Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia

A Review of the Evidence

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Context Neuropsychiatric symptoms of dementia are common and associated with poor outcomes for patients and caregivers. Although nonpharmacological interventions should be the first line of treatment, a wide variety of pharmacological agents are used in the management of neuropsychiatric symptoms; therefore, concise, current, evidence-based recommendations are needed.

Objective To evaluate the efficacy of pharmacological agents used in the treatment of neuropsychiatric symptoms of dementia.

Evidence Acquisition A systematic review of English-language articles published from 1966 to July 2004 using MEDLINE, the Cochrane Database of Systematic Reviews, and a manual search of bibliographies was conducted. Inclusion criteria were double-blind, placebo-controlled, randomized controlled trials (RCTs) or meta-analyses of any drug therapy for patients with dementia that included neuropsychiatric outcomes. Trials reporting only depression outcomes were excluded. Data on the inclusion criteria, patients, methods, results, and quality of each study were independently abstracted. Twenty-nine articles met inclusion criteria.

Evidence Synthesis For typical antipsychotics, 2 meta-analyses and 2 RCTs were included. Generally, no difference among specific agents was found, efficacy was small at best, and adverse effects were common. Six RCTs with atypical antipsychotics were included; results showed modest, statistically significant efficacy of olanzapine and risperidone, with minimal adverse effects at lower doses. Atypical antipsychotics are associated with an increased risk of stroke. There have been no RCTs designed to directly compare the efficacy of typical and atypical antipsychotics. Five trials of antidepressants were included; results showed no efficacy for treating neuropsychiatric symptoms other than depression, with the exception of 1 study of citalopram. For mood stabilizers, 3 RCTs investigating valproate showed no efficacy. Two small RCTs of carbamazepine had conflicting results. Two meta-analyses and 6 RCTs of cholinesterase inhibitors generally showed small, although statistically significant, efficacy. Two RCTs of memantine also had conflicting results for treatment of neuropsychiatric symptoms.

Conclusions Pharmacological therapies are not particularly effective for management of neuropsychiatric symptoms of dementia. Of the agents reviewed, the atypical antipsychotics risperidone and olanzapine currently have the best evidence for efficacy. However, the effects are modest and further complicated by an increased risk of stroke. Additional trials of cholinesterase inhibitors enrolling patients with high levels of neuropsychiatric symptoms may be warranted.

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Up to 50% of community-dwelling elderly individuals older than 85 years have dementia, with Alzheimer disease (AD), vascular dementia, and dementia with Lewy bodies accounting for most cases.[1,2] Although cognitive deficits are the clinical hallmark of dementing illnesses, noncognitive symptoms are common and can dominate disease presentation. These include an array of neuropsychiatric symptoms, such as agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among other symptoms. Neuropsychiatric symptoms have been observed in 60% to 98% of patients with dementia,[3-7] especially in later stages, and are associated with caregiver stress and depression, as well as reduced caregiver employment and income.[8-13]

Neuropsychiatric symptoms are also associated with increased hospital lengths of stay[14] and commonly lead to nursing home placement.[15-17] Federal expenditures for dementia are expected to triple in the next 10 years[18] and 30% of the cost of caring for patients with AD is attributed directly to the management of neuropsychiatric

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symptoms.[19] Thus, interventions aimed at treating neuropsychiatric symptoms could have a tremendous impact on patients, caregivers, and society.

Although there are multiple classes of drugs in use for neuropsychiatric symptoms, including antipsychotics, anticonvulsants, antidepressants, anxiolytics, cholinesterase inhibitors, and *N*-methyl-D-aspartate–receptor modulators, there is no clear standard of care and treatment is often based on local pharmacotherapy customs. We provide a comprehensive systematic review of pharmacological interventions for neuropsychiatric symptoms of dementia. Our goal is to provide the generalist physician with a clinically useful, evidence-based assessment of available pharmacological interventions for neuropsychiatric symptoms.

EVIDENCE ACQUISITION

To identify articles, we systematically searched the MEDLINE database for English-language articles published between 1966 and July 2004, the Cochrane Database of Systematic Reviews, and performed a manual search of the reference lists of relevant retrieved articles. In MEDLINE, we combined the results of searches in 3 separate domains: dementia (MeSH terms *dementia*; *Alzheimer disease*; *dementia, vascular*; or *Lewy body disease*), neuropsychiatric symptoms (*behavior*; *neurobehavioral manifestations*; *perceptual disorders*; *psychomotor disorders*; *mood disorders*; or keyword *neuropsychiatric*), and drug therapy (*cholinesterase inhibitors*; *tranquilizing agents*; *serotonin uptake inhibitors*; *anticonvulsants*; *valproic acid*; *benzodiazepines*; *trazodone*; *memantine*; or *psychotropic drugs*). A total of 253 articles were identified through database searches. The titles and abstracts were read by 2 authors (K.M.S. and K.F.H.) and if the article appeared to meet inclusion criteria or if we were uncertain, the full study was obtained. A total of 187 articles were excluded based on reviewing titles and abstracts; therefore, 66 articles were obtained for full review and an additional 12 articles were identified in the manual search of references.

Studies were selected for inclusion in our systematic review if they met all of the following inclusion criteria: double-blind, placebo-controlled, randomized controlled trials (RCTs) or meta-analyses of RCTs; intervention consisting of any drug therapy for patients with dementia (generally defined in accordance with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria and including AD, vascular dementia, mixed, or dementia with Lewy bodies); and outcomes for neuropsychiatric symptoms were reported (eg, hallucinations, delusions, combativeness, verbal aggression, psychomotor agitation, wandering). Trials reporting only depression outcomes were excluded. For the sake of summarizing a large body of evidence succinctly, if a meta-analysis was available, results from that analysis were presented along with any RCTs published since the meta-analysis. Because the goal of this review was to be clinically useful, studies were excluded if the drug was not available for use in the United States or was no longer in wide clinical use (eg, tacrine). Studies were also excluded if they were post hoc analyses of trials already selected for inclusion or were duplicate publications. Data on the inclusion criteria, patients, methods, results, and quality of each study were independently abstracted by 2 authors (K.M.S. and K.F.H.). Disagreements were discussed and if consensus was not reached, a third author (K.Y.) was the final arbitrator. From 78 articles that were reviewed, only 25 RCTs and 4 meta-analyses met our inclusion criteria.

