RECOGNITION AND TREATMENT OF PSYCHIATRIC DISORDERS:

A PSYCHOPHARMACOLOGY HANDBOOK FOR PRIMARY CARE PHYSICIANS

First Edition

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Under development

Under development

INTRODUCTION

Under development; will include overview on how to use the handbook, format/contents. Will state that the book focuses on psychopharmacology rather than psychotherapy and only adults are considered. Focus is on psychiatric disorders most commonly seen in primary care.

ALZHEIMER'S DISEASE

Alzheimer's Disease (AD) is the most common primary, progressive degenerative dementia in the elderly and the fourth leading cause of death in the United States (Keefover, 1996; Raskind, 1993). At an annual cost of more than $67 billion in the US alone, AD has important public health implications, especially in concert with the unparalleled growth of the aged population (Keefover, 1996).

Epidemiology

Alzheimer's disease afflicts up to 4 million US adults (Keefover, 1996), a figure that may double by the year 2000 (Price et al, 1995). The prevalence of AD clearly increases with advancing age and some estimate that up to 50% of US adults older than 85 years of age have the disorder (Evans et al, 1989). Overall estimates of the incidence of AD (1%/y) are hindered by a lack of reliable data (Keefover, 1996). The presence of AD greatly reduces life expectancy; median survival is 5 to 8 years after diagnosis (Keefover, 1996) but the illness can persist up to 20 years until death (Cohen, 1995). Life expectancy is lower in men with AD than in women with AD and in also those with significantly impaired cognition at the time of diagnosis. Risk factors for AD are shown in Table 1 (Keefover, 1996).

Table 1. Possible risk factors for AD (Keefover, 1996; Sandson et al, 1995)

Risk factor	Comments
Aluminum ingestion	Unresolved; ↑ aluminosilicate concentrations found in NFT and plaques of persons with AD but aluminum inhalation or ingestion (including aluminum-containing antacids) does not produce AD
Apolipoprotein E4	Presence of the E4 allele is a strong risk factor for late-onset AD but not a diagnostic test
Diet	Possible trend toward delayed onset of dementia in vegetarians versus heavy meat eaters
Education level	AD occurs more often in undereducated persons
Estrogen deficiency	Postmenopausal women not using estrogen supplements may be at risk for AD
Family history	Positive family history ↑ risk of AD
Female gender	Unresolved whether females are at greater risk for AD than males
Head injury	Head injury causing loss of consciousness or retrograde amnesia has been associated with ↑ risk of AD in men in later life
Maternal age	Late maternal age may ↑ risk of AD in offspring
Thyroid disease	Unconfirmed association between thyroid disease and AD

See Glossary for abbreviations.

Pathophysiology

Although the cause of AD is unknown, a genetic component is likely (Small, 1996). The primary degenerative central nervous system (CNS)

changes in AD include prominent cerebral atrophy in cortical association areas, neuronal losses, neurofibrillary tangles [NFT], and neuritic or senile plaques. The latter two are hallmark neurohistologic lesions of AD and were first described in the early 1900s by Alois Alzheimer. Because of these degenerative changes, patients with AD have deficits of several neurotransmitters, primarily acetylcholine (ACH), but also of monoamines (eg, dopamine, norepinephrine, serotonin), somatostatin, and gamma aminobutyric acid (GABA). Low ACH levels may be caused by reduced activity of enzymes (eg, choline acetyltransferase [ChAT], acetylcholinesterase) involved in ACH synthesis (Schneider and Tariot, 1994).

Presentation

Insidious memory loss is the hallmark feature of AD (Table 2); short-term memory loss occurs in the early stages of AD and is eventually followed by long-term memory loss (Price et al, 1995; Raskind, 1995).

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Table 2. Typical presentation of AD

- Appears usually after 65 years of age
- Reduced cognitive abilities
  - memory, performance speed, problem-solving skills
- Language disorders (word-finding difficulties, aphasia)
- Altered spatial perceptions, judgment (eg, personal safety)
- Progressive inability to perform or inattentiveness toward activities of daily living and personal hygiene
- Disruptive behavioral changes
  - nonpsychotic (eg, physical and verbal abuse, aggression, agitation, screaming, wandering, uncooperativeness)
  - psychotic (eg hallucinations, simple paranoid delusions)

At least 40% of patients with AD develop disruptive, agitated behavior during the course of the disorder; this behavior may adversely affect cognitive function by interfering with motivation or attentiveness (Raskind, 1993).

Hallucinations and delusions often appear in a patient with AD usually during the early or middle stages of the disorder. In contrast to the more complex, grandiose delusions of schizophrenia, delusions of AD are usually simple, paranoid beliefs related to memory loss. Typical delusions of AD might include perceived theft of money or personal items, a belief that a long-deceased acquaintance is still alive, or a

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belief that one's spouse is an imposter. These differences between delusions of schizophrenia and those of AD may explain why antipsychotic drugs are less effective in the latter disorder.

Depression often coexists with AD and can aggravate simple memory loss. In advanced stages of AD, patients have profound dementia, aphasia, and usually are bedridden, incontinent, and unable to remain alone or in a home setting without constant care.

