoms</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Insomnia, anxiety</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation, nausea, dyspepsia, sialorrhea</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Agranulocytosis (clozapine only)</td>
</tr>
</tbody>
</table>


### TABLE 39

**CONVENTIONAL ANTIPSYCHOTICS FREQUENTLY USED TO TREAT AGITATION AND PSYCHOSIS IN DEMENTIA**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-Life (Haldol)</th>
<th>Starting Dose</th>
<th>Range of Usual Treatment</th>
<th>Metabolic Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>20 hours</td>
<td>0.5 mg/day</td>
<td>2–3 mg/day</td>
<td>CYP 2D6 (major), 3A4 (major), 1A2 (minor)</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>33 hours</td>
<td>0.5 mg/day</td>
<td>3–10 mg/day</td>
<td>CYP 2D6 (major)</td>
</tr>
</tbody>
</table>

* Intramuscular formulations available for both agents in this Table. CYP=cytochrome P450.


### TABLE 40

**SIDE EFFECTS MOST COMMONLY REPORTED WITH CONVENTIONAL ANTIPSYCHOTICS**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Side Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, tachycardia, abnormal T waves</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Parkinsonism, akathisia, dystonic reaction, tardive dyskinesia, neuroleptic malignant syndrome, headache, drowsiness, confusion</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Insomnia, depression, agitation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, constipation</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Amenorrhea, galactorrhea</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash, hyperpigmentation, alopecia</td>
</tr>
</tbody>
</table>


### TABLE 41

**ANTIDEPRESSANTS FREQUENTLY USED TO TREAT DEPRESSION IN DEMENTIA**

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Half-Life</th>
<th>Starting Dose</th>
<th>Range of Usual Treatment</th>
<th>Metabolic Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>Escitalopram (Lexapro)</td>
<td>27–32 hours</td>
<td>10 mg/day</td>
<td>10–20 mg/day</td>
<td>CYP 3A4 (major), 2C19 (major)</td>
</tr>
<tr>
<td></td>
<td>Citalopram (Celexa)</td>
<td>24–48 hours</td>
<td>10 mg/day</td>
<td>20–40 mg/day</td>
<td>CYP 3A4 (major), 2C19 (major), 2D6 (minor)</td>
</tr>
<tr>
<td></td>
<td>Sertraline (Zoloft)</td>
<td>26 hours (metabolite - 66 hours)</td>
<td>25 mg/day</td>
<td>50–100 mg/day</td>
<td>CYP 2D6 (major), 2C19 (major), 2B6 (minor), 2C8/9 (minor)</td>
</tr>
<tr>
<td></td>
<td>Paroxetine (Paxil)</td>
<td>21 hours</td>
<td>10 mg/day</td>
<td>20–40 mg/day</td>
<td>CYP 2D6 (major)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine (Prozac)</td>
<td>1–3 days (acute administration), 4–6 days (chronic administration); metabolite 4–16 days</td>
<td>10 mg/day</td>
<td>10–40 mg/day</td>
<td>CYP 2D6 (major), 2C8/9 (major), 1A2 (minor), 2B6 (minor), 2C19 (minor), 2E1 (minor), 3A4 (minor)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Venlafaxine (Effexor)</td>
<td>3–7 hours</td>
<td>25 mg</td>
<td>25–37.5 mg BID</td>
<td>CYP 2D6 (major), 3A4 (major), 2C19 (minor), 2C8/9 (minor)</td>
</tr>
<tr>
<td></td>
<td>Duloxetine (Cymbalta)</td>
<td>12 hours</td>
<td>20 mg</td>
<td>20–30 mg BID</td>
<td>CYP 2D6 (major), 1A2 (major)</td>
</tr>
<tr>
<td>TCAs*</td>
<td>Nortriptyline (Pamelor)</td>
<td>28–31 hours</td>
<td>25 mg</td>
<td>50–150 mg/day</td>
<td>CYP 2D6 (major), 1A2 (minor), 2C19 (minor), 3A4 (minor)</td>
</tr>
<tr>
<td></td>
<td>Desipramine (Norpramin)</td>
<td>7–60 hours</td>
<td>10 mg/day</td>
<td>75–100 mg/day</td>
<td>CYP 2D6 (major), 1A2 (minor)</td>
</tr>
</tbody>
</table>

* TCAs have anticholinergic side effects and should be avoided in the elderly unless patients have proven intolerant of, or unresponsive to, other agents.

SSRIs=selective serotonin reuptake inhibitors; CYP=cytochrome P450; SNRIs=serotonin noradrenaline reuptake inhibitors; TCAs=tricyclic antidepressants.