EVIDENCE SYNTHESIS

Typical Antipsychotics

Two meta-analyses[20,21] covering 12 RCTs and 2 additional RCTs[22,23] of typical (or conventional) antipsychotics were reviewed (TABLE 1 and TABLE 2). Trials varied in length from 17 days to 16 weeks. In an early meta-analysis[21] of antipsychotic drugs (including haloperidol, thioridazine, thiothixene, chlorpromazine, trifluoperazine, and acetophenazine) covering 7 RCTs, the authors concluded that "18 of 100 patients benefited from neuroleptics (beyond that of placebo)." There was no difference in efficacy among the different typical antipsychotics on neuropsychiatric symptoms. An RCT of thioridazine vs placebo[23] found significant improvements in agitation, but the trial was of poor quality with no mention of effect size, methods for randomization and allocation concealment, or the number of patients who completed the trial. A recent Cochrane review[20] comparing haloperidol with placebo for the treatment of agitation in dementia concluded that aggression, but not agitation, behavioral symptoms as a whole, or clinical global impression of change was improved by treatment with haloperidol. Whether the statistically significant result for the aggression subscale represents a true benefit on aggression vs a chance finding in the setting of multiple hypothesis testing is unclear. In addition, the authors reported that dropouts due to adverse events, such as extrapyramidal symptoms and somnolence, were more than twice as likely to occur among those individuals randomized to haloperidol than placebo (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.2-5.2). Lastly, perphenazine was not found to be of benefit compared with placebo in a 17-day trial of hospitalized patients.[22]

There is no clear evidence that typical antipsychotic drugs are useful for treating neuropsychiatric symptoms defined broadly. There may be a slight benefit for haloperidol with aggression (doses of 1.2-3.5 mg/d) but it is unclear if this benefit outweighs the adverse effects, particularly extrapyramidal symptoms and sedation. There is no evidence that any one typical antipsychotic is more efficacious than another.

Atypical Antipsychotics

Atypical antipsychotics, also known as second-generation antipsychotics, include clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Four of 6 RCTs of atypical

antipsychotics (olanzapine and risperidone) reported benefit in the treatment of neuropsychiatric symptoms of dementia (Table 1 and Table 2).[24-29] These trials ranged from 24 hours to 12 weeks and were all conducted among nursing home residents, generally with moderate to severe dementia (mean Mini-Mental State Examination score, 5.5-13.7). The first trial of oral olanzapine reported that doses of 5 and 10 mg but not 15 mg were associated with a statistically significant decrease in the primary outcome of the sum of 3 Neuropsychiatric Inventory (NPI) core symptoms (agitation/aggression, hallucinations, and delusions).[26] Only the 5-mg dose was associated with improvement in total NPI score (mean, 8.8 point improvement over placebo; range, 0-144; $P=.005$). Another trial comparing varying doses of olanzapine with placebo for patients with dementia-related psychosis found no significant difference between any of the doses and placebo in either of the primary outcomes.[29] However, the authors show that the 7.5-mg dose was better than placebo in some secondary analyses. Finally, results from a 24-hour trial of intramuscular olanzapine (2.5 or 5.0 mg) reported a statistically significant improvement in the primary outcome at 2 hours in those individuals treated with either dose of olanzapine compared with placebo.[27]

In 1 fixed-dose trial of risperidone,[25] 45% of patients receiving 1.0 mg and 50% patients receiving 2.0 mg compared with 33% receiving placebo had at least 50% reduction in the Behavioral Pathology in Alzheimer Disease Rating Scale (BEHAVE-AD) score ($P=.02$ and $P=.002$ vs placebo, respectively). A 2.0-mg dose was not more efficacious than 1.0-mg dose and resulted in significantly higher adverse events, including extrapyramidal symptoms and somnolence. A subgroup analysis of patients who were not somnolent found similar benefit for risperidone vs placebo, suggesting that somnolence was not the mechanism for efficacy. Another trial[24] of 229 patients did not report a significant benefit of risperidone (mean dose, 1.1 mg/d) in their primary outcome (≥30% reduction in BEHAVE-AD total score) but did report significant results for several secondary analyses. This trial found

Table 1. Studies of Typical and Atypical Antipsychotics: Study Characteristics

Source	Study Design	No. of Patients	Length of Study	Funding Sponsor	Drug	Patient Residence	Dementia Type and Severity
Typical							
Schneider et al,[21] 1990	Meta-analysis of 7 RCTs	252	3-8 wk	NIH	Haloperidol, thioridazine, thiothixene, chlorpromazine, trifluoperazine, acetophenazine (75-267 mg/d in chlorpromazine equivalents)	Mostly nursing home	"Senile" dementia, vascular dementia
Lonergan et al,[20] 2002	Meta-analysis of 5 RCTs	573	3-16 wk	UK National Health Service	Haloperidol (0.25-6.0 mg/d)	Community and nursing home	AD and vascular dementia: mild, moderate, and severe
Stotsky,[23] 1984	RCT	358	4 wk	Not specified	Thioridazine (10-200 mg/d)	Nursing home and hospital	"Senile"; severity not specified
Pollock et al,[22] 2002	RCT	54	17 d	NIH	Perphenazine (mean dose, 6.5 mg/d)	Geropsychiatry ward	AD, vascular dementia, mixed, dementia with Lewy bodies MMSE score, 7.7
Atypical							
De Deyn et al,[24] 1999	RCT	229	12 wk	Janssen	Risperidone (mean dose, 1.1 mg/d)	Nursing home	AD, vascular dementia, mixed MMSE score, 8.7
Katz et al,[25] 1999	RCT	625	12 wk	Janssen	Risperidone (0.5, 1.0, or 2.0 mg/d)	Nursing home	AD, vascular dementia, mixed MMSE score, 6.6
Street et al,[26] 2000	RCT	206	6 wk	Eli Lilly	Olanzapine (5, 10, or 15 mg/d)	Nursing home	AD MMSE score, 6.9
Meehan et al,[27] 2002	RCT	204	24 h	Eli Lilly	Intramuscular olanzapine (2.5 or 5.0 mg)	Nursing home, hospital	AD, vascular dementia, mixed MMSE score, 11.8
Brodaty et al,[28] 2003	RCT	345	12 wk	Janssen	Risperidone (mean dose, 0.95 mg/d)	Nursing home	AD, vascular dementia, mixed MMSE score, 5.5
De Deyn et al,[29] 2004	RCT	652	10 wk	Eli Lilly	Olanzapine (1, 2.5, 5, or 7.5 mg/d)	Nursing home	AD MMSE score, 13.7

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; NIH, National Institutes of Health; RCT, randomized controlled trial.

