Elderly Patients With Dementia-Related Symptoms of Severe Agitation and Aggression: Consensus Statement on Treatment Options, Clinical Trials Methodology, and Policy

Carl Salzman, M.D.; Dilip V. Jeste, M.D.; Roger E. Meyer, M.D.; Jiska Cohen-Mansfield, Ph.D.; Jeffrey Cummings, M.D.; George T. Grossberg, M.D.; Lissy Jarvik, M.D., Ph.D.; Helena C. Kraemer, Ph.D.; Barry D. Lebowitz, Ph.D.; Katie Maslow, M.S.W.; Bruce G. Pollock, M.D., Ph.D.; Murray Raskind, M.D.; Susan K. Schultz, M.D.; Philip Wang, M.D.; Julie M. Zito, Ph.D.; and George S. Zubenko, M.D., Ph.D.

Objective: Atypical antipsychotic drugs have been used off label in clinical practice for treatment of serious dementia-associated agitation and aggression. Following reports of cerebrovascular adverse events associated with the use of atypical antipsychotics in elderly patients with dementia, the U.S. Food and Drug Administration (FDA) issued black box warnings for several atypical antipsychotics titled "Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia." Subsequently, the FDA initiated a meta-analysis of safety data from 17 registration trials across 6 antipsychotic drugs (5 atypical antipsychotics and haloperidol). In 2005, the FDA issued a black box warning regarding increased risk of mortality associated with the use of atypical antipsychotic drugs in this patient population.

Participants: Geriatric mental health experts participating in a 2006 consensus conference (Bethesda, Md., June 28–29) reviewed evidence on the safety and efficacy of antipsychotics, as well as nonpharmacologic approaches, in treating dementia-related symptoms of agitation and aggression.

Evidence/Consensus Process: The participants concluded that, while problems in clinical trial designs may have been one of the contributors to the failure to find a signal of drug efficacy, the findings related to drug safety should be taken seriously by clinicians in assessing the potential risks and benefits of treatment in a frail population, and in advising families about treatment. Information provided to patients and family members should be documented in the patient's chart. Drugs should be used only when nonpharmacologic approaches have failed to adequately control behavioral disruption. Participants also agreed that there is a need for an FDA-approved medication for the treatment of severe, persistent, or recurrent dementia-related symptoms of agitation and aggression (even in the absence of psychosis) that are unresponsive to nonpharmacologic intervention.

Conclusions: This article outlines methodological enhancements to better evaluate treatment approaches in future registration trials and provides an algorithm for improving the treatment of these patients in nursing home and non–nursing home settings.

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Received June 26, 2007; accepted Oct. 2, 2007. *From Harvard Medical School, Boston, Mass. (Drs. Salzman and Wang); University of California, San Diego (Drs. Jeste and Lebowitz); Best Practice Project Management, Inc., Bethesda, Md. (Dr. Meyer); University of Washington, Seattle (Drs. Cohen-Mansfield and Raskind); University of California, Los Angeles (Drs. Cummings and Jarvik); Saint Louis University Medical Center, Mo. (Dr. Grossberg); Stanford University, Palo Alto, Calif. (Dr. Kraemer); Alzheimer's Association, Washington, D.C. (Ms. Maslow); University of Toronto, The Rotman Research Institute, Ontario, Canada (Dr. Pollock); University of Iowa, Carver College of Medicine, Iowa City (Dr. Schultz); University of Maryland, Baltimore (Dr. Zito); and University of Pittsburgh, Pa. (Dr. Zubenko).*

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Corresponding author and reprints: Carl Salzman, M.D., Department of Psychiatry, Harvard Medical School, 25 Shattuck St., Boston, MA 02115 (e-mail: carl_salzman@bidmc.harvard.edu).

The observation of behavioral disturbances in dementia began over a century ago with Alzheimer's description of his first patient. Frequent and severe dementia-related behavioral symptoms can be extremely distressing to the individual, the family, and caregivers. Since there has been no U.S. Food and Drug Administration (FDA)–approved treatment for these patients for more than 50 years, off-label prescribing of antipsychotic

drugs has been commonly employed to treat symptoms of aggression and agitation in patients with dementia.[1] Practitioners tend to use these medications for short periods and in low doses. Although believed to be modestly helpful, first-generation antipsychotic drugs sometimes produce substantial side effects, such as tardive dyskinesia, as well as extrapyramidal and anticholinergic symptoms.[2] More recently, use of conventional neuroleptics has been associated with increased mortality in older patients with various diagnoses.[3,4] For the most part, these drugs have been replaced during the past decade by atypical antipsychotics for off-label treatment of patients with dementia-related behavioral symptoms. Industry-sponsored clinical (registration) trials have failed to establish the efficacy of antipsychotic drugs for treating dementia-related psychosis and behavioral disruption, a finding which has been confirmed by a Cochrane analysis[5] and by a multisite National Institute of Mental Health (NIMH)–sponsored study of the effectiveness of atypical antipsychotics for outpatients with dementia (published after this conference).[6] In the latter study, atypical antipsychotic drugs were not reliably more effective than placebo for psychotic symptoms of dementia.

