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ACNP White Paper: Update on Use of Antipsychotic Drugs in Elderly Persons with Dementia

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Abstract

In elderly persons, antipsychotic drugs are clinically prescribed off-label for a number of disorders outside of their Food and Drug Administration (FDA)-approved indications (schizophrenia and bipolar disorder). The largest number of antipsychotic prescriptions in older adults is for behavioral disturbances associated with dementia. In April 2005, the FDA, based on a meta-analysis of 17 double-blind randomized placebo-controlled trials among elderly people with dementia, determined that atypical antipsychotics were associated with a significantly (1.6−1.7 times) greater mortality risk compared with placebo, and asked that drug manufacturers add a 'black box' warning to prescribing information for these drugs. Most deaths were due to either cardiac or infectious causes, the two most common immediate causes of death in dementia in general. Clinicians, patients, and caregivers are left with unclear choices of treatment for dementia patients with psychosis and/or severe agitation. Not only are psychosis and agitation common in persons with dementia but they also frequently cause considerable caregiver distress and hasten institutionalization of patients. At the same time, there is a paucity of evidence-based treatment alternatives to antipsychotics for this population. Thus, there is insufficient evidence to suggest that psychotropics other than antipsychotics represent an overall effective and safe, let alone better, treatment choice for psychosis or agitation in dementia; currently no such treatment has been approved by the FDA for these symptoms. Similarly, the data on the efficacy of specific psychosocial treatments in patients with dementia are limited and inconclusive. The goal of this White Paper is to review relevant issues and make clinical and research recommendations regarding the treatment of elderly dementia patients with psychosis and/or agitation. The role of shared decision making and caution in using pharmacotherapy for these patients is stressed.

BACKGROUND: PSYCHOSIS AND AGITATION IN DEMENTIA PATIENTS

Among US adults over age 65, prevalence estimates of dementia range from 5% to 15%, with Alzheimer Disease (AD) being the most common type of dementia (Kaplan and Sadock, 1998; Evans et al., 1989; Losonczy et al., 1998). A recent review estimated that worldwide 24 million people have dementia, and that this number will double by the year 2020 (Ferri et al., 2005).

Behavioral and psychiatric symptoms develop in as many as 60% of community-dwelling dementia patients (Wragg and Jeste, 1988; Lyketsos et al., 2000) and in more than 80% of patients with dementia living in nursing homes (Testad et al., 2007; Zuidema et al., 2006); the lifetime risk of such complications approaches 100% (Lyketsos et al., 2000). Psychosis of AD is characterized by delusions or hallucinations (Jeste and Finkel, 2000). The reported prevalence of delusions in AD patients ranges from 9% to 63% (median 36%), and that for hallucinations from 4% to 41% (median 18%) (Ropacki and Jeste, 2005). Rates of physical aggression among community-dwelling dementia patients range from 11% to 46%, whereas rates from institutional settings range from 31% to 42% (Brodaty and Low, 2003). The range of prevalence estimates for agitation in dementia is even wider — from 20% to over 80% (Tractenberg et al., 2003; Ryu et al., 2005). Agitation may be conceptualized as a

single symptom or a symptom complex, and may co-occur with psychosis or depression (Jeste et al., 2006).

Neuropsychiatric symptoms frequently have several adverse clinical repercussions. Psychosis and agitation in patients with dementia decrease quality of life (Matsui et al., 2006; Banerjee et al., 2006) and may portend a worse prognosis. Several studies indicate that psychosis is associated with more rapid cognitive decline among persons with dementia (Drevets and Rubin, 1989; Rosen and Zubenko, 1991; Wilson et al., 2006). Some evidence suggests that agitation and/or psychosis in dementia might be associated with increased mortality, though this finding has been inconsistent. Walsh et al. (1990) demonstrated that behavioral disturbances in general (relative risk 1.5, 95% CI 1.0−2.5), and wandering combined with falls in particular (relative risk 3.1, 95% CI 1.4−6.6) were associated with decreased survival over 6+ years of follow-up, although on multivariate analysis these relative risks failed to reach significance. One study found that nursing home residents who later died had displayed more verbal agitation than those who survived during the same follow-up period (t=2.03, effect size 0.51) (Allen et al., 2005); however, another study reported that the association between mortality and agitation in dementia disappeared on multivariate analysis (Bowen et al., 1996). Likewise, some investigations have demonstrated an association between psychosis of dementia and increased mortality (Wilson et al., 2006), whereas other researchers have not found such a relationship (Samson et al., 1996; Rosen and Zubenko, 1991).

Psychosis and agitation in patients with different types of dementias have been consistently associated with increased caregiver distress (Kaufer et al., 1998); (Fuh et al., 2001; Donaldson et al., 1998; Aarsland et al., 2007; Mourik et al., 2004). The myriad of adverse psychological and physical consequences of caregiver stress have been reviewed (Pinquart and Sorensen, 2003). One reported association of caregiver distress is early patient institutionalization. In a large prospective study, both caregiver burden and behavioral symptoms were independently associated with nursing home placement of persons with dementia (Yaffe et al., 2002). Forty-six percent of caregivers in another study reported behavioral problems as a reason for the decision to place persons with dementia outside the home, and caregiver stress was higher among persons opting for nursing home placement (Buhr et al., 2006). A combination of the various adverse effects of neuropsychiatric symptoms in dementia likely leads to increased system-wide healthcare costs (Murman and Colenda, 2005).

Summary

Psychosis and agitation are not only common but also have serious clinical consequences in persons with dementia.

EFFICACY OF ANTIPSYCHOTICS IN DEMENTIA PATIENTS

Historical Background

With the discovery of the first dopamine-blocking typical (or conventional or first-generation) antipsychotic chlorpromazine in 1952, a revolution in psychiatric therapeutics occurred that radically changed the treatment of schizophrenia and other severe mental illnesses. Over the subsequent decades, adverse long-term consequences of these antipsychotic agents, especially tardive dyskinesia, became evident, but effective and safe therapeutic alternatives did not exist. With the advent of clozapine (FDA approval in 1989) followed by other atypical (or second-generation) antipsychotics (risperidone in 1993, olanzapine in 1996, quetiapine in 1997, ziprasidone in 2001, and aripiprazole in 2002), therapeutic options for psychosis expanded. Atypical antipsychotics demonstrated significantly lower risks of motor side effects and somewhat better overall tolerability

compared to the typical agents (Glazer, 2000; Jeste et al., 1999a; Ritsner et al., 2004; Stanniland and Taylor, 2000). The atypical antipsychotics came to be used widely in different patient populations, including older adults with dementia, who were especially susceptible to the motor side effects of the typical agents (Jeste, 2000). However, based primarily on studies conducted in younger adult populations, the newer agents eventually proved to have their own liabilities, mainly in terms of metabolic side effects (e.g. weight gain, type-II diabetes mellitus, and dyslipidemia) (Jin et al., 2004). In addition, studies have called into question the degree to which atypical antipsychotics (excluding clozapine) represent a significant advance in therapeutic effectiveness compared to the typical agents in schizophrenia (Lieberman et al., 2005; Jones et al., 2006).