Table 2. Studies of Typical and Atypical Antipsychotics: Outcomes

Source	Outcomes	Significance of Primary Outcome		Adverse Events and Comments
		Statistical	Clinical	
Typical				
Schneider et al,[21] 1990	Standardized effect size* (r = 0.18, P = .004); 18 of 100 benefited from neuroleptics	Yes	Possibly	Also examined 11 RCTs comparing thioridazine or haloperidol to another antipsychotic; no difference between drugs
Lonergan et al,[20] 2002	"Behavioral symptoms,"* agitation, aggression, CGIC Only aggression was statistically different for haloperidol vs placebo	No		Dropouts due to adverse events more common in haloperidol than placebo group (OR, 2.5; 95% CI, 1.2-5.2)
Stotsky,[23] 1984	Hamilton Anxiety Scale* Patients taking thioridazine showed significantly greater improvement in all 8 symptoms of Hamilton Anxiety Scale, including agitation and behavioral changes (P<.01 each)	Yes	Not able to comment	Magnitude of change was not reported No mention of number of dropouts
Pollock et al,[22] 2002	Neurobehavioral Rating Scale* No significant difference between perphenazine and placebo	No		High dropout rate: 55% of perphenazine and 57% of placebo patients, P = .92 No significant difference between groups in extrapyramidal or autonomic symptoms
Atypical				
De Deyn et al,[24] 1999	BEHAVE-AD (≥30% reduction),* CMAI, CGIS No difference between risperidone and placebo for primary outcome Significant results for several secondary analyses	No		Somnolence more common for risperidone than placebo (12.2% vs 4.4%) Also had a haloperidol group to compare tolerability of haloperidol with risperid one No difference in extrapyramidal symptoms between risperidone and placebo, but more common for haloperidol (P<.05)
Katz et al,[25] 1999	BEHAVE-AD (≥50% reduction),* BEHAVE-AD psychosis subscale, CMAI, CGIS 33% Placebo vs 45% with 1 mg and 50% with 2 mg of risperidone (P = .02 and P=.002, respectively) had ≥50% reduction in total BEHAVE-AD score	Yes	Probably	27% Placebo and 42% in 2-mg risperidone group dropped out; primarily due to adverse events Significantly more extrapyramidal symptoms in 2-mg risperidone vs placebo; dose response increase in somnolence (8%-28%) No difference in efficacy for 1 vs 2 mg
Street et al,[26] 2000	Sum of 3 NPI/NH core symptoms (agitation/aggression, hallucinations, delusion),* NPI/NH total, individual NPI items, BPRS 5 and 10 mg but not 15 mg had a significant decrease in the sum of core symptoms vs placebo; only 5 mg showed improvement in total NPI/NH score	Yes	Probably for 5 and 10 mg	18% of placebo group dropouts were due to adverse events vs 44% of olanzapine-treated patients Somnolence was 5 to 8 times greater and gait disturbance 7.5 to 11 times more common for olanzapine than placebo No difference in extrapyramidal symptoms between groups
Meehan et al,[27] 2002	PANSS-EC,* CMAI, ACES Significant mean change in PANSS-EC 2 h after injection for both olanzapine doses vs placebo	Yes	Probably	Adverse events not significantly different across groups Also had an intramuscular lorazepam group; no difference between olanzapine and lorazepam
Brodaty et al,[28] 2003	CMAI total aggression score,* CMAI nonaggression score and subscale scores, BEHAVE-AD, CGIC Patients treated with risperidone improved more on CMAI-aggression subscale than placebo (4.4-point difference, P<.001; scale of 14-98); similar results for other outcomes	Yes	Possibly	Serious adverse events occurred in 16.8% of risperidone vs 8.8% of placebo group, including 5 strokes and 1 TIA, all in the risperidone group Somnolence, injury, and falls were most common adverse events
De Deyn et al,[29] 2004	Psychosis subscale of NPI/NH,* CGIC,* NPI/NH total and item scores, BPRS total and item scores, occupational disruptiveness score No significant differences in primary outcomes between any olanzapine dose and placebo	No		No difference in dropouts due to adverse events across groups (P = .35), but weight gain, anorexia, and urinary incontinence more common with olanzapine No difference in motor function or anticholinergic adverse effects Significant psychosis was an entry criteria

Abbreviations: CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; TIA, transient ischemic attack. See Box for guide to neuropsychiatric symptom rating scales.
*Primary outcomes; all other outcomes listed are secondary outcomes.

no difference between risperidone and haloperidol in the primary outcome, although extrapyramidal symptoms were more common with haloperidol. In the most recent trial of risperidone,[28] mean doses of 0.95 mg/d were found to be more efficacious than placebo on the primary outcome (4.4-point difference on Cohen-Mansfield Agitation Inventory aggression score [scale of 84 points], $P<.001$) and several secondary outcomes. In this trial, 16.8% of the patients randomized to risperidone (vs 8.8% of placebo group) had serious adverse events, including 5 strokes and 1 transient ischemic attack. All of the cerebrovascular events reported in the trial occurred with risperidone. However, all of these patients also had stroke risk factors (5 of 6 patients had atrial fibrillation).

Doses of 5 to 10 mg/d of olanzapine or 1.0 mg/d of risperidone appear to be at least modestly effective for treating neuropsychiatric symptoms of dementia in patients with AD or vascular dementia. The incidence of extrapyramidal symptoms appears to be low when receiving these doses of olanzapine and risperidone, but somnolence remains a concern. To our knowledge, there have been no published RCTs of clozapine, quetiapine, ziprasidone, or aripiprazole for neuropsychiatric symptoms of dementia. Furthermore, there have been no published RCTs designed to compare the efficacy of typical and atypical agents.

Antidepressants

Of the 5 RCTs that have investigated the use of serotonergic antidepressants for the treatment of neuropsychiatric symptoms (sertraline, fluoxetine, citalopram, and trazodone),[22,30-33] only the trial of citalopram found benefit (TABLE 3 and TABLE 4). This 17-day study of hospitalized patients found a 10-point change (of 168 points) in the Neurobehavioral Rating Scale for patients randomized to citalopram compared with a 2.3-point change for placebo ($P<.001$).[22] Of the 7 subscales examined, only agitation and lability were significantly improved with citalopram compared with placebo. The trial had a high dropout rate, with more than half of patients in each group failing to complete the study, most commonly due to lack of efficacy. Lyketsos et al[31] found sertraline to be effective in the treatment of depression among patients with dementia. However, there was no significant benefit of sertraline on neuropsychiatric symptoms. The authors did report that in subgroup analyses of full responders vs nonresponders (in terms of depression symptoms), full responders had significantly greater improvement on