Other studies have suggested that risperidone,[7,8] olanzapine,[9] and quetiapine[10] may be more effective for treating the symptoms of agitation and aggression than for hallucinations and delusions in the psychosis of dementia. Small-scale studies of treatment with drugs other than antipsychotics have produced equivocal results. Trazodone,[11–13] anticonvulsant mood stabilizers,[14] selective serotonin reuptake inhibitors (SSRIs),[15,16] benzodiazepines,[17,18] and cognitive enhancers[19,20] may reduce symptoms of agitation and aggression in a proportion of patients with dementia, although the overall results are inconsistent. The available data are limited by small numbers of subjects or shortcomings in study design, and a number of these drugs have their own adverse effects. None of these drugs have been approved by the FDA for treatment of behavioral symptoms of dementia.

Given the frequency, severity, and distress caused by behavioral and psychotic symptoms in patients with dementia, there is a need for increased research and development of FDA-approved treatment approaches, including newer safe and effective drugs for these symptoms. In order to address an apparent discrepancy between the public health need for safe and effective treatment and the lack of FDA-approved treatments, the Department of Psychiatry at Harvard Medical School (Beth Israel Deaconess Medical Center, Boston, Mass.) and Best Practice Project Management, Inc., Bethesda, Md., convened a consensus development conference on June 28–29, 2006, in Bethesda, Md. Attendees included 40 participants from leading academic centers, the pharmaceutical industry, the FDA, the Centers for Medicare and Medicaid Services, the National Institutes of Health (NIH), the medical leadership group in the nursing home industry, and advocates for patients and families with dementia. This article represents a consensus of the participants. Three themes were addressed at the conference: (1) A review of current data on the safety and efficacy of antipsychotic drugs for the treatment of symptoms of agitation and aggression in patients with dementia, with or without the diagnosis of psychosis; (2) A review of and recommendations to improve clinical trial methodology for assessing the efficacy of treatments for symptoms of agitation and aggression in patients with dementia; and (3) Recommendations to strengthen monitoring systems for postmarketing surveillance of drug safety in patients with dementia in nursing homes and other venues.

NEED FOR FDA-APPROVED INDICATION FOR PHARMACOLOGIC TREATMENT OF DEMENTIA-RELATED SYMPTOMS OF AGITATION AND AGGRESSION

Despite extensive clinical experience with off-label prescribing, as well as published clinical trials[21] of conventional (typical) and atypical antipsychotic drug treatment of symptoms of agitation and aggression in dementia, the efficacy of these drugs for psychosis and these behavioral symptoms has not been established in FDA-required registration trials. In the past decade, in an effort to encourage research and improve clinical practice, geriatric psychiatrists[22] placed the behavioral and psychotic symptoms of Alzheimer's disease into a new diagnostic category of "psychosis of Alzheimer's disease and related dementias." By 2000, the FDA had accepted this new diagnosis, which made possible the diagnostic differentiation of dementia-associated psychosis from late-life schizophrenia and other late-life psychoses.[23]

Data from functional imaging studies[24] and neuropathology[25] suggest that among the multiple causes of symptoms of agitation and aggression in Alzheimer's disease, patients may have an identifiable pathophysiology. Since reliable and valid measurement instruments are now available to quantify dementia-associated symptoms of agitation and aggression, it may be possible to define a distinct syndrome that would represent an FDA-approvable target for appropriate use of antipsychotic and other medications to treat these symptoms of dementia even in the absence of psychosis, with the caveat that the symptoms should be severe, persistent or recurrent, and unresponsive to nonpharmacologic interventions. This diagnostic category would also promote further research into the treatment of these difficult behaviors.

