Published in final edited form as:
Curr Psychiatr. 2008 June 1; 7(6): 50–65.

Beyond the Black Box: What is The Role for Antipsychotics in Dementia?

Thomas W. Meeks, M.D. [Assistant Professor of Psychiatry] and
University of California, San Diego

Dilip V. Jeste, M.D. [Estelle and Edgar Levi Chair in Aging; Director of the Sam and Rose Stein Institute for Research on Aging; Professor of Psychiatry and Neurosciences]
University of California, San Diego and VA San Diego Healthcare System

Deck

There is a small but well-established increase in the risk of death and stroke when using atypical antipsychotics in older adults with dementia. Clinicians and patients/caregivers are left with a seemingly "no-win" clinical conundrum of how to deal with serious dementia-related psychosis and aggression, which are themselves associated with serious morbidity.

Please address correspondence to Thomas W. Meeks, M.D., UCSD Senior Behavioral Health, 8950 Villa La Jolla Drive, Suite C209, Mail Code 0839, La Jolla, CA 92037.

RELATED RESOURCES:
Jeste DV, Blazer D, Casey D, Meeks T, et al. ACNP White Paper: Update on Use of Antipsychotic Drugs in Elderly Persons with Dementia. Neuropsychopharmacology. 2007 Jul 18; [Epub ahead of print]
American Association for Geriatric Psychiatry Position Statement: Principles of Care for Persons with Dementia Resulting from Alzheimer Disease: http://www.aagponline.org/prof/position_caredmnalz.asp

DRUG-BRAND NAMES
Alprazolam * Xanax
Aripiprazole * Abilify
Atenolol * Tenormin
Buspirone * Buspar
Carbamazepine * Tegretol
Citalopram * Celexa
Clozapine * Clozaril
Diphenhydramine * Benadryl
Divalproex * Depakote
Donepezil * Aricept
Galantamine * Razadyne
Haloperidol * Haldol
Hydrocodone/acetaminophen * Vicodin/Lortab
Lorazepam * Ativan
Memantine * Namenda
Olanzapine * Zyprexa
Oxazepam * Serax
Oxybutynin * Ditropan
Paroxetine * Paxil
Propranolol * Inderal
Quetiapine * Seroquel
Risperdone * Risperdal
Rivastigmine * Exelon
Trazodone * Desyrel
Ziprasidone * Geodon

INTRODUCTION

Alzheimer disease (AD) likely affects over 5 million Americans, with this number expected to grow nearly exponentially over the upcoming decades (1). Additionally, millions of Americans are afflicted with other types of dementia. Regardless of the etiology, dementias share certain diagnostic features regarding cognitive and functional decline. Yet, for many patients and their families, the nearly ubiquitous neuropsychiatric symptoms of dementias (e.g. depression, psychosis, aggression, sleep disturbance) are the most problematic aspects of these illnesses, leading to caregiver morbidity, poor patient quality of life, and early patient institutionalization (2). Psychosis, for instance, affects approximately 40% of persons with AD, while agitation occurs in 80% or more of persons with dementia at some point in the illness (3). Although empirical research regarding the treatment of neuropsychiatric manifestations of dementia has been sparse relative to the growing public health significance of this problem, no medication has been FDA-approved for the treatment of these symptoms. Psychotropic medications, especially antipsychotics, have often been used off-label in attempts to ameliorate these symptoms. Yet, this has not been without controversy, as some public perception (at times validated by unfortunate institutional practices) has viewed the use of antipsychotics in dementia as a means of creating "zombies" in order to lighten the work burden of healthcare workers. Nonetheless, psychosis and severe agitation/aggression in dementia can pose significant risks to patients and those around them, such that efforts to treat these symptoms are indeed warranted. While possibly underutilized because of time constraints, reimbursement issues, and lack of training, non-pharmacological strategies to treat aggression and psychosis are appealing alternatives to "knee-jerk" antipsychotic prescriptions; nonetheless, the empirical evidence base for non-pharmacological strategies to control psychosis and/or agitation in dementia remains generally inadequate as well (4).