Diagnosis

Dementia is only one possible diagnosis in an older individual with reduced cognitive function. Other causes of impaired memory include that due to normal aging processes, encephalopathies (eg, from anoxia, head trauma), vascular or multi-infarct dementia, or an acute confusional state related to a metabolic, toxic, or infectious disorder (Sandson et al, 1995). These alternative diagnoses should be ruled out.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) task force has established commonly used diagnostic criteria for possible, probable, or definite AD (McKhann et al, 1984). However, a definitive diagnosis of AD can only be made on autopsy.

To establish progressive deterioration in memory and cognitive skills, the primary care physician must perform a careful patient evaluation, including a detailed family history, medication history, past medical history, and a complete physical, neuropsychologic, and laboratory workup (Table 3). Referral for neuroimaging studies may be useful in selected cases (McKhann et al, 1984; Price et al, 1995; Sandson et al, 1995).

Table 3. Diagnostic approach to the patient with suspected AD (McKhann et al, 1984; Sandson et al, 1995)

Evaluation	Goal	Approach
Medical history	Establish history of progressive memory deterioration and inability to perform tasks.	Interview patient, family, close acquaintances. Obtain detailed family history, medication history (prescription and nonprescription), past medical history (eg, stroke, seizures, head trauma, psychiatric history)
Clinical examination	Document diagnostic inclusion and exclusion criteria	Perform physical examination, mental status testing (eg, MMSE), neurologic testing
Neuropsychological evaluation	Provide additional information on diagnosis of dementia	Recognition Span Test, Boston Naming Test, Wechsler Adult Intelligence Scale, Continuous Performance Test, Gollin Incomplete Pictures Test, Wisconsin Card Sorting Test, Philadelphia Geriatrics Center forms[6]

Table 3 (cont'd). Diagnostic approach to the patient with suspected AD (McKhann et al, 1984; Sandson et al, 1995)

Evaluation	Goal	Approach
Laboratory testing	Enhance diagnostic accuracy	Obtain routine blood, electrolyte, renal, liver, metabolic studies. Also, Vitamin B_{12}, folic acid, thyroid function tests, erythrocyte sedimentation rate, syphilis or HIV (if risk factors present)
Neuroimaging studies	Identify potentially treatable causes of dementia (eg, tumors, abscess, subdural hematoma)	CT or MRI
	Identify ↓ regional glucose metabolism and blood flow in parietal and temporal lobes	PET or SPECT (mainly research tools)

See **Glossary** for abbreviations.

* See McKhann et al, 1984 for more detailed information.

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Screening Tools: In the office setting, the Mini Mental State Examination (MMSE) (Folstein et al, 1975), the Blessed Dementia Scale, (Blessed et al, 1968), or the Short Portable Mental Status Questionnaire (Pfeiffer, 1975) may be used to screen a patient in whom dementia is suspected. On the MMSE, a score of 26 or less is abnormal in a high school graduate and a score of 27 to 30 with evidence of cognitive decline should prompt more detailed neuropsychological testing (Peskind, 1996). More detailed neuropsychologic testing as outlined by the NINCDS-ADRDA (McKhann et al, 1984) should follow if clinical suspicion is raised. Patients with AD will show a reduction of 3 to 4 points/y on the Blessed Memory Concentration Test or a reduction of 2 to 3 points/y on the MMSE (Price et al, 1995).

Referrals

A multidisciplinary approach that addresses medical, social, psychological, and environmental issues is needed not only for the patient's benefit, but also for the family or caregiver's sake (Cohen, 1995; Sky and Grossberg, 1994). Alzheimer's disease extracts a substantial burden on the patient's family and caregivers; these individuals often become the "second patients." It has been estimated that up to 80% of spousal caregivers experience clinically significant symptoms of anxiety or depression as well as more frequent medical illness associated with chronic stress during the course of the patient's disorder (Cohen, 1995). Thus, the primary care physician

plays an important role in referring family members or caregivers to local support services (see **Glossary**) that may alleviate some of these stresses. For example, having the patient attend an "adult day care" setting once or twice weekly may provide the caregiver with sorely needed personal time.

ANXIETY DISORDERS

Panic Disorder

Agoraphobia

Obsessive-Compulsive Disorder (OCD)

Posttraumatic Stress Disorder (PTSD)

Generalized Anxiety Disorder (GAD)

Social Phobia

EATING DISORDERS

Anorexia Nervosa (with subtypes)

Bulimia Nervosa (with subtypes)

MOOD DISORDERS

Depressive Disorders

Mania

Bipolar Disorder

SCHIZOPHRENIA

SLEEP DISORDERS

Primary Insomnia

SOMATIZATION DISORDER

SUBSTANCE USE/ABUSE DISORDERS

Cocaine Abuse

Alcohol Abuse

Opiate/Opioid Abuse

Before prescribing any drug to a patient, readers are encouraged to consult a current and more complete source of prescribing information, such as the *Physician's Desk Reference* (1997), *AHFS Drug Information* (1997), or other similar source. Unless otherwise cited, information in this chapter has been compiled from these and similar secondary resources.