METHODOLOGICAL CONCERNS RAISED BY PREVIOUS NEGATIVE REGISTRATION TRIALS

Previous industry-sponsored registration trials involved persons with dementia (probable and possible Alzheimer's

disease) with psychosis and/or agitation. The studies were placebo-controlled and lasted for 6 to 12 weeks, typically 10 to 12 weeks. They were parallel-group, fixed-dose range or adjustable/titrated-dose trials involving 200 to 650 patients. Most of these trials were nursing home studies and included patients with a mean age > 80 years; 75% were women. The clinical trial endpoints were based on behavior rating scales, including the Brief Psychiatric Rating Scale, Behavioral Pathology in Alzheimer's Disease Rating Scale, Neuropsychiatric Inventory, Positive and Negative Syndrome Scale and Positive and Negative Syndrome Scale Excited Component, Cohen-Mansfield Agitation Inventory and subscales (proxy based more common than direct observation), global assessments, and activities of daily living scales.

A number of methodological flaws limit the conclusions that can be drawn from these studies and indicate a need for better-designed future research. Some studies required long periods of continuous symptomatology (as much as 3 weeks) to establish eligibility. This requirement disproportionately eliminated the most severe cases requiring immediate treatment, who may have been more likely to respond to a drug than to placebo. This disproportionate requirement of continuous symptomatology could explain the failure to establish drug/placebo differences. Among subjects studied, there was a wide degree of variation in type and severity of symptomatology, which diminished the likelihood of coherent results. Additional design problems included the (nonrandom) statistical distribution of behavior test scores and lack of consideration of effect size.

The conference identified 3 additional aspects of clinical trial design that would improve the correct identification of improved and nonimproved subjects.

(1) When considering appropriate primary outcomes, endpoint measures and prechange and postchange scores may be misleading because they are not sensitive to changes over time. Rating trajectory over time (repeated-measures design) is more likely to accurately reflect improvement, would substantially reduce the need for "last observation carried forward" to implement analyses by intention to treat, and would generally increase the power to detect treatment effects.
(2) In older, medically fragile patients, there is a higher risk of harm (side effects) and/or benefit compromised by harm. As serious adverse events are more likely in drug-treated patients versus control groups, the primary outcome should examine the balance between harm and benefit. Moreover, there may be more than one benefit and more than one negative consequence. The balance between harm and benefit, therefore, depends both upon the multivariate assessment of harm-to-benefit ratio in individual patients and the correlation between harm and benefit across patients.
(3) The same drugs may not be equally effective and/or safe in all elderly patients. Thus, it is important after each randomized clinical trial to investigate possible moderators of treatment response and baseline variables that differentiate between responders and nonresponders.

SAFETY OF ATYPICAL AND TYPICAL ANTIPSYCHOTIC DRUGS

In general, older persons are more sensitive to common and severe drug side effects, in part as a consequence of age-related pharmacokinetic changes that can result in higher and/or more variable drug concentrations.[26,27] In addition to adverse consequences of age-related changes in pharmacologic disposition and sensitivity to antipsychotic drugs, specific concern has emerged regarding apparent increases in mortality when antipsychotic drugs were given to patients with dementia. Following reports of cerebrovascular adverse events associated with the use of atypical antipsychotics in elderly patients with dementia, the FDA issued black box warnings for several atypical antipsychotics titled "Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia." Subsequently, on April 11, 2005, the FDA issued a public health advisory for atypical antipsychotic drugs prescribed for the treatment of behavioral disorders in elderly patients requesting that the manufacturers "include a boxed warning in their labeling describing mortality risk and noting that these drugs are not approved for the treatment of behavioral disturbances in elderly patients with dementia."[28] The safety warning was based on an FDA analysis of 17 placebo-controlled trials comparing 6 antipsychotic drugs to placebo. That analysis showed a statistically significant elevated risk of death—a rate that was 71% greater than the death rate of placebo-treated patients. More than 5000 individuals (average age of 81 years) were included in the FDA analysis, and two thirds received an antipsychotic drug over a 6- to 12-week period. The increased mortality was seen with all atypical antipsychotic medications, in spite of differences in receptor-binding profiles, a finding consistent with later meta-analyses[4,5] of placebo-controlled, randomized clinical trials. This risk should be taken seriously by clinicians in assessing the potential risks and benefits of treatment in a generally frail population and in advising family members about treatment options.

Subsequently, in an observational study of patients in a pharmacy benefit program for the elderly,[3] researchers reported that all-cause mortality associated with conventional antipsychotics was similar to that of patients taking atypical antipsychotic drugs. In this study, frail elderly subjects and those with serious medical illness were not

separated from other less susceptible nursing home residents.[3] Additional studies are needed to verify this finding, preferably with greater control of severity of dementia, medical comorbidities, and length of drug exposure.