Adding another layer of complexity onto the use of antipsychotics in treating dementia-related psychosis and/or agitation are the recent FDA black-box warnings regarding atypical agents in this patient population. Beginning with a warning regarding increased risk of "cerebrovascular adverse events including stroke" in dementia patients treated with risperidone versus placebo in 2003, a cascade of warnings for this class of agents has ensued. Similar cerebrovascular black-box warnings have been issued for olanzapine and aripiprazole. While the absolute risk difference was generally 1–2 % between antipsychotic- and placebo-treated patients, the relative risk was approximately two times higher (due to the overall low prevalence of these events in both groups) (5). Perhaps even more daunting, after a meta-analysis of 17 placebo-controlled trials using atypical antipsychotics in dementia, the FDA issued a black-box warning (Table 1) citing an increased risk of mortality for patients receiving atypical antipsychotics (relative risk 1.6–1.7) versus placebo. This warning was applied to atypical antipsychotics as a class, and as with the cerebrovascular risks, the absolute risk difference was between 1–2% (6). Indeed, the public is well-served by evidence-based pharamaco-vigilance that identifies previously unrecognized risks associated with prescription medications, but the FDA data does little to answer the question, "***And so, what now***?" for the millions of families grappling with these symptoms. Recognizing the limits of answering this question without solid empirical evidence, we attempt to address this question that lingers for clinicians, patients, and caregivers, who must deal with these symptoms while science tries to provide a more definitive answer to this question.

TEXT

HYPOTHETICAL CASE EXAMPLE: Mrs. B is an 82-year old Caucasian woman diagnosed 7 years ago with Alzheimer disease who resides in an assisted living facility with a "dementia waiver," indicating that their staff has some training in dealing with issues unique to providing care to older persons with dementia. Despite attempts to provide more one-to-one attention

and verbal reassurance, Mrs. B has demonstrated an escalating pattern of psychosis and aggression over the past two months. At first the psychosis was restricted to occasional accusations of rape during assisted bathing, and the aggression was primarily manifested by Mrs. B banging her hand repetitively on furniture (occasionally causing skin tears). However, over the prior week, Mrs. B has spent much of the day accusing staff and other patients of having stolen her personal belongings and even assaulted both a staff member (causing minor bruises to the staff member's forearm) and another resident (pushing another female over, prompting an emergency room evaluation for this resident's fall). This latter incident finally prompted supervisors at the assisted living to advise Mrs. B's family that she could no longer stay there and suggested that they take her to a local emergency room. From the emergency room, the patient is admitted involuntarily to the nearest geriatric psychiatry inpatient unit.

"And so, what now?"

Table 2 summarizes an approach to the initial evaluation of persons with dementia presenting with psychosis and/or agitation/aggression (7). For this patient (and most older adults), a list of current medications (including "as needed" medications from records at a facility or from family report) will be important to review. A review of the medication administration record from the assisted living reveals potentially relevant information: atenolol 25 mg daily, aspirin 81 mg daily, oxybutynin extended release 10 mg at bedtime, psyllium one packet daily, hydrocodone/acetaminophen 5/500 mg every 4 hours as needed for pain, lorazepam 1 mg every 6 hours as needed for agitation, diphenhydramine 25 mg at bedtime, in and out catheter every 8 hours as needed for urinary retention, paroxetine 20 mg daily, haloperidol 5 mg at bedtime, and memantine 10 mg twice daily. This medication list is revealing for many reasons that are unfortunately not rare. There are several anticholinergic medications (oxybutynin, diphenhydramine, and paroxetine) that may be worsening mental status and behavior directly through central nervous system effects, possibly in combination with frequent benzodiazepine use. Anticholinergics can also lead to behavioral changes via peripheral side effects—constipation and urinary retention may cause significant discomfort that is "acted out" rather than verbalized in the aphasic patient. The patient may be having pain related to these side effects and receiving opioid analgesics for pain, which ironically worsen constipation and urinary retention. However, uncontrolled pain related to musculoskeletal disease or neuropathy may merit treatment and reduce behavioral disturbances. The invasive and unpleasant nature of urinary catheterization is likely to worsen behavior directly and risks causing one of the most common "asymptomatic" etiologies of behavioral symptoms in dementia—urinary tract infection.

After admission, and having recognized all these factors, the patient's polypharmacy is reduced by limiting medications to atenolol, aspirin, psyllium, memantine, and a taper of lorazepam and paroxetine. Complete laboratory, radiological, and physical examinations reveal a urinary tract infection, fecal impaction, bladder distension, and mild hyponatremia. The patient is given an enema, antibiotic therapy, and integrated into the milieu of the unit. Despite one-to-one nursing care, frequent re-orientation, and attempts to interest the patient in art therapy, the patient remains agitated and postures to strike staff and other patients. The patient denies pain or discomfort. The nurse pages the psychiatrist on duty because she fears for the safety of the Mrs. B, staff, and other patients.