Trials of Antipsychotics in Dementia

Approximately half of the clinical trials of antipsychotics in dementia patients recruited individuals with psychosis, while the other half selected individuals with agitation or global behavioral disturbance. Yet, most trials of psychosis did not exclude agitation, and *vice versa*, resulting in many trials including persons with elevated symptom scores for both psychosis and agitation (Schneider et al., 2006a).

Psychosis

Overall, atypical antipsychotic drugs appear to have modest efficacy for treating the psychosis of AD (Ballard and Waite, 2006; Sink et al., 2005), although studies have not always found significant advantage over placebo in terms of psychotic symptoms (Kindermann et al., 2002; Schneider et al., 2006a). Schneider et al. (2006a) reviewed 15 RCTs of atypical antipsychotics for agitation and/or psychosis of dementia that pre-dated the CATIE-AD trial (3 with aripiprazole, 4 with olanzapine, 4 with risperidone, 1 comparing olanzapine and risperidone, and 3 with quetiapine). Eleven trials were conducted in nursing homes and four in outpatient settings. A vast majority of subjects included had AD (87%), and were women (70%), with a mean age of 81 years. Overall, in these trials it is somewhat difficult to disentangle the efficacy of antipsychotics for psychosis from their efficacy for global neuropsychiatric disturbance or for agitation. Several trials included patients with heterogenous mixtures of psychosis and agitation. The trials used a variety of outcome measures, and when primary outcomes measures were reported, they often represented a global measure of neuropsychiatric symptoms. Combining data for individual drugs, psychosis scores improved significantly only in trials of risperidone. On the other hand, global neuropsychiatric symptoms improved with active treatment in pooled analysis of aripiprazole and risperidone. In the six studies that assessed operationally defined psychosis of AD, there was no significant effect in any of the trials on psychosis rating scales. Subgroup analysis revealed better overall response in patients without (versus with) psychosis, those in nursing home (versus outpatient) settings, and those with severe (versus moderate) cognitive impairment.

In the CATIE-AD trial, the largest (N=421) non-industry sponsored study of atypical antipsychotics for psychosis or agitation/aggression in people with dementia, olanzapine, quetiapine, and risperidone were no better than placebo for the primary outcome (time to discontinuation for any reason) or the secondary outcome (Clinical Global Impression or CGI) (Schneider et al., 2006b). Time to discontinuation due to lack of efficacy favored olanzapine and risperidone, while time to discontinuation due to adverse events favored placebo. The CATIE-AD outcome measures were selected to assess effectiveness by focusing on more clinically meaningful or relevant outcomes, in contrast to many previous trials, which used psychopathologic rating scales such as the Neuro-Psychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS), and BEHAVE-AD to assess efficacy (Bech et al., 1988; Reisberg et al., 1996; Cummings, 1997). The CATIE-AD trial was, however, not

without limitations. The authors have noted such issues as possible underdosing of antipsychotics (especially regarding quetiapine) and the relatively high discontinuation rates compared to previous efficacy trials (Schneider et al., 2006a; Schneider et al., 2007). Although the design of CATIE-AD might have led to elevated rates of treatment discontinuation (e.g., through relatively quick decisions to stop therapy and move on to phase 2 of the study), this may also reflect real-world clinical decision-making as it was more of an effectiveness than an efficacy study. Finally, CATIE-AD was conducted with outpatients, a group noted above to demonstrate possibly less response to atypical antipsychotics than nursing home residents or more cognitively impaired patients.

Efficacy data reported as “Number Needed to Treat” (NNT), the number of patients that need to receive a given therapy in order to successfully treat one person, may be especially meaningful for clinicians. In a meta-analysis of large-scale RCTs of atypical antipsychotics in dementia, the NNT ranged from 5 to 14, depending on the outcome measure, the criterion for improvement, and methodology used (2006a). The overall average treatment effect was about 18%, a figure remarkably similar to that found in a meta-analysis of studies of conventional antipsychotics in this population (Schneider et al., 1990).

Agitation

Only a few studies of antipsychotics specifically targeted agitation or aggression. It is noteworthy that, as mentioned before, Schneider et al. (2006a) reported better response in trials of atypical antipsychotics for dementia patients without (versus with) psychosis; thus, patients with agitation alone may preferentially respond to these medications (though common comorbidities such as depression and anxiety were not fully characterized in these patients with agitation). In another meta-analysis, Lonergan et al. (2001) found that haloperidol was beneficial for dementia patients with aggression, but not for general agitation (i.e., wandering, verbal agitation, etc.). Similarly, in recent trials, no significant therapeutic effects were found for haloperidol compared to placebo and trazodone (Teri et al., 2000), compared to placebo and quetiapine (Tariot et al., 2006), and compared to risperidone and placebo (De Deyn et al., 1999). Some, though not all, RCTs with risperidone, olanzapine, and aripiprazole have shown modest efficacy for reducing aggression and overall agitation in AD (Ballard and Waite, 2006; Sink et al., 2005).

Comparisons with Typical Antipsychotics

Because of the recent black-box warnings about strokes and mortality with atypical antipsychotics (see below), some clinicians have begun to switch to the older typical antipsychotic agents. However, there have been only four RCTs comparing these two classes of antipsychotics in persons with dementia: three comparing risperidone with haloperidol (Chan et al., 2001; De Deyn et al., 1999; Suh et al., 2004), and one comparing quetiapine and haloperidol (Tariot et al., 2006). Only one of the four trials found a significantly greater efficacy with the atypical than with the typical agent; the others found no significant difference in this respect. However, in all four studies, haloperidol was associated with more EPS than the atypical agent. Atypical antipsychotics are less likely than most typical antipsychotics (especially haloperidol) to cause or exacerbate EPS and tardive dyskinesia in dementia patients but no other advantages in terms of efficacy or safety have been demonstrated. Likewise, the typical antipsychotics have no proven therapeutic advantages over atypical agents, but typical drugs are less expensive, and individual typical drugs may have less propensity to cause certain side effects (e.g. anticholinergic, hypotensive, metabolic) compared to certain individual atypical agents.