### TABLE 42

<table>
<thead>
<tr>
<th>Body System</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>Insomnia, somnolence, dizziness, headache, fatigue, tremors</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, diarrhea, weight gain</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Anxiety, agitation</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash</td>
</tr>
</tbody>
</table>


### TABLE 43

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-Life</th>
<th>Starting Dose</th>
<th>Range of usual treatment</th>
<th>Metabolic Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem (Ambien)</td>
<td>2.5 hours</td>
<td>5 mg</td>
<td>5–10 mg/night</td>
<td>CYP 3A4 (major), 1A2 (minor), 2C8/9 (minor), 2C19 (minor), 2D6 (minor)</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>1 hour</td>
<td>5 mg</td>
<td>5–20 mg/night</td>
<td>CYP 3A4 (minor)</td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>1.0–2.6 hours</td>
<td>8 mg</td>
<td>8 mg/night</td>
<td>CYP 1A2 (major), 3A4 (minor), 2C family (minor)</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>6 hours</td>
<td>1 mg</td>
<td>1–2 mg/night</td>
<td>CYP 3A4 (major), 2E1 (minor)</td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td>7–8 hours</td>
<td>50 mg</td>
<td>50–200 mg/night</td>
<td>CYP 3A4 (major), 2D6 (minor)</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>9.5–12.4 hours</td>
<td>15 mg</td>
<td>15–30 mg/night</td>
<td>CYP minor substrate for 2D6, 2C8/9, 2C19, 3A4</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>1.7–5.0 hours</td>
<td>0.0625 mg/night</td>
<td>0.0625–2.5 mg/night</td>
<td>CYP 3A4 (major)</td>
</tr>
</tbody>
</table>

CYP=cytochrome P450.


### TABLE 44

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life</th>
<th>Starting Dose</th>
<th>Range of usual treatment</th>
<th>Metabolic pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>19–50 hours</td>
<td>0.125 mg</td>
<td>0.125–0.5 BID</td>
<td>CYP 3A4 (major)</td>
</tr>
<tr>
<td>Buspirone (Buspar)</td>
<td>2.4 hours</td>
<td>7.5 mg</td>
<td>7.5–15 mg BID</td>
<td>CYP 3A4 (major), 2D6 (minor)</td>
</tr>
</tbody>
</table>


### FIGURE 13

**THERAPEUTIC APPROACH TO PARKINSON’S DISEASE**

- Parkinson’s Disease Diagnosis
- Initial therapy with MAOI, Levodopa/Carbidopa (sustained or immediate release), dopamine agonist
- Add Levodopa/Carbidopa if begun on dopamine agonist; add dopamine agonist if begun on Levodopa/Carbidopa
- Add Entacapone or Tolcapone (Liver Enzyme Monitoring Required with Tolcapone) with each Levodopa Dose

* Steps represent responses to worsening disease.

MAO-I=monoamine oxidase inhibitor.


### FIGURE 14

**THERAPEUTIC APPROACH TO PARKINSON’S DISEASE WITH MOTOR FLUCTUATIONS AND DYKINESIAS**

- Parkinson’s Disease with Off-Time and/or Dyskinesia
  - First Line: Entacapone or Rasagiline; Second Line: Pramipexole or Ropinirol
  - Medical Therapy: Amantadine
  - Surgical Therapy: Deep Brain Stimulation of Subthalamic Nucleus


### FIGURE 15

**THERAPEUTIC APPROACH TO PARKINSON’S DISEASE WITH BEHAVIORAL COMPLICATIONS**

- Parkinson’s Disease with Behavioral Complications
  - Depression
  - Psychosis
  - First Line: SSRI or SNRI
  - Second Line: Tricyclic Antidepressant*
  - First Line: Clozapine†
  - Second Line: Quetiapine

* If TCAs are selected, agents with fewer anticholinergic side effects such as desipramine or nortriptyline should be chosen.

† Use of clozapine required weekly white blood cell counts for the first 6 months, every other week for the second 6 months, and every 4 weeks thereafter.

SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant.