"And so, what now?"

When faced with an emergent situation of this nature, and with the knowledge that well-trained staff have assessed for common reversible proximal causes of agitation and have tried several reasonable non-pharmacological means of calming the patient, few people would argue against the use of medication for preservation of a safe environment for the patient and others. The nurse calls Mrs. B's husband, who has durable power of attorney for her healthcare, to advise

him of the circumstances and the need for medication. She advises the husband that the psychiatrist has ordered risperidone 0.5 mg by mouth, but he immediately interjects that the psychiatrist at the assisted living facility told him to use haloperidol for his wife's symptoms because other antipsychotics can cause strokes and death.

"And so, what now?"

Ideally, informed consent for medications that are anticipated as possible agents to be used during a hospitalization is obtained from the patient or (more likely) the proxy decision-maker at admission so that such issues and questions do not arise in a crisis. The nurse may have to delay medication administration while putting the husband and psychiatrist in contact. The larger question brought up here is the implication that typical antipsychotics are now preferred for dementia-related psychosis/agitation because the FDA has not issues the same global black-box warnings for this class of agents. Astute clinicians realize, however, that lack of evidence of harm is not evidence of lack of harm. In fact, since the black-box warnings for atypical antipsychotics in dementia emerged, several studies have examined whether the same risks exist for typical agents, mostly via retrospective database analysis (prospective head-to-head comparisons between atypical and typical antipsychotics in dementia are scarce, and future prospective studies to address this question would be plagued with ethical quandaries) (8–15). Table 3 summarizes available evidence regarding typical antipsychotics and risk of stroke/death in dementia. Overall, no evidence suggests that typical agents mitigate the risks of stroke or death in dementia compared to atypical agents; in fact, what is clearly known is that typical agents are more likely than atypical agents to cause movement related side effects (especially tardive dyskinesia and parkinsonism) in older adults with dementia (16).

After an explanation of these data (and the lack of FDA-approved treatments), Mrs. B's husband consents to treat her acute agitation with risperidone. This medication provides moderate relief of the patient's aggression and paranoia per nursing observations. The next day Mrs. B's husband visits the unit and asks to speak with the psychiatrist. While appreciative of the staff's caring attitude toward his wife, he posits, "There must be safer or better ways to deal with these symptoms than these medications like risperidone. I just don't want the guilt of causing my wife to have a stroke or to pass away."

"And so, what now?"

There are several important issues that this conversation should address. First, although we have said a lot about the risks of antipsychotics in dementia, we have not given much attention to their efficacy and effectiveness—an equally important and not always agreed upon issue. A recent meta-analysis of 15 randomized controlled trials of atypical antipsychotics for agitation and/or psychosis in dementia included studies with risperidone, olanzapine, aripiprazole, and quetiapine (5). The majority of study participants were institutionalized, female, and had Alzheimer disease. Psychosis scores clearly improved in pooled studies of risperidone, whereas global neuropsychiatric disturbance clearly improved with risperidone and aripiprazole. Effects were more notable in persons without psychosis, those living in nursing homes, and those with severe cognitive impairment. Subsequent placebo-controlled trials (using agents such as risperidone, quetiapine, and aripiprazole) published after this meta-analysis further argue that the preponderance of evidence indicates that antipsychotics (atypical and typical) have modest efficacy in reducing aggression and psychosis in dementia (most studies focusing on AD) according to symptom scales. However, the largest non-industry funded study conducted to address this question, the National Institute of Mental Health CATIE-AD trial, called this conclusion into question to some extent (17). While risperidone and olanzapine (but not quetiapine) were efficacious in that fewer patients taking them versus placebo dropped out due to lack of efficacy, they were overall not effective because all-cause discontinuation rates (the primary outcome) were similar for all three antipsychotics and placebo. This indicates that

on average these medications' side effect burden may offset their efficacy, though individual cases may vary from the "mean" lack of effectiveness.

Mrs. B's husband also raises the issue of treatment alternatives. In the case of dementia with psychosis and/or agitation, these include no treatment, non-pharmacological methods, and other psychotropic medications. Whereas no treatment may be viable in mild-moderate cases, severe psychosis or agitation will usually bring a consensus among clinicians and caregivers that the absence of treatment is impractical (e.g. compromising safety or leaving the patient without any feasible housing options). "No treatment" does not mean to imply no assessment or intervention at all. Examination for iatrogenic, medical, obvious psychosocial, or other clear precipitants of these behavioral symptoms should always be conducted. Table 4 summarizes what is known about treatment alternatives for psychosis and/or agitation in dementia, including non-pharmacological interventions and other psychotropic medications (4,7).

