

# Psychopharmacology of Noncognitive Abnormal Behaviors in Alzheimer's Disease

Murray A. Raskind, M.D.

Disruptive agitation and psychotic symptoms are important problems in the management of Alzheimer's disease and are major determinants of nursing home placement. This article reviews interpretable, placebo-controlled studies of psychopharmacologic approaches to the treatment of these "noncognitive" psychiatric and behavioral problems. Clinical trials of antipsychotic drugs demonstrate modest efficacy for psychosis and agitation, but adverse effects are common. Trials of serotonin selective reuptake inhibitors suggest they may be effective for emotional disturbances complicating Alzheimer's disease. Trials of drugs that enhance central cholinergic activity (certain cholinesterase inhibitors and selective M<sub>1</sub> muscarinic cholinergic agonists) demonstrate positive effects on both cognitive deficits and noncognitive psychiatric and behavioral problems. Further clinical studies are needed to provide guidelines for the management of noncognitive psychiatric and behavioral problems in Alzheimer's disease.

(*J Clin Psychiatry* 1998;59[suppl 9]:28-32)

Since the original description of Alzheimer's disease in 1907,<sup>1</sup> it has been recognized that so-called "noncognitive" behavioral abnormalities such as disruptive agitation and psychotic symptoms are major clinical problems in this disease. Although cognitive and functional impairments are central to Alzheimer's disease, disruptive agitation and psychotic symptoms may be the most important determinants of eventual placement in long-term care.<sup>2</sup> These noncognitive problems become more common as Alzheimer's disease progresses.<sup>3</sup>

Although the use of psychotropic medications for the management of noncognitive psychiatric and behavioral problems in Alzheimer's disease is widespread,<sup>4</sup> the number of interpretable, placebo-controlled studies of psychotropic medications in the psychiatrically and behaviorally disturbed patient with Alzheimer's disease remains remarkably small. However, interest in this important area is growing, and several recent studies extend our limited database. Furthermore, certain drugs developed for cognitive enhancement in Alzheimer's disease appear to possess positive effects on noncognitive behavioral problems in

this disorder.<sup>5,6</sup> This review will focus on interpretable, placebo-controlled trials of antipsychotic drugs, serotonin selective reuptake inhibitor (SSRI) antidepressant drugs, and drugs that enhance brain cholinergic activity. Other classes of psychotropic medications with sedative, anti-anxiety, or mood-stabilizing activity have been reported anecdotally to improve noncognitive problem behaviors in Alzheimer's disease.<sup>4</sup> Because of the demonstrated therapeutic effect of placebo, even in severely cognitively impaired persons with Alzheimer's disease,<sup>7</sup> the clinician is cautioned to use discretion when evaluating enthusiastic claims of efficacy in anecdotal reports derived from uncontrolled studies.

## ANTIPSYCHOTIC DRUGS

### Typical Antipsychotics

Antipsychotic drugs have been widely prescribed to patients with Alzheimer's disease for noncognitive psychiatric and behavioral problems almost since their introduction. Despite this widespread use, only a handful of trials of antipsychotic drugs in patients with Alzheimer's disease are available that provide criteria-based diagnostic assessment and a placebo-controlled design. In these trials, indications for inclusion were usually disruptive, agitated behaviors (e.g., uncooperativeness with necessary care, motoric hyperactivity, verbal or physical aggression), psychotic symptoms (e.g., delusions, auditory hallucinations), or both. Because these 2 categories of noncognitive abnormal behaviors often appear linked, attempting to separate patients with psychotic signs and symptoms and those with nonpsychotic disruptive abnormal behaviors may not be possible or even preferable.

---

*From the Veteran's Administration Puget Sound Health Care System, Mental Health Service, and the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle.*

*Presented at the closed symposium "New Strategies for Treating Alzheimer's Disease," held August 2, 1997, Chicago, Ill., which was supported by an unrestricted educational grant from Bayer Corporation.*

*Reprint requests to: Murray A. Raskind, M.D., Veteran's Administration Puget Sound Health Care System, Mental Health Service (116), 1660 S. Columbian Way, Seattle, WA 98108.*

