ALZHEIMER DISEASE: TREATMENT OF NONCOGNITIVE BEHAVIORAL ABNORMALITIES

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The original patient described by Dr. Alois Alzheimer in 1907 (1) was remarkable for both her progressive cognitive impairment and her prominent noncognitive behavioral abnormalities. Clinical interest in the noncognitive abnormalities in Alzheimer disease (AD) has been substantial because of their high prevalence (2–4) and because noncognitive behavioral problems complicate patient management and often precipitate institutionalization (3,5–12). The real or apparent resemblance of delusions, hallucinations, depressed mood, agitation, hostility, and other noncognitive behavioral abnormalities of AD to the signs and symptoms expressed in such classic psychiatric disorders as depression, schizophrenia, and mania has prompted the widespread use of psychotropic drugs in the management of AD (13–16). However, widespread use does not imply established efficacy. In fact, data establishing the efficacy of psychotropic drugs for noncognitive behavioral problems in AD and other dementing disorders remain limited. Although reports of treatment outcome studies incorporating reliable and valid outcome measures, well-defined patient samples, and randomization to an adequate trial of active medication or placebo continue to appear, their number remains small. This chapter reviews informative studies of the psychopharmacologic management of noncognitive behavioral problems in AD. These include depression (or depressive signs and symptoms), psychotic symptoms (delusions and hallucinations), and disruptive agitated behaviors (e.g., physical and verbal aggression, motoric hyperactivity, and uncooperativeness with activities necessary for personal hygiene and safety). Placebo-controlled studies are emphasized, but results of other studies and reports are discussed when they suggest directions for future investigation or are the only studies available.

DEPRESSION IN ALZHEIMER DISEASE

Diagnostic Challenges

The diagnosis and treatment of depression complicating the course of AD have received considerable attention. Because depression *per se* can impair cognitive function (17), it is reasonable to hypothesize that effective treatment of depression in the patient with AD may maximize potential cognitive capacity. Furthermore, the consensus is that reduction of depressive signs and symptoms improves quality of life (18). Unfortunately, the apparently straightforward goal of treating depression complicating AD becomes complex when the problems involved in the diagnosis of depression in the context of AD or other dementing illnesses are considered. A fundamental problem is the substantial overlap of signs and symptoms between depression and AD. Common to both disorders are apathy and loss of interest, impaired ability to think and concentrate, psychomotor changes (both retardation and agitation), and sleep disturbance. The ability to diagnose depression in AD is further compromised by the patient's lack of insight and poor recollection of symptoms.

Prevalence

Even if investigators agreed on uniform diagnostic criteria for syndromal depression in AD and used uniform assessment instruments and interviews, discrepant prevalence rates would likely arise from the differential characteristics of the samples of AD patients studied. Prevalence rates of AD with concurrent depression derived from clinical populations are higher than those derived from research registries that select "pure" AD subjects without a history of major

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depressive disorder. For example, in an outpatient geriatric clinic, Reifler et al. (19) found that 20% of patients with AD met DSM-III criteria for major depressive episode. In contrast, Burke et al. (20) found no incident case of major depression in an AD research registry population followed longitudinally through the course of illness. The latter study included a longitudinally followed normal control group matched for age, sex, race, and social position. Signs and symptoms of depression occurred in both patients with AD and controls, but criterion-based major depression could not be diagnosed. A similarly low prevalence of major depression in a sample of subjects with AD screened to exclude those with a past history of major psychiatric disorders was reported by Kumar et al. (5). Although depressed mood was more frequent in the AD subjects than in age-matched normal controls, depressed mood in the AD subjects was unaccompanied by classic vegetative signs and symptoms of depression. These investigators, therefore, interpreted depressed mood as reflecting "demoralization" rather than major depressive disorder. Given these problems, it is not surprising that estimates of the prevalence of depression in AD are widely disparate. Perhaps the true prevalence of concurrent depression in AD lies somewhere between these disparate estimates. As early as 1955, Sir Martin Roth (21) addressed the issue of differentiating the common "affective coloring" seen in dementia patients from the relatively uncommon "sustained depressive symptom complex." He found that the latter syndrome, which can probably be equated with DSM-IV major depressive episode, occurred in only 3% of patients with dementia.

Psychopharmacologic Approaches

It continues to be disappointing that the extensive interest in defining the prevalence of depression complicating AD has generated few interpretable studies evaluating the outcome of antidepressant treatment in such patients. The database consists primarily of anecdotal case reports and non–placebo-controlled outcome studies. These reports suggest that depression complicating AD may respond to tricyclic antidepressants (22,23), monoamine oxidase inhibitor (MAOI) antidepressants (24), or selective serotonin reuptake inhibitors (SSRI) (25). In an open trial of nortriptyline, given in doses sufficient to achieve therapeutic plasma concentrations, or electroconvulsive therapy in eight inpatients with AD complicated by depression, Reynolds et al. (26) reported a significant reduction in mean Hamilton Depression Scale (HAM-D) scores (27) from 17 before treatment to 9 after treatment. Although the reduction in depressive signs and symptoms was substantial in AD patients with concurrent depression, it was less robust than in a similarly treated group of elderly nondemented depressed patients. Another open trial of "naturalistic" somatic antidepressant treatment of inpatients with dementia and concurrent depression was reported by Greenwald et al. (28). This

study carefully documented the presence of major depressive episode in six patients with AD and four with multiinfarct dementia (MID). Patients were treated for a mean duration of 11 weeks with a variety of conventional somatic antidepressants (doses not reported), electroconvulsive therapy, or both. HAM-D scores significantly and substantially decreased from a mean of 19 on admission to a mean of 5 at discharge. This degree of improvement did not differ significantly from that in an elderly, nondemented, depressed inpatient group treated in a similar naturalistic manner. However, the mean length of stay to achieve comparable improvement in the elderly nondemented, depressed group was substantially shorter than that in the demented, depressed group. Possible differential treatment responses between AD subjects with major depression and MID subjects with major depression were not reported. Both Reynolds et al. (26) and Greenwald et al. (28) interpreted their results as suggesting that major depression complicating dementia is responsive to somatic antidepressant treatments, but both investigators acknowledged that standardized, double-blinded, placebo-controlled studies of antidepressants in dementia patients with major depression are needed.

