

# Atypical Antipsychotics for the Management of Patients With Dementia and Psychotic Symptoms

Dilip V. Jeste, MD (Chair)  
Lon Schneider, MD  
Peter Paul De Deyn, MD, PhD, MMPP

Joel E. Streim, MD (Chair)  
J. Michael Ryan, MD

## Educational Objectives

- Identify the differences between antipsychotic agents, with particular emphasis on efficacy, safety, and tolerability.
- Describe novel antipsychotic mechanisms of action and associated clinical implications.
- Discuss factors that influence the choice of outcome measures in clinical trial design, and distinguish the design and outcome measures of large clinical trials of antipsychotics.

On August 18 and 19, 2003, two symposia entitled “Effective Management of Patients With Dementia and Psychotic Symptoms” and “Atypical Antipsychotic Drugs for the Treatment of Psychotic Symptoms of Dementia” were presented at the 11th International Congress of the International Psychogeriatric Association in Chicago, IL. The potential impact, efficacy, and safety profiles of atypical antipsychotics on the treatment of psychosis of dementia were reviewed. Presenters also discussed regulatory issues in the design of antipsychotic clinical trials, and the study of medication effectiveness in the “real world.”

## POTENTIAL IMPACT OF ATYPICAL ANTIPSYCHOTICS ON THE TREATMENT OF PSYCHOSIS OF DEMENTIA

Lon Schneider, MD, Professor, Department of Psychiatry and Behavior Science, Keck School of Medicine, University of Southern California, Los Angeles, CA, provided an overview of the symptoms and prevalence of psychosis in Alzheimer's disease, and the available evidence on the efficacy, safety, and tolerability of atypical antipsychotics.

### *Symptoms and Prevalence of Psychosis in Alzheimer's Disease*

The behavioral symptoms of Alzheimer's disease include agitation, anxiety, aggression, hostility, apathy, and wandering. Psychological symptoms include disorganized or illogical thought processes, perceptual disturbances (hallucinations), and non-reality-based thought content (delusions).<sup>1,2</sup>

*Psychosis of Alzheimer's disease*, as defined by Jeste and Finkel,<sup>3</sup> occurs after the onset of Alzheimer's disease at the exclusion of schizophrenia or other causes of psychotic symptoms. The associated hallucinations or delusions are late-onset, present intermittently for 1 or more months, and cause disruption to patient functioning. Patients may also have associated agitation, negative symptoms, and depression (Table I).<sup>3</sup>

### *Pharmacotherapy for the Psychosis of Alzheimer's Disease*

The objectives when treating psychosis associated with Alzheimer's disease are to lessen symptomatology and minimize adverse drug reactions.

***First-Generation (Conventional or Typical) Antipsychotics.*** First-generation antipsychotic drugs were the mainstay of

treatment in nursing homes in the United States until the 1990s. In clinical studies, first-generation antipsychotics were effective in about one-third of cases,<sup>4</sup> and exhibited a modest but consistent improvement rate of approximately 18% greater than placebo.<sup>5</sup> In these studies, relatively low doses were usually effective.

First-generation antipsychotics were characterized by their range of side effects and the need for individual dosing. There was definitely room for improvement.

***Second-Generation (Atypical) Antipsychotics.*** Advantages of second-generation antipsychotics are lower liability for extrapyramidal symptoms and tardive dyskinesia, less impairment or possibly improvement in cognition, and decreased liability for hyperprolactinemia with some agents.<sup>6</sup> Limitations include somnolence, dose-dependent extrapyramidal symptoms and prolactin liability (with some agents), metabolic side effects, cerebrovascular concerns, and inadequate response.<sup>6</sup>

A summary of completed placebo-controlled trials of second-generation antipsychotics (risperidone, olanzapine, quetiapine, and aripiprazole) in dementia is shown in Table II.<sup>7-18</sup> Many of the studies were conducted in nursing home patients, and a few were done in outpatients. Each study showed symptomatic improvement on one or several instruments.

### *Summary*

The psychosis of Alzheimer's disease is common and disruptive. This condition can be managed with antipsychotic agents, but treatment requires special considerations. Second-generation antipsychotic drugs offer advantages over first-generation agents in terms of extrapyramidal symptoms or tardive dyskinesia liability, but other efficacy, safety, and tolerability concerns remain. The role of medications needs further research.