Table 3. Studies of Antidepressants and Mood Stabilizers: Study Characteristics*

Source	No. of Patients	Length of Study	Funding Sponsor	Drug	Patient Residence	Dementia Type and Severity
Antidepressants						
Auchus and Bissey-Black,[32] 1997	15†	6 wk	NIH and institutional grant	Fluoxetine (20 mg/d)	Community	AD MMSE score, 15.2
Teri et al,[33] 2000	73	16 wk	NIH	Trazodone (mean dose, 200 mg/d)	Community	AD MMSE score, 13.5
Pollock et al,[22] 2002	52	17 d	NIH	Citalopram (20 mg/d)	Hospital	AD, vascular dementia, mixed, dementia with Lewy bodies MMSE score, 8.5
Lyketsos et al,[31] 2003	44	12 wk	NIH	Sertraline (mean dose, 95 mg/d)	Community	AD MMSE score, 16.9
Finkel et al,[30] 2004	245	12 wk	Pfizer	Sertraline (mean dose, 126 mg/d)	Community	AD MMSE score, 17.8
Mood stabilizers						
Tariot et al,[34] 1998	51	6 wk	NIH, drugs donated by Ciba-Geigy Corp	Carbamazepine (mean dose, 304 mg/d)	Nursing home	AD, vascular dementia, mixed MMSE score, 6.0
Olin et al,[35] 2001	21	6 wk	NIH	Carbamazepine (mean [SD] dose, 388 [44] mg/d)	Nursing home	AD MMSE score, 6.0
Porsteinsson et al,[36] 2001	56	6 wk	Alzheimer's Association, NIH, and Abbott Laboratories	Divalproex sodium (mean [SD] dose, 826 [216] mg/d)	Nursing home	AD, vascular dementia, mixed MMSE score, 6.8
Tariot et al,[37] 2001	172	6 wk	Abbott Laboratories	Divalproex sodium (median, 1000 mg/d)	Nursing home	AD, vascular dementia, mixed MMSE score, 7.4
Sival et al,[38] 2002	42	3 wk	Van Helten Foundation, government	Rapid-acting sodium valproate (480 mg/d)	Nursing home	AD, vascular dementia, mixed, Parkinson disease MMSE score, 11.4

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; NIH, National Institutes of Health. See Box for guide to abbreviations of neuropsychiatric symptom rating scales.
*All studies were randomized controlled trials.
†Number of patients in total study was 15, split between 3 groups (haloperidol, fluoxetine, or placebo); actual number of patients in each group was not reported.

Table 4. Studies of Antidepressants and Mood Stabilizers: Outcomes

Source	Outcomes	Significance of Primary Outcome		Adverse Events and Comments
		Statistical	Clinical	
Antidepressants				
Auchus and Bissey-Black,[32] 1997	No positive treatment effect for CMAI,* BEHAVE-AD, CSI	No		Mean number of adverse events was higher for fluoxetine than for placebo (15.4 vs 7.3, $P = .05$) Patients receiving fluoxetine had worse CMAI score than patients receiving placebo at 6 wk Also had a haloperidol group (data in Lonergan et al[20]) (Table 2)
Teri et al,[33] 2000	No difference between trazodone and placebo on CGIC,* CMAI, BRSD, RMBPC, ABID, SCB	No		No significant differences in adverse events or dropouts between trazodone and placebo Also included 34 patients in a haloperidol group (data in Lonergan et al[20]) (Table 2) and 41 patients in a behavioral-management group; there was no difference between any of the drug groups and placebo
Pollock et al,[22] 2002	Change in NRS total score* significantly greater for citalopram than placebo (10 vs 2.3 points; $P<.001$) Of 7 subscales,* agitation and lability significantly improved with citalopram vs placebo (<1 point on 7-point scale)	Yes	Possibly	52% Citalopram and 57% placebo patients dropped out; 30% dropouts due to adverse events, 50% due to lack of efficacy Also had a perphenazine group (Table 1)
Lyketsos et al,[31] 2003	No significant difference in total NPI or NPI-NM scores between groups	Depression: yes Agitation: no		No significant difference in adverse events between groups Primary goal was to treat depression in patients with dementia, for which sertraline was successful
Finkel et al,[30] 2004	No significant difference between groups on NPI,* CGIC,* CGIS,* CMAI, BEHAVE-AD, CBQ, 4-item NPI, 3-item BEHAVE-AD	No		12% Dropped out in both groups due to adverse events; diarrhea significantly more common with sertraline (27.4% vs 11.7%, $P<.05$) All patients were also taking donepezil Behavior symptoms were a selection criteria for study
Mood stabilizers				
Tariot et al,[34] 1998	Agitation improved more in carbamazepine vs placebo group on all measures (BPRS,* CGIC,* OAS, BRSD); 77% of patients taking carbamazepine vs 21% placebo rated as improved by CGIC	Yes	Probably	Significantly more adverse events in drug group than placebo (59% vs 29% $P = .03$); all 4 dropouts in drug group Physician titrating the dose was not blinded, but raters were
Olin et al,[35] 2001	No difference between groups on BPRS,* CGIC,* 21-item Ham-D; 56% carbamazepine and 58% placebo improved on CGIC	No		Adverse events were mild and occurred in 4 of 9 patients taking carbamazepine and 8 of 12 taking placebo
Porsteinsson et al,[36] 2001	No difference in the change in total scores between drug and placebo on BPRS,* OAS, BRSD, CMAI, CGIC	No		Adverse effects significantly more frequent with drug than placebo, $P = .03$; sedation most common adverse event (39% divalproex vs 11% placebo), also weakness, respiratory problems Physician titrating dose of drug was not blinded, but raters were
Tariot et al,[37] 2001	No difference between groups on BRMS* or BPRS; change in CMAI total score was slightly greater for drug group (–3.2 vs –1.0, $P = .04$); however, divalproex patients were slightly worse on CGIC than placebo ($P = .04$)	No		Study was discontinued early due to significantly higher adverse event rate in the divalproex group (predominantly somnolence) Patients had to exhibit manic symptoms to be included
Sival et al,[38] 2002	No difference between groups on SDAS-9,* CGIS,* or nurses' observations; benefit was reported for 3 of 14 GIP subscales	No		Data on specific adverse events not presented, but mean incidence of reported adverse events was low (0.17 divalproex vs 0.02 placebo) 14 of 42 patients did not have an MMSE score because dementia was too severe

Abbreviations: MMSE, Mini-Mental State Examination. See Box for guide to abbreviations of neuropsychiatric symptom rating scales.
*Primary outcomes; all other outcomes listed are secondary outcomes.

nonmood items of the NPI than nonresponders.