ANTIDEPRESSANTS

BENZODIAZEPINES

NONBENZODIAZEPINE ANXIOLYTICS

ANTIPSYCHOTICS

Traditional

Atypical (olanzapine, risperidone, clozapine)

DRUGS FOR EXTRAPYRAMIDAL SYMPTOMS

COGNITIVE ENHANCERS

Ergoloid Mesylates

Ergoloid mesylates (Hydergine,® Sandoz Pharmaceuticals Corporation; dihydroergotoxine, dihydrogenated ergot alkaloids) are indicated for symptomatic relief of age-related mental capacity decline (in persons >60 years of age), such as that which might occur in AD (Table 4).

Table 4. Overview of ergoloid mesylate therapy

Feature	Comments
Mechanism	Unknown , may ↑ cerebral blood flow
Pharmacokinetics	Rapid oral absorption, extensive hepatic metabolism, drug interactions not reported
Efficacy	Modest ↑ in cognition
Safety	Transient nausea, GI disturbances
Dosing	Start with 1 mg TID; titrate up to 12 mg/d in divided doses; response usually requires ≥ 6 mg/d for 6 months

Mechanism: Ergoloid mesylates may increase cerebral blood flow although the exact mechanism is unknown. Unlike natural ergot alkaloids, this product does not have vasoconstrictive properties.

Pharmacokinetics: Ergoloid mesylates are rapidly absorbed in the gastrointestinal (GI) tract after oral administration and are quickly and extensively metabolized in the liver. Drug interactions have not been reported.

Efficacy: In 12-week studies using the Sandoz Clinical Assessment Geriatric Rating Scale, modest but statistically significant improvements have been observed in mental alertness, confusion, orientation, emotional lability, recent memory, self-care, depression, anxiety, cooperation, sociability, appetite, dizziness, fatigue, and overall improvement in clinical status.

Safety: Ergoloid mesylates are generally well tolerated but can cause transient nausea or other GI disturbances.

Warnings/Precautions: Reversible and potentially treatable causes of dementia should be ruled out before ergoloid mesylate therapy is prescribed. Periodically reevaluate any perceived benefit of therapy to the patient.

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Dosing Guidelines: The usual starting dose is 1 mg TID; doses may be increased up to 12 mg/d (divided). Results may not be detected for 3 or 4 weeks and treatment with a minimal dose of 6 mg/d may be needed for at least 6 months to detect any benefit. This product is available in tablet, liquid, and liquid capsule formulations.

Cholinesterase Inhibitors

Because of the known deficit of cortical ACH in persons with AD (ie, the cholinergic hypothesis), drug development research has focused on agents that will restore levels of this neurotransmitter either directly (ie, cholinergic agonists) or indirectly (ie, cholinesterase inhibitors). In 1993, the first cholinesterase inhibitor, tacrine (Cognex®, Parke-Davis; tetrahydroaminoacridine, THA), was approved for the treatment of mild to moderate cognitive impairment of AD. Although tacrine is only modestly effective and carries a relatively significant adverse effect profile, it may offer respite (albeit temporary) for selected patients with AD (Table 5).

Table 5. Overview of tacrine therapy

Feature	Comments
Mechanism	↑ ACH concentrations via nonspecific inhibition of brain cholinesterase
Pharmacokinetics	Rapid oral absorption, extensive hepatic metabolism
Efficacy	Minimal but significant improvement in ADAS cog, and global impressions in trials lasting ≤30 weeks. High rate of withdrawal due to side effects
Safety	GI distress, myalgia, ataxia, anorexia (dose-related). ↑ LFTs require extensive and prolonged monitoring
Dosing	Start with 10 mg QID (empty stomach, between meals) for ≥ 6 weeks; ↑ to 20 mg QID if LFTs normal and tolerance good. Discontinue if no response in 6 months.

Mechanism: Tacrine is a centrally active, reversible, nonspecific cholinesterase inhibitor that increases ACH concentrations by minimizing or preventing its breakdown after ACH is released from functioning cholinergic neurons. Tacrine does not change the natural, progressive course of AD and it is relatively ineffective in advanced stages of AD when few cholinergic neurons remain viable.

Pharmacokinetics: Taken orally, tacrine is rapidly absorbed and has a duration of action of 4 to 6 hours. Food does not affect tacrine absorption if the drug is taken at least 1 hour before meals (ie, on an empty stomach, between meals if possible). Tacrine is extensively metabolized by hepatic cytochrome P450 enzymes, primarily CYPIA2 (see Table 6) but not CYPIID6. Advanced age and renal disease have no clinically important influence on tacrine elimination. However, liver disease may reduce the elimination of tacrine and its metabolites. Tacrine serum concentrations are 50% higher in females than in males and about 33% lower in smokers than in nonsmokers.