## PHARMACOTHERAPY FOR THE MANAGEMENT OF PSYCHOSIS ASSOCIATED WITH DEMENTIA

In patients with Alzheimer's disease and dementia, medications must be well tolerated with minimal associated

TABLE I

### Diagnostic Criteria for Psychosis of Alzheimer's Disease<sup>3</sup>

- Diagnosis of Alzheimer's dementia
- Exclusion of schizophrenia or other causes of psychotic symptoms
- Hallucinations and/or delusions
  - Late-onset
  - Present intermittently for  $\geq 1$  month
  - Disruptive to patient functioning
- Associated agitation, negative symptoms, and depression
- Disturbances do not correlate exclusively with delirium

## Completed Placebo-Controlled Trials of Atypical Antipsychotics in Dementia

Antipsychotic	Study	Pub?	N	Duration (wk)	Location	Efficacy Results
Risperidone	Katz et al <sup>7</sup>	Yes	625	12	Nursing home	Improved symptoms
	De Deyn et al <sup>8</sup>	Yes	344	13	Nursing home	Improved symptoms
	Brodaty et al <sup>9</sup>	Yes	337	12	Nursing home	Improved symptoms
	Ris-USA-232 <sup>10</sup>	No	408	12	Nursing home	?
	Ris-Ger-16 <sup>11</sup>	No	818		Outpatient	?
Olanzapine	HGGU <sup>12</sup>	No	434	10	Outpatient	?
	Satterlee et al <sup>13</sup>	No	238	8	Outpatient	No difference
	Street et al <sup>14</sup>	Yes	206	6	Nursing home	Improved symptoms
	De Deyn et al <sup>15</sup>	Poster	650	10	Nursing home	Improved symptoms
	HGGU <sup>16</sup>	No	434	10	Outpatient	?
Quetiapine	Tariot et al <sup>17</sup>	Poster	294	12	Nursing home	Improved symptoms
Aripiprazole	De Deyn et al <sup>15</sup>	Poster	208	10	Outpatient	Improved symptoms
	005 <sup>18</sup>	No	256	10	Nursing home	Improved symptoms

adverse events and safety risks. Maintenance or improvement of cognitive function is also important. The adverse effects and potential comorbidities associated with the management of psychosis in geriatric patients was discussed by both J. Michael Ryan, MD, Assistant Professor of Psychiatry, Program in Neurobehavioral Therapeutics, University of Rochester Medical Center, and Director of Psychiatric Consultation Services, Monroe Community Hospital, Rochester, NY; and Dilip V. Jeste, MD, Estelle and Edgar Levi Chair in Aging, Professor of Psychiatry and Neurosciences, and Chief of the Division of Geriatric Psychiatry, University of California, VA San Diego Healthcare System, San Diego, CA.

### Common Medication-Related Adverse Effects

Short-term effects associated with antipsychotic agents may include somnolence, extrapyramidal symptoms, anorexia, abnormal gait, postural hypotension, falls, and fractures. Extrapyramidal symptoms and tardive dyskinesia are associated with incoordination, feeding problems, disfigurement, social isolation, falls, and fractures. Sedation can interfere with everyday activities. Postural hypotension can lead to falls and fractures.

Elderly patients with dementia are also sensitive to anticholinergic effects. Central anticholinergic effects can cause confusion and memory impairment. Peripheral anticholinergic effects can lead to blurred vision, urinary retention, constipation, and dry mouth.

Tardive dyskinesia is one long-term effect that is especially problematic in elderly patients.<sup>19</sup> The risk factors for development of tardive dyskinesia include longer duration of treatment with antipsychotic medication and greater cumulative amounts. Fortunately, the newer second-generation antipsychotic medications have a significantly lower risk of tardive dyskinesia than the older drugs.<sup>20</sup>

Other considerations in pharmacotherapy include age-related differences in drug metabolism and the issue of polypharmacy. For example, there may be additive effects of layering medications that each have their own side-effect profiles. Medications should be chosen in an attempt to minimize these consequences as much as possible.

Sometimes one drug can cause an adverse effect and another drug is prescribed to counterbalance the side effect. This is the so-called "prescribing cascade."<sup>21</sup> It is important to choose a medication that matches the patient's medical profile and overall drug regimen, and will not lead to the cascade of adverse events.

### Key Clinical Trials of Second-Generation Antipsychotics

Some of the key clinical trials that have been conducted on psychosis of Alzheimer's disease or dementia were discussed.

**Risperidone.** Katz et al<sup>7</sup> conducted a prospective, 12-week, multicenter trial of fixed-dose risperidone (0.5, 1, or 2 mg per day) versus placebo in 625 patients with psychosis of dementia.

Patients taking the 1- and 2-mg doses of risperidone showed statistically significant improvements on the global Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) scale, as well as on the psychosis and aggression subscales, compared with placebo. There were dose-related increases in somnolence and extrapyramidal symptoms, which led to the conclusion that 1 mg is the optimal dose for risperidone.