The SSRI antidepressants are theoretically attractive drugs for the treatment of depression in AD. Decreased numbers of serotoninergic neurons in the dorsal raphe nucleus and decreased concentrations of the serotonin metabolite 5-hydroxyindolacetic acid in forebrain and cerebrospinal fluid are consistent with a serotoninergic deficit in AD (29, 30). Enhancing serotoninergic neurotransmission by inhibiting serotonin reuptake theoretically might alleviate depression in AD. Furthermore, the adverse effect profile of SSRIs is relatively benign compared with those of the tricyclics and MAOIs. SSRIs are not anticholinergic, nor do they produce orthostatic hypotension. These theoretic advantages likely account for the increasing use of SSRIs in elderly patients (16,31,32).

Placebo-Controlled Outcome Trials

Despite the widespread use of antidepressants in patients with AD and other dementing disorders (32), it is clear that this use is not grounded in an adequate empiric database. Only three placebo-controlled trials of an antidepressant in AD patients with depression have been published thus far, and only one of these evaluated an antidepressant from the increasingly prescribed class of SSRIs.

Reifler et al. (33) randomly assigned to either imipramine ($n = 13$) or placebo ($n = 12$) subjects who met DSM-III criteria for both primary degenerative dementia of the Alzheimer type and major depressive episode. AD outpatients (mean age, 72) had a mean Mini-Mental State Examination (MMSE) score of 17 [very comparable with the mean MMSE scores of the demented, depressed patients studied openly by Greenwald et al. (28) and Reynolds et al. (26)]

and were suffering from a similarly moderate degree of depression (mean HAM-D score, 19). Imipramine (mean dose, 83 mg/d; mean plasma level of imipramine plus desmethylimipramine, 116 ng/mL) or placebo was prescribed for 8 weeks. Substantial, highly significant, and almost identical improvements occurred in mean HAM-D scores in both the imipramine subjects (19.3 before treatment vs. 11.5 following treatment) and placebo subjects (18.6 before treatment vs. 10.8 following treatment). Imipramine was generally well tolerated in these subjects. However, its central anticholinergic effect likely accounted for subtle decrements in cognitive function in the imipramine group. The improvement in HAM-D scores was similar to that achieved in the open inpatient studies reported by Greenwald et al. (28) and Reynolds et al. (26). This outpatient study demonstrated that depressive signs and symptoms can be reduced in outpatients with AD, but the mechanism of treatment efficacy does not appear to be a specific antidepressant effect of imipramine.

Petracca et al. (34) randomly assigned 24 patients meeting criteria for AD with DSM-III-R depression to treatment with either clomipramine or placebo in a randomized, double-blinded, placebo-controlled crossover study. As in the imipramine trial reported by Reifler et al. (33), both active drug (in this case clomipramine) and placebo were associated with significant improvement in depression ratings. However, in this study, the improvement in depression in the active drug group was modestly greater than that in the placebo group. One subject in the clomipramine group dropped out of the study because of an acute confusional episode likely attributable to the central anticholinergic activity of clomipramine.

Nyth et al. (35) have reported the only placebo-controlled trial of an SSRI in patients with dementia and concomitant depression. In this study, subjects were randomized to 20 mg of citalopram per day or placebo for 6 weeks. Twenty-three patients with dementia (presumably including a substantial number of patients with AD) were "nested" in a larger controlled trial of depressed elderly persons ($n = 149$), the majority of whom were not suffering from dementia. The inclusion criterion for "depression" was an HAM-D score of at least 14. In the 23 subjects with dementia who completed the 6-month trial, modest but significant differences were noted favoring citalopram over placebo in the observer-rated fear/panic, depressed mood, and impaired recent memory items of the dementia rating scale of Gottfries et al. (36). As in the imipramine and clomipramine studies described above, a substantial antidepressant response to placebo occurred in these subjects, but citalopram was modestly superior to placebo and was well tolerated. Although the effects of citalopram on psychometric tests were not reported, observer-rated improvement in memory is supportive of other studies suggesting that SSRIs do not have an adverse effect on cognitive function (37).

These limited data from placebo-controlled studies of antidepressants in outpatients with AD and concurrent depression have several implications. First, the robust responses of the placebo group make it essential to include a placebo group in future antidepressant drug outcome trials in dementia patients if the results are to be interpretable. They also suggest that the "nonpharmacologic" aspects of trial participation contribute to a reduction of depressive signs and symptoms in patients with AD. A recent placebo-controlled trial demonstrating efficacy of behaviorally based psychotherapy for depression in AD outpatients is consistent with this interpretation (38). Second, the absence of SSRI adverse effects on cognitive function or blood pressure regulation is an advantage for this class of antidepressant in older patients (37,39). More placebo-controlled trials of SSRIs (and other newer antidepressants, such as venlafaxine and nefazodone) in AD patients with concomitant depression would be informative.