Despite the lack of an FDA-approved indication, the largest number of atypical antipsychotic prescriptions in older adults are for behavioral disturbances in persons with

dementia (Weiss et al., 2000). This suggests a need for designing and conducting further clinical trials of appropriate medications for dementia-associated psychosis and/or agitation. While advances in defining phenotypes of psychosis in dementia have been made (e.g. operationalized criteria for psychosis (Jeste and Finkel, 2000)), these were not used in early clinical trials. Careful consideration must also be given to the validity of outcome measures used for psychosis and other neuropsychiatric symptoms, such as how these may relate to clinically meaningful outcomes.

Summary

The RCTs examining antipsychotics for psychosis and/or agitation associated with dementia, in aggregate, suggest modest efficacy in symptom reduction with active treatment compared to placebo. However, several individual trials have yielded negative results.

ADVERSE EFFECTS OF ANTIPSYCHOTICS IN DEMENTIA PATIENTS

During the past decade, atypical antipsychotics have largely replaced typical agents in the treatment of psychosis, aggression, and agitation in patients with dementia because of perceived greater tolerability and lesser risk for acute EPS, and because of the documented lower risk for tardive dyskinesia compared to typical agents (Glazer, 2000; Dolder and Jeste, 2003; Jeste et al., 1999a; Ritsner et al., 2004; Stanniland and Taylor, 2000). On the other hand, most of these drugs have other acute and subacute side effects in elderly persons such as sedation, postural hypotension, and falls, especially at higher doses. There have been no large-scale published studies of antipsychotic-associated diabetes, obesity, and dyslipidemia among elderly dementia patients. However, during the last three years, two serious adverse events have been associated with the use of atypical antipsychotics in dementia patients, resulting in black-box warnings by the FDA: cerebrovascular adverse events (CVAEs) and death.

Cerebro-Vascular Adverse Events (CVAEs)

In 2003, the FDA issued a warning titled “Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia”. It referred to CVAEs (e.g., stroke, transient ischemic attack), including fatalities, reported in patients (mean age 85 years; age range 73−97) in trials of risperidone in elderly patients with dementia-related psychosis and/or agitation. In placebo-controlled trials, there was a significantly higher incidence of CVAEs in patients treated with risperidone compared to those treated with placebo. In 2003, Janssen (manufacturer of risperidone), in consultation with the FDA, added the following warning to risperidone prescribing information regarding stroke risk in older dementia patients.

> “Combining data from all the 3 published large-scale double-blind placebo-controlled trials of risperidone, (De Deyn et al., 1999; Katz et al., 1999; Brodaty et al., 2003) 12 out of 744 patients on risperidone compared to 4 out of 562 on placebo developed serious cerebrovascular events. Of these patients, 4 on risperidone and 2 on placebo died. At this time, no cause-and-effect relationship can be established between risperidone and strokes; nonetheless, such a possibility cannot be ruled out.”

Combining data from three published placebo-controlled RCTs of risperidone with those from three unpublished trials, Janssen reported the rates of risperidone- versus placebo-associated serious CVAEs were not significantly different (15/1009=1.5% for risperidone vs. 4/712=0.6% for placebo, p=0.27). However, using the same data, risperidone-treated patients had significantly higher rates of non-serious CVAEs than did placebo-treated patients (18/1009=1.8% and 4/712=0.6%, respectively; p=0.026) (Herrmann and Lanctot, 2005).

Soon thereafter, a similar warning was applied to olanzapine and aripiprazole. In the five olanzapine trials, the relative risk of CVAEs was 1.8 (95% CI 0.5, 6.3), which was not statistically significant (p = 0.36). Collectively, the 11 risperidone/olanzapine studies suggested that 48 of 2,187 (2.2%) drug-treated subjects experienced CVAEs compared with 10 of 1,190 (0.8%) placebo-treated subjects (Herrmann and Lanctot, 2005); the combined relative risk was 2.7 (95% CI 1.4, 5.3). In placebo-controlled trials with aripiprazole in psychosis of AD (two flexible dose trials and one fixed dose study), there was an increased incidence of CVAEs (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients, (mean age: 84 years; range: 78−88 years) (Abilify prescribing information, 2006). The relative risk of CVAEs is not directly reported in the prescribing information for aripiprazole. In the fixed-dose study, there was a statistically significant dose response relationship for CVAEs in patients treated with aripiprazole. Analysis of data combined from two studies of quetiapine versus placebo in dementia yielded rates of CVAE's of 0.9% versus 1.9%, respectively (relative risk 0.5, 95% CI 0.1−2.0) (Schneider LS, Tariot PN, Mintzer J et al (unpublished)). However, the data with quetiapine in dementia patients are somewhat more limited than those with risperidone, olanzapine, or aripiprazole. A meta-analysis found that pooled rates of CVAEs were 1.9% in atypical antipsychotic treated patients versus 0.9% in placebo-treated patients, yielding an odds ratio of 2.1 (95% CI 1.2, 3.8) (Schneider et al, 2006a).

Limitations of CVAE Data

The increased risk for CVAEs was determined from RCTs, and is based on unbiased estimates. However, interpretation of the risk is limited by several facts including the following:

a) These studies were designed and powered to determine efficacy, not a cause-and-effect relationship between atypical antipsychotics and CVAEs.

b) The category of serious CVAEs was broad and not operationally defined while designing the trials. The diagnoses of serious CVAEs were based on spontaneously reported adverse events; these were not validated. Nevertheless, whatever the events were, they were being determined in an unbiased fashion in double-blind, placebo-controlled trials, and occurred more frequently with atypical antipsychotics than with placebo. It is thus possible that some of the actual events could have been characterized as non-“cerebrovascular” in origin, although this does not mitigate concern about their seriousness.

c) Typical vs. Atypical Antipsychotics: Gill et al. (2005) in a retrospective cohort study reported that, after adjustment for potential confounders, participants receiving atypical antipsychotics showed no significant increase in the risk of ischemic stroke compared with those receiving typical antipsychotics (adjusted hazard ratio 1.0, 95% CI 0.8, 1.3). This finding was consistent in subgroup analyses of individual atypical antipsychotic drugs (risperidone, olanzapine, and quetiapine) and selected subpopulations of the total sample. This was similar to the results reported by other authors (Herrmann et al., 2004) that typical antipsychotics appeared similar to atypical agents in stroke risk. However, the retrospective data bases used for these analyses were not intended to address the issue of CVAEs with antipsychotics. Among the four previously described RCTs comparing typical versus atypical antipsychotics, none reported a differential incidence of CVAEs with typical or atypical antipsychotics although sample sizes were smaller than might be needed to demonstrate such differences (Chan et al., 2001; De Deyn et al., 1999; Suh et al., 2004).