In a more recent 12-week, double-blind study, Brodaty et al<sup>9</sup> randomized 305 nursing home patients with Alzheimer's disease, vascular dementia, or mixed dementia to either flexible-dose risperidone (mean, 0.95 mg per day) or placebo. After 4 weeks, 8 weeks, and at endpoint, there was significant improvement in the Cohen-Mansfield Agitation Inventory (CMAI) total aggression score for risperidone.

Risperidone was associated with a slightly higher incidence of somnolence and extrapyramidal symptoms compared with placebo, although this difference was not statistically significant. Six patients in the risperidone group experienced serious cerebrovascular adverse events compared with none in the placebo group. However, all of these patients had significant predisposing factors for cerebrovascular events.

Dolder and Jeste<sup>20</sup> compared the incidence of tardive dyskinesia in older patients taking either haloperidol (1 mg per day, n = 61) or risperidone (1 mg per day, n = 61). After 9 weeks, the rate of tardive dyskinesia was five- to sixfold higher with haloperidol than with risperidone.

**Olanzapine.** Street et al<sup>14</sup> conducted a prospective, 6-week, multicenter study of fixed-dose olanzapine (5, 10, or 15 mg per day) versus placebo in 206 nursing home patients with Alzheimer's disease.

On the Neuropsychiatric Inventory-Nursing Home (NPI-NH) total score, lower doses (5 and 10 mg) of olanzapine were more effective than placebo. However, the 15-mg dose was not significantly different than placebo. There was a dose-dependent increase in the

incidence of somnolence. The incidence of abnormal gait was significantly higher for the 5- and 15-mg doses compared with placebo.

**Quetiapine.** Tariot et al<sup>17</sup> conducted a prospective, 10-week, double-blind, multicenter trial on 284 nursing home patients with Alzheimer's disease who were randomized to flexible-dose quetiapine (mean, 120 mg per day), flexible-dose haloperidol (mean, 2 mg per day), or placebo.

Psychosis, as measured on the Brief Psychiatric Rating Scale (BPRS) total score, improved in all groups and there was no difference between the treatment groups and the placebo group. However, on the BPRS agitation subscale (which consists of tension, hostility, uncooperativeness, and excitement), both haloperidol and quetiapine were more effective than placebo.

Both quetiapine and haloperidol were associated with a high incidence of somnolence, but quetiapine had a favorable motor profile and was associated with low incidence of extrapyramidal adverse events. Haloperidol was associated with worsening functional status, an effect that was not seen in the group treated with quetiapine.

### *Advantages and Limitations of Second-Generation Antipsychotic Drugs*

The advantages of second-generation antipsychotic drugs include decreased extrapyramidal symptoms and tardive dyskinesia, decreased liability of hyperprolactinemia, and cognitive improvement with some agents.

However, limitations of second-generation antipsychotics may include somnolence, dose-dependent extrapyramidal symptoms, prolactin liability, metabolic side effects, and cerebrovascular diseases.<sup>6</sup>

There is now the concern that tardive dyskinesia is being replaced with newer tardive side effects such as obesity, hyperlipidemia, hypertension, and diabetes.

Diabetes poses an increased risk of cardiovascular disease, macrovascular complications, and microvascular effects.<sup>22</sup> Koro et al<sup>23</sup> investigated a large database of 19,600 patients with schizophrenia and found that olanzapine was associated with a statistically significantly

higher incidence of diabetes compared with conventional antipsychotics and placebo.

### Summary

The second-generation antipsychotic drugs are safer than first-generation agents in terms of movement disorders. However, they have other important side effects and they differ in both their efficacies and adverse-effect profiles. Careful dosing can minimize adverse effects, but the optimal dose still needs to be established for some agents.

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## NEW CLINICAL FINDINGS OF A NEXT-GENERATION ANTIPSYCHOTIC

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Peter Paul De Deyn, MD, PhD, MMPP, Professor of Neurology and Behavioral Physiology, University of Antwerp, Middelheim Hospital, Antwerp, Belgium; and Joel E. Streim, MD, President of the American Association for Geriatric Psychiatry, and Associate Professor of Psychiatry, University of Pennsylvania, Philadelphia VA Medical Center, Philadelphia, PA, presented efficacy, safety, and tolerability data from two recent trials of a new antipsychotic agent, aripiprazole, in the treatment of psychiatric symptoms associated with dementia.