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Table 6. Drug and food interactions with tacrine

Substance	Effect of tacrine
Anticholinergics	May interfere with activity of anticholinergics
Cholinergic agonists (eg, bethanechol), cholinesterase inhibitors (eg, physostigmine), succinylcholine	May have a synergistic effect with these drugs
Theophylline	Prolongs elimination of theophylline and ↑ plasma concentrations. Monitor theophylline concentrations and ↓ dose accordingly
Cimetidine	Cimetidine ↑ concentrations of tacrine by inhibiting its metabolism
Food	Food ↓ plasma tacrine levels by one-third; take tacrine between meals if possible

Efficacy: Tacrine has been shown to be effective in placebo-controlled trials in patients with mild to moderate probable AD. In two key studies of up to 30 weeks' duration, most patients taking tacrine (20 to 160 mg/d) showed minimal but statistically significant improvement in the Alzheimer's Disease Assessment Scale (ADAS cog; Rosen et al, 1984)

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and clinician's global impression measures (Davis et al, 1992; Farlow et al, 1992; Knapp et al, 1994). The ADAS cog examines memory attention, reason, language, and praxis. However, there were a wide range of responses and a substantial number of patients were unable to tolerate tacrine therapy and withdrew from the trials. Importantly, the beneficial effects of tacrine tended to diminish with time, even in patients who experienced an initial beneficial response

Safety: Tacrine has an extensive adverse effect profile. Common adverse events are nausea, vomiting, diarrhea, dyspepsia, and other GI symptoms, elevated LFTs (see **Warnings/Precautions**), myalgia, anorexia, and ataxia. Except for LFT abnormalities and myalgia, these effects are dose related. The safety and efficacy of tacrine have not been tested in demented children; tacrine should not be given to pregnant or lactating women (Pregnancy Category C; see **Glossary**).

Warnings/Precautions: Use tacrine carefully in patients with current or past liver dysfunction (ie, elevated LFTs). Tacrine commonly increases LFTs in persons without a prior history of liver disease and may cause clinically significant sequelae (eg, jaundice). However, prompt withdrawal of tacrine in such circumstances will only rarely result in liver injury and LFTs should return to normal limits within 4 to 6 weeks. Patients who develop clinical jaundice (total bilirubin >3 mg/dL) or those with clinical signs or symptoms of hypersensitivity

with elevated LFTs should permanently stop tacrine therapy (see **Dosing Guidelines** below and prescribing information for LFT monitoring advice). Tacrine stimulates cholinergic activity and should be used cautiously in selected patients (Table 7).

Table 7. Cautions related to cholinergic activity of tacrine

Tacrine may cause:	**Use with caution in:**
Bradycardia	"Sick sinus syndrome," conduction abnormalities, bradyarrhytmia
↑ Gastric acid secretion	Patients at risk for ulcers (eg, history of ulcer disease, current NSAID users). Monitor for active or occult GI bleeding
Bladder outflow obstruction	Bladder dysfunction
Seizures	Limited potential; seizures also may be due to AD itself
Asthma	History of asthma

Dosing Guidelines: Prescribe tacrine only when a caregiver can monitor patient compliance with drug administration at regular intervals.

Usual starting dose: 10 mg QID; do not increase dose for at least 6 weeks to observe potential delayed LFT elevation. Tacrine is available in 10-, 20-, 30-, and 40-mg capsules.

Dose titration: Increase to 20 mg QID if LFTs are normal and patient is tolerating therapy. Higher doses (eg, 30 to 40 mg QID) may be given at 6-week intervals unless side effects appear. It may take up to 6 months to see any benefit and if none is seen within this time, tacrine should be discontinued.

LFTs: After tacrine therapy is initiated, monitor LFTs every other week for at least the first 16 weeks, monthly for 2 months, every 3 months subsequently. The dose of tacrine should be reduced by 40 mg/d if LFTs are between three and five times the upper limit of normal (ULN). Tacrine should be discontinued if LFTs are greater than five times ULN. If treatment is stopped and restarted for any reason, resume weekly monitoring as described above.

Cholinergic Agonists

Although theoretically appealing, no commercially available drugs of this class have provided clinical utility in patients with AD. Although patients with AD taking bethanechol have shown some improvement on the MMSE, the drug must be given intracerebroventricularly because it does not cross the blood-brain barrier. Other oral agents (eg, pilocarpine) have been ineffective or have required frequent intravenous administration (eg, arecoline). A number of newer orally active cholinergic agonists are under study (Schneider and Tariot, 1994).

Miscellaneous

Selegiline (Eldepryl,® Somerset Pharmaceuticals, Inc; formerly known as L-deprenyl) is currently indicated for adjunctive use in Parkinson's disease to prolong the efficacy of levodopa. However, this drug has been shown to be effective in improving cognitive function and disturbed behavior (eg, anxiety, cooperation, agitation) in patients with AD (Schneider and Tariot, 1994) (Table 8).