Another prominent issue is the value system of the patient/caregiver. Proxy decision makers should try to examine the treatment decisions at hand in terms of how they believe the patient would view treatment alternatives, although in the absence of very specific advanced directives, even well-intentioned proxy decision makers are likely to "contaminate" the decisions with their own personal values/interests. After a discussion of what is known about the risks and benefits of various treatments, a useful question might be, for example, "If Mrs. B could have foreseen her behaviors ten years ago, what do you think she would have wanted us to do in this situation? Some people might have been mortified by the thought that they are attacking other people, whereas other people would not mind this as much as the fear of being 'overmedicated.' Which end of the spectrum do you think she would have leaned toward?" In the end, when medical research does not offer clear answers for the "right" next clinical step (which happens in a plethora of other clinical scenarios), clinicians should acknowledge the limits of their own and human knowledge, engage the caregiver (or less commonly the patient) in a process of shared decision-making, recognizing some people will appreciate this opportunity for "equal partnership" while others will ultimately want the physician to decide based on his or her own best clinical judgment.

Mrs. B's husband decides that the level of risk involved in using an atypical antipsychotic for his wife is acceptable given that he believes quality of life is more important than quantity of life and given that he believes his wife would have wanted to try a medication with a moderate chance at relieving the internal distress that paranoia brings and preventing her from harming anyone else, as she had never been a violent person before the dementia. Mrs. B's husband then asks, "How long will she have to take this medication?"

"And so, what now?"

Once again the evidence base leaves clinicians largely floundering on their own in regards to this question. What is known is that neuropsychiatric symptoms such as psychosis and agitation exhibit variable patterns over the course of dementia. The symptoms may wax and wane for unclear reasons. As such, and given the tenuous nature of the risk-benefit profile for atypical antipsychotics in dementia, persons with dementia who remain relatively asymptomatic for 3–6 months after successful treatment with an atypical antipsychotic should be considered for a gradual taper off the medication, with close monitoring for symptom recurrence (7).

For patients such as Mrs. B, in particular, in whom several possibly reversible precipitants of psychosis and aggression were identified, careful consideration should be given to the necessary duration of antipsychotic therapy. Patients may have a delayed beneficial response to the correction of precipitating factors such as medical illness, physical discomfort, or medication side effects. Although this case example used risperidone as the treatment agent for demonstration purposes, evidence for efficacy and safety in dementia-related psychosis or

agitation does not yet significantly distinguish among the atypical agents, with the exception of the relative dearth of data for ziprasidone or clozapine in this population. Typical starting and target doses for atypical antipsychotics are given in Table 6 (18).

BOTTOM LINE

No solid evidence-based treatment exists for psychosis or agitation in dementia. Atypical antipsychotics carry a black-box warning for increased risk of death and cerebrovascular events in dementia, although typical antipsychotics appear no safer. When treatment becomes necessary, atypical antipsychotics are one of several off-label treatment options but, if chosen, should be used judiciously in the context of shared-decision making, close monitoring, and minimization of dose/treatment duration.

REFERENCES

1. Hebert LE, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol 2003;60:1119–1122. [PubMed: 12925369]
2. Yaffe K, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. JAMA 2002;287:2090–2097. [PubMed: 11966383]
3. Jeste DV, Meeks TW, Kim DS, Zubenko GS. Research agenda for DSM-V: Diagnostic categories and criteria for neuropsychiatry syndromes in dementia. J Geriatr Psychiatry Neurol 2006;19:160–171. [PubMed: 16880358]
4. Livingston G, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry 2005;162:1996–2021. [PubMed: 16263837]
5. 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]
6. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943. [PubMed: 16234500]
7. Jeste DV, et al. ACNP White Paper: update on the use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology. 2007 July 18;[Epub ahead of print]
8. Nasrallah HA, White T, Nasrallah AT. Lower mortality in geriatric patients receiving risperidone and olanzapine versus haloperidol: preliminary analysis of retrospective data. Am J Geriatr Psychiatry 2004;12:437–439. [PubMed: 15249282]
9. Schneeweiss S, et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007;176:627–632. [PubMed: 17325327]
10. Wang PS, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341. [PubMed: 16319382]
11. Trifirò G, et al. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. Pharmacoepidemiol Drug Saf 2007;16:538–544. [PubMed: 17036366]
12. Gill SS, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007;146:786.
13. Kales HC, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 2007;164:1568–1576. [PubMed: 17898349]
14. Gill SS, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ 2005:330–445. [PubMed: 16081446]
15. Liperoti R, et al. Cerebrovascular events among elderly nursing home patients treated with conventional or atypical antipsychotics. J Clin Psychiatry 2005;66:1090–1096. [PubMed: 16187764]
16. Jeste DV, Lacro JP, Nguyen HA, et al. Incidence of tardive dyskinesia with risperidone versus haloperidol. Journal of American Geriatric Society 1999;47:716–719.
17. Schneider LS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–1538. [PubMed: 17035647]