Possible Mechanisms

Mechanisms underlying antipsychotic- associated CVAEs are unknown. It is conceivable that such mechanisms could be somewhat different for different drugs. Hypotheses could include: orthostatic hypotension (α_1-receptor blockade); tachycardia (α_1- and M_2-receptor blockade); metabolic derangements due to atypical antipsychotics such as insulin resistance, weight gain, dyslipidemia (possibly due to H_1-, M_3-, $5HT_2$-receptor blockade); sedation (e.g. D_2-, $5HT_2$-, H_1-receptor blockade) and/or EPS (D_2-receptor blockade) leading to venous stasis and consequent activation of pro-coagulant pathways; and hyperprolactinemia (D_2-receptor blockade), which has been associated with impaired endothelial function, decreased insulin-sensitivity, and increased platelet aggregation (Herrmann and Lanctot, 2005). All of the above mentioned mechanisms are speculative, and not shown to be causally related to CVAEs with antipsychotics. The relationship of antipsychotic dose or drug-drug interactions to CVAEs is unclear.

Mortality

The FDA issued the following warning in May 2004 for all atypical antipsychotics based on their examination of published and unpublished proprietary clinical trials data:

> "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."

A meta-analysis of 15 RCTs documented the risk of mortality with atypical antipsychotics compared to placebo as 3.5% vs. 2.3%, respectively (OR 1.5; 95% CI 1.1, 2.2) (Schneider et al., (2005a). Using the concept of "Number Needed to Harm" (NNH), similar to NNT, for every 100 (95% CI 53,1000) dementia patients treated with an atypical antipsychotic over 10 to 12 weeks, there would be 1 death due to atypical drug use. Given the above mentioned NNT calculations, the likelihood of benefit versus serious risk would be modest: for every 9 to 25 persons helped with these medications there would be 1 death.

Limitations of Mortality Data

As with the CVAEs, there are important limitations to the above mentioned data on mortality in the published RCTs.

a) Insufficient information is available on individual cases, causes or circumstances of death, baseline clinical characteristics, medical conditions, and concurrent medications. Most deaths were due to either cardiac or infectious disorders, which are also the two most common immediate causes of death in patients with dementia in general (Keene et al, 2001; Kammoun et al, 2000).

b) Typical vs Atypical Antipsychotics: A meta-analysis noted that, in two RCTs including haloperidol, the increased risk of death in dementia patients treated with haloperidol relative to placebo (OR 1.7, 95% CI 0.7−3.9) was similar to the average increase in risk reported with atypical drugs relative to placebo (Schneider et al 2005). Cerebrovascular adverse events and quetiapine: a pooled analysis in elderly patients with dementia. Presented at the 18th Annual Meeting of the American Association for Geriatric Psychiatry; San Diego, CA

March 3−6.). Although the difference in mortality rates between haloperidol and placebo was not statistically significant, this does not equate to a lack of concern. In a recent paper, Wang et al. (2005) reported the results of a retrospective cohort study of mortality involving 22,890 patients, 65 years of age or older, treated with antipsychotics. Typical antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications at all intervals studied (≤180 days: relative risk, 1.4; 95% CI, 1.3 to 1.5; <40 days: relative risk, 1.6; 95% CI, 1.4 to 1.8; 40 to 79 days: relative risk, 1.4; 95% CI, 1.2 to 1.6; and 80 to 180 days: relative risk, 1.3; 95% CI, 1.1 to 1.4), and in all subgroups defined according to the presence or absence of dementia or nursing home residency. Similar results (i.e. higher mortality with typical than with atypical antipsychotics among older adults) were reported in two other retrospective analyses of large health system databases (Nasrallah et al., 2004; Schneeweiss et al., 2007). A Finnish study of 254 frail elderly patients with dementia in nursing homes and hospitals found no increase in mortality with either typical or atypical antipsychotics over a two-year period (Raivio et al., 2007). These studies have the usual limitations that accompany retrospective data analyses, and researchers have pointed to other limitations such as a lack of statistical control for possible confounds including medical illness and demographics in at least one investigation (Blazer, 2004).

Possible Mechanisms

As with CVAEs, several mechanisms may be postulated for antipsychotic-associated deaths, although they are all speculative. These include metabolic derangements, cardiac conduction disturbances, sedation leading to aspiration, with secondary pneumonia, and other mechanisms listed above with CVAEs.

Summary

The incidence of mortality is significantly higher with atypical antipsychotics as a group (and that of CVAEs with several agents in this class) than with placebo in patients with dementia, based on large-scale RCTs. However, several aspects of this association remain unknown.

ALTERNATIVES TO ANTIPSYCHOTICS IN DEMENTIA PATIENTS

The alternatives to antipsychotics for treating psychosis and agitation in persons with dementia include no treatment, use of other psychotropic drugs, and psychosocial and psychotherapeutic interventions. The consequences of these options are considered below.

No Specific Treatment

Not initiating any specific treatment may be a viable option in mild-to-moderate cases, or if symptoms are not overtly disturbing for the patient and are not resulting in impaired functioning. However, serious consequences are generally associated with persistent or severe psychosis and agitation in persons with dementia that may make non-specific treatment impractical and even dangerous in certain cases.