Table 8. Overview of selegiline therapy

Feature	Comments
Mechanism	Irreversible selective inhibition of MAO-B at low doses (≤10 mg/d)
Pharmacokinetics	Orally absorbed, extensive hepatic metabolism
Efficacy	↑ cognition and behavior
Safety	Nausea, dizziness, abdominal pain confusion, hallucinations headache, dry mouth, dyskinesia
Dosing	5 mg BID maximum. Higher doses ↑ side effects and do not improve efficacy

Mechanism: Selegiline is an irreversible and, at low doses (ie, ≤10 mg/d), selective inhibitor of monoamine oxidase type B (MAO-B). At

higher doses, the drug loses its selectivity and also inhibits MAO-A. Monoamine oxidase is responsible for the breakdown of dopamine, serotonin, and norepinephrine and the B type is found primarily in the brain. Selegiline also may increase dopaminergic activity by other unknown mechanisms. Emerging evidence indicates that selegiline may retard the progression of AD by reducing oxidative stress in neurons (Schneider and Tariot, 1994).

Pharmacokinetics: The bioavailability of selegiline increases up to four times when the drug is taken with food. Selegiline is extensively metabolized in the liver and one metabolite has clinical activity. Data are not available regarding the pharmacokinetic fate of selegiline or its metabolite in patients with renal or hepatic impairment. It is not known if selegiline is excreted in breast milk.

Efficacy: Results of several randomized, placebo-controlled trials indicate that selegiline (10 mg/d) appears to impart beneficial effects on cognition and behavior in patients with AD (Schneider et al, 1994). Additional trials are needed to confirm these findings. Whether the benefit of selegiline is related to increased MAO-B activity that has been reported in AD or related to improvement in mood is not clear.

Safety: Safety data from controlled clinical trials is limited but nausea, dizziness, abdominal pain, confusion, hallucinations, dry mouth,

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vivid dreams, dyskinesia, and headache have been reported. Selegiline has not been studied in children. Selegiline is rated as Pregnancy Category C (see **Glossary**).

Warnings/Precautions/Drug Interactions: Do not increase the dose selegiline higher than 10 mg/d. CNS toxicity (including hyperpyrexia, severe agitation, hallucinations, and death) has occurred in some patients taking selegiline with TCAs, SSRIs, or meperidine. Hypertensive crises have occurred in patients taking selegiline and the sympathomimetic agent, ephedrine.

Dosing Guidelines: The dose of selegiline is 5 mg administered BID, with breakfast and lunch. Higher doses are not more effective and should be avoided to prevent side effects. In trials of AD patients, any clinical benefit was evident within a few weeks.

SEDATIVE-HYPNOTICS

STIMULANTS

OVERVIEW OF DRUG THERAPY: GENERAL PRINCIPLES

Elderly

Pregnancy/Lactation (see **Glossary** for FDA definitions)

TREATMENT ALGORITHMS FOR COMMON PSYCHIATRIC DISORDERS

Alzheimer's Disease

Because AD is a chronic, progressive disorder, by necessity, treatment approaches must be continually customized and adjusted according to the patient's current situation. A multidisciplinary approach should involve both nonpharmacologic and pharmacologic avenues for the patient with AD and his or her family (Figure 1). Nonpharmacologic approaches include behavioral counseling (for patients and caregivers) and home safety evaluation (eg, providing living arrangements on a single level of the home to eliminate need to use stairs, enhance lighting in dark hallways to reduce disorientation, lower hot water temperature, etc).