The conference raised questions regarding the increased and diverse causes of mortality. While there may be an association between risperidone, olanzapine, and aripiprazole and risk of stroke,[5] the reported causes of death in the 17 studies were mainly related to cardiovascular events and infection. It is possible that mortality by infection, specifically pneumonia, could be related to sedation and aspiration. Finally, in addition to the specific mortality risk associated with use of atypical antipsychotics in dementia, the FDA has also applied a class label to risk of weight gain, metabolic syndrome, hyperlipidemia, and type 2 diabetes.[29] Obviously, elderly subjects are also susceptible to these metabolic effects.

NONPHARMACOLOGIC INTERVENTIONS

Since dementia-related agitation and aggression can occur from many causes, it is important to identify any contributing factors that can be modified without the use of medication. Nonpharmacologic interventions are based on the principle that a clinical care system serving patients with dementia must address issues in the physical environment and in the care system (and its policies) that may contribute to the emergence of symptoms of agitation and aggression. Research has shown that verbal/vocal behaviors may be associated with pain, loneliness, or depression.[30] Agitation may be associated with boredom and the need for activity and stimulation. Aggressive behaviors may be associated with avoiding discomfort, the communication of needs, or a demand for personal space.[31] All treatment approaches should start with rigorous attempts to identify any reversible causes of these behaviors and eliminate or mitigate these factors. Typical precipitants of agitation and aggression include pain, medical illness, boredom, loneliness, depression, and social and environmental stressors. Identified causes should be addressed through individualized and/or systemic efforts to mitigate the triggers of agitation and/or aggression. Other individualized nonpharmacologic interventions for the person with dementia include tools to improve or stabilize cognitive function, behavior modification, self-affirming exercises such as reminiscence therapy, and structured socialization such as pet therapy and viewing family videotapes. The efficacy of these interventions has been demonstrated in a series of small studies[32] and in some larger studies.[33–35] Given the promising results reported, there is a need for additional scientifically sound, adequately powered studies designed to assess the effectiveness of nonpharmacologic interventions, which should be initiated with government and/or private-sector support. These studies are necessary in order to recommend any "evidenced-based" treatment for severe agitation or aggression associated with dementia.

Training programs for family caregivers of people with dementia, such as Savvy Caregiver, Staff Training in Assisted-Living Residences-Caregivers, and Resources for Enhancing Alzheimer's Caregiver Health, have resulted in decreased agitation in people with dementia who live at home and reduced feelings of burden and depression for family caregivers.[36–42] One study that compared the effectiveness of 4 interventions—nonpharmacologic behavior management intervention, haloperidol, trazodone, and placebo—found no significant differences in outcomes, but did find fewer adverse events (e.g., bradykinesia and parkinsonian gait) in subjects who received the nonpharmacologic intervention.[43] At this stage, nonpharmacologic treatments directed to the person with dementia (and/or the family caregiver[s]) can be incorporated into clinical practice and clinical trials as part of a treatment algorithm and/or decision tree in clinical practice in assessing the need for medication and as adjuncts to medication treatment in clinical trials for people with dementia who are living at home or in nursing homes or in assisted-living facilities.

CONSENSUS FINDINGS AND RECOMMENDATIONS

Improving Clinical Trial Methodology

Given the identified risks observed in this population, it is incumbent on sponsors and investigators to ensure that only patients at lowest risk, who stand to benefit most, be entered into phase 2 trials. If there is a good signal of efficacy in the treatment of dementia-related symptoms of agitation and aggression in these patients, later phase 3 studies, as well as specific safety studies, should inform the FDA approval process and the use of pharmacotherapy in a broader group of patients with dementia and these behavioral symptoms. If the signal of efficacy is not statistically significant, there is no need to expose the test compound to a wider sample of patients. The black box warning for the atypical antipsychotic drugs highlights the potential for harm.

The methodological recommendations for clinical trials by the conference may strengthen study designs for any medication proposed for the treatment of dementia-related symptoms of agitation and aggression in patients with dementia. These recommendations are made with the following caveats: (1) they have not been empirically validated and are not known to enhance detection of a drug-placebo difference, (2) they would be further strengthened by additional analyses of data from the 17 industry-sponsored trials, and (3) the methodology of any trial will need to be adjusted to reflect the specific questions to be answered by the trial; general recommendations will not optimize the design of all trials. Trial recommendations are as follows.