Other Psychotropics

Psychotropics from other medication classes have been proposed for treating psychosis and agitation in dementia (Sink et al., 2005). Compared to antipsychotics, even less evidence base exists regarding the use of non-antipsychotic medications for these symptoms. We searched PubMed through November 1, 2006 for RCTs of non-antipsychotic medications primarily targeted at psychosis or agitation associated with AD or dementia in general. We used the following search terms combined with “dementia” and limited to “clinical trials”: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, tricyclic,

bupropion, duloxetine, mirtazapine, moclobemide, nefazodone, reboxetine, trazodone, venlafaxine, carbamazepine, divalproex, gabapentin, lamotrigine, phenytoin, topirimate, valproic acid, lithium, benzodiazepine, alprazolam, clonazepam, diazepam, lorazepam, oxazepam, buspirone, donepezil, galantamine, rivastigmine, tacrine, memantine, propranolol, and estrogen. Additionally we searched "dementia and agitation," "dementia and psychosis," and "dementia and aggression" with a limit of "randomized controlled trials." Table 1 summarizes the studies (n= 17) we found that were explicitly designed to assess efficacy for psychosis and/or agitation, and included 20 or more subjects. Many trials had important methodological limitations (e.g. small sample sizes). Overall, these trials yielded, at best, mixed results regarding therapeutic efficacy and tolerability.

Cholinesterase inhibitors and memantine have been reported to have small-to-medium effect size effects on neuropsychiatric symptoms, including psychosis and agitation; however, these data were obtained from secondary outcome measures and post-hoc analyses of patients who often did not have clinically significant behavioral symptoms at baseline, and yet other trials have shown no effect of cognitive enhancers on behavior (Cummings et al., 2006b; Sink et al., 2005; McKeith et al., 2000; Trinh et al., 2003; Cummings et al., 2006a; Hermann et al., 2005). A prospective trial of donepezil for neuropsychiatric symptoms in outpatients with mild-moderate AD showed improvement in global neuropsychiatric symptoms during open-label treatment for 3 months, followed by symptomatic worsening only in placebo-treated patients during the subsequent randomized discontinuation phase of the trial (Holmes et al., 2004). Yet, these patients had relatively modest levels of behavioral symptoms. A recent placebo-controlled RCT of donepezil, the British Medical Research Council-sponsored CALM-AD trial showed no effect of donepezil on behavior in AD patients with both severe dementia and substantial behavioral symptoms (Howard R, unpublished data). One small RCT compared quetiapine, rivastigmine, and placebo specifically to assess efficacy for agitation in dementia patients, and found no difference among the treatment groups (Ballard et al., 2005)

As with antipsychotics, no other psychotropic medications have been approved by the FDA for the treatment of psychosis or agitation in dementia. Nonetheless, some of these agents may be considered on a case-by-case basis, taking into account the risk-benefit ratio for each individual patient. There is a paucity of clinical trials with psychotropics in older adults in general and in dementia patients in particular, with consequent lack of evidence-based therapeutic alternatives. Several factors contribute to this dearth of clinical trials in older adults – e.g., pharmaceutical companies tend to shy away from studying older adults because of their increased medical comorbidity, polypharmacy, cognitive deficits, and a greater risk for most side effects (Roose and Sackeim, 2002; Ownby, 2001; Schneider et al., 2003).

Psychosocial and Psychotherapeutic Interventions

In the RCTs of antipsychotics in patients with dementia summarized earlier, the placebo response rate was generally 30−50%. This relatively high placebo response rate may be attributed, in part, to nonspecific therapeutic factors such as improved attention and care for patients enrolled in clinical trials, suggesting a possible value of psychosocial and behavioral treatments for this patient population. Clinical experience as well as several small studies support the usefulness of specific interventions of this type in individual patients. Unfortunately, the evidence base for the efficacy of most psychosocial interventions in dementia patients is limited (Cohen-Mansfield, 2001; Livingston et al., 2005). Livingston and colleagues (2005) recently reviewed psychosocial treatment trials for neurospychiatric symptoms of dementia and noted several promising treatments (e.g. cognitive stimulation therapy, behavioral management techniques, music therapy, caregiver education). However, only 9 of 162 studies included in the review were graded as "level 1 evidence" using

guidelines from the Oxford Centre for Evidence-Based Medicine, and several studies focused on outcomes other than psychosis or agitation (e.g. depression). Similarly, Ayalon and colleagues (2006) recently published a systematic review of nonpharmacological treatments for neuropsychiatric symptoms of dementia, and using strict inclusion criteria suggested by the American Psychological Association, found only three RCTs that met these criteria. All three RCTs evaluated caregiving interventions, and the results were inconclusive.

The published studies of psychosocial/behavioral treatments have a number of methodological limitations. Many, if not most, of the patients included in such studies had mild symptoms, so that these treatments might only be useful in mild to moderate cases. Additionally, assessments of adverse outcomes in many such trials were not as systematically conducted as in pharmaceutical trials. This leaves open a possibility that adverse effects might not have been adequately evaluated and reported. Despite these limitations, it should be emphasized that lack of evidence is not the same as evidence of lack of efficacy for psychosocial treatments in dementia-related psychosis and agitation. An individualized approach to psychosocial treatments using behavioral and other strategies may be a reasonable choice for certain patients with these symptoms.

There is clearly a need for conducting well designed RCTs of behavioral and psychosocial interventions in patients with dementia. It is true there would be obstacles to widespread implementation of even evidence-based psychosocial and psychotherapeutic treatments, including a lack of financial resources, the increased training and time necessary to implement them, and a lack of reimbursement for providing them. Nonetheless, there is some limited evidence that certain psychosocial interventions can be successfully implemented. For instance, Ray, et al. (1993) demonstrated that a comprehensive program to reduce antipsychotic drug use through education of physicians, nurses, and other nursing home staff was effective in two rural community nursing homes. The number of days of antipsychotic use decreased by 72% in the education homes compared to 13% in the control homes ($p < .001$). A more recent study demonstrated that a training and support intervention delivered to nursing home staff decreased the use of antipsychotics (Fossey et al., 2006). Additionally, collaborative care management in primary care settings, when compared to augmented usual care, showed improvements in overall severity of neuropsychiatric symptoms (Callahan et al., 2006). Thus, possible problems in dissemination and implementation should not stand in the way of carrying out methodologically sound RCTs of nonpharmacological interventions in patients with dementia.

Summary

The efficacy and safety of pharmacological and psychosocial/behavioral treatment alternatives to antipsychotics for managing patients with dementia complicated by psychosis and/or agitation remain unclear.

Summary of What is Known and What is Not Known regarding Antipsychotics for Psychosis and Agitation in Patients with Dementia

The following is a summary of what is known and what is not regarding the use of antipsychotic drugs in dementia-associated psychosis and agitation, based largely on the literature discussed above.