### *Dopamine Hypothesis and Effects of Dopamine Antagonism*

There are four dopaminergic pathways that are related both to symptomatology and to side effects from antipsychotic treatment. One is the mesolimbic pathway; hyperactivity in this pathway results in positive symptoms. A second is the mesocortical pathway, and hypoactivity in this pathway causes negative symptoms and cognitive impairment. Third, the nigrostriatal pathway is responsible for the extrapyramidal symptomatology observed after treatment with classical antipsychotic agents. Finally, there is the tuberoinfundibular pathway; dopaminergic antagonism occurs in this pathway and causes inhibition of prolactin release.<sup>24</sup>

Partial agonists, such as the new novel generation antipsychotic drug aripiprazole, induce a partial effect to the receptor, which results in modulation of dopaminergic neurotransmission. The partial agonistic nature of aripiprazole at the mesolimbic level results in

improvement of positive symptoms. Its partial agonistic effects on the nigrostriatal and tuberoinfundibular pathways lead to the minimal appearance of extrapyramidal symptoms and the lack of hyperprolactinemia.

### *Aripiprazole for Psychosis of Alzheimer's Disease: Placebo-Controlled Trials*

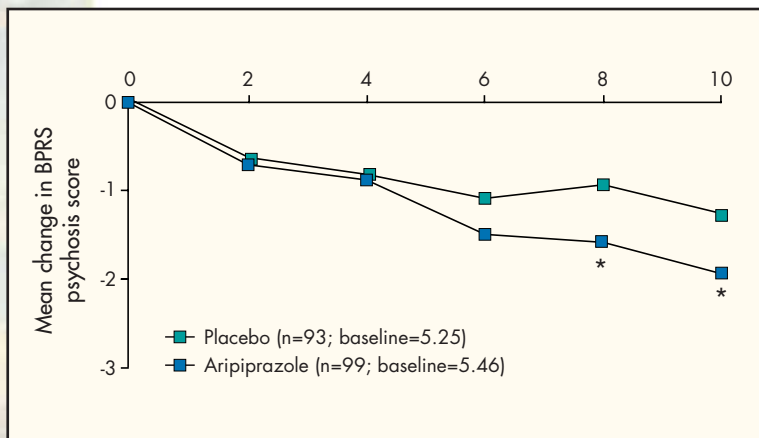
Dr. De Deyn and Dr. Streim discussed efficacy and safety data from two trials conducted on aripiprazole in psychosis associated with Alzheimer's disease.

**Outpatient Study of Aripiprazole vs Placebo.** The first trial, by De Deyn et al,<sup>15</sup> was a 10-week, multicenter study of 208 outpatients with psychosis of Alzheimer's disease (an open-label extension phase of an additional 130 weeks is still ongoing). Patients were ambulatory, community-dwelling individuals aged 55-95 years. All patients had a Mini-Mental State Examination (MMSE) score between 6 and 24, had been experiencing delusions or hallucinations for over 1 month, and had an NPI score of at least 6.

Dosing of aripiprazole was flexible and ranged from 2-15 mg per day. The recommended titration was 2 mg in weeks 1 and 2, 5 mg in weeks 3 and 4, 10 mg in weeks 5 and 6, up to 15 mg in weeks 7-10. This dosing titration schedule could be adjusted more rapidly based on the investigator's clinical evaluation, and the dose could be reduced for tolerability. The optimal dose was not reached until the endpoint of the trial. The mean dose at endpoint was 10 mg per day.

Improvement on the NPI psychosis subscale was numerically greater with aripiprazole than with placebo at weeks 6 and 10, but the differences were not statistically significant.

Aripiprazole was associated with greater reductions in Brief Psychiatric Rating Scale (BPRS) total scores compared to placebo, but the differences were statistically significant only at week 6. However, on the BPRS core subscale (which measures conceptual disorganization, suspiciousness, hallucinations, and unusual thought), and on the BPRS psychosis subscale (which measures all hallucinations and unusual thought), the aripiprazole-treated group achieved greater improvement in scores compared to the placebo group, with differ-



**Figure 1.** Aripiprazole for psychosis of Alzheimer’s disease (outpatient): Brief Psychiatric Rating Scale (BPRS) psychosis subscale—change from baseline.<sup>15</sup>  
 \*  $P < 0.05$  vs placebo; LOCF analysis.  
 BPRS psychosis subscale = hallucinations and unusual thought content.

ences that reached statistical significance at week 8 and were sustained through week 10 (Figure 1).<sup>15</sup>

The discontinuation rates for placebo and aripiprazole were 18% and 17%, respectively. The one adverse event of note was somnolence, which occurred at a rate of 8% for aripiprazole and 1% for placebo. Somnolence was mild-to-moderate, occurred at the higher doses of 10 and 15 mg, and tended to resolve with dose reductions. There was no difference between aripiprazole and placebo in terms of extrapyramidal-related events (dyskinesia, extrapyramidal symptoms, hypokinesia, and tremor). The rates of occurrence of cardiovascular effects and weight changes were low in both the placebo and treatment groups.