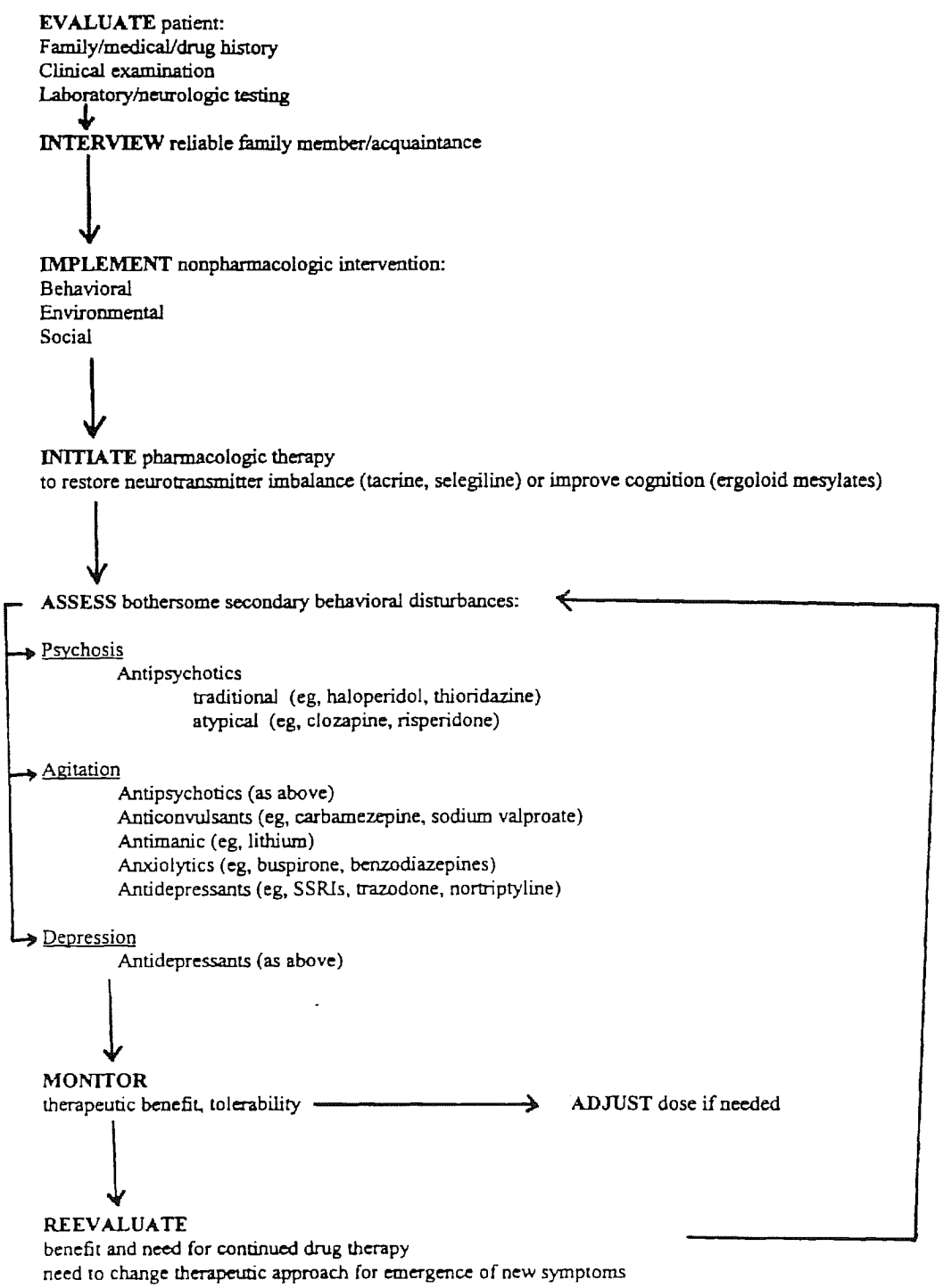

Figure 1. Treatment approach to the patient with AD.

Pharmacotherapy cannot delay or prevent the onset of AD but can be directed at restoring primary underlying neurotransmitter deficits (ie, low central ACH levels). Currently, only tacrine (see Page 19) is indicated in the US for the treatment of the dementia of AD. Ergoloid mesylates (see Page 18) have been used in elderly demented patients but with little clinical success. A number of new compounds are actively being studied (Schneider and Tariot, 1994; Schneider, 1996).

Pharmacotherapy for patients with AD also can be directed at managing secondary behavioral disturbances such as aggression or agitation, depression, or psychosis (Tables 9 and 10) (Raskind, 1995).

Table 9. Secondary behavioral symptoms of AD and the expected response to drug therapy (Sky and Grossberg, 1994)

More likely to respond:	Nonspecific hyperactivity, physical or verbal agitation, classic psychoses or delusions, depressive symptoms, hallucinations
Less likely to respond:	Wandering, public disrobing, hoarding or hiding objects and possessions, repetitive questioning, social inappropriateness

Antipsychotics: Data supporting the use of antipsychotics and antidepressants in patients with AD are limited; much of the data have been extrapolated from studies in younger, demented patients. More trials are needed in elderly patients with strictly defined AD.

Antipsychotics have demonstrated limited efficacy and only a marginal benefit over placebo in AD (Table 10) (Raskind, 1995; Schneider et al, 1990). According to a meta-analysis, no antipsychotic drug offers substantial clinical advantage over another. Antipsychotics are most effective for managing classic psychotic symptoms (eg, grandiose, complex delusions) and less effective in patients who are not agitated, hyperactive, or not experiencing hallucinations or delusions (Raskind, 1993).

Table 10. Pharmacotherapy of behavioral disturbances in patients with AD (Raskind, 1993; Schneider and Tariot, 1994; Sky and Grossberg, 1994; Tariot, 1996)

Drug class	Behavioral features	Typical regimen	Cautions	Comments
Antipsychotic	Symptoms resembling classic psychosis (eg, hyperactivity, grandiose or complex hallucinations, delusions)	Haloperidol 1 mg, thioridazine 20 mg; ↑ dose every 3 days as tolerated until therapeutic effect. Divide higher doses (eg, haloperidol up to 4.6 mg/d or thioridazine up to 150 mg/d) BID or TID. Discontinue (taper) regimen after 3 months to avoid long-term drug exposure and EPS	EPS more common with high-potency drugs (eg, haloperidol) whereas anticholinergic effects (eg, urinary retention, constipation, dry mouth, blurry vision, sedation, orthostatic hypotension, delirium) more common with low-potency drugs (eg, thioridazine)	Only marginal benefit vs placebo. Most effective in those with classic psychotic symptoms. Excess sedation and EPS limit clinical utility. Emerging data with clozapine and risperidone.