What is known

(1) Psychosis, aggression, and agitation are common problems in patients with dementia, and when severe or persistent, can cause considerable patient distress and disability, as well as caregiver strain and early institutionalization.

(2) There is no FDA-approved indication for a drug to treat psychosis or agitation in persons with dementia. However, unlabeled (or "off-label") use of pharmacotherapy, especially antipsychotics, is common practice.

(3) More RCTs have been done in dementia patients with psychosis and/or agitation for atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) and for haloperidol than for other classes of psychotropic drugs. Most of these trials have included patients with AD or dementia of unspecified etiology. The RCTs examining antipsychotics for agitation and/or psychosis associated with dementia, in aggregate, suggest modest efficacy in symptom reduction with active treatment compared to placebo. However, several individual trials have yielded negative results. The recent CATIE-AD trial suggested that side effect burden may negate the clinical effectiveness of these agents.

(4) The incidence of mortality is significantly higher with atypical antipsychotics as a group (and that of CVAEs with several agents in this class) than with placebo in patients with dementia, based on large-scale RCTs. This has prompted the addition of an FDA black-box warning regarding these risks to the prescribing information for atypical antipsychotics. The overall risk difference is 1−2% over 8−12 weeks. These risks in addition to acute and subacute adverse effects such as excessive sedation, postural hypotension, and falls should be taken into account when considering treatment.

(5) Atypical antipsychotics are less likely than most first generation antipsychotics (especially haloperidol) to cause or exacerbate EPS and tardive dyskinesia in dementia patients. However, no other differences in efficacy or safety have been demonstrated between typical and atypical agents, although typical antipsychotics are less expensive. Individual typical or atypical drugs may have less propensity to cause certain side effects (e.g. anticholinergic, hypotensive, metabolic) compared to certain other individual agents in specific patients.

(6) The placebo response rate in RCTs testing antipsychotics in dementia is relatively high (generally 30−40%). Nonspecific therapeutic factors such as improved attention and care for patients enrolled in clinical trials likely account for a substantial portion of this improvement.

What is unknown

(1) Direct comparisons of typical and atypical antipsychotics in controlled trials in persons with dementia have been limited. As such, differential effects of these medication classes on symptom improvement and various adverse reactions (including CVAEs and death) remain undetermined. Likewise, individual antipsychotics within the same class may have differences in serious side effect profiles, but head-to-head comparisons among atypical antipsychotics have been uncommon.

(2) Given the relatively brief duration of most RCTs, the risks for CVAEs and death beyond 8−12 weeks are unknown, as are any potential long-term benefits from continued antipsychotic treatment.

(3) No specific risk or protective factors related to antipsychotic-associated CVAEs or deaths are known. It is possible that as-yet undetermined factors (e.g. medical comorbidity,

etiology or stage of dementia, concomitant medications, antipsychotic dose, genetic factors) mediate risks in individual patients. The same is true regarding possible mediators/ moderators of therapeutic effects.

(4) The efficacy and safety of treatment alternatives to antipsychotics are unclear. No psychotropic drug has well-established efficacy and safety in patients with dementia complicated by agitation or psychosis. The same is true for psychosocial interventions.

(5) The behavioral effects of treatments for dementia targeted at cognitive symptoms (i.e., cholinesterase inhibitors and memantine) are unclear, but appear to be modest at best, based on existing data.

(6) Whereas advances have been made in understanding the neurobiology of psychiatric complications of dementia, these findings have not yet established the most proximal causes of these symptoms. As such, specifically targeted pharmacotherapies for psychosis and agitation in dementia are unavailable; current treatments are primarily an extrapolation of treatments for related but somewhat different syndromes (e.g., schizophrenia). Future treatments more specific to underlying pathological processes in dementia may yield better results.

CLINIAL AND RESEARCH RECOMMENDATIONS

CLINICAL RECOMMENDATIONS

(1) Determining Etiology of Symptoms—Psychosis or agitation may result from multiple causes in people with dementia. Seeking to identify the underlying causative factors for the symptoms in a given individual should be the first step in management. For example, these symptoms may be a part of a delirium secondary to anticholinergic toxicity; in such cases, reducing the anticholinergic load would be warranted. Likewise, agitation may be a result of psychosocial stressors that may be correctable.

(2) General Therapeutic Considerations—Good clinical care, independently from pharmacotherapy, may be helpful for patients with dementia-related psychosis and/or agitation, and their caregivers, through nonspecific and specific interventions. Nonspecific interventions such as empathy and attention to interpersonal and social issues may be particularly helpful, as evidenced in several studies and by the improvements in the placebo groups in nearly all clinical trials. Specific interventions include environmental, psychosocial, behavioral, and medical interventions to reduce or mitigate possible antecedents as well as consequences of the behaviors.

(3) Shared Decision Making—Clinicians and their patients should make decisions based on the patients' and families' values regarding quality of life goals. Providers should engage caregivers, family members, and patients (whenever possible), in the decision-making process for treating psychosis, agitation, and other disruptive behaviors. This will include offering appropriate information about what is known regarding overall risks and benefits of different treatment options. Such information should be tailored to the educational/ intellectual level of the recipient, and also respect the individual's desire for autonomy in medical decisions. Thus, some people may want to fully engage in a detailed risk/benefit analysis, and be equal partners in treatment decisions. Others may be more deferential to the clinician out of habit or anxiety about making a wrong decision, but even these individuals should be provided with all relevant information (including risks and benefits of no treatment and of possible environmental/psychosocial interventions) along with opportunities to participate in decisions to the extent they are comfortable. Clinicians should document the fact that a discussion of these issues was conducted.

(4) Identifying Target Symptoms—It is important to identify target signs and symptoms, and to establish a time frame in which to expect and evaluate an intervention's effectiveness and in which to decide on continuing or altering treatment. Both expert clinical opinion and RCT evidence demonstrate that a sizable proportion of both drug-and placebo-treated patients improve within 2 to 4 weeks.