Because antipsychotic drugs have been highly effective for the amelioration of psychotic symptoms in nondemented persons suffering from schizophrenia, it is not surprising that antipsychotic drugs have been widely prescribed to treat psychotic symptoms and related behavioral problems in Alzheimer's disease.<sup>8</sup> Why then are the antipsychotic drugs not as effective for the behaviorally disturbed patient with Alzheimer's disease as they are for young persons with schizophrenia? Part of the answer may lie in phenomenological differences between the psychotic features of Alzheimer's disease and the psychotic features of schizophrenia. In Alzheimer's disease, the most common delusions are relatively unelaborated paranoid beliefs, such as that money or property has been stolen. Often, these delusions can be traced to the forgetfulness of the patient with Alzheimer's disease concerning misplaced objects or objects long since discarded. Complex and bizarre delusions such as those typical of schizophrenia are uncommon in Alzheimer's disease. Whether these phenomenological differences reflect underlying neurobiological differences between the pathophysiology of delusions in Alzheimer's disease and schizophrenia remains unknown.

Several placebo-controlled, antipsychotic drug trials performed in elderly dementia patients have used explicit diagnostic criteria for Alzheimer's disease and multi-infarct dementia, and have required that psychotic symptoms and disruptive psychiatric and behavioral problems be present as target symptoms. These studies have been carried out in outpatients, in patients in a state hospital setting, and in patients in typical nursing homes. In an outpatient study,<sup>9</sup> haloperidol was compared with placebo in 9 persons with Alzheimer's disease complicated by both clear psychotic behaviors (delusions and hallucinations) and disruptive problem behaviors. In this crossover design study, haloperidol was significantly superior to placebo for target symptoms. However, deteriorated cognitive function and extrapyramidal adverse effects limited improvement in quality of life achieved by subjects whose psychotic and agitated symptoms had improved during haloperidol therapy. In a study performed at a large state psychiatric hospital, haloperidol, loxapine, and placebo were compared in 64 older subjects (mean age = 73 years) who had Alzheimer's disease and multi-infarct dementia.<sup>10</sup> Both haloperidol and loxapine were more effective than placebo for the target symptoms of suspiciousness, hallucinations, excitement, hostility, and uncooperativeness. Global ratings of improvement favored active medication, but only modestly. Thirty-two percent of loxapine patients and 35% of haloperidol patients were rated as moderately or markedly improved compared with 9% of patients receiving placebo.

Two studies have been performed in typical community nursing home settings. In the first, subjects met criteria for either Alzheimer's disease or multi-infarct dementia com-

plicated by psychotic and/or disruptive problem behaviors, and were of advanced old age (mean age = 83 years).<sup>7</sup> Both thioridazine and loxapine were significantly more effective than placebo on the Brief Psychiatric Rating Scale<sup>11</sup> items of "excitement" and "uncooperativeness." Although the items "suspiciousness" and "hostility" improved in active drug conditions, these 2 important symptoms also improved in the placebo condition. Only one third of these very elderly dementia patients randomly assigned to active medication were rated as either moderately or markedly improved on a clinical global impression scale. That both "suspiciousness" and "hostility" significantly improved with placebo underlines the importance of including a placebo condition in studies of therapeutic response to behaviorally active drugs in dementia patients. It also demonstrates the ability of dementia patients to respond to a placebo condition despite the presence of substantial cognitive impairment.

A second study comparing an antipsychotic drug to placebo in agitated nursing home patients with dementia recently has been reported.<sup>12</sup> This trial also was conducted in a typical community nursing home facility in very elderly patients (mean age = 85 years). Thiothixene was compared with placebo for disruptive problem behaviors including physical aggression (hitting, kicking, and pushing), physical nonaggressive agitation (pacing and repetitive mannerisms), and verbal aggression (screaming and cursing). The presence and nature of psychotic delusions and hallucinations were not specified in this study. Thiothixene was more effective than placebo in this 11-week, parallel-design study, but differences between groups did not become apparent until 6 weeks of treatment had been completed. The positive effects of thiothixene appeared to persist for 3 to 6 weeks after drug discontinuation. The persistence of thiothixene drug effects for weeks is consistent with persistence of both therapeutic and adverse haloperidol drug effects noted in the outpatient study described above.<sup>9</sup> A meta-analysis of studies evaluating antipsychotic drugs in dementia patients with psychotic and/or disruptive problem behaviors concluded that the antipsychotic drugs are modestly superior to placebo in these patients.<sup>13</sup> This effect size of antipsychotic drugs is substantially smaller than that seen in young, nondemented persons suffering from schizophrenia.

### Atypical Antipsychotics

A major problem in the use of traditional antipsychotic drugs to manage psychiatric and behavioral problems in Alzheimer's disease and other dementing disorders is the frequent emergence of pseudoparkinsonian rigidity, tremor, and bradykinesia. Patients with the Lewy body variant of Alzheimer's disease appear particularly susceptible to these adverse effects.<sup>14</sup> The new atypical antipsychotic drugs such as clozapine, risperidone, and olanzapine offer the theoretical advantage of reduced or minimal

incidence of pseudoparkinsonism. Unfortunately, only anecdotal reports of atypical antipsychotic drug use in small numbers of behaviorally disturbed dementia patients are available. These studies recently have been reviewed.<sup>15</sup> The efficacy and tolerability of these drugs in the patient who has Alzheimer's disease with noncognitive behavioral problems must await data from well-designed, placebo-controlled outcome studies.

### **Withdrawal of Antipsychotic Drugs in Behaviorally Stable Patients**

Both good practice and federal guidelines for long-term care suggest that periodic attempts be made to reduce or even eliminate maintenance antipsychotic drug therapy in dementia patients whose psychotic or other noncognitive problem behaviors appear to be well controlled. Two studies of antipsychotic drug withdrawal in behaviorally disturbed dementia patients are available and support this practice.

Placebo was substituted for maintenance antipsychotic medication in 9 male patients with Alzheimer's disease or vascular dementia (mean age = 65 years) who had been maintained on antipsychotic medication for at least 90 days and whose target symptoms had improved and stabilized.<sup>16</sup> At the end of a 6-week placebo substitution period, only 1 patient had developed disruptive behavior severe enough to warrant restarting antipsychotic medication. Of the remaining 8 patients, 5 were less agitated than prior to drug discontinuation. Two were unchanged, and 1 was more agitated than prior to medication withdrawal.

In a larger study<sup>17</sup> performed in 36 community nursing home patients (mean age = 82 years) who met criteria for probable or possible Alzheimer's disease, patients were randomly assigned to either continuation of antipsychotic medication or placebo substitution withdrawal from antipsychotic medication. Of the 22 patients withdrawn from antipsychotic medication, 20 (91%) were able to complete the 4-week, double-blind withdrawal. Only 2 of the patients were requested by the nursing home staff to discontinue the study because of emergencies involving unacceptable levels of agitation. There was no significant difference between the incidence of emergent physically aggressive behavior between patients withdrawn from antipsychotic medication and those maintained on antipsychotic medication. Half of the patients withdrawn from antipsychotic medication remained off these drugs for an extended period of time after the end of the study, even after the blind had been broken. These 2 studies demonstrate that an attempt at withdrawal from antipsychotic medication in behaviorally stable dementia patients is feasible.

### **SEROTONIN SELECTIVE REUPTAKE INHIBITORS**

The SSRIs are effective drugs for depression and panic disorder in nonelderly persons without cognitive impair-

ment. Several studies suggest that these agents may also be helpful in the management of noncognitive problem behaviors in elderly persons with Alzheimer's disease or vascular dementia.

In a multicenter Scandinavian study,<sup>18</sup> the SSRI citalopram was more effective than placebo for the target symptoms of irritability, fear/panic, depressed mood, and restlessness. Improvement was limited to patients with Alzheimer's disease. No significant effects of citalopram were noted in patients with vascular dementia. Cognitive function was unaffected by either citalopram or placebo, and citalopram was well tolerated by the elderly subjects in this study.

In another Scandinavian study,<sup>19</sup> the SSRI fluvoxamine tended to be more effective on the target symptoms of confusion, irritability, anxiety, fear/panic, mood level, and restlessness than was placebo. The differences between fluvoxamine and placebo, however, failed to reach standard levels of statistical significance.

This study of fluvoxamine was less encouraging than the study using citalopram. However, given the relatively benign adverse effect profile of the SSRIs compared with antipsychotic medications, further studies of SSRIs in the management of noncognitive behavioral problems in Alzheimer's disease are indicated. Such studies should include psychotic symptoms (delusions and hallucinations) as specific target symptoms. These important symptoms were not specifically addressed in the 2 SSRI studies described above.