Serotoninergic	Symptoms resembling classic psychosis (eg, hyperactivity, hallucinations, delusions	Trazodone 25 to 400 mg/d (divided) Buspirone 10 to 45 mg/d (divided)	Trazodone: orthostatic hypotension, sedation Buspirone: dizziness, sedation, headache	Uncontrolled, anecdotal data
Benzodiazepines	Anxiety, agitation, wandering, restlessness	Use low dose of a short- or intermediate-acting agent with inactive metabolites (eg, oxazepam 20 to 80 mg/d, lorazepam, 1 to 1.5 mg/d)	Tolerance or dependence with chronic use, ataxia, sedation, impaired cognition, confusion	No large, well controlled studies

Antimanic drugs	Violent behavior, impulsiveness	Carbamezepine 50 to 100 mg BID (up to 1000 mg/d maintenance) Sodium valproate plasma levels of 30 to 90 µg/mL reported beneficial Lithium 250 to 1200 mg/d	Carbamezepine: sedation, ataxia, leukopenia, skin rash, hepatotoxicity Lithium: EPS, confusion, ataxia	Controlled data needed; therapeutic serum level monitoring must be implemented
Antidepressants	Apathy, sleep or appetite changes, psychomotor agitation or retardation	Select agent with low anticholinergic activity (eg, SSRI, trazodone, secondary amine)		Very limited controlled clinical trial data

β Blockers	Agitation, hostility	Propranolol 40 to 520 mg/d (divided) Pindolol 60 to 100 mg/d (divided)	Use with caution in heart failure, obstructive pulmonary disease, asthma, diabetes, hyperthyroidism; drug interactions common	

Because functional improvements are often limited by excess sedation and substantial EPS, clinicians should consider the impact of drug therapy on the quality of life of the AD patient and their caregivers. If the patient and caregiver can tolerate certain disruptive behavior, antipsychotic drug therapy could be withheld, at least temporarily. On the other hand, however, some evidence indicates that psychotic symptoms may be associated with faster cognitive deterioration (Raskind, 1995). Thus, outcome trials are needed to determine usefulness of antipsychotic drugs in patients with AD.

Antidepressants: Antidepressants have not been well studied in depressed patients with AD and the response to placebo is very high (Table 10) (Alexopoulos, 1996). Thus, early "response" to an antidepressant may forecast an early "relapse." These drugs may improve mood or disturbed sleep-wake cycles but have no effect on cognitive functioning. Clinicians should select a low dose of an antidepressant with few anticholinergic properties such as an SSRI, a secondary amine (eg, nortriptyline, desipramine) and increase the dose gradually. If improvement is not noted, select another agent. Some evidence indicates that plasma levels considered therapeutic in nondemented depressed individuals may not apply to demented depressed patients (Alexopoulos, 1996).

MENTAL HEALTH ORGANIZATIONS

Alzheimer's Disease (Cohen, 1995)

Alzheimer's Association (AA)

70 E Lake Street, Chicago, IL 60601

TEL: 312-853-3060 or 800-272-3900

National organization with extensive family-oriented information and newsletter. Local chapters are an excellent resource for information on community services (eg, adult day care, respite programs).

American Association of Retired Persons (AARP)

TEL: 800-424-3410

Provides literature on services and programs for older adults.

Area Agency on Aging

TEL: Check local listing for nearest Area Agency on Aging.

Division of the US Department of Health and Human Services; coordinates a large network of offices on aging to provide information and referrals.

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Alzheimer's Disease Education and Referral Program (ADEAR)

TEL: 800-438-4380.

Sponsored by the National Institute on Aging. ADEAR performs free literature searches for clinicians and researchers on AD.

Alzheimer's Disease Centers (ADC)

Offers diagnosis and management services (costs are variable), information about AD and local resources, opportunities to participate in drug trials. Contact ADEAR (above) for nearest center.

PATIENT ADVOCACY GROUPS

PUBLICATIONS

INTERNET RESOURCES

ACH: acetylcholine.

AD: Alzheimer's disease.

ADAS cog:

BID: twice daily.

ChAT: choline acetyltransferase.

CNS: central nervous system.

CT: computed tomography.

Cytochrome P450 system (CYP450): Proteins that catalyze oxidative drug metabolism. Many families and subfamilies of isoenzymes. Cytochromes (CYP) IA2, IIC, IID6, and IIIA4 are relevant to metabolism of many psychotherapeutic agents and clinically important drug interactions.

EPS: Extrapyramidal side effects; common with antipsychotic therapy. Includes acute dystonic reactions (eg, facial grimacing, oculogyric crisis), akathisia (ie, subjective feeling of restlessness), pseudoparkinson features (eg, slowed movement, masked facies, rigidity, resting tremor) and tardive dyskinesia (ie, irregular facial movements). EPS are treatable with antiparkinsonian drugs.

GABA: gamma aminobutyric acid.

GI: gastrointestinal.

HIV: human immunodeficiency virus.

LFTs: liver function tests such as alanine aminotransferase (ALT [formerly SGPT]), aspartate aminotransferase (AST [formerly SGOT]), gamma-glutamyl transpeptidase (GGT), bilirubin.

MAOI: monoamine oxidase inhibitor.

MMSE: Mini Mental State Examination: a short (<10 minutes to administer), structured (11 questions) clinician-administered examination of cognitive aspects of mental function (Folstein et al, 1975). Good for initial and serial measurement of mental function; reliable over time.