18. Jeste D, Meeks T. To prescribe or not to prescribe? Atypical antipsychotic drugs in patients with dementia. South Med J 2007;100:961–963. [PubMed: 17943030]

19. Cohen-Mansfield J. Nonpharmacologic interventions for inappropriate behaviors in dementia: a review and critique. Am J Geriatr Psychiatry 2001;9:361–381. [PubMed: 11739063]

20. Pollock BG, et al. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. Am J Geriatr Psychiatry 2007;15:942–952. [PubMed: 17846102]

TABLE 1

The FDA Black Box Warnings Regarding Atypical Antipsychotics in Dementia

"Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 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 about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. These drugs are not approved for the treatment of patients with dementia-related psychosis."
"Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients…in trials of DRUG X* in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with DRUG X compared to patients treated with placebo. DRUG X is not approved for the treatment of patients with dementia-related psychosis."

* Applies to risperidone, olanzapine, and aripirazole.

TABLE 2

Suggested Approach to the Evaluation of Patients with Dementia Presenting with Psychosis and or Agitation*/ Agression

1)	Establish the dangerousness of the situation.	
	•	If the physical safety of the patient or others is at significant risk, and the patient does not respond quickly to behavioral strategies (e.g. verbal redirection/reassurance, stimulus reduction, change of environment), acute treatment with pharmacotherapy could be considered. For instance, offer the patient oral antipsychotic medication (possibly in dissolvable tablets for ease of administration) and then if necessary consider intramuscular medications (e.g. olanzapine, aripiprazole, haloperidol, lorazepam).
	•	For less acute situations, conduct a more thorough investigation of the symptom etiology and an informed consent process prior to any treatment.
2)	Establish a clear diagnosis/etiology (to the extent possible) for the symptoms.	
	•	Rule out delirium (e.g. urinary tract infection, subdural hematoma, pneumonia) through appropriate physical examination and diagnostic studies.
	•	Rule out iatrogenic causes (e.g. explore recent changes in medications).
	•	Rule out physical discomfort (e.g. arthritis pain, unrecognized fracture, constipation).
	•	Explore for common antecedents to symptom flares that are potentially modifiable (e.g. seeing a certain person, increased noise level, social isolation).
	•	Explore other common causes of behavioral disturbances in dementia (e.g. depression, anxiety, insomnia).
3)	Establish the severity and frequency of the symptoms, including:	
	•	Impact on patient quality of life
	•	Impact on caregiver quality of life
	•	Instances in which the physical safety of the patient or others have been jeopardized
	•	Clear delineation/description of prototypical examples of the symptoms
4)	Explore past treatments/caregiver strategies used to address the symptoms and their level of success and/or problematic outcomes of such treatments	
5)	Discuss what is known (and probably more importantly what is not known) about possible risks and benefits of treatments (pharmacological and non-pharmacological) for psychosis and agitation/aggression in dementia, including atypical antipsychotics	

*Agitation for the purposes of this paper is defined as “inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual (19).”

TABLE 3

Studies examining risks stroke and mortality with *typical* antipsychotics.