We conclude from these trials that although serotonergic agents are well tolerated, they do not appear to be very effective in the treatment of neuropsychiatric symptoms of dementia other than depression.[39,40]

Mood Stabilizers

Three RCTs have investigated valproate[36-38] and 2 studies have investigated carbamazepine for neuropsychiatric symptoms[34,35] (Table 3 and Table 4). Valproate does not appear to be effective for the treatment of neuropsychiatric symptoms of dementia whether in short- or long-acting preparations. In addition, valproate caused significantly more adverse events than placebo, sedation being the most common. Therefore, we do not recommend the use of valproate in the management of neuropsychiatric symptoms of dementia. Based on 2 small trials (1 positive[34] and 1 negative[35]), there is currently not enough evidence of benefit to recommend the use of carbamazepine for treatment of neuropsychiatric symptoms, especially in light of the black box warning for hematologic toxicity and the potential drug-drug interactions between carbamazepine and other drugs commonly prescribed to elderly individuals. To our knowledge, there have been no published placebo-controlled RCTs of lithium for the treatment of neuropsychiatric symptoms of dementia.

Cholinesterase Inhibitors

Two meta-analyses[41,42] and 6 additional RCTs[43-48] of various cholinesterase inhibitors with neuropsychiatric symptom outcomes have been published (TABLE 5 and TABLE 6) with 5 of the 8 studies reporting statistically significant benefit. In a recent meta-analysis of cholinesterase inhibitors,[42] the authors reported a small but statistically significant benefit from cholinesterase inhibitors with NPI scores (summary estimate 1.72-point improvement vs placebo on a scale of 0-120) but not Alzheimer Disease Assessment Scale, noncognitive portion scores. The statistically significant effect on NPI scores was most likely driven by 2 studies of metrifonate, which was never approved by the Food and Drug Administration for use in the United States due to toxicities.

A Cochrane review of galantamine for AD reported 2 RCTs of galantamine that included the NPI as an outcome.[41] In one trial, there was no benefit of either galantamine 24-mg/d or 32-mg/d dose vs placebo.[51] In the second trial, the intention-to-treat analysis found only the 16-mg/d dose to be significantly better than placebo (mean difference of 2.1 points, $P=.03$) with no benefit for the other doses.[52] One additional RCT using 24-mg/d dose of galantamine also reported a

Table 5. Studies of Cholinesterase Inhibitors and Memantine: Study Characteristics

Source	Study Design	No. of Patients	Length of Study	Funding Sponsor	Drug	Patient Residence	Dementia Type and Severity
Cholinesterase inhibitors							
McKeith et al,[45] 2000	RCT	120	20 wk	Novaritis	Rivastigmine (mean, 9.4 mg/d)	Community	Dementia with Lewy bodies MMSE score, 17.9
Feldman et al,[44] 2001	RCT	290	24 wk	Pfizer	Donepezil (74% taking 10 mg/d, 26% 5 mg/d)	Community, assisted living	AD MMSE score, 11.8
Tariot et al,[46] 2001	RCT	208	24 wk	Pfizer and Eisai	Donepezil (mean, 9.5 mg/d)	Nursing home	AD MMSE score, 14.4
Erkinjuntti et al,[43] 2002	RCT	592	24 wk	Janssen	Galantamine (24 mg/d)	Community	Vascular dementia, mixed MMSE score, 20.5
Olin and Schneider,[41] 2003	Meta-analysis of 2 RCTs*	1364	12-20 wk	Meta-analysis funded by NIH, both studies analyzed funded by Janssen	Galantamine (8, 16, 24, 32 mg/d)	Community	Mild to moderate AD
Trinh et al,[42] 2003	Meta-analysis of 16 RCTs	5529	6 wk-1 y	NIH and American Federation for Aging Research	Metrifonate, tacrine, galantamine, donepezil, velnacrine, physostigmine	Community	Mild to moderate AD
Courtney et al,[47] 2004	RCT	565	Up to 4 y (n = 4 in year 4)	UK National Health Service	Donepezil (5 or 10 mg/d)	Community	AD, mixed MMSE score, 19
Holmes et al,[48] 2004	RCT	96	12 wk	Pfizer	Donepezil (10 mg/d)	Not specified	AD MMSE score, 21
Memantine							
Reisberg et al,[49] 2003	RCT	252	28 wk	Merz Pharmaceuticals and NIH	Memantine (20 mg/d)	Community	AD MMSE score, 7.9
Tariot et al,[50] 2004	RCT	404	24 wk	Forest Laboratories	Memantine (20 mg/d)	Community	AD MMSE score, 10

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; NIH, National Institutes of Health; RCT, randomized controlled trial.
*Six trials contributed to analyses, but only 2 had data on neuropsychiatric symptoms.