(1) Pharmaceutical manufacturers of antipsychotic drugs should be encouraged to collaborate with research leaders to review the data from the 17 trials to see if the rating instruments used were sensitive to change in agitation/aggression.
(2) Pilot studies are needed to test newly proposed methods for assessment. These should not be used as the basis for power calculations for larger trials, as sampling errors for the effect size from these small trials are often unreasonably large. Instead, these studies should be used to check the feasibility of sampling, measurement, treatment delivery, and outcome assessment proposals.
(3) Participation in trials should be offered to those most likely to benefit from pharmacologic therapy and for whom there is minimal reason to expect serious side effects. Although it is not always feasible, a nonpharmacologic intervention should be attempted before enrolling a patient in a clinical trial. This may be facilitated by encouraging a standardized nonpharmacologic intervention for all patients at all sites. The intervention should be long enough to identify patients who respond to nonpharmacologic intervention and not so long as to make it difficult for patients with more severe symptom levels to be enrolled in the trial.
(4) Patients enrolled in clinical trials should have severe and persistent or recurrent symptoms of agitation and/or aggression that are unresponsive to nonpharmacologic interventions. Enrollment should follow a central eligibility process to verify that the patient meets enrollment criteria. By establishing these entry criteria, early dropouts will be reduced.
(5) The trajectory of response is superior to an endpoint analysis as a measure of treatment efficacy. This requires a repeated-measures design and contrasting the course of the response to drug or placebo over time. This design not only increases power to detect treatment effects, but it also facilitates intention-to-treat analysis and uses a measure more sensitive to change than any endpoint or change score using the same instrument.
(6) A meaningful effect size should be prespecified prior to trial initiation. This effect size should be the area under the curve, which equals the probability that a patient in the treatment group has a response clinically preferable to one in the control group. With the area under the curve, one can incorporate consideration of multiple benefits and multiple harms into one clinically interpretable index.
(7) Multivariate analysis of effectiveness expressed as the number-needed-to-treat analyses may be the most readily interpretable type of data for clinicians, but further assessment with this approach is recommended.
(8) Since deaths from atypical antipsychotics involved cardiovascular and infectious causes, it is prudent to monitor the medical status of patients very closely during clinical trials and for the protocol to explicitly state criteria for termination of a subject's participation in the study.
(9) Sedation may contribute to adverse events as well as treatment success and should be measured in clinical trials for agitation and aggression.
(10) Additional scientifically sound, adequately powered studies designed to assess the effectiveness of nonpharmacologic interventions should be initiated. The clinical trial methodology for essential multisite trials remains to be established. Initial support should be provided by governmental agencies (e.g., NIH) and private sources. Pharmaceutical companies should pay increased attention to the appropriate combination/integration of pharmacologic and nonpharmacologic interventions in safety and efficacy studies of the treatment of agitation and aggression in patients with dementia.
(11) Consensus could not be reached on the question of ongoing nonpharmacologic treatments across all treatment arms over the course of medication trials in this population of patients with dementia and serious symptoms of agitation and/or aggression. Some conference participants did not recommend that ongoing standardized nonpharmacologic treatment should be continued over the course of the trial in all treatment arms because of the absence of more definitive data on the efficacy of nonpharmacologic interventions. These participants felt that ongoing standardized nonpharmacologic treatment continued over the course of the trial in all treatment arms may well confound pharmacologic effects. They also argued that if standardized nonpharmacologic intervention is necessary in the interest of the patient's and/or caregiver's welfare, then these clinical trials need to be clearly identified as studies of combined pharmacologic and nonpharmacologic treatment—with both modalities clearly specified.
(12) To advance drug trials in elderly individuals with dementia, better definitions of acute and chronic agitation and/or aggression are needed. The definition should provide specific diagnostic criteria for a syndrome of agitation and aggression associated with dementia.
(13) Reliable and valid rating scales are necessary to quantify the severity of agitation and aggression and changes with treatment in registration trials. Other worthy outcomes that may be secondary or primary in clinical trials include quality of life, mobility, drowsiness, mood, and independence in addition to emotional stability. A specific level of sever-

ity may be required for trial enrollment. Repeated-measurement analyses are essential. Selection of scales will vary by trial, population, venue, and proposed analytic strategy. Commonly used scales for agitation and aggression include the Cohen-Mansfield Agitation Inventory and Neuropsychiatric Inventory, including family or nursing home versions. Measurement accuracy can be improved by the use of standardized raters, better training of raters and observers, and advances in measurement methods. In some cases, technological advances may augment clinical measures, e.g., actigraph recording of activity levels. Variability is characteristic of the phenomenon being measured (agitation and/or aggression) and must be anticipated in trials.

(14) Stratifying the sample for severity of agitation and aggression may ensure an adequate number of more severely agitated patients, but stratification is to be avoided unless there is prior evidence that a baseline variable moderates treatment response.

(15) Many classes of drugs may reduce agitation and may warrant testing in clinical trials, including antipsychotics, SSRIs, mood stabilizers, anxiolytics, cholinesterase inhibitors, memantine, and analgesics, as well as novel pharmacologic agents.