Study	Population	Summarized Results
MORTALITY		
Nasrallah et al. 2004	VA patients over age 65 taking haloperidol or an atypical antipsychotic (n=1553)	Approximately 4 times higher rate of death in those receiving haloperidol compared to those receiving atypicals
Wang et al. 2005	Adults age 65+ taking with prescription coverage taking antipsychotics in Pennsylvania (n=22,890)	Typicals had higher relative risk of death at all time points over 180 days (RR 1.27–1.56), both in persons with and without dementia; higher risk associated with increased typical doses
Gill et al. 2007	Canadians age >65 with dementia (n=27,259 matched pairs)	Rate of death higher for users of typical versus atypical antipsychotics (RR 1.26–1.55)
Kales et al. 2007	VA patients age 65+ prescribed psychotropics after a dementia diagnosis (n=10,615)	Risk of death similar for atypical and typical antipsychotics
Schneeweiss et al. 2007	Canadians age 65+ free of cancer taking antiosychotics (n=37,241)	Higher mortality rates for those taking typical antipsychotics than those taking atypical (RR 1.47); higher mortality associated with higher typical doses
Trifiro et al. 2007	Adults age 65+ with dementia receiving antipsychotics in Italy (n=2385)	Equivalent rates of mortality in those taking typical and atypical antipsychotics
STROKE		
Gill et al. 2005	Canadians age 65+ with dementia receiving antipscyhotics (n=32,710)	Equivalent rates of ischemic stroke in those taking atypical and typical agents
Liperoti et al. 2005	Nursing home residents with dementia hospitalized for stroke or TIA and matched controls(n=4788)	Rates of cerebrovascular adverse events equivalent between users of atypical and typical antipsychotics

n = sample size; VA = Veterans Affairs; RR = relative risk; TIA = transient ischemic attack

TABLE 4

Evidence base for treatment alternatives to antipsychotics for psychosis or agitation in dementia.

Treatment	Evidence/Results
PHARMACOTHERAPIES	
Selective Serotonin Reuptake Inhibitors	Two positive studies with citalopram (1-better for agitation than PBO and 2-equivalent to risperidone for psychosis and agitation with better tolerability (20)); two negative trials with sertraline
Other Antidepressants	One study showed trazodone equivalent to haloperidol for agitation with better tolerability; another study showed trazodone no different from PBO; other agents only have case reports/ open-label trials
Anticonvulsants	Three trials showing divalproex equivalent to placebo; two positive trials for carbamazepine but problems with tolerability in both; other agents only tried in case reports or open-label trials
Benzodiazepines/Anxiolytics	Three trials showing effects on agitation for oxazepam, alprazolam, diphenhydramine, and buspirone were equivalent to haloperidol but no PBO control in any trial; problematic methodology in trials and worries over cognitive worsening with some of these agents (especially diphenhydramine)
Cognitive enhancers	Some evidence of modest benefit in mostly post-hoc data analysis in trials designed to assess cognitive variables and often among participants with overall mild psychiatric symptom severity; prospective studies of rivastigmine and donepezil specifically designed to assess neuropsychiatric symptoms have found no difference versus PBO
Miscellaneous drugs	Failed trial of transdermal estrogen in men; small study showing propranolol (average dose 106 mg/day) better than placebo
PSYHCHOSOCIAL/BEHAVIORAL THERAPIES*	
Caregiver psychoeducation/support	Several positive RCTs (evidence grade A)
Music therapy	6 RCTs generally positive in the short term (evidence grade B)
Cognitive stimulation therapy	¾ of RCTs showed some benefit (evidence grade B)
Sonezelen theraoy	3 RCTs with positive short term benefits (evidence grade B)
Behavioral management therapies (by professionals)	Largest RCTs with some benefits (grade B)
Staff training/education	Several positive studies of fair-to-good methodological quality (evidence grade B)
Reality orientation therapy	Best RCT showed no benefit (evidence grade D)
Teaching caregivers behavioral management techniques	Overall inconsistent results (evidence grade D)
Stimulate presence therapy	Only one RCT which was negative (evidence grade D)
Validation therapy	1-year RCT with mixed results (evidence grade D)
Reminiscence therapy	A few small studies with mixed methodologies (evidence grade D)
Therapeutic activity programs	Varied methods (e.g. exercise, puzzle play) and inconsistent results (evidence grade D)
Physical environmental stimulation (e.g. altered visual stimuli, mirrors, signs)	Generally poor methodology and inconsistent results (best results with obscuring exits to decrease exit-seeking) (evidence grade D)

PBO = placebo; RCT = randomized controlled trial

*These summaries include recent evidence grades assigned to various therapies in a systematic review conducted by Livingston et al. in 2005 (4).

TABLE 5

Suggested starting and target doses for atypical antipsychotics in dementia.

DRUG	STARTING DOSE	TARGET DOSE
Aripirazole	2.5-5 mg/day	7.5-12.5 mg/day
Olanzapine	2.5-5 mg/day	5-10 mg/day
Quetiapine	12.5-25 mg/day	50-200 mg/day
Risperidone	0.25-0.5 mg/day	0.5-1.5 mg/day