PSYCHOSIS AND DISRUPTIVE AGITATION

Prevalence

The prevalence rates of psychotic symptoms (delusions and hallucinations) complicating AD cluster between 20% and 40% in carefully performed cross-sectional studies (2,4,7, 40). Because psychotic symptoms can emerge at any time during the course of AD and probably are more prevalent in the later stages of the illness, longitudinal studies reveal even higher prevalence rates (6). Drevets and Rubin (41) longitudinally followed subjects with AD from the early through the later stages of illness and documented the occurrence of psychotic symptoms both cross-sectionally and cumulatively. This study was strengthened by the inclusion of a longitudinally followed age-matched normal control population (psychotic symptoms developed in none of them during the course of the study). Slightly more than 50% of the AD subjects manifested psychotic symptoms at some point during the course of their illness. The subjects were not considered positive for psychotic symptoms if they occurred only rarely or only in the context of a possible delirium. As in other studies of psychotic symptoms in AD (2, 4,7), delusions were usually simple and persecutory, most commonly involving theft. Systematized delusions were uncommon. Hallucinations were most frequently visual, although auditory hallucinations were also common.

Disruptive agitated behaviors such as verbal and physical aggression, motor hyperactivity, uncooperativeness with essential care, persistent irritability, and repetitive vocalizations are highly prevalent in moderately to markedly demented patients with AD (8,11). Less severely demented patients with AD who are still able to reside in the community also manifest disruptive behaviors. Ryden (42) surveyed the caregivers of outpatients with AD and found a prevalence of aggressive behavior occurring at least once a week in 31% of subjects and daily in 16% of subjects.

Although psychotic symptoms and "nonpsychotic" disruptive agitated behaviors may not always reflect the same underlying pathophysiologic process or processes, these two classes of noncognitive behavioral problems often are expressed together. Lopez et al. (43) evaluated the presence of belligerence, uncooperativeness, and physical and verbal aggression in psychotic AD patients with delusions and hallucinations ($n = 17$) and nonpsychotic AD patients without delusions and hallucinations ($n = 17$). A greater proportion of psychotic AD patients (11 of 17) manifested these behavioral disturbances than did the nonpsychotic AD patients (1 of 17). A study addressing the relationship between psychotic symptoms and physical aggression in AD patients was reported by Deutsch et al. (40). Delusions (most commonly persecutory) and mistaken identifications (e.g., patients believing that their house is not their home or that strangers are living in the house) frequently preceded and were significantly associated with episodes of physical aggression. However, the presence of delusions could account for episodes of physical aggression in only a minority of cases. Therefore, factors other than apparent psychosis were involved in the precipitation of physically aggressive behavior.

Psychotic Symptoms and Disease Progression

A number of studies have consistently suggested that the presence of psychotic symptoms in AD is associated with more rapid deterioration of cognitive function. Stern et al. (44) were the first to report this phenomenon, and the association between psychotic symptoms and more rapid decline has since been confirmed by other groups. Lopez et al. (43) reported that AD patients with delusions and hallucinations had a more rapid decline in MMSE scores during a 1-year follow-up than did nonpsychotic AD patients, and they appeared to manifest a specific defect in receptive language. Drevets and Rubin (41) reported that the presence of psychotic symptoms predicted an increased rate of cognitive deterioration. Jeste et al. (45) compared the performance over time of delusional and nondelusional AD patients on a neuropsychological test battery. Patients with delusions had a more rapid rate of dementia progression than nondelusional AD patients. It is possible that the presence of psychotic symptoms reflects a more malignant pathobiologic process that adversely affects both behavior and neurodegeneration. The inadvertent inclusion in these studies of patients now more accurately classified as having dementia with Lewy bodies (DLB) also may have contributed to the apparent association between psychotic symptoms and more rapid cognitive deterioration. DLB is characterized by an early incidence and high prevalence of psychotic symptoms (46), and these patients appear to manifest a more rapidly deteriorating course of dementia (47).

Antipsychotic Drug Use for Psychotic and Disruptive Behaviors: Rationale

Psychotropic drugs are widely prescribed to patients with AD in long-term care facilities (16). In fact, repeated documentation of the widespread practice of prescribing antipsychotic and other psychotropic drugs in the long-term care setting, often for extended periods of time (13–16), has prompted the implementation of federal regulations designed to limit the use of such drugs to short-term treatment regimens with clear indications (48).

The rationale for the use of antipsychotic drugs in AD is partially attributable to the superficial phenomenologic similarities of delusions, hallucinations, and other disruptive behaviors occurring in AD to the symptoms of schizophrenia. Unfortunately, this analogy to psychotic and other behavioral signs and symptoms in schizophrenia is very imperfect. Hallucinations in AD usually are visual, whereas hallucinations in schizophrenia typically are auditory. Delusions in AD often are unelaborated persecutory beliefs, such as delusions of theft. Systematized, complex, and grandiose delusions are uncommon (9). In addition, the memory deficits of AD often appear to play a role in the development of delusional beliefs. For example, patients with AD who forget where an item has been placed and who do not understand their cognitive deficits may assume that it has been stolen. Or, a patient with AD can stubbornly insist in a delusional manner that a long-deceased person who still remains alive in available memory traces is, in fact, alive. Although such beliefs of theft, of a deceased person who continues to exist, or of a spouse who is an impostor may meet formal criteria for delusions, they are phenomenologically dissimilar to the typical delusions of schizophrenia for which the antipsychotic drugs have been demonstrated so effective. These phenomenologic differences may reflect underlying neurobiologic differences, and they may explain why the effect size of antipsychotic drugs in AD is modest (49) and much less robust than in schizophrenia.