(16) Biological markers for drug response and adverse event susceptibility should be sought in clinical trials in order to determine if response (or failure) can be predicted and to determine whether side effect patterns can also be predicted.

(17) Time to emergence of behavioral events is an important measure of treatment success in trials of both symptomatic and disease-modifying agents for neurodegenerative disorders.

(18) Most studies in this population will require a data and safety monitoring board, not only for review of adverse events and serious adverse events, but also to evaluate the research protocol and monitor fidelity to the clinical trial design and to help investigators deal with unexpected problems that often arise in large, randomized, placebo-controlled trials.

Improved Monitoring of Postmarketing Drug Safety Surveillance in Patients With Dementia

Recommendations to improve drug safety monitoring need to be considered in the context of the unique characteristics of the patient population, including the fact that patients in nursing homes are taking an average of 8 to 9 medications for the treatment of multiple chronic and acute medical problems. The interaction between drugs with different pharmacologic and metabolic characteristics and various diseases makes this population more vulnerable to adverse drug reactions. Moreover, the average age of these patients is > 80 years, with 25% of nursing home residents > 90 years. Nursing home oversight varies considerably by state. In spite of the complexity of monitoring drug safety and effectiveness in these patients, it is critical that a better system of monitoring be established to supplement the limited data collected prior to drug approval. The following recommendations are meant to address this issue.

(1) Collaboration between the FDA and the Centers for Medicaid and Medicare Services should be encouraged to assure population-based observational studies from existing databases and to incorporate an active drug surveillance system within one of the Medicare initiatives. With a new data set commencing from Medicare Part D, there is some potential for gathering more information relative to drug utilization and to link acute episodes of care and/or mortality data to recent medication history. Annual prevalence of the use of psychotropic medications in the elderly should be reported to increase our knowledge of U.S. community-based practices and to generate hypotheses for studies of off-label indications of complex combinations lacking adequate evidence of safety.

(2) The goal of the monitoring program should be to look for signals to identify markers in this patient population relative to the safety of these medications. To aid in this endeavor, it would be helpful to collaborate with drug registries in Western Europe (including the United Kingdom, The Netherlands, and Denmark) as well as other nations with linkable pharmacoepidemiologic data sources.

(3) It would be desirable to develop nursing home staff rater standardization to assure improved reporting of adverse events and serious adverse events. Consideration should be given to mandated training and certification of nursing home staff to improve awareness of safety and tolerability issues relative to medication as well.

(4) Public and pharmaceutical industry funding is needed to assure support for additional phase 4 (postmarketing) studies and to utilize nonpharmacologic interventions as comparator treatments in these drug studies. In order to refine criteria for medication treatment, the phase 4 studies should include studies in specific patient subgroups and acute treatment and maintenance components.

Improving Treatment for Patients With Dementia in Various Settings

Non–nursing home setting recommendations.

(1) Emphasis should be placed on appropriate assessment, which can be challenging in the home or in a setting with limited oversight. An in-home visit should be included, when necessary, in order to complete an assessment, and on-going assessments

are necessary to evaluate changing symptoms and severity.

(2) For patients unresponsive to interventions that address potential psychosocial, environmental, or medical causes of the behavior or those with residual agitation and aggression, pharmacologic management may be considered. The selection of medications will depend on future clinical trials as well as currently available research and clinical practice. Not all patients with dementia respond to the same types of medications. Patients with Lewy body dementia are more vulnerable to the side effects of antipsychotics, both conventional and atypical. Frontotemporal dementias may not respond to cholinesterase inhibitors. In view of the cardiovascular risks that have been identified, patients with vascular dementia may have greater risk for cardiovascular or cerebrovascular events with atypical antipsychotic drugs.