**Nursing Home Study of Aripiprazole vs Placebo.** This 10-week, randomized, placebo-controlled study had similar design and enrollment requirements as the previous study, except that subjects were residents of nursing homes or assisted living facilities.<sup>18</sup> Two hundred fifty-six institutionalized patients with psychosis of Alzheimer’s disease were randomized to aripiprazole or placebo. There was an additional open-label extension phase of 42 weeks.

The flexible dosing schedule in this study was similar to that of the previous trial. The recommended titration was 2 mg per day in week 1, 5 mg in weeks 2 and 3, 10 mg in weeks 4 and 5, up to 15 mg in weeks

6-10. The dose could be adjusted more rapidly based on the investigator’s clinical evaluation, or reduced for tolerability. The mean dose at endpoint was 9 mg per day.

Improvement on the NPI-NH psychosis subscale was comparable in the aripiprazole and placebo groups, with no statistically significant differences between treatment groups. However, on the NPI-NH total scale, the aripiprazole-treated group had statistically significantly greater reductions in total scores at weeks 6, 8, and 10 compared to the placebo group (Figure 2).<sup>18</sup> Many patients in the active treatment group had more than twice as much improvement of symptoms.

On the BPRS, reductions in total score were significantly greater with aripiprazole compared with placebo at weeks 8 and 10.

On the Clinical Global Impression (CGI) of improvement scale, aripiprazole outcomes were better than placebo, with statistically significant difference in global ratings at weeks 2, 3, 6, 8, and 10. In post hoc analyses, both the Cohen-Mansfield Agitation Inventory and the Cornell Scale for Depression in Dementia showed statistically significant improvements in the aripiprazole group compared with placebo.

Discontinuation rates were relatively low at 19% for placebo and 21% for aripiprazole. Accidental injury was the most often reported adverse event, and there were more accidental injuries in the placebo group than the treatment group.

Mild somnolence occurred more often in the aripiprazole group compared with placebo. The incidence rates of extrapyramidal side effects were low and there were no substantial differences between drug and placebo. Cardiovascular effects and weight changes were minimal in both the placebo and treatment groups.

### Summary

Aripiprazole, a partial dopamine agonist, is the first of a new, novel generation of atypical antipsychotic agents. Aripiprazole is efficacious for psychiatric symptoms of Alzheimer’s disease and exhibits a favorable safety and tolerability profile for the geriatric population.

## REGULATORY PRESSURES, CLINICAL VALUE, AND ETHICAL CONSIDERATIONS IN THE DESIGN OF STUDIES

Dr. Streim discussed the multiple stakeholders to whom the treatment outcomes of antipsychotic drugs are important. These include consumers (patients, families, and caregivers), health care professionals (providers and clinical researchers), industry (pharmaceutical and health care companies and insurers), and regulatory agencies.

### Health Care Provider Perspective

The health care provider focuses primarily on the psychiatric concomitants of dementia. They treat not only the cognitive domains in dementia, but also depression, delirium, delusions, and disturbances of behavior as they occur in patients with dementing illness.

### Clinical Research Perspective

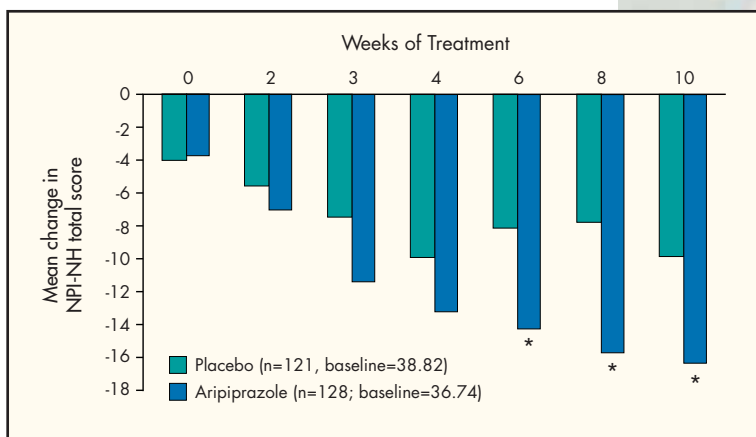
Clinical researchers are interested in the expanded concept of behavioral and psychological symptoms of dementia (BPSD), which broadly includes agitation, aggression, psychosis, depression, apathy, and manic symptoms. Researchