Published in final edited form as:

Am J Geriatr Psychiatry. 2008 July ; 16(7): 523–527. doi:10.1097/JGP.0b013e318178416c.

Neuropsychiatric Symptoms in Alzheimer Disease and Related Disorders: Why Do Treatments Work in Clinical Practice but Not in the Randomized Trials?

Helen Lavretsky, M.D., M.S.

Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA

Among US adults over age 65, prevalence of dementia ranges from 5%–15% with Alzheimer disease being the most common type of dementia. Because of the growing number of elderly people worldwide, increasing numbers of patients suffering of Alzheimer disease and related dementias is projected to double by the year 2020.¹ The prevalence of neuropsychiatric symptoms is estimated in 60% of community-dwelling dementia patients² and in more than 80% of those in nursing homes, with a lifetime risk of such complications approaching 90%–100%.² Over the past decade, researchers and clinicians realized that these behavioral symptoms result in premature placement into the nursing home, overmedication, and physical restraint, as well as decreased quality of life and increased caregiver burden.^{3,4} Improved understanding of pathophysiology and management of neuropsychiatric symptoms becomes especially important.^{4,5}

The most common difficult-to-manage behaviors in patients with dementia include agitation and aggression (rate ranges 20%–80%),^{6,7} and psychosis with delusions and hallucinations (rate ranges 20%–40%).⁸ Apathy is another common symptom associated with dementia.⁹ Apathy is defined as a lack of feeling, emotion, interest, concern, or motivation. Using Marin's criteria, Starkstein¹⁰ found that 14% of patients with A.D. met the criteria for apathy only, 22% met the criteria for depression only, 23% met the criteria for both, and 41% met the criteria for neither. Frontal-temporal or vascular dementias are both associated with greater prevalence of apathy, asplontaneity, and indifference due to the damage of frontal and fronto-subcortical circuits, either due to degeneration or vascular injury.¹¹ Treatment of apathy may require different approaches enhancing cholinergic and dopaminergic neurotransmitter system that has received only limited attention from researchers.⁹ Overall, successful treatment of behavioral disturbances can reduce suffering of the patient, the burden on the family, and the economic cost of dementia care and caregiver burden.

EFFICACY OF ANTIPSYCHOTICS IN DEMENTIA PATIENTS

Over the five decades of antipsychotic drug use and development, antipsychotic drugs have been widely used and studied in dementia patients with agitated and aggressive behaviors with or without psychosis. Approximately half of the clinical trials examining the efficacy of antipsychotics in dementia patients recruited individuals with psychosis, whereas the other half selected individuals exhibiting agitation and global behavioral disturbances. Most trials included participants with both agitation and psychosis.¹²

Although typical antipsychotics were consistently found to be moderately effective for the treatment of agitation and psychosis, the downside of potentially serious side-effects, such as tardive dyskinesia, the development of the second generation atypical antipsychotics brought about excitement in the field.⁴ Atypical antipsychotics demonstrated significantly lower risks of motor side-effects and somewhat better overall tolerability compared with the typical agents.^{13,14} A distinct side effect profile of atypicals included a metabolic syndrome that is undesirable in the elderly with dementia.¹⁵ The efficacy of these newer agents was based on the handful of the phase IV clinical trials and appeared to be modest on average^{16,17} before the results of the large-scale nonindustry sponsored National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness- Alzheimer Disease (CATIE-A.D.) study that were released in 2007.¹⁸ In that trial, olanzepine, quetiapine, and risperidone were no better than placebo for the primary (time to discontinuation) or the secondary (Clinical Global Impression (CGI) score) outcomes. Time to discontinuation due to efficacy favored olanzepine and risperidone, whereas time to discontinuation due to side effects favored placebo. The limitations of the CATIE-A.D. trial included possible underdosing of the atypicals, and especially, quetiapine, and had higher discontinuation rates compared with other trials.¹⁸ The disappointing message of the CATIE-A.D. was not much different from the preceding meta-analysis by Schneider et al.¹² of 15 trials of atypicals that included placebo-controlled trials and active-drug comparisons. In this meta-analysis, psychosis scores improved only in the studies of risperidone, and global agitation improved with treatment in the pooled analyses of aripiprazole and risperidone. The common problem in the CATIE-A.D. and in all other studies of patients with dementia and neuropsychiatric symptoms was that it was difficult to separate the overall agitation from psychosis because of the recruitment strategy that included subjects with heterogeneous neuropsychiatric symptoms and coexisting agitation and psychosis. In fact, presence of psychosis in patients with dementia may not be essential for clinical improvement in agitated behavior that occurs with antipsychotic treatment.¹⁹

In aggregate, the randomized clinical trials (RCT) examining antipsychotics for psychosis and/or agitation associated with dementia suggest modest efficacy in symptom reduction with active treatment compared with placebo. The comparative safety of typical and atypical neuroleptics in just a few trials do not find any advantage in efficacy of either class, and the selection can be based on safety profile and cost considerations.¹⁴ Atypicals are less likely to cause extrapyramidal symptoms and TD, but typical neuroleptics are less expensive, and some typical agents may cause fewer anticholinergic, orthostatic, or metabolic side-effects compared with some atypicals.⁴

CHOLINESTERASE INHIBITORS AND MEMANTINE

Growing evidence suggests that the neurobiological basis of behavioral disturbances of A.D. and related dementias is a loss of cholinergic neurons and a resultant decline in acetylcholine in brain regions, which regulate behavioral and emotional responses, such as the limbic system.^{20–23} Preliminary evidence also indicates that cholinesterase inhibitors and memantine use for treatment of cognitive symptoms of A.D. and related dementias may have beneficial effects on apathy, depression, psychosis, and agitation.^{21–24}

EFFICACY OF OTHER PSYCHOTROPIC DRUGS IN DEMENTIA PATIENTS WITH NEUROPSYCHIATRIC SYMPTOMS

Although the majority of RCT for behavioral disturbances of dementia included antipsychotics, a number of studies studied antidepressants and anticonvulsants for the treatment of agitation.^{25–28} Trazodone, citalopram, and other serotonergic medications were also effective and well-tolerated when prescribed to treat agitated behavior in patients with dementia, although there are limited data from controlled trials.^{23,25} Initially, great hope was placed onto the clinical

and research use of anticonvulsants, more recent large RCTs failed to find the drug-placebo differences in drug response.^{26,28} Despite negative research results, anticonvulsants are widely used in clinical practice to treat behavioral disturbances of dementia.

Dopaminergic and stimulant medications can be used in the treatment of apathy, amotivation, and social withdrawal associated with depression or dementia.^{9,29} An early placebo-controlled study demonstrated efficacy of the stimulant methylphenidate hydrochloride in the treatment of withdrawn apathetic geriatric patients.³⁰ Although dopaminergic deficits occur in many neurodegenerative dementias, such as A.D., Lewy body dementia (LBD), progressive supranuclear palsy (PSP), and other “Parkinson plus” dementias that can manifest with depression and apathy, the role of dopaminergic agents in their treatment is understudied.³¹

NONPHARMACOLOGIC INTERVENTIONS FOR NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA

Behavioral management of neuropsychiatric symptoms of dementia is usually attempted first. Although, traditionally psychosocial and behavioral studies followed the design and methodology of pharmaceutical trials,³² more recently the trend included individualized or tailored intervention, such as recently published by Gitlin et al.³³ the results of the Tailored Activity Program with customized activities that reduced the number of problem activities compared with the wait list control. Similarly, Cohen-Mansfield et al.³⁴ reported the positive results of the trial of systematic individualized intervention designed to match the person’s cognitive, physical, and sensory abilities. Davison et al.³⁵ reported successful individualized behavioral interventions for treatment resistant patients with dementia and behavioral disturbances in a nursing home. The theme of individualized or personalized treatments is permeating behavioral and caregiver research in dementia.

THERAPEUTIC DILEMMA

The remaining dilemma is the insufficient evidence of effective and safe treatments in the face of increasing prevalence of dementia and coexisting neuropsychiatric symptoms in the United States and around the world. We offer treatments that are modestly effective to our patients and their families as evident from the recent large-scale studies of antipsychotics and valproic acid, as well as behavioral studies, and caregiver trials. The most frequently reported improvement on global scores of multiple behavioral scales commonly used in these trials (e.g., Neuropsychiatric Inventory (NPI) or BPSD) is neither specific nor informative. Although we can successfully manage our patients and help caregivers in our practices, we are unable to provide solid scientific support to back up our clinical successes. The reasons for such state of affairs are not entirely clear, but the four articles published in the current issue reflect this dilemma.

In the current issue, four articles address different aspects of behavioral disturbances of dementia. The article from Selbaek et al.³⁶ describes the prevalence of behavioral disturbances and the psychotropic drug use in the residents of nursing homes in Norway. The authors found that neuropsychiatric symptoms are common and persistent in a 12-month follow-up study. Agitation and apathy were the most persistent behavioral symptoms that lead to prolonged psychotropic drug use. These findings support the common knowledge that the behavioral disturbances are common and persistent accumulated throughout decades of research. The authors contrast their findings to the fact that the data on the psychotropic drug use for the control of behavioral disturbances in dementia shows only a modest response to psychotropic agents compared with that of a placebo.

The second article by Streim et al.³⁷ reports the results of the 10-week randomized, double-blind, placebo-controlled, flexible-dose trial of aripiprazole for the treatment of psychosis and agitation in 256 nursing home residents with A.D., and it echoes Selbaeks paper by reporting no drug-placebo difference on primary outcomes of the study that reflect the severity of psychosis and dementia. Nevertheless, a greater improvement occurred in the aripiprazole group in the secondary measures, mostly total scores of several other scales measuring the overall agitation and depression, and improvement over time. The adverse effects were not different between the drug and placebo except for somnolence and the mean dose of aripiprazole was 9 mg. The study was conducted before the FDA warning about the risk of atypical neuroleptic use in the elderly with dementia. The results are comparable with those of other atypical neuroleptic trials and show no advantage of aripiprazole, except possibly in the management of depression associated with A.D. But it mirrors the story of the available psychotropic drugs for treatment of agitation in dementia.

In contrast, Lanctot et al.³⁸ report contains new information that can advance our understanding of the underlying mechanisms and approaches to management of apathy associated with A.D. that can be present in up to 70% of patients. The authors assessed the use of *d*-amphetamine to assess response in apathetic and nonapathetic patients. They found a blunted subjective response to *d*-amphetamine, suggesting dysfunction in the Brain Reward System that opens the doors to the use of dopaminergic agents and stimulant drugs that are likely to improve apathy in contrast to serotonergic drugs. Although the reports of cognitive enhancers shows a modest rate of improvement in apathy,³⁹ the use of dopaminergic agents is also appropriate to correct the dopaminergic deficit in the brain reward system. Perhaps, we should allow a new look at the use of stimulants in dementia that will require new studies of the stimulant use as augmentation of the standard dementia treatments.

Clearly, the field of geriatric psychiatry is in an urgent need of new paradigms of therapeutic development to treat behavioral disturbance in dementia, including new classes of drugs and the new uses of available drugs and other therapeutic agents (e.g., supplements). Although the field is at odds with the state of affairs in pharmacological management, the behavioral research is offering new and better solutions that lie in the development of personalized interventions. The fourth article in this issue by Tune⁴⁰ reports behavioral management of sexually inappropriate behaviors of a male patient, in whom medications were ineffective in controlling his behaviors. The patient responded to a large 3-ft tall pink panther stuffed animal. Although the patient grasped and fondled the Pink Panther, he became less intrusive with fellow patients and staff, and later was discharged to a nursing facility along with the Pink Panther, and continued to refrain from disrupting fellow residents. This proves that while the behavioral approaches do not stop the behavior, they can prevent harm to other patients and staff. This observation calls for creativity in providing individualized approaches.

It is becoming clear that there is not an easy solution to pharmacotherapy of neuropsychiatric symptoms of dementia. The current database exclusively uses averages and group means in documenting response in the drug trials or behavioral studies, which is responsible for the discrepancy between the disappointing results of the research studies and individual successes in clinical practice. We have learned by now that there is not a single prescription for everyone, and creating personalized approaches could be the way to build evidence for our colleagues, and demonstrate to our patients and their families that our treatments work. The question remains whether the pharmaceutical industry and academia can be flexible enough in designing such studies and whether there is an agency that will fund them. The National Institute of Health Roadmap initiative calls for such creative solutions to designing effective treatments using personalized approaches.⁴¹ This is an opportunity to rethink the way research is being conducted in developing effective treatments for neuropsychiatric symptoms of A.D. and related dementias.

In addition to developing effective pharmacotherapy, it would be important to increase evidence base for alternative and complementary approaches that are already widely used by our patients and their families such as spiritual activities, meditation, life style, exercise, energy treatments, light and music therapy, and many others. The use of multiple interventions in an individual patient are likely to replace the use of a single treatment and will need to be tested in research, such as psychosocial treatments, caregiver training and support, antidepressants and acetylcholinesterase inhibitors, as well as other drugs developed for the treatment and prevention of Alzheimer disease.

Acknowledgments

This work was supported by the NIH grants R01 MH077650 and R-21 AT003480 (to HL).

References

1. Ferri CP, Prince M, Brayne C, et al. Alzheimer's Disease International Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366:2112–2117. [PubMed: 16360788]
2. Lyketsos CG, Steinberg M, Tschanz JT, et al. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000;157:708–714. [PubMed: 10784462]
3. Matsui T, Nakaaki S, Murata Y, et al. Determinants of the quality of life in Alzheimer's disease patients as assessed by the Japanese version of the Quality of Life-Alzheimer's disease scale. *Dement Geriatr Cogn Disord* 2006;21:182–191. [PubMed: 16401890]
4. Jeste DV, Blazer D, Casey D, et al. ACNP white paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology* 2008;33:957–970. [PubMed: 17637610]
5. Cummings JL. Cognitive and behavioral heterogeneity in Alzheimer's disease: seeking the neurobiological basis. *Neurobiol Aging* 2000;21:845–861. [PubMed: 11124429]
6. Tractenberg RE, Weiner MF, Patterson MB, et al. Comorbidity of psychopathological domains in community-dwelling persons with Alzheimer's Disease. *J Geriatr Psychiatry* 2003;16:94–99.
7. Ryu SH, Katona C, Rive B, et al. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. *Am J Geriatr Psychiatry* 2005;13:976–983. [PubMed: 16286441]
8. Ballard C. Agitation and psychosis in dementia. *Am J Geriatr Psychiatry* 2007;15:913–917. [PubMed: 17974863]
9. Mizrahi R, Starkstein SE. Epidemiology and management of apathy in patients with Alzheimer's disease. *Drugs Aging* 2007;24:547–554. [PubMed: 17658906]
10. Starkstein SE. Apathy and withdrawal. *Int Psychogeriatr* 2000;12:135–137. [PubMed: 10937535]
11. Lavretsky H, Ballmaier M, Pham D, et al. Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. *Am J Geriatr Psychiatry* 2007;15:386–394. [PubMed: 17463189]
12. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006;14:191–210. [PubMed: 16505124]
13. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. *J Clin Psychiatry* 2000;61:16–21. [PubMed: 10724129]
14. Jeste DV, Lacro JP, Bailey A, et al. Incidence of tardive dyskinesia with risperidone versus haloperidol. *J Am Geriatr Society* 1999;47:716–719.
15. Jin H, Meyer JM, Jeste DV. Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res* 2004;71:195–212. [PubMed: 15474892]
16. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev* 2006;1:CD003476. [PubMed: 16437455]

17. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *J Am Med Assoc* 2005;293:596–608.
18. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;355:1525–1538. [PubMed: 17035647]
19. Sultzer, D.; Lavretsky, H. Antipsychotic medications in the elderly. In: Sadock, B.; Sadock, V., editors. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 3096–3100.
20. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int J Geriatr Psychiatry* 2008;23:537–45. [PubMed: 18058838]
21. Cummings JL, McRae T, Zhang R, et al. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. *Am J Geriatr Psychiatry* 2006;14:605–612. [PubMed: 16816014]
22. Cummings JL, Schneider E, Tariot PN, et al. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 2006;67:57–63. [PubMed: 16832078]
23. Tariot PN. Contemporary issues in the treatment of Alzheimer's disease: tangible benefits of current therapies. *J Clin Psychiatry* 2006;67:15–22. [PubMed: 16649847]
24. Trinh NH, Hoblyn J, Mohanty S. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *J Am Med Assoc* 2003;289:210–216.
25. Sultzer DL, Gray KF, Gunay I. Does behavioral improvement with haloperidol or trazodone treatment depend on psychosis or mood symptoms in patients with dementia? *J Am Geriatr Soc* 2001;49:1294–1300. [PubMed: 11890487]
26. Tariot PN, Raman R, Jakimovich L, et al. Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: a randomized, controlled trial. *Am J Geriatr Psychiatry* 2005;13:942–949. [PubMed: 16286437]
27. Porsteinsson AP. Divalproex sodium for the treatment of behavioural problems associated with dementia in the elderly. *Drugs Aging* 2006;23:877–886. [PubMed: 17109566]
28. Loneragan ET, Cameron M, Luxenberg J. Valproic acid for agitation in dementia. *Cochrane Database Syst Rev* 2004;2:CD003945. [PubMed: 15106227]
29. Roth RM, Flashman LA, McAllister TW. Apathy and its treatment. *Curr Treat Options Neurol* 2007;9:363–370. [PubMed: 17716600]
30. Lavretsky H. Therapy of depression in dementia. *Expert Rev Neurotherapeutics* 2003;3:89–97.
31. Lavretsky H, Kumar A. Clinically significant non-major depression: old concepts, new insights. *Am J Geriatr Psychiatry* 2002;10:239–255. [PubMed: 11994211]
32. Teri L, Logsdon RG, Peskind E, et al. Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. *Neurology* 2000;55:1271–1278. Erratum, *Neurology* 2001; 56:426. [PubMed: 11087767]
33. Gitlin LN, Winter L, Burke J, et al. Tailored activities to manage neuropsychiatric behaviors in persons with dementia and reduce caregiver burden: a randomized pilot study. *Am J Geriatr Psychiatry* 2008;16:229–239. [PubMed: 18310553]
34. Cohen-Mansfield J, Libin A, Marx MS. Nonpharmacological treatment of agitation: a controlled trial of systematic individualized intervention. *J Gerontol A Biol Sci Med Sci* 2007;62:908–916. [PubMed: 17702884]
35. Davison TE, Hudgson C, McCabe MP, et al. An individualized psychosocial approach for “treatment resistant” behavioral symptoms of dementia among aged care residents. *Int Psychogeriatr* 2007;19:859–873. [PubMed: 16973098]
36. Selbaek G, Qyvind K, Knut E. The course of psychiatric and behavioral symptoms and the use of psychotropic medications in patients with dementia in Norwegian nursing homes: a 12 month follow-up study. *Am J Geriatr Psychiatry* 2008;16:528–536. [PubMed: 18591573]
37. Streim JE, Porsteinsson AP, Breder CD, et al. A randomized double-blind placebo-controlled study of aripiprazole for the treatment of psychosis in nursing home patients with Alzheimer's disease. *Am J Geriatr Psychiatry* 2008;16:537–550. [PubMed: 18591574]

38. Lanctot KL, Herrmann N, Black SE, et al. Apathy associated with Alzheimer's disease: use of dexamphetamine challenge. *Am J Geriatr Psychiatry* 2008;16:551–557. [PubMed: 18591575]
39. Cummings JL, Jeste DV. Pharmacotherapy of neuropsychiatric syndromes in neurologic disorders: definitional and regulatory aspects. *Psychopharmacol Bull* 2007;40:89–98. [PubMed: 18227780]
40. Tune LE. Nonpharmacological treatment of inappropriate sexual behavior in dementia: the case of the Pink Panther. *Am J Geriatr Psychiatry* 2008;16:612–616. [PubMed: 18591581]
41. Zerhouni EA. Translational research: moving discovery to practice. *Clin Pharmacol Therapeutics* 2007;81:126–28.