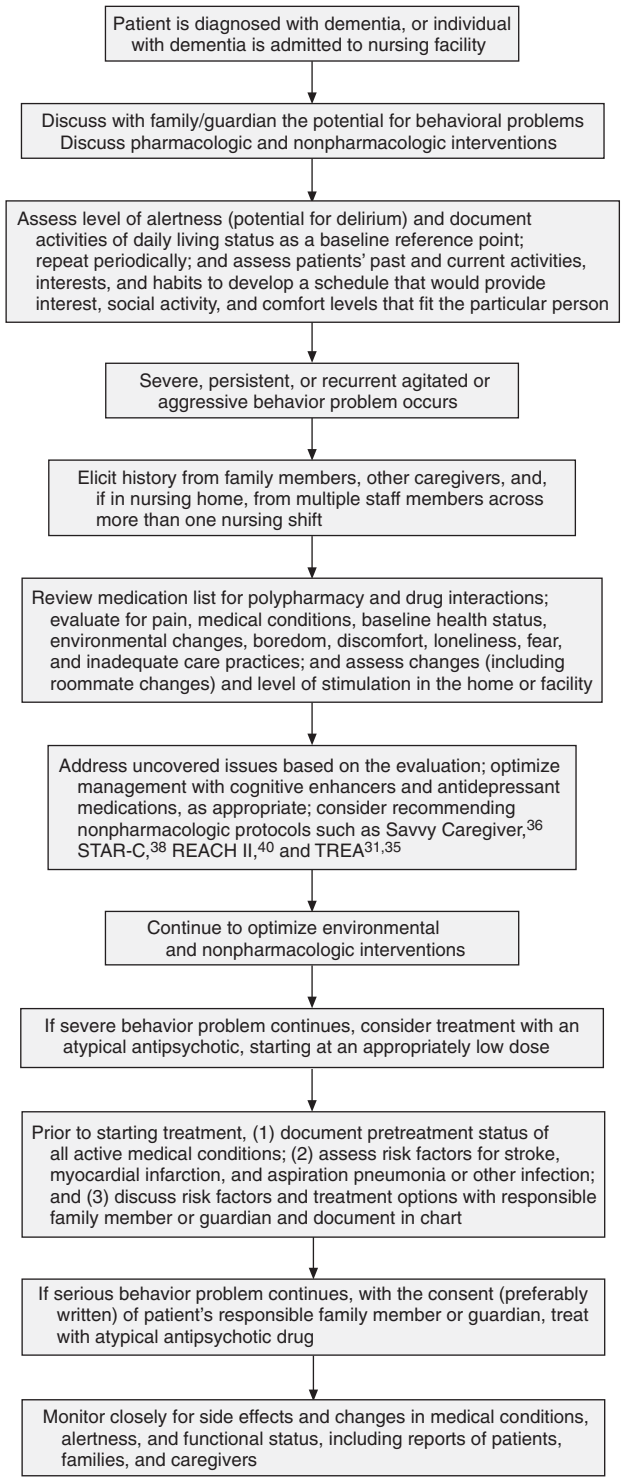
(3) If a decision is made to initiate treatment with a medication that has not been approved by the FDA for that indication and for which there is a black box warning, patients and families need to be adequately informed of risks and potential benefits in the context of the disease, the symptom picture, frequent and rare adverse events, and the consequences of nontreatment as well as alternative treatment of the symptoms. This information should be provided by the physician and documented in the patient's chart. The physician should be able to supplement the information with a take-home brochure. Figure 1 offers a treatment algorithm for patients with dementia and symptoms of agitation and aggression in various settings.

Nursing home recommendations.

(1) Upon admission, before an episode of aggression occurs, the staff and physician should discuss the needs of future care in the facility, including background information about habits and preferences that could inform care.

(2) Once aggression or a syndrome of acute agitation and aggression has occurred, rigorous attempts should be directed toward identifying any reversible cause of the agitation and/or aggression and eliminating it if possible. Typical causes of agitation include pain, medical illness, medications, drug interactions, loneliness, fear, boredom, or environmental stress. Assessment of agitation should include medication review emphasizing polypharmacy and drug interactions and intensive medical evaluation (including blood chemistries for liver, renal, and cardiac functions, as well as metabolic laboratory values and a more complete neurologic examination). A quantifiable evaluation of alert-

Figure 1. Treatment Algorithm for Individuals With Dementia Who Develop Symptoms of Severe, Persistent, or Recurrent Agitation and Aggression, Whether Residing at Home or in a Nursing Facility



Abbreviations: REACH II = Resources for Enhancing Alzheimer's Caregiver Health, STAR-C = Staff Training in Assisted-Living Residences-Caregivers, TREA = Treatment Routes for Exploring Agitation.

ness, sedation, and cognitive function and assessment of activities of daily living and subjective well-being and quality of life should also be included.

(3) The potential benefits and risks of all clinical decisions should be shared with family members and their consent obtained (in writing if possible). This provides an opportunity to obtain proxy consent and to discuss antidepressants, antipsychotics, and other medications and their potential side effects. Specifically with respect to antipsychotics, most long-term care settings can effectively have their clients benefit from antipsychotic management, even in the face of medical comorbidity, with proper monitoring and very careful dose titration, as long as the risk/benefit ratio is low and there is ongoing dialogue and reassessment with an eye toward dose reduction or discontinuation in place.