### **CHOLINERGIC DRUGS**

The well-demonstrated CNS presynaptic cholinergic deficiency in Alzheimer's disease has promoted the use of drugs that enhance CNS cholinergic activity in these patients.<sup>20</sup> It has been widely assumed that this cholinergic deficiency contributes to the cognitive symptoms of Alzheimer's disease. However, careful analysis of the results of large, placebo-controlled trials of drugs that enhance cholinergic activity in patients who have Alzheimer's disease suggests that some of these agents may improve noncognitive psychiatric and behavioral problems as well as cognitive function in these patients. Neurobiological rationale for the involvement of decreased cholinergic activity in noncognitive behavioral problems and anecdotal studies suggesting that cholinesterase inhibitor therapy can improve such symptoms have been recently reviewed.<sup>21</sup> Data from large, multicenter trials now provide support for these theoretical considerations and anecdotal reports.

The effect of the cholinesterase inhibitor tacrine on noncognitive behavioral problems was examined retrospectively in outpatients who had Alzheimer's disease and were enrolled in a previously reported multicenter, double-blind, 30-week trial that established the effective-

ness of tacrine for cognitive deficits.<sup>6,22</sup> The study population included all patients randomly assigned to treatment with 160 mg/day of tacrine hydrochloride (N = 238) and subjects randomly assigned to placebo (N = 181). Only those subjects who had noncognitive behavioral problems at baseline were included in this exploratory analysis. Compared with the placebo group, the percentage of patients receiving tacrine whose noncognitive behavioral problems either improved or stabilized was significantly greater for the target symptom items cooperation, delusions, and pacing.

Placebo-controlled multicenter trials of the cholinesterase inhibitor metrifonate also demonstrate positive drug effects on noncognitive psychiatric and behavioral problems in Alzheimer's disease (Bayer Pharmaceuticals, data on file). Collectively, these trials show that metrifonate significantly reduced hallucinations, depression, apathy, agitation, aggression, and aberrant motor behaviors (Bayer Pharmaceuticals, data on file).

The effects of xanomeline, an experimental M<sub>1</sub> muscarinic cholinergic receptor agonist, on behavioral symptoms in Alzheimer's disease were evaluated in a large, 6-month, randomized, double-blind, placebo-controlled, parallel study.<sup>5</sup> Xanomeline was more effective than placebo in the reduction of treatment-emergent noncognitive behavioral problems including vocal outbursts, suspiciousness, delusions, agitation, and hallucinations. However, xanomeline treatment was also associated with a high incidence of adverse events and a high premature study discontinuation rate.

It should be noted that in both the study of tacrine and the study of xanomeline, exclusion criteria for entry included the presence of severe noncognitive behavioral problems. Also, only outpatients with mild or moderate dementia were studied. Thus, these data must be interpreted cautiously as to the efficacy of drugs that enhance cholinergic activity in patients who have Alzheimer's disease with advanced dementia or severe noncognitive, behavioral problems. At the least, these data suggest that cholinesterase inhibitors and M<sub>1</sub> agonists are unlikely to produce noncognitive behavioral problems when used to treat cognitive deficits in Alzheimer's disease. Further studies of drugs enhancing CNS cholinergic activity are necessary to determine their role in the clinical management of noncognitive behavioral problems in Alzheimer's disease.

### BEHAVIORAL AND ENVIRONMENTAL APPROACHES TO NONCOGNITIVE BEHAVIORAL PROBLEMS

Before a drug is prescribed for the management of noncognitive problems in the patient with Alzheimer's disease, it is essential that the clinician carefully evaluate the patient's general medical status and medication regimen to rule out the possibility that disruptive behavior is a function of an underlying medical illness (such as painful ar-

thritis or urinary tract infection) or an adverse effect of a nonpsychotropic medication (such as theophylline or levodopa). It is also important to evaluate the possibility that the noncognitive problem behavior is a function of interpersonal or environmental factors that can be approached nonpharmacologically.

If a precipitating event clearly leading to a noncognitive behavioral problem can be identified, modification of the caregiver's behavior may alleviate the patient's problem behavior. Most clinicians agree that behavioral and environmental approaches to disruptive agitation are useful,<sup>23</sup> but controlled studies evaluating these approaches have yet to be reported.

It is particularly important to recognize that aimless pacing, a common problem behavior in the middle and later stages of Alzheimer's disease, is unlikely to respond positively to psychotropic medication. In fact, akathisia from antipsychotic drugs can exacerbate pacing and motor restlessness. Pacing is best managed by providing a secure environment in which dementia patients can safely pace at times of their choosing.