Typical Antipsychotic Drugs: Outcome Studies before DSM-III

The interpretation of typical antipsychotic drug outcome studies in patients with dementia that were performed before the introduction of DSM-III is often hampered by the use of unclear diagnostic nomenclature. For example, the term *senile psychosis* connoted dementia with severe cognitive impairment rather than the presence of delusions and hallucinations. In addition, early studies were usually performed in state hospital populations, which included patients with a mixture of degenerative neurologic dementing disorders (at least a subgroup of whom presumably had AD) and patients with chronic schizophrenia who had grown old in the institutional setting. In such early studies targeting psychosis and disruptive agitation, chlorpromazine (50,51),

acetophenazine (52), and haloperidol (53) were each modestly more effective than placebo, but adverse effects such as excessive sedation, falls, unsteady gait, and pseudoparkinsonism were more common in the active drug groups.

It is not surprising that early studies of typical antipsychotic drugs in patients with dementia who did not manifest psychotic disruptive behaviors as target symptoms and signs found antipsychotic drugs no more effective than placebo (54,55). For example, a comparison of the effects of trifluoperazine and placebo on target symptoms of apathy, withdrawal, and cognitive and behavioral deterioration (loss of ambulation, disorientation, and incontinence) demonstrated no therapeutic effect of the active medication, and the findings were most remarkable for a high prevalence of trifluoperazine-induced sedation and extrapyramidal signs and symptoms (54). One of these studies, however, is particularly instructive concerning the substantial placebo response that can be seen in elderly patients with dementia despite the presence of cognitive impairment. In a comparison of the effects of thiothixene and placebo on cognitive deficits in a group of demented patients (55), the majority of patients in both groups were rated as globally improved (13 of 22 patients receiving thiothixene and 11 of 20 patients receiving placebo).

Typical Antipsychotic Drug Studies: Outcome Studies since DSM-III

Since the introduction of DSM-III, a small number of placebo-controlled studies have evaluated the efficacy of typical antipsychotic drugs in patients with dementia in both outpatient and institutional settings. Because of the use of operationalized diagnostic criteria for AD and MID, one can be more confident that elderly patients with chronic psychiatric disorders beginning in early life, such as schizophrenia, were excluded from these studies. In addition, the studies have clearly targeted psychotic or disruptive agitated behaviors as outcome measures.

Several studies have compared typical antipsychotics with placebo in either state hospital or community nursing home institutional settings. Petrie et al. (56) compared low-dose haloperidol and loxapine with placebo in 64 inpatients of a state psychiatric hospital (mean age, 73 years). The sample included subjects who met diagnostic criteria for either AD or MID. Both antipsychotic medications were more effective than placebo in reducing hallucinations, suspiciousness, hostility, excitement, and uncooperativeness. Global improvement ratings, however, only modestly favored the active medications. Thirty-five percent of haloperidol subjects and 32% of loxapine subjects, in comparison with 9% of placebo subjects, were rated as moderately or markedly improved. Not only were therapeutic responses to active drugs in these elderly demented patients lower than would have been predicted from outcome studies in younger subjects with schizophrenia, but adverse drug effects, including sedation and extrapyramidal signs and symptoms, were frequent. In a placebo-controlled study of antipsychotic drugs in a typical community nursing home sample of elderly demented patients, Barnes et al. (57) randomized 60 behaviorally disturbed patients with dementia (mean age, 83 years) to thioridazine, loxapine, or placebo. All subjects met diagnostic criteria for either AD or MID. Both active antipsychotic drugs were more effective than placebo for reducing excitement and uncooperativeness. Although suspiciousness and hostility tended to improve more with active drugs than with placebo, substantial improvements in these two factors also were documented in subjects receiving placebo. Like Petrie et al. (56), Barnes et al. (57) found that only approximately one-third of patients in the active medication conditions achieved global ratings of either moderate or marked improvement. Finkel et al. (58) compared the typical antipsychotic drug thiothixene with placebo in agitated nursing home patients with dementia (mean age, 85 years). Disruptive problem behaviors included physical aggression (hitting, kicking, and pushing), physical nonaggressive agitation (pacing and repetitive mannerisms), and verbal aggression (screaming and cursing). The presence and nature of psychotic delusions and hallucinations were not specified in this study. Thiothixene was more effective than placebo in this 11-week, parallel-design study, but differences between groups did not become apparent until 6 weeks of treatment had been completed. The positive effects of thiothixene appeared to persist for 3 to 6 weeks after drug discontinuation. Taken together, these three studies suggest that low-dose typical antipsychotic drugs are modestly effective for treating psychotic and nonpsychotic disruptive behaviors in patients with AD residing in long-term care facilities. However, parkinsonian rigidity and sedation occurred in some patients in each of these studies.

In a well-designed and well-executed study of the acute efficacy and adverse effects of a typical antipsychotic in AD outpatients with psychosis and disruptive behaviors, Devanand et al. (59) randomized 71 subjects to 6 weeks of standard-dose haloperidol (2 to 3 mg/d), low-dose haloperidol (0.5 to 0.75 mg/d), or placebo for 6 weeks. When an *a priori* response criterion of at least 25% improvement in one of three quantifications of target symptoms was used, response rates were significantly greater in the standard-dose (55% to 60%) than in either the low-dose (25% to 35%) or placebo (25% to 35%) groups. Although effect sizes were modest, standard-dose haloperidol clearly was effective for both psychosis and agitation. Not surprisingly, moderate to severe extrapyramidal signs developed in a subgroup of standard-dose haloperidol subjects (20%). Low-order but significant correlations were found between haloperidol blood levels and symptomatic improvement, and a stronger correlation between haloperidol blood levels and extrapyramidal signs. Haloperidol was effective for treating psychosis and agitation in AD outpatients in this study, but

the therapeutic window was narrow. A similar narrow therapeutic window in such patients may also exist for several of the newer atypical antipsychotics (see below). In a recently reported multicenter placebo-controlled comparison of haloperidol, trazodone, and behavioral management for disruptive agitation and psychosis in AD outpatients, haloperidol (mean dose, 2 mg/d) was not more effective than placebo (60). The reasons for the discrepant findings between this study and the positive study reported by Devanand et al. (59) in AD outpatients are unclear. One possibility is that the subjects in the study of Devanand et al. may have manifested more severe behavioral symptoms. In an early, placebo-controlled trial of haloperidol (53), it was in the more severely behaviorally disturbed patients that a positive effect of haloperidol was detectable.