Table 6. Studies of Cholinesterase Inhibitors and Memantine: Outcomes

Source	Outcomes	Significance of Primary Outcome		Adverse Events and Comments
		Statistical	Clinical	
Cholinesterase inhibitors				
McKeith et al,[45] 2000	No difference in mean change in NPI-4 (delusions, hallucinations, apathy, depression)* or NPI total scores between rivastigmine and placebo on ITT analyses; no significant difference in mean CIBIC-plus scores at week 20	No		23% Dropout rate, no difference between groups; nausea, vomiting, anorexia, and somnolence significantly more common in rivastigmine vs placebo; no difference in serious adverse events
Feldman et al,[44] 2001	Mean difference in CIBIC-plus* scores at week 24: 0.54, $P<.001$; 63% of donepezil and 42% placebo group rated as improved or unchanged ($P<.001$); 5.6-point treatment difference on NPI scores (of 144) favoring donepezil ($P<.001$)	Yes	Possibly	8% of donepezil and 6% placebo dropped out due to adverse events; diarrhea, headache, and arthralgias occurred at least twice as frequently in donepezil vs placebo group
Tariot et al,[46] 2001	No significant difference in mean change on NPI-NH* total score or any individual item for donepezil vs placebo	No		18% of placebo vs 11% donepezil dropped out due to adverse events; weight loss, abdominal pain, nausea, tremor, and myasthenia at least twice the frequency in donepezil vs placebo group
Erkinjuntti et al,[43] 2002	74% of galantamine vs 59% placebo patients rated as unchanged or improved on CIBIC-plus* at 6 mo ($P = .001$); mean treatment difference in NPI scores was 2.2 points (of 120), favoring galantamine ($P<.05$)	Yes	Unlikely	20% of galantamine vs 8% placebo group dropped out due to adverse events; nausea and vomiting more common reason for withdrawal in galantamine than placebo (16% vs 3%; no measure of statistical significance given) Neuropsychiatric symptoms not primary outcome; patients had low levels at baseline
Olin and Schneider,[41] 2003	NPI*; study 1: no significant difference in NPI scores between galantamine and placebo for 24 or 32 mg/d; study 2: in ITT analysis only 16 mg/d was significantly better than placebo (mean difference, 2.1 [of 120], $P = .03$). No difference between galantamine and placebo for 8- or 24-mg doses	Yes, for 16 mg only	Unlikely	Adverse event data from 6 trials: no difference vs placebo for 8 mg, but increasing adverse events with increasing doses above 8 mg; gastrointestinal most common
Trinh et al,[42] 2003	NPI*: 6 trials; summary estimate, 1.72-point improvement over placebo (scale, 0-120) (95% CI, 0.87-2.57); ADAS-noncog*: 10 trials; summary estimate, 0.03-point improvement over placebo (scale, 0-50) (95% CI, 0.00-0.05)	NPI: yes ADAS: no	Unlikely	Statistically significant improvement in NPI was driven by metrifonate, not approved for use in United States; no statistically significant benefit for donepezil (1 trial) or galantamine (2 trials, see Olin and Schneider[41])
Courtney et al,[47] 2004	No significant difference in risk of nursing home placement,* development of disability,* or mean change in NPI scores between groups	No		6% of donepezil vs 1% placebo dropped out due to adverse events at 12 weeks, $P = .001$; after the first 12 wk, 7% of donepezil vs 3% placebo dropped out due to adverse events
Holmes et al,[48] 2004	6.2-point (of 120) treatment difference on NPI* score at 12 wk, favoring donepezil ($P = .02$); 2.8-point (of 50) difference in NPI caregiver distress scale, favoring donepezil ($P = .01$)	Yes	Possibly	Significant neuropsychiatric symptoms was an entry criterion; no difference in dropout rates between groups after randomization (18% placebo, 15% drug)
Memantine				
Reisberg et al,[49] 2003	LOCF analysis for CIBIC-plus* not statistically different between groups (4.5 vs 4.8, $P = .06$); 28-week analysis was significantly better for memantine vs placebo (4.4 vs 4.7, $P = .03$); NPI change scores not significantly different between groups for either LOCF or 28-wk analyses ($P = .33$ and .60)	Global impression: no (LOCF) Behavioral: no		17% of placebo and 10% memantine group dropped out due to adverse events, with agitation being most common reason; incidence of any adverse event no more than 2% higher for memantine than placebo Also measured caregiver hours and found 45.8 h/mo fewer for patients taking memantine vs placebo ($P = .01$)
Tariot et al,[50] 2004	Mean change on NPI significantly better among patients receiving memantine (–0.1 vs +3.7; $P = .002$); CIBIC-plus score significantly better for memantine vs placebo (4.41 vs 4.66, $P = .03$); 55% memantine and 45% placebo group rated as improved or unchanged	Cognitive and functional: yes Behavioral: yes	Possibly	Significantly more dropouts in placebo group than memantine (25% vs 15%, $P = .01$); confusion more common in memantine than placebo group (7.9% vs 2%, $P = .01$) Primary outcomes were cognitive and functional for which the trial was positive; CIBIC-plus was a rating of global, not behavioral, improvement

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LOCF, last observation carried forward. See Box for guide to abbreviations of neuropsychiatric symptom rating scales.
*Primary outcomes; all other outcomes listed are secondary outcomes.

mean treatment difference in NPI scores of 2.2 points ($P<.05$).[43] However, a 2-point difference on the NPI (range, 0-120) is unlikely to be clinically significant.

Four additional RCTs using donepezil have reported conflicting results. In a 24-week trial of 208 patients in a nursing home, there was no difference between treatment groups in the mean change in NPI scores.[46] In subgroup analyses using the NPI items as categorical outcomes, only agitation/aggression was better for those individuals randomized to donepezil vs placebo (45% improved vs 28%, $P=.04$). A 24-week trial of patients living in the community or assisted-living facilities found a slightly larger treatment difference of 5.6 points on the NPI in favor of donepezil ($P<.001$), with statistically significant benefit on the apathy, depression, and anxiety subscales.[44] A similar magnitude of benefit was reported in a 12-week trial of 96 patients who had significant neuropsychiatric symptoms on enrollment.[48] However, in the longest trial of cholinesterase inhibitors to date, there was no significant difference in the mean changes in NPI scores between those individuals randomized to donepezil (5 or 10 mg) or placebo at any time point up to 4 years of follow-up.[47]

An RCT of patients with mild to moderate dementia with Lewy bodies found no difference in NPI scores between rivastigmine and placebo on either a 4-item NPI "dementia with Lewy bodies cluster" (delusions, hallucinations, apathy, and depression) or the full 10-item NPI.[45] However, using a predefined cutoff of at least 30% improvement, significantly more patients receiving rivastigmine showed improvement compared with placebo (47.5% vs 27.9%, $P=.03$).

Although some trials of cholinesterase inhibitors have shown statistically significant differences, the magnitude of effect has been small and of questionable clinical significance. Most of the patients enrolled in the cholinesterase inhibitor trials had little neuropsychiatric symptoms with only 2 trials,[46,48] requiring significant neuropsychiatric symptoms as part of the entry criteria.

Other Drugs

Memantine, an *N*-methyl-D-aspartate receptor antagonist, was recently approved in the United States for the treatment of moderate to severe AD. Two RCTs of community-dwelling patients with moderate to severe AD have included neuropsychiatric symptoms as secondary outcomes (Table 5 and Table 6).[49,50] In 1 trial,[49] NPI scores were not significantly different between groups. In the other trial,[50] there was a statistically significant difference in NPI change scores, largely because those individuals randomized to placebo got worse. Patients receiving memantine improved their NPI score by an average of 0.1 points, whereas patients receiving placebo declined 3.7 points ($P=.002$). This difference is of unclear clinical significance. We conclude that although memantine may be of benefit in cognitive and functional domains, there does not appear to be a clinically significant benefit in the treatment of neuropsychiatric symptoms for patients with moderate to severe AD.

Only 1 placebo-controlled RCT has been published on the use of benzodiazepines for the management of neuropsychiatric symptoms of dementia.[27] This 24-hour trial of intramuscular olanzapine (2.5 mg or 5 mg) vs intramuscular lorazepam (1 mg) vs placebo is described in the section on atypical antipsychotics in Table 2. To our knowledge, there have been no published placebo-controlled RCTs on buspirone for the management of neuropsychiatric symptoms of dementia.