### CONCLUSION

Typical antipsychotic drugs are effective and remain widely used in the treatment of psychotic or nonpsychotic disruptive behavioral problems in patients with Alzheimer's disease, but cause troublesome adverse side effects. Preliminary studies suggest that SSRIs and drugs enhancing CNS cholinergic function may be effective for at least some noncognitive behavioral problems in persons with Alzheimer's disease. Placebo-controlled studies of atypical antipsychotic drugs, SSRIs, and cholinergic-enhancing drugs in patients who have Alzheimer's disease with disruptive agitated behaviors clearly are needed.

*Drug names:* clozapine (Clozaril), fluvoxamine (Luvox), haloperidol (Haldol and others), levodopa (Larodopa), loxapine (Loxitane), olanzapine (Zyprexa), risperidone (Risperdal), tacrine (Cognex), theophylline (Aminophylline and others), thioridazine (Mellaril and others), thiothixene (Navane).

### REFERENCES

1. Alzheimer A, Jarvik L, Greenson G, trans. About a peculiar disease of the cerebral cortex. *Alzheimer Dis Assoc Disord* 1987;1:7-8
2. Cummings JL, Miller B, Hill MA, et al. Neuropsychiatric aspects of multi-infarct dementia and dementia of the Alzheimer type. *Arch Neurol* 1987;44:389-393
3. Reisberg B, Borenstein J, Salob SP, et al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry* 1987;48(5, suppl):9-15
4. Raskind MA. Alzheimer's disease: treatment of noncognitive behavioral problems. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York, NY: Raven Press; 1995:1426-1435
5. Bodick NC, Offen WW, Levey AI, et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer's disease. *Arch Neurol* 1997;54:465-473
6. Raskind MA, Sadowsky CH, Sigmund WR, et al. Effect of tacrine on language, praxis, and noncognitive behavioral problems in Alzheimer disease.

- Arch Neurol 1997;54:836–840
7. Barnes R, Veith R, Okimoto J, et al. Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. *Am J Psychiatry* 1982;139:1170–1174
  8. Raskind MA, Peskind ER. Neurotransmitter abnormalities and the psychopharmacology of Alzheimer's disease. In: Heston LL, ed. *Progress in Alzheimer's Disease and Similar Conditions*. Washington, DC: American Psychiatric Press; 1997:245–257
  9. Devanand DP, Sackheim HA, Brown RP, et al. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. *Arch Neurol* 1989;46:854–857
  10. Petrie WM, Ban TA, Berney S, et al. Loxapine in psychogeriatrics: a placebo- and standard-controlled clinical investigation. *J Clin Psychopharmacol* 1982;2:122–126
  11. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1961;10:799–812
  12. Finkel SI, Lyons JS, Anderson RL, et al. A randomized, placebo-controlled trial of thiothixene in agitated, demented nursing home patients. *Int J Geriatr Psychiatry* 1994;10:129–136
  13. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc* 1990;38:553–563
  14. Lee H, Cooney JM, Lawlor BA. The use of risperidone, an atypical neuroleptic, in Lewy body disease. *Int J Geriatr Psychiatry* 1993;9:415–417
  15. Kumar V. Use of antipsychotic agents in geriatric patients: a review. *Int J Geriatr Psychopharmacol* 1997;1:15–23
  16. Risse SC, Cubberley L, Lampe TH, et al. Acute effects of neuroleptic withdrawal in elderly dementia patients. *J Geriatr Drug Ther* 1987;2:65–67
  17. Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study. *J Geriatr Psychiatry Neurol* 1997;10:119–126
  18. Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. *Br J Psychiatry* 1990;157:894–901
  19. Olafsson K, Jørgensen S, Jensen HV, et al. Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. *Acta Psychiatr Scand* 1992;85:453–456
  20. Whitehouse PJ, Price DL, Clark AW, et al. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol* 1981;10:122–126
  21. Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. *Neurology* 1996;47:876–883
  22. Knapp MJ, Knopman DS, Solomon PR, et al, and 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
  23. Teri L, Rabins P, Whitehouse P, et al. Management of behavior disturbance in Alzheimer disease: current knowledge and future directions. *Alzheimer Dis Assoc Disord* 1992;6:77–88

© 1998 Physicians Postgraduate Press, Inc.  
One personal copy may be printed