### TABLE 45
AGENTS USED TO TREAT PARKINSON’S DISEASE

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent (Trade Name)</th>
<th>Half-Life (hours)</th>
<th>Initial Dose</th>
<th>Target Dose (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Precursor</td>
<td>Levodopa+Carbidopa (Sinemet, Parcopa)</td>
<td>1–1.5 (levodopa)</td>
<td>1/2 of 25/100 mg TID</td>
<td>Titrate in divided doses to maximum of 200 mg carbidopa and 2,000 mg levodopa daily</td>
</tr>
<tr>
<td></td>
<td>Levodopa+Carbidopa sustained release tablets (Sinemet-SR)</td>
<td>1–1.5 (levodopa)</td>
<td>1 capsule BID</td>
<td>Titrate as needed to maximum of 8 tablets per day</td>
</tr>
<tr>
<td></td>
<td>Levodopa+Carbidopa+Entacapone (Stalevo; 1:4 ratio of levodopa+carbidopa+200 mg entacapone)</td>
<td>1–1.5 (levodopa)</td>
<td>1 table BID</td>
<td>Advance as needed for symptomatic improvement</td>
</tr>
<tr>
<td>Dopamine Agonist</td>
<td>Bromocriptine (Parlodel)</td>
<td>12–15</td>
<td>1.25 mg BID</td>
<td>2.5–5 mg TID</td>
</tr>
<tr>
<td></td>
<td>Pramipexole (Mirapex)</td>
<td>8–12</td>
<td>0.375 mg TID</td>
<td>0.5–1.5 mg TID</td>
</tr>
<tr>
<td></td>
<td>Ropinirole (Requip)</td>
<td>6–8</td>
<td>0.25 mg TID</td>
<td>8 mg TID</td>
</tr>
<tr>
<td></td>
<td>Rotigotine (Neupro) patch</td>
<td>5–7</td>
<td>2 mg patch daily</td>
<td>6 mg patch daily</td>
</tr>
<tr>
<td></td>
<td>Apomorphine injection (Apokyn)</td>
<td>30–60 minutes</td>
<td>0.2 mL (2 mg); administered while patient is in the off state</td>
<td>0.6 mL (6 mg)</td>
</tr>
<tr>
<td>COMT-Inhibitor</td>
<td>Entacapone (Comtan)</td>
<td>Two phases: Phase 1: 0.4–0.7; Phase 2: 2–4</td>
<td>200 mg TID (with levodopa dose)</td>
<td>Maximum of 1,600 mg in divided doses</td>
</tr>
<tr>
<td></td>
<td>Tolcapone (Tasmar)*</td>
<td>2–3</td>
<td>100 mg TID (with levodopa dose)</td>
<td>200 mg TID</td>
</tr>
<tr>
<td>MAO-B Inhibitor</td>
<td>Selegiline (Eldepryl)</td>
<td>10</td>
<td>5 mg with breakfast and lunch</td>
<td>5 mg with breakfast and lunch</td>
</tr>
<tr>
<td></td>
<td>Zydus Selegiline (sublingual formulation) (Zelapar)</td>
<td>10</td>
<td>1.25 mg sublingual before breakfast</td>
<td>2.5 mg sublingual before breakfast</td>
</tr>
<tr>
<td></td>
<td>Rasagiline* (Azilect)</td>
<td>3</td>
<td>0.5 mg TID</td>
<td>1 mg TID</td>
</tr>
<tr>
<td>Dopamine Release Enhancer</td>
<td>Amantadine (Symmetrel)</td>
<td>16±6</td>
<td>100 mg QD</td>
<td>100 mg TID</td>
</tr>
<tr>
<td>Anticholinergic Agents</td>
<td>Benztrapine (Cogentin)</td>
<td>3–24</td>
<td>0.5–1 mg QD</td>
<td>2–3 mg BID</td>
</tr>
<tr>
<td></td>
<td>Trihexyphenidyl (Artane)</td>
<td>4</td>
<td>1 mg TID</td>
<td>6 mg TID</td>
</tr>
</tbody>
</table>

* Tolcapone has been associated with elevated hepatic enzymes and liver enzymes must be monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter.
† Patients on rasagiline must avoid tyramine containing foods and drugs with sympathomimetic amines such as pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine.
‡ Anticholinergics should be avoided in elderly patients and in those with dementia.
SR=sustained release; COMT=Catechol-O-methyltransferase (inhibits metabolism of levodopa); MAO-B= monoamine oxidase B.

TABLE 46
SIDE EFFECTS OF PARKINSON'S DISEASE PHARMACOLOGIC TREATMENTS

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>Hallucinations, delusions, nausea, dizziness, nervousness, orthostatic hypotension; repetitive or impulsive behaviors occur in a minority of patients including dopamine dysregulation syndrome (hedonistic homeostatic dysregulation), hypersexuality, paraphilias, punding</td>
</tr>
<tr>
<td>Dopamine Agonists</td>
<td>Hallucinations, delusions, dyskinesias, somnolence, insomnia, nausea, constipation, diarrhea, dyspepsia; repetitive or impulsive behaviors occur in a minority of patients including pathologic gambling, compulsive eating, hypersexuality</td>
</tr>
<tr>
<td>Levodopa + dopamine agonists</td>
<td>Hallucinations, delusions, dyskinesias, somnolence, insomnia, nausea, constipation, diarrhea, dyspepsia; repetitive or impulsive behaviors may occur in a minority of patients including pathologic gambling, compulsive eating, hypersexuality, paraphilias, punding (specific patients may be predisposed to these behaviors)</td>
</tr>
<tr>
<td>COMT-Inhibitor</td>
<td>Administered with levodopa and the side effects are the same as those seen with levodopa/carbidopa as above; tolcapone has been associated with elevated liver enzymes and these must be monitored regularly (every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter)</td>
</tr>
<tr>
<td>MAO-B Inhibitor</td>
<td>Hallucinations, delusions, insomnia, dreams/nightmares, anxiety, peripheral edema, hypotension, hypertension, anorexia, diarrhea</td>
</tr>
<tr>
<td>Dopamine Release Enhancer (Amanantadine)</td>
<td>Hallucinations, leg edema, livedo reticularis (of legs)</td>
</tr>
<tr>
<td>Anticholinergic Agents</td>
<td>Dry mouth, narrow angle glaucoma, constipation, urinary retention, memory impairment, confusion, hallucinations</td>
</tr>
</tbody>
</table>

COMT=Catechol-O-methyltransferase; MAO-B=monoamine oxidase B.


REFERENCES