MRI: magnetic resonance imaging.

Neuritic plaques: also called senile plaques. Like NFT, a hallmark neurohistologic feature of AD. Neuritic plaques have a central core of insoluble β amyloid protein surrounded by distended and abnormal dendrites and small axons.

NFT: neurofibrillary tangles. A neurohistologic feature of AD consisting of filament bundles in cell bodies, axons, dendrites found in the cerebral cortex and hippocampus. NFT density closely correlated with degree of cognitive impairment.

NSAID: nonsteroidal anti-inflammatory drug (eg, ibuprofen, indomethacin, naproxen, etc).

PET: positron emission tomography.

Pregnancy Categories: The Food and Drug Administration has established five categories for classifying drugs for use during pregnancy.

Category A: Adequate studies in pregnant women have not demonstrated fetal risk in the first trimester and there is no evidence of risk in later trimesters.

Category B: No fetal risk in animal studies but no adequate studies in pregnant women. OR, animal studies have shown adverse effect but adequate studies in pregnant women have not demonstrated fetal risk during the first trimester and no evidence of risk in later trimesters.

Category C: No adverse effect in animal studies but no adequate studies in humans. Benefits from use of the drug by pregnant woman may be acceptable despite these risks. Or, no animal reproduction studies and no adequate studies in humans.

Category D: Evidence of human fetal risk but potential benefits from the drug in a pregnant women may be acceptable despite these risks.

Category X: Studies in animals or humans demonstrate fetal abnormalities or evidence of fetal risk; the risk of use clearly outweighs any possible benefit.

QID: four times daily.

SPECT: single positron emission computed tomography.

SSRI: selective serotonin reuptake inhibitor. Class of antidepressants includes fluoxetine, paroxetine, sertraline.

TCA: tricyclic antidepressant.

TID: three times daily.

Alexopoulos GS. The treatment of depressed demented patients. *J Clin Psychiatry*. 1996;57(suppl 14):14-20.

American Hospital Formulary Service (AHFS). *AHFS Drug Information*. Bethesda, MD: American Society of Health Systems Pharmacists; 1996.

Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114:797-811.

Cohen GD. Management of Alzheimer's disease. *Adv Intern Med*. 1995;40:31-67.

Davis KL, Thal LJ, Gamzu ER, et al, for the Tacrine Collaborative Study Group. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. *N Engl J Med*. 1992;327:1253-1259.

Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA*. 1989;262:2551-2556.

Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J, for the Tacrine Study Group. A controlled trial of tacrine in Alzheimer's disease. *JAMA*. 1992;268:2523-2529.

Folstein M, Folstein S, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.

Keefover RW. The clinical epidemiology of Alzheimer's disease. *Neurol Clin*. 1996;14:337-351.

Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI, for the Tacrine Study Group. A 30-week, randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. *JAMA*. 1994;271:985-991.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984;34:939-944.

Peskind ER. Question and answer session, In: Clinical developments in Alzheimer's disease. *J Clin Psychiatry.* 1996;57(suppl 14):39-44.

Pfeiffer E. A short, portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc.* 1975;23:433-441.

Physicians' Desk Reference. 51st ed. Montvale, NJ: Medical Economics Company, Inc; 1997.

Price DL, Walker LC, Martin LJ, Borchelt DR, Wong PC, Sisodia SS. Biology of Alzheimer's disease and animal models. In: *Textbook of Psychopharmacology.* Washington, DC: American Psychiatric Press Inc; 1995;523-535.

Raskind MA. Treatment of Alzheimer's disease and other dementias. In: *Textbook of Psychopharmacology.* Washington, DC: American Psychiatric Press Inc; 1995;657-667.

Raskind MA. Management of late-life depression and the noncognitive behavioral disturbances of Alzheimer's disease. *Psych Clin North Am.* 1993;16:815-827.

PAR000011040

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.

Sandson TA, Sperling RA, Price BH. Alzheimer's disease: an update. *Compr Ther*. 1995;21:480-485.

Schneider LS. New therapeutic approaches to Alzheimer's disease. *J Clin Psychiatry*. 1996;57(suppl 14):30-36.

Schneider LS, Tariot PN. Emerging drugs for Alzheimer's disease. Mechanisms of action and prospects for cognitive-enhancing medications. *Med Clin North Am*. 1994;78:911-934.

Schneider LS, Tariot PN, Goldstein B. Therapy with *l*-deprenyl (selegiline) and relation to abuse liability. *Clin Pharmacol Ther* 1994;56:750-756.

Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc*. 1990;38:553-563.

Sky AJ, Grossberg GT. The use of psychotropic medication in the management of problem behaviors in the patient with Alzheimer's disease. *Med Clin North Am*. 1994;78:811-822.

Small GW. Neuroimaging and genetic assessment for early detection of Alzheimer's disease. *J Clin Psychiatry*. 1996;57(suppl 14):9-13.

Tariot PN. Treatment strategies for agitation and psychosis in dementia. *J Clin Psychiatry*. 1996;57(suppl 14):21-29.

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OPTIONAL; need decision regarding its inclusion after review of Draft I.