CONTROVERSIES

Interpretation of Data

There are several important methodological issues in neuropsychiatric symptom trials that limit the interpretation of the data and generate controversies on pharmacological management of neuropsychiatric symptoms of dementia. One controversy is how to define clinically significant improvement in neuropsychiatric symptoms. A particularly good example of this problem is highlighted with the cholinesterase inhibitor trials in which several trials reported very small but statistically significant changes in the NPI scores. Because there are no gold standard outcomes for neuropsychiatric symptoms, it is difficult to interpret small changes in scale scores and also to compare results across trials using different scales to measure neuropsychiatric symptoms (BOX). To address this, we attempted to calculate standardized response means,[53] but the vast majority of trials did not present the data needed to calculate such a measure. Clinically useful outcomes such as nursing home placement, quality of life, and caregiver burden and depression would enhance a clinician's ability to interpret trial results and counsel patients and families regarding risks and benefits of treatment.

Another problem with the current literature is that most trials report on multiple outcomes from several different scales and subscales. What does it mean if the score was significantly improved on 1 scale but not on 4 others? This multiple comparison testing raises the concern for type I error. In addition, when reporting their results, many of the studies downplay the negative primary outcome while emphasizing positive secondary outcomes, especially in the abstract and discussion sections. The majority of these trials have been funded by the pharmaceutical industry. In this review, we have focused on the primary outcome as specified by the authors.

Clinical Dilemmas

The current evidence appears to suggest that, if behavioral interventions have failed, neuropsychiatric symptoms of dementia are best treated with the atypical antipsychotic agents (risperidone and olanzapine). However, the product label warning for cerebrovascular events (strokes and transient ischemic attacks) for these drugs creates a clinical dilemma. The pooled incidence of cerebrovascular events across 6 RCTs of risperidone in the patients with dementia (N=1721) was re-

ported to be 3.3% for risperidone vs 1.1% for placebo ($P=.03$).[54] Similarly, combining data from 5 RCTs of olanzapine in 1656 patients with dementia-related psychosis revealed the incidence of cerebrovascular events in patients treated with olanzapine was significantly higher than in the placebo group (1.3% vs 0.4%, $P=.02$), even after adjustment for age, sex, and type of dementia.[55] Therefore, physicians considering the prescription of risperidone or olanzapine should discuss the potential risks and benefits of such treatment with patients and their surrogate decision makers, especially for patients with risk factors for cerebrovascular disease.

Another area of clinical uncertainty pertains to the treatment of neuropsychiatric symptoms in patients with dementia with Lewy bodies, increasingly recognized as a common form of dementia.[2,56,57] Very few trials regarding the treatment of neuropsychiatric symptoms have included patients with dementia with Lewy bodies. Therefore, no conclusions can be drawn regarding the efficacy of drug treatment for neuropsychiatric symptoms occurring in this setting. However, antipsychotics should be used cautiously in patients suspected to have dementia with Lewy bodies as these patients have been reported to have marked sensitivity, including life-threatening neuroleptic malignant syndrome, to typical and atypical antipsychotics.[57-61] Although dementia with Lewy bodies is characterized by fluctuating levels of impairment, hallucinations (often visual), and parkinsonism, the diagnosis may be overlooked, especially in later stages of the illness, until the patient experiences significant extrapyramidal symptoms while receiving an antipsychotic. If this occurs, the drug should be discontinued and a diagnosis of dementia with Lewy bodies entertained.

Box. Neuropsychiatric Symptom Rating Scales

Agitated Behavior Inventory for Dementia (ABID)

Agitation-Calmness Evaluation Scale (ACES)

Alzheimer Disease Assessment Scale, noncognitive portion (ADAS-noncog)

Bech-Rafaelsen Mania Scale (BRMS)

Behavior Observation Scale for Intramural Psychogeriatric Patients (GIP)

Behavior Rating Scale for Dementia (by the Consortium to Establish a Registry for Dementia) (BRSD)

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

Brief Psychiatric Rating Scale (BPRS)

Caregiver Burden Questionnaire (CBQ)

Clinical Global Impression of Change (1=very much improved to 7=very much worse) (CGIC)

Clinical Global Impression Scale (CGIS)

Clinicians Interview Based Impression of Change plus caregiver input (CIBIC-plus)

Cohen-Mansfield Agitation Inventory (CMAI)

Hamilton Rating Scale for Depression (Ham-D)

Iowa Caregiver Stress Inventory (CSI)

Neurobehavioral Rating Scale (0=not present to 7=extremely severe), derived from the Brief Psychiatric Rating Scale (NRS)

Neuropsychiatric Inventory (usually 10 items, 120 points) (NPI)

Neuropsychiatric Inventory-Nursing Home version (12 items, 144 points) (NPI-NH)

Neuropsychiatric Inventory minus 5 "mood" items (NPI-NM)

Overt Aggression Scale (OAS)

Positive and Negative Syndrome Scale-Excited Component (PANSS-EC)

Revised Memory and Behavior Problem Checklist (RMBPC)

Screen for Caregiver Burden (SCB)

Social Dysfunction and Aggression Scale (SDAS-9)

CONCLUSIONS AND PERSPECTIVES

Among the many drugs in use for the treatment of neuropsychiatric symptoms, we found only the atypical antipsychotics, risperidone and olanzapine, to have convincing evidence of efficacy for neuropsychiatric symptoms. In addition, trials of cholinesterase inhibitors have had remarkably consistent, albeit small positive effects on neuropsychiatric symptoms. However, it is clear that none of the drugs in use for neuropsychiatric symptoms offer a "magic pill." The effect sizes have been modest at best, with treatment differences on the NPI scale of about 2 points for cholinesterase inhibitors and up to 8 points for olanzapine.

Potential Treatment Strategies

The management of neuropsychiatric symptoms in dementia should always begin with an assessment of the patient for medical (eg, pain and delirium) and environmental causes of the behavior. If the problem persists after these have been addressed, nonpharmacological interventions should be attempted before moving to drug therapy. Although a comprehensive review of nonpharmacological interventions is outside the scope of this article, several interventions have been shown in small studies to have varying degrees of success including but not limited to music therapy,[62,63] aromatherapy,[64,65] and pet therapy.[66] Caregiver (either formal or informal) education is also an integral part of the management.[67] Larger, well-designed, controlled trials