Atypical Antipsychotic Drug Studies

A major problem in the use of traditional antipsychotic drugs to manage psychiatric and behavioral problems in AD and other dementing disorders is the frequent emergence of pseudoparkinsonian rigidity, tremor, and bradykinesia. Patients with DLB are particularly susceptible to these adverse effects (61). The atypical antipsychotic drugs such as clozapine, risperidone, olanzapine, and quetiapine offer the theoretic advantage of a reduced or minimal incidence of pseudoparkinsonism. The atypical antipsychotics may also theoretically prove more efficacious than the typical antipsychotics for psychosis and disruptive agitation in AD. The efficacy and tolerability of these drugs in AD patients with psychosis or disruptive agitation recently have been addressed in several large, well-designed, placebo-controlled outcome studies.

Katz et al. (62) reported the results of a large, double-blinded, placebo-controlled study of efficacy and safety of risperidone in institutionalized dementia patients with psychotic and disruptive behaviors (mean age, 83 years). Among the subjects, 73% met criteria for AD, 15% for vascular dementia, and 12% for mixed AD and vascular dementia. At the end of the 12-week study, BEHAVE-AD total scores, in addition to psychosis and aggressiveness subscale scores, were significantly more reduced in patients receiving either 1 or 2 mg of risperidone per day than in those receiving placebo. In contrast, a 0.5-mg low-dose group did not differ from the placebo group at 12 weeks except for a slightly greater reduction in the aggressiveness subscale of the BEHAVE-AD. Extrapyramidal adverse effects did not differ between the 0.5-mg group or the 1-mg group versus placebo. However, significantly more subjects (21%) in the group receiving 2 mg/d manifested extrapyramidal adverse effects than in the placebo group (7%). The efficacy of risperidone in this study was modest and comparable in magnitude with that reported in studies of typical antipsychotics in this type of institutionalized, very elderly sample

(57,58). The authors concluded that 1 mg of risperidone per day is likely to be the optimal dose for the majority of dementia patients of this age and with cognitive and behavioral symptoms of this degree of severity. Another large, double-blinded, placebo-controlled trial of risperidone, haloperidol, and placebo generally supports the equivalent efficacy of these atypical and typical antipsychotics, but it also suggests an advantage of risperidone in terms of extrapyramidal adverse effects (63). Institutionalized patients with dementia (mean age, 81 years) were randomized to risperidone (mean dose, 1.1 mg/d), haloperidol (mean dose, 1.2 mg/d), or placebo for 12 weeks. Both the risperidone and haloperidol groups had significantly lower aggression cluster scores on the BEHAVE-AD at week 12 in comparison with the placebo group. The severity of extrapyramidal symptoms at endpoint did not significantly differ between the risperidone and placebo groups but was significantly greater in the haloperidol group than in the risperidone group.

The atypical antipsychotic drug olanzapine also has been studied in large, placebo-controlled trials in AD patients with psychosis and other behavioral disturbances. In an 8-week double-blinded, placebo-controlled trial that included 238 outpatients with AD and psychosis (mean age, 79 years), olanzapine (mean dose, 2.4 mg/d) was not significantly more effective than placebo in improving BEHAVE-AD scores, nor were adverse effects such as extrapyramidal signs more common in the olanzapine group (64). In a subsequent large, placebo-controlled study in AD patients residing in nursing facilities and manifesting psychosis and other behavioral disturbances (65), subjects were randomized to placebo or to 5 mg, 10 mg, or 15 mg of olanzapine per day. Clinically significant improvement, defined a reduction from baseline on the Neuropsychiatric Inventory (NPI) total score of 50% or more (66), was demonstrated in 66% of the patients receiving 5 mg/d, 57% receiving 10 mg/d, 43% receiving 15 mg/d, and 36% of the patients receiving placebo. These differences were significant for the groups receiving 5 or 10 mg/d but not for the group receiving 15 mg/d. In addition, the high-dose subjects had a significantly increased incidence of somnolence and abnormal gait. This study suggests that 5 mg per day may be an optimal dose of olanzapine for AD patients with psychosis and other disruptive agitated behaviors.

Taken together, studies of the atypical antipsychotics suggest that the efficacy of these newer agents is comparable with that of the typical antipsychotics and that, somewhat surprisingly, they may have a narrow "therapeutic window." However, because the incidence of parkinsonism and tardive dyskinesia associated with the atypical antipsychotics is low, it is likely that they will be increasingly used to manage psychosis and disruptive agitation in patients with AD, despite their higher cost.

Maintenance Antipsychotic Drug Therapy in Dementia

When a satisfactory response to an antipsychotic drug has been achieved with an acute treatment regimen, the clinician must next decide how long to maintain the patient on the drug. This question was addressed by Risse et al. (67) in a small but informative antipsychotic drug discontinuation study in behaviorally disturbed elderly patients with dementia who appeared to have benefited from an acute course of antipsychotic medications and had then been maintained on these medications on a long-term basis. Placebo was substituted for maintenance antipsychotic medication in nine men with dementia (mean age, 65 years) who had shown a clear reduction in noncognitive behavioral problems following treatment with antipsychotic medication and who subsequently had been maintained on antipsychotic medication for at least 90 days. At the end of the 6-week placebo-substitution period, disruptive behaviors severe enough to warrant reinstitution of antipsychotic medication had developed in only one patient. Of the remaining eight patients, five actually were less agitated, two were unchanged, and only one was rated as more agitated than when he had been receiving maintenance antipsychotic medication. This small study supports the wisdom of periodic discontinuation of long-term antipsychotic medication to evaluate the need for maintenance. In a larger study performed in 36 community nursing home patients (mean age, 82 years) who met criteria for probable or possible AD, patients were randomly assigned to either continuation of antipsychotic medication or withdrawal from antipsychotic medication and substitution of placebo (68). Of the 22 patients withdrawn from antipsychotic medication, 20 (91%) were able to complete the 4-week, double-blinded withdrawal. In only two cases did the nursing home staff request that the patients be withdrawn from the study because of emergencies involving unacceptable levels of agitation. No significant difference in the incidence of emergent physically aggressive behavior was found between patients withdrawn from antipsychotic medication and those maintained on antipsychotic medication. Half of the patients withdrawn from antipsychotic medication remained off the drugs for an extended period of time after the end of the study, even after the blind had been broken. These two studies demonstrate that an attempt at withdrawal from antipsychotic medication in behaviorally stable patients with dementia is feasible.

Dementia with Lewy Bodies: Implications for Psychopharmacology

It is increasingly clear that a subgroup of patients meeting formal criteria for probable AD (69) are more accurately classified diagnostically as having DLB (46).

The defining neuropathologic feature of DLB is the presence of Lewy bodies in the forebrain. These α-synuclein-containing intracytoplasmic inclusions are the classic histopathologic lesion of Parkinson disease, but substantial numbers of Lewy bodies rarely are expressed outside the substantia nigra in this latter disorder. In DLB, numerous Lewy bodies are found in neocortex, limbic brain areas, and other parts of the forebrain. In most cases of DLB, modest numbers of the amyloid plaques and neurofibrillary tangles characteristic of classic AD are also found. In addition, the presynaptic cholinergic deficit present in AD (70,71) is very prominent in DLB (72). The parkinsonian features and cholinergic deficit of DLB have implications for the pharmacologic management of the noncognitive behavioral aspects of this disorder. First, the parkinsonian features of DLB make these patients extremely sensitive to dopaminergic blockade by typical antipsychotics (61). The atypical antipsychotics appear preferable for the management of psychosis in DLB (73). Also, several studies suggest that compensating for the profound cholinergic deficit of DLB with cholinesterase inhibitor therapy improves psychotic and other noncognitive behavioral problems in this disorder (26, 74,75).

Other Pharmacologic Approaches to the Management of Agitated Behaviors in Alzheimer Disease

Despite their somewhat disappointing therapeutic effect size, the consensus is that antipsychotic drugs should be prescribed for clear and troublesome delusions and hallucinations. However, the rationale for prescribing antipsychotic drugs as the drug class of choice for AD patients with disruptive agitation in the absence of clear psychotic symptoms is less compelling. In such patients, attempts to demonstrate efficacy for other types of psychotropic drugs are both reasonable and important. Unfortunately, the database derived from well-designed clinical trials of psychotropic drugs other than the antipsychotics for the management of disruptive behaviors in AD is even less robust than that for the antipsychotic drugs. The following review, therefore, relies heavily on anecdotal reports and non–placebo-controlled studies when data from interpretable placebo-controlled studies are not available.

Benzodiazepines

The use of benzodiazepines in patients with AD and other dementing disorders has been reviewed (76). In a group of "emotionally disturbed" elderly patients (mean age, 81 years), Sanders (77) evaluated the efficacy of oxazepam in comparison with placebo in an 8-week treatment trial. Oxazepam was superior to placebo, particularly for reduction of agitation and anxiety. Interpretation of this study is ham-

pered by the vagueness of the diagnoses and the likelihood that many of the subjects were not demented. Coccaro et al. (78) compared oxazepam, haloperidol, and the sedating antihistamine diphenhydramine in elderly institutionalized patients. The mean age of these subjects was 75 years, most met criteria for AD, and target signs and symptoms included tension, excitement, aggressiveness, pacing, and increased motor activity. Ratings of target signs and symptoms improved during an 8-week period in all treatment groups. Although statistically significant differences between the groups did not emerge, a trend for greater improvement with diphenhydramine or haloperidol than with oxazepam was noted. The lack of a placebo group in this study complicates interpretation of the modest improvements in objective ratings of disruptive behaviors.

Salzman et al. (79) tapered and then discontinued benzodiazepines in 13 elderly nursing home residents and compared memory function and ratings of depression, anxiety, irritability, and sleep between the subjects who discontinued benzodiazepine and 12 nursing home residents who continued their benzodiazepine regimens. The group in which the drug was discontinued showed greater improvements in memory than did the group that continued to take benzodiazepine, and no differences between the groups were found in measures of depression, anxiety, irritability, or sleep. This study suggests that at least a subgroup of patients maintained for an extended time on short-acting benzodiazepines may benefit from a trial of drug discontinuation. In addition to adverse effects on cognitive function, benzodiazepines have been associated with falls in geriatric psychiatric inpatients (80). Taken together, these studies of benzodiazepines in behaviorally disturbed patients with dementia suggest that the use of benzodiazepines is best limited to short-term treatment of acute anxiety and agitation, and that benzodiazepines are a poor choice for long-term management of disruptive agitation in AD.

Buspirone

Buspirone is a partial 5-hydroxytryptamine subtype 1A (5-HT_{1A})-receptor agonist with antianxiety activity and a relatively benign adverse effect profile. Two uncontrolled studies of buspirone in dementia patients with agitated behavior have been reported. Sakauye et al. (81) prescribed buspirone to 10 patients with AD complicated by agitated behaviors in an open-label study. A modest but statistically significant overall reduction of agitated behaviors was noted, as was a substantial variability in response, with 4 of the 10 patients demonstrating marked declines in disruptive behaviors. In a similar study, Hermann and Eryavec (82) prescribed buspirone to a group of elderly nursing home residents with heterogeneous types of dementia (AD, MID, and alcoholic dementia). All subjects had demonstrated severe behavioral disturbances, including agitation and aggression, and all had failed to improve with previous trials of other types of psy-

chotropic medications, principally antipsychotic drugs. Six of 16 patients were rated as much or very much improved in terms of agitation and aggressive behavior. Levy (83) used buspirone to treat 20 patients with AD and behavioral disturbances rated as at least moderately troublesome on the BEHAVE-AD in a single-blinded dose-escalation study. After a 2- to 4-week psychotropic drug washout period, subjects were given placebo for 1 week and then progressively increasing weekly doses (15, 30, 45, and 60 mg) of buspirone. A dose–response improvement in anxiety rating occurred. As in the study of Barnes et al. (57) of antipsychotic drugs, placebo had a significant effect on delusions. In these studies of buspirone, adverse effects were unusual. Given the low toxicity of this drug, further placebo-controlled investigations appear warranted.

Serotoninergic Drugs

Selective Serotonin Reuptake Inhibitors

The clear serotoninergic deficit demonstrated in AD (29, 30) and the relationship between low central nervous system serotoninergic activity and aggressive behaviors in nondemented persons (84) provide the rationale for studies addressing the behavioral efficacy of drugs that enhance central serotoninergic neurotransmission in AD patients with agitated behaviors. In a recently reported multicenter trial, AD subjects selected for the presence of psychosis or disruptive agitation were first treated openly with the cholinesterase inhibitor donepezil and then randomized to the addition of either the SSRI sertraline or placebo (85). Sertraline had a modest positive effect on agitated behaviors (but not psychosis) in comparison with placebo. Two multisite Scandinavian studies have evaluated SSRIs in demented patients with a variety of predominantly nonpsychotic behavioral disturbances. These patients were not reported to have met diagnostic criteria for depression. In demented patients with either AD or vascular dementia, the SSRI citalopram was more effective than placebo for the target symptoms of irritability, fear/panic, depressed mood, and restlessness (86). Improvement was limited to demented patients with AD. No significant effects of citalopram were noted in patients with vascular dementia. Cognitive function was unaffected by either citalopram or placebo, and citalopram was well tolerated by the elderly subjects in this study. In another study of demented patients with AD or vascular dementia (87), the SSRI fluvoxamine tended to be more effective than placebo on the target symptoms of confusion, irritability, anxiety, fear/panic, mood level, and restlessness. The differences between fluvoxamine and placebo, however, failed to reach statistical significance. Although more studies are needed to evaluate the possible roles of the SSRIs for disruptive agitation, results to date do not support their use as first-line agents for this indication.

Other Serotoninergic Drugs

Trazodone is a sedating antidepressant with serotoninergic agonist activity. Simpson and Foster (88) treated four de-

mented patients who manifested disruptive behaviors with trazodone after antipsychotic drug treatment had proved ineffective. In this anecdotal report, trazodone in doses of 200 to 500 mg daily was associated with decreased agitation and aggressive behavior. Pinner and Rich (89) treated seven demented patients with trazodone for symptomatic aggressive behavior. Again, all subjects had failed to improve with antipsychotic drug therapy. Three of the seven patients demonstrated an apparent marked decrease in aggressive behavior following 4 to 6 weeks of trazodone at doses ranging from 200 to 350 mg/d. In a recently reported multisite study comparing haloperidol, trazodone, behavioral management, and placebo, the results with trazodone (mean dose, 200 mg/d) did not differ from those with placebo (59). In a double-blinded, placebo-controlled crossover study, Lawlor et al. (90) treated 10 patients with AD and behavioral complications (troublesome agitation, depression, psychosis, or anxiety) with trazodone (up to 150 mg/d), buspirone (30 mg/d), or placebo. Trazodone produced a small but significant behavioral improvement in comparison with placebo, whereas buspirone had no apparent effect.

Anticonvulsant Drugs

Because the hyperactive and aggressive behaviors encountered in the manic phase of bipolar disorder at least superficially can resemble agitated behaviors in AD and other dementias, the anticonvulsant drugs effective in the treatment of mania may benefit behaviorally disturbed patients with dementia. Lithium has not been helpful for behavioral symptoms in AD (91). Marin and Greenwald (92) treated two AD patients and one MID patient with carbamazepine in an attempt to reduce combative, agitated behaviors. Within 2 weeks of carbamazepine treatment at doses ranging from 100 to 300 mg/d, behavioral improvement was noted in all subjects. In a larger open study of AD patients who had failed to respond to antipsychotic drugs (93), reduction in hostility, agitation, and uncooperativeness was noted in five of nine patients. In this study, two patients whose agitated behaviors decreased manifested ataxia and confusion, which resolved with reduction of the carbamazepine dose. The mean dose of carbamazepine in this study was 480 mg/d. In contrast to enthusiastic authors of these small reports, Chambers et al. (94) noted no overall benefit from carbamazepine in 19 elderly patients with dementia who were prescribed carbamazepine at doses of 100 to 300 mg/d. Target symptoms in this study were wandering, overactivity, and restlessness. Tariot et al. (95), in a 6-week placebo-controlled, randomized, multisite, parallel-group study, evaluated the efficacy, safety, and tolerability of the anticonvulsant drug carbamazepine in demented patients in long-term care facilities with disruptive agitated behaviors. The modal carbamazepine dose at 6 weeks was 300 mg/d, with a mean serum level of 5.3 μg/mL. Statistical

superiority of carbamazepine compared with placebo was attributable primarily to a greater decrease in agitation and aggression in the carbamazepine group.

Sodium valproate is another anticonvulsant drug with demonstrated antimanic activity. Mellow et al. (96) treated four patients with AD who manifested disruptive and agitated behaviors with doses of valproate ranging from 500 mg twice daily to 500 mg three times daily; treatment lasted for 1 to 3 months. Substantial behavioral improvement was noted in two of the four patients, and adverse effects did not appear. A recently reported multisite study of the anticonvulsant valproate sodium has been less encouraging (97). Because of a high frequency of adverse effects, primarily excessive somnolence, the study was terminated prematurely. Although at the end of the study agitation was reduced more in valproate subjects than in placebo subjects, it is possible that this apparent therapeutic effect reflected the high degree of sedation experienced by the subjects in the active treatment group. Methodologically, this study was designed to address "mania-like" symptoms in persons with AD, and the higher doses of valproate typically prescribed for the treatment of mania in a younger population were achieved. Lower doses of valproate may have beneficial therapeutic effects with a more tolerable adverse effect profile.

Cholinergic Enhancement

That drugs that enhance cholinergic neurotransmission in the central nervous system decrease agitation and psychotic symptoms in persons with mild to moderate AD has been an unanticipated finding of large, multisite outcome trials demonstrating modest positive effects of these agents on cognitive function (98–100). The contribution of a presynaptic cholinergic deficit to memory and other cognitive impairments in AD (69,70) has been a cornerstone of AD drug development. Interest in a potential contribution of this cholinergic deficit to noncognitive behavioral problems in AD increased after Cummings (101) observed that the agitation and psychotic symptoms characteristic of delirium induced by anticholinergic drug toxicity resemble some noncognitive behavioral symptoms occurring spontaneously in AD (e.g., hallucinations, agitation). Cummings reasoned that enhancing brain cholinergic neurotransmission might improve such noncognitive symptoms. Empiric support for this hypothesis came from a carefully performed single-case study in which the cholinesterase inhibitor physostigmine reduced psychotic symptoms in a patient with AD (102) and from a double-blinded crossover study in which physostigmine and the typical antipsychotic haloperidol equally reduced psychotic and agitated behaviors in 13 patients with advanced AD (103). Further support has come from *post hoc* and secondary outcome analyses of large, multicenter cholinesterase inhibitor outcome trials in AD. In addition to demonstrating modest effects on cognitive func-

tion, the cholinesterase inhibitors tacrine (104), galantamine (105), donepezil (106), metrifonate (107), and (in DLB subjects) rivastigmine (108) significantly improved such noncognitive behaviors as delusions, hallucinations, pacing, and uncooperativeness more than did placebo. However, these large, multicenter cholinesterase inhibitor studies excluded AD patients with substantial noncognitive behavioral problems. It is just such severely disturbed patients who must be studied prospectively to establish the clinical importance of cholinesterase inhibitors in the management of noncognitive behavioral problems in AD.

Perhaps the most impressive data supporting positive effects of cholinergic enhancement on noncognitive symptoms in AD come from a multicenter trial of the selective M1 muscarinic cholinergic agonist xanomeline (109). Although the effects of xanomeline on cognitive function disappointingly did not differ from those of placebo, this investigational cholinergic agonist both decreased psychotic and agitated behaviors present at study entry and reduced emergence of these symptoms during the 6-month duration of the study. Furthermore, a clear dose–response effect was observed over the three doses of xanomeline administered. That xanomeline decreases activity of A10 dopaminergic neurons in preclinical studies suggests a possible interaction between cholinergic enhancement and more traditional dopaminergic antagonist approaches to the reduction of psychotic symptoms.

β-*Adrenergic Antagonists*

Despite substantial loss of noradrenergic locus ceruleus neurons in AD, studies measuring the concentrations of norepinephrine and its metabolites in either postmortem brain tissue or cerebrospinal fluid (110–112) suggest that noradrenergic outflow is maintained in AD, apparently through compensatory up-regulation of remaining noradrenergic neurons in the locus ceruleus. In addition, patients with AD manifest an enhanced behavioral agitation response to brain noradrenergic stimulation (113). An uncontrolled study suggested that the centrally active β-adrenergic antagonist propranolol reduces disruptive agitated behaviors in AD (114). In a recently reported placebo-controlled pilot study of Peskind et al. (115), propranolol was superior to placebo in reducing disruptive agitated behaviors in elderly nursing home residents with AD. These patients' disruptive behaviors had been unresponsive to antipsychotic or other psychotropic medications. Propranolol was well tolerated in this small but very elderly population. These neurobiological findings and pilot clinical data warrant larger-scale placebo-controlled trials of propranolol in AD patients with disruptive agitated behaviors.

CONCLUSION

The database supporting guidelines for the pharmacologic management of noncognitive behavioral abnormalities in AD remains limited despite the prevalence of these problems and their impact on patient management. Extrapolating from psychopharmacologic outcome studies in younger, nondemented patients with such diseases as depression and schizophrenia has not been a satisfactory approach to developing effective pharmacologic treatments for noncognitive behavioral disturbances in elderly patients with AD and other dementing disorders. The clear placebo responses noted in several carefully performed pharmacologic trials in AD patients with noncognitive behavioral problems emphasize the necessity for inclusion of a placebo condition if a study is to be interpretable. More must be learned about the neurobiological substrates of psychotic and disruptive agitated behaviors in AD. Such knowledge is essential to the rational development of more effective pharmacotherapeutics for these disturbing and costly problems.

DISCLOSURE

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