(5) Choice of Pharmacotherapy—Not all psychotic symptoms or agitations need pharmacotherapy. Only severe symptoms that are persistent or recurrent and cause clinically significant functional disruption would generally be considered appropriate for ongoing pharamcologic management. At this time, there is no single treatment algorithm that can be routinely recommended for all patients with dementia. Individual patients may tolerate and benefit from antipsychotic medications such that their use in patients with severe and persistent or recurrent symptoms may be justified, but these medications are not an unequivocal first-line treatment. Use of antipsychotics after shared decision making with patients and/or caregivers and followed by close clinical monitoring is within the realm of reasonable practice. There is no evidence to support overall better safety profiles with typical (compared to atypical) antipsychotics, and these drugs, as a class, may *not* be considered as therapeutic alternatives for the purpose of minimizing these risks (although there may be individual exceptions). There is a lack of evidence to support efficacy or safety when other agents (e.g. antidepressants, anticonvulsants, benzodiazepines) are used for treating psychosis or agitation in people with dementia.

(6) Dosages—One should use the lowest medication dosages required and for the shortest time period necessary. This may include medication tapering or discontinuation in patients who have symptomatic remission. An examination of therapeutic and adverse effects of these medications in elderly persons with dementia suggests target doses of 0.5−1.5 mg/day of risperidone; 5−10 mg/day of olanzapine; 50−200 mg/day of quetiapine; and 7−12 mg/day of aripiprazole, although these dose ranges are not universally considered as evidence-based (Katz et al., 1999; Alexopoulos et al., 2005; Jeste et al., 1999a; Zhong et al., 2007; Jeste et al., 1999b; Street et al., 2000; De Deyn et al., 2005; Tariot et al., 2006).

(7) Monitoring Effectiveness—The clinician should regularly assess treatment response in terms of effectiveness. Although a number of instruments for evaluating clinical outcomes associated with neuropsychiatric symptoms in dementia have been used in research, these have not generally been shown to be feasible or useful tools for everyday clinical practice. Several recent reviews have summarized the relative strengths and weaknesses of scales designed to measure such outcomes in studies of dementia (Rockwood, 2007; Ready and Ott, 2003; De Deyn and Wirshing, 2001). Individual clinicians should consider the following domains in monitoring treatment effectiveness: symptom severity and frequency, daily functioning, quality of life, and global impressions of clinicians, caregivers, and (when possible) patients.

(8) Monitoring Safety—Elderly persons with dementia constitute a fragile population in whom introduction of any prescription medication may carry some appreciable risks. Treatment approaches should, therefore, be frequently reassessed. The clinician should regularly monitor relevant adverse effects of antipsychotics, including EPS, tardive dyskinesia, blood pressure, body weight, and blood glucose and lipid levels. The physical assessments may be conducted at baseline and then every 3 months whereas the lab testing may be done at baseline, months 3 and 6 and every 6 months thereafter. These are general recommendations, and the exact intervals may be shorter or longer depending on an individual patient's medical profile. Additional medical evaluations may be needed for patients with specific risk factors.

(9) Education of Patients and Caregivers—In addition to the information regarding risks/benefits discussed during the informed consent process, it is necessary to educate patients, caregivers, and family members about actions to take if and when side effects occur. Also the clinician should assess the caregivers' ability to monitor beneficial and adverse effects of the treatment plan, including medication initiation and withdrawal.

(10) Considering Discontinuing or Switching Pharmacotherapy—Absence of significant improvement in target symptoms or occurrence of certain adverse effects (e.g., weight gain, hyperglycemia, tardive dyskinesia) may warrant considerations for discontinuation of medication or switching to another treatment with a putatively safer profile for the particular side effects.

(11) Given the complex array of medical illnesses typical of such patients, physicians should coordinate patient care with other health care professionals (especially, primary care physicians) to minimize risks of treatments—In view of limited empirical evidence to guide many clinical decisions, clinicians will often have to make choices based on their clinical experience and judgment. The serious consequences of psychosis and agitation in dementia, the problematic risk-benefit profile of antipsychotic medications for such symptoms, and the paucity of data on other treatment alternatives combine to create a clinical conundrum for which there are no immediate or simple solutions.

RESEARCH RECOMMENDATIONS

There is an urgent need for additional research in this area of considerable public health significance. Below we list some examples of suggested research.

(1) Patient-level meta-analyses of existing data from clinical trials so as to identify predictors of efficacy as well as factors related to increased risk of CVAEs and death in subpopulations of patients and with specific aspects of treatment (e.g., lower vs. higher doses).

(2) Establishing clinically significant treatment outcomes and goals from the perspectives of patients and caregivers—e.g. via qualitative studies.

(3) Exploring biological mechanisms (including non-dopaminergic ones) underlying psychosis and agitation in dementia, and using such data to continually refine these diagnostic constructs/phenotypes.

(4) Search for biomarkers that may allow risk/benefit prediction on an individualized level (e.g., genetic markers related to neurotransmitters or vascular risk factors; functional neuroimaging).

(5) Development and testing of novel pharmacological targets (pharmacological agents that more directly affect underlying pathophysiologic changes) for psychosis and agitation in dementia, including neuroprotective agents; in light of the recent safety concerns, much needed research to discover effective treatments for these syndromes may not be undertaken by pharmaceutical industry.

(6) Studies of mechanism of action for antipsychotic effects on cardio/cerebrovascular systems.

(7) Exploring effects of nonpharmacological somatic treatments for psychosis and agitation in dementia (e.g. light therapy, electroconvulsive therapy, transcranial magnetic stimulation).

(8) Conducting additional trials of psychosocial treatments for dementia-related neuropsychiatric symptoms.

(9) Research on the shared decision-making process and its effects on consumer satisfaction in this clinical setting.

(10) Investigations with a focus on delaying or preventing the emergence of psychosis and agitation in persons with dementia.

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Table 1

Randomized controlled trials using non-antipsychotic medication for psychosis and/or agitation in persons with dementia

Authors (year)	Psychotropic (daily dose)	Sample (n)	Outcome Measure	Results	Comments
Antidepressants					
Sultzer et al. (1997)	Trazodone (50−250 mg)	Inpatients with dementia and agitation or aggression (28)	CMAI, OAS, CGI	Trazodone = haloperidol (1−5 mg/d); trazodone better tolerated than halodperidol	Small sample size; heterogeneous dementia etiologies included; no PBO control group; chloral hydrate as rescue med
Teri et al. (2000)	Trazodone (50−300 mg)	AD patients with agitation (149)	ADCS-CGIC	Trazodone = PBO on efficacy and side effects	4-armed trial (including PBO, haloperidol, and cognitive behavioral therapy management) failed to distinguish among any treatment group; heterogeneous target symptoms
Levkovitz wt al. (2001)	Fluvoxamine (50 mg)	AD patients with psychosis concomitantly treated with perphenazine 12 mg/day (20)	BPRS, CGI	Perphenazine + fluvoxamine better than perphenazine + PBO on total BPRS only	No change in positive symptoms with fluvoxamine augmentation; small sample; fluvoxamine can increase antipsychotic blood levels; little description of concomitant meds or adverse events; crossover design could cause SSRI withdrawal to confound observations; fixed, low dose for brief duration
Pollock et al. (2002)	Citalopram (20 mg)	Inpatients with dementia-associated psychosis and/or agitation/aggression (85)	Neuro-behavioral Rating Scale	Citalopram better than PBO for total score and lability + agitation subscales; citalopram = PBO for tolerability	Modest sample size; heterogeneous target symptoms; heterogeneous dementia etiologies; lorazepam as rescue med; relatively high attrition in severely ill population; third arm treated with perphenazine, which did not differ from citalopram or PBO
Lanctot et al. (2002)	Sertraline (100 mg)	Institutionalized persons with severe AD with NPI score >7 but without major depression (22)	NPI, CMAI, BEHAVE-AD, CGI	Sertraline = PBO on efficacy and tolerability	Small sample size; limited rescue med with lorazepam; higher prolactin response to fenfluramine challenge somewhat predictive of better reponse to sertraline
Finkel et al. (2004)	Sertraline (50−200mg)	AD patients with NPI score >5, taking donepezil 10 mg/d (276)	NPI, CGI, BEHAVE-AD	Sertraline = PBO; more diarrhea in sertraline group	Heterogeneous target symptoms; 8-week open treatment with donepezil as lead-in to sertraline trial could have influenced behavioral symptoms; large sample size and relatively long treatment duration (12 weeks)
Anticonvulsants					
Tariot et al. (1998)	Carbamazepine (CBZ) (mean=304 mg)	Dementia patients with agitation in nursing homes (51)	BPRS, CGI	CBZ better than PBO; more side effects (e.g. ataxia, disorientation) with CBZ	Small sample size; vascular, Alzheimer's, and mixed dementias included; chloral hydrate as rescue med; CBZ dose adjusted by non-blinded physician; some baseline differences between treatment groups

Authors (year)	Psychotropic (daily dose)	Sample (n)	Outcome Measure	Results	Comments
Olin et al. (2001)	Carbamazepine (CBZ) (400 mg)	Dementia patients with agitation unresponsive to antipsychotics (21)	BPRS, CGI	CBZ better than PBO but trend for worsened hallucinations with CBZ	Small sample size; chloral hydrate as rescue medication; average CBZ level = 4.9 mcg/ml
Porsteinsson et al. (2001)	Divalproex (mean=826 mg)	Dementia patients with agitation in nursing homes (56)	BPRS, CGI	Divalproex=PBO	Modest sample size; average VPA level = 45 mcg/ml; multiple dementia diagnoses included; VPA dose adjusted by non-blinded physician
Sival et al. (2001)	Valproate (VPA) (480 mg)	Dementia patients with aggression (42)	SDAS-9, CGI	VPA = PBO	Any dementia type included; secondary beneficial effects on restless/anxious behaviors noted for VPA but with multiple comparisons; treatment duration only 3 weeks
Tariot et al. (2005)	Divalproex (mean=800mg)	AD patients with agitation in nursing homes (153)	BPRS (agitation)	Divalproex=PBO	Relatively large sample size with adequate power; average VPA level (52.8 mcg/ml); VPA-treated patients had more diarrhea and “nervous system” side effects; lorazepam and zolpidem allowed as rescue meds
Other					
Coccaro et al. (1990)	Oxazepam (10−60mg) Diphenhydramine (25−200 mg)	Dementia patients with agitation in long-term care facilities (59)	BPRS	Oxazepam, haloperidol, and diphenhydramine were all equivalent	No placebo control; limited assessment of adverse effects; diphenhydramine now often listed among medications to avoid in the elderly because of anticholinergic effects; heterogeneous dementia population
Cantillon et al. (1996)	Buspirone (mean 15 mg)	AD patients with agitation/aggression living in a nursing home (26)	BPRS	Buspirone = haloperidol	No placebo comparison; small sample; no concomitant psychotropics except benztropine
Christensen and Benfield (1998)	Alprazolam (1 mg)	Dementia patients with agitation living in nursing homes (48)	CGI, SCAG	Alprazolam = haloperidol	Entry criterion was treatment with haloperidol at 1 mg/day or less (not specific symptomatology); cross-over design may create drug withdrawal effects
Ballard et al. (2005)	Rivastigmine* (9−12 mg)	AD patients with agitation in long term care facilities (93)	CMAI	Rivastigmine = PBO	Third treatment arm of quetiapine also failed to separate from PBO or rivastigmine; modest sample size; quetiapine may have worsened cognition
Hall et al. (2005)	Transdermal estrogen (50−100 mcg)	Male dementia patients with aggressive behaviors (27)	RAGE	Estrogen = PBO	Small sample size; “rebound” worsening when estrogen withdrawn; adverse effects of hormonal treatments may occur over longer term; concomitant antipsychotic and benzodiazepine treatment allowed
Peskind et al. (2005)	Propranolol (mean=106mg)	AD patients with agitation (31)	NPI, CGI	Propranolol better than PBO	Small sample size; effects not maintained at 6-month open-label follow-up; participants on average were on two other psychotropics during study

AD (Alzheimer disease);

ADCS-CGIC (Alzheimer's Disease Cooperative Study Clinical Global Impression of Change);

BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease Rating Scale);

BPRS (Brief Psychiatric Rating Scale);

CBZ (carbamazepine);

CGI (Clinical Golbal Impression);

CMAI (Cohen-Mansfield Agitation Inventory);

NPI (Neuropsychiatric Inventory);

OAS (Overt Aggression Scale);

PBO (placebo);

RAGE (Rating Scale for Aggressive Behavior in the Elderly)

SCAG (Sandoz Clinical Assessment Geriatric scale);

SDAS-9 (Social Dysfunction and Aggression Scale-9);

VPA (valproic acid)

* We did not include most published trials of cholinesterase inhibitors and memantine that reported behavioral effects, because these trials were designed primarily to assess cognition, with only secondary post-hoc analysis of behavioral symptoms.