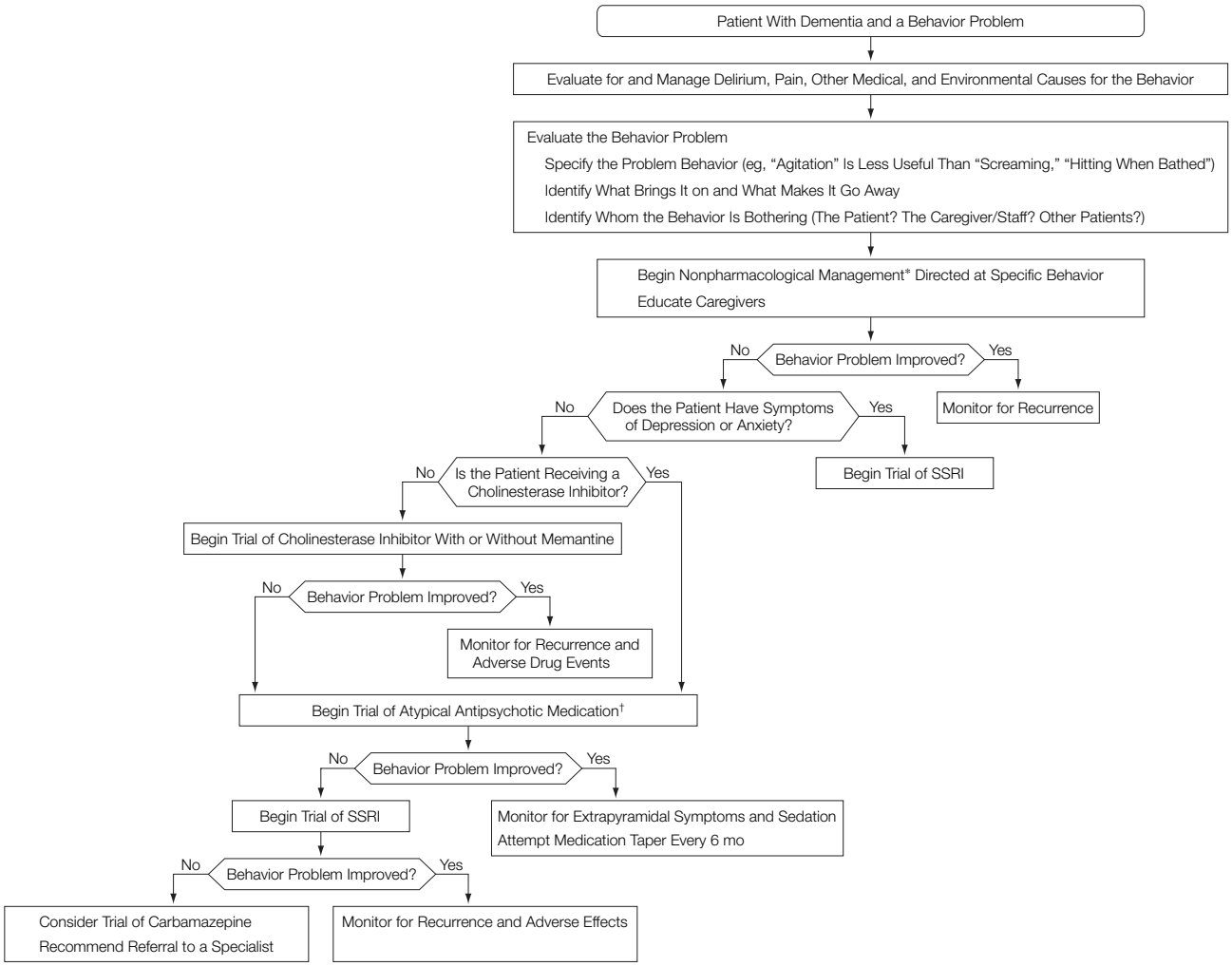
of nonpharmacological interventions are needed.

Until there are better answers, if drug therapy is to be instituted, there are 2 reasonable approaches to the management of neuropsychiatric symptoms, each with its merits and pitfalls. One approach would be to identify the target symptom and choose a drug that is known to treat a symptom most closely related to the one the patient is exhibiting. For example, one might use an antipsychotic for psychotic symptoms or an antidepressant for anxiety symptoms, such as repetitive vocalizations or pacing. Although this approach is intuitive, RCTs have not been designed to confirm that this approach is effective and secondary analyses suggest it might not be.[68]

An alternative approach is one guided by the current state of evidence in combination with the goal of minimizing adverse effects (FIGURE). For example, although the evidence for cholinesterase inhibitors as effective treatments for neuropsychiatric symptoms is not as convincing as that for risperidone or olanzapine, we recommend beginning with a cholinesterase inhibitor if the patient is not already receiving one because they are well tolerated and may benefit cognition and function, even if they are not beneficial for neuropsychiatric symptoms.[67] Additionally, typical antipsychotics do not appear in the suggested algorithm because there is less evidence of benefit and more adverse effects compared with the atypical antipsychotics.

Benzodiazepines are not part of the recommended management of neuropsychiatric symptoms and should be avoided, especially for long-term management. Although the only RCT us-

Figure. Recommended Algorithm for Management of Neuropsychiatric Symptoms of Dementia



SSRI indicates selective serotonin reuptake inhibitor.
*Music therapy, aromatherapy, pet therapy, or other approaches.
†Caution is advised in patients with dementia with Lewy bodies.

ing a benzodiazepine for acutely agitated patients with dementia (Table 2)[27] did not report a significant difference in adverse events in the 24 hours after intramuscular injection, case reports and anecdotal evidence suggest that benzodiazepines lead to increased confusion, falls, and may paradoxically increase agitation in patients with dementia.[69,70] Consistent with this information, the report published by the Expert Consensus Panel for Agitation in Dementia generally recommended against the use of benzodiazepines except for short-term or occasional use for anxiety symptoms.[71] In addition, no psychoactive medication prescribed to treat neuropsychiatric symptoms of dementia should be continued indefinitely and attempts at drug withdrawal should be made regularly.[72] Many patients who are prescribed antipsychotics for neuropsychiatric symptoms will no longer need them when the drug is later discontinued.[73] Physical restraints should be avoided as they are associated with injury, not protection, of patients who are confused.[74]

Directions for Future Research

Because there is no "magic pill" for neuropsychiatric symptoms of dementia, it is especially important to continue efforts to better understand the pathophysiology of the symptoms and whether they vary by dementia type; perform high-quality trials of nonpharmacological treatments, especially in combination with drug therapy; include nursing home placement and caregiver outcomes in trials[47]; and support non–industry-funded trials aimed specifically at treating patients with neuropsychiatric symptoms. The results from the National Institute of Mental Health–funded Clinical Antipsychotic Trials of Intervention Effectiveness trial[75] will be particularly valuable. This trial is a multicenter RCT comparing risperidone, olanzapine, quetiapine, citalopram, and placebo for up to 36 weeks for the treatment of psychosis and agitation in patients with AD.[75] This will be the first and longest placebo-controlled, head-to-head trial of atypical antipsychotic drugs.

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Acquisition of data: Sink, Holden.
Analysis and interpretation of data: Sink, Holden, Yaffe.
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