SUMMARY

Atypical antipsychotic drugs have been commonly used off-label in clinical practice for treatment of serious dementia-associated agitation and aggression, although they have not been approved by the FDA for such use. Following reports of cerebrovascular adverse events associated with the use of atypical antipsychotics in elderly patients with dementia, the FDA issued black box warnings for several atypical antipsychotics titled "Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia." Subsequently, the FDA initiated a meta-analysis of safety data from 17 registration trials across 6 antipsychotic drugs (5 atypical antipsychotic drugs and haloperidol) and issued a black box warning regarding mortality with the use of these drugs in this patient population.*

Experts in the field of geriatric mental health who participated in this consensus conference reviewed the available evidence regarding the safety and efficacy of antipsychotic drugs, as well as nonpharmacologic approaches for the treatment of dementia-related symptoms of agitation and aggression. They concluded that problems in clinical trial design may have been a significant contributor to the negative results. Among many criticisms noted, participants emphasized the wide variation in type and severity of symptoms required for eligibility, inadequate statistical power, and absence of clinically interpretable effect sizes to determine the true risk of these drugs; a prolonged drug-free baseline before randomization leading to potential bias that could favor placebo response; and the use of outcome measures and assessments that failed to differentiate agitation and aggressive behavior from psychosis. These issues could have influenced the negative trial results. Future studies should assess the balance of risk and benefit of treatment in this frail population, and they should be adequately powered to assess both benefit and risk.

Participants agreed that there is a need for an FDA-approved indication for treating dementia-related symptoms of severe and persistent or recurrent agitation and aggression, even in the absence of psychosis. Participants further agreed that agitation and aggression associated with Alzheimer's disease be considered an appropriate target for treatment development and ultimate registration. At present, many clinicians use atypical antipsychotic drugs as the off-label treatment for behavioral symptoms[21,22] of dementia, despite the fact that the elderly are more sensitive to their side effects than young and middle-aged adults. The FDA analysis of the 17 registration trials across 6 antipsychotic drugs indicated a statistically significant elevated risk of death in drug-treated patients (either heart related or from infections) that was 1.6 times greater than placebo-treated patients. These findings should be taken seriously by clinicians in assessing the potential risks and benefits of treatment in a generally frail population and in advising family members about treatment options. In general, drugs may be used only when nonpharmacologic approaches have failed to adequately control serious behavioral disruption within 5 to 7 days.

Conference participants were unanimous in their call for additional research to further define pharmacologic as well as nonpharmacologic treatment approaches for individuals with dementia and behavioral disruption. Among the new methodologies that were recommended, the following received particular emphasis:

(1) Lowest risk patients should first be studied in phase 2 trials of new compounds.

(2) If feasible, subjects should be those who are likely to respond to pharmacotherapy and who have failed an adequate course of a nonpharmacologic intervention.

(3) The trajectory of response should be used rather than endpoint analysis, and a meaningful effect size must be specified prior to trial initiation and the study adequately powered to detect effect at or above that effect size. After the study is concluded, the p value should be reported as well as the estimated effect size, which can be compared with the preset standard.

*The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) results were published after the consensus conference was held,[6] so the data could not be discussed during the conference. The trial showed that there was no significant difference among the atypical antipsychotic medications studied on the primary outcome measure (i.e., time to discontinuation). There was no evidence of increased stroke or cardiac complications, although the CATIE study was not powered to examine this issue.

(4) More rigorous use of patient sampling and statistical techniques, as well as attention to diagnostic subgroups of dementia and their response to treatment interventions, are necessary. This includes use of annual prevalence of use data from community populations to discern practice patterns.
(5) Improved postmarketing passive and active surveillance monitoring of new drugs (especially newly marketed drugs) for safety and efficacy in patients with dementia is essential; the development of markers to signal potential safety problems was encouraged.

In their concluding discussions, participants developed recommendations for improving the treatment of patients with dementia in the nursing home as well as in non–nursing home settings. Treatment algorithms were proposed, and nonpharmacologic interventions were encouraged as the initial treatment of choice. In view of the clinical need to treat very sick patients in the absence of perfectly safe and effective alternatives, treatment algorithms should support prescribing by physicians if a decision is made to initiate treatment with agents that have not been approved by the FDA for this indication and for which there is a black box warning. Clearly, patients and families must be adequately informed of risks and potential benefits in the context of the disease, the symptom picture, the adverse event profile, and the consequences of nontreatment of the symptoms. Treatment should only be initiated following preferably written consent by the responsible family member to such treatment, after being adequately informed of risks and potential benefits. The information provided by the physician should be documented in the patient's chart.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), memantine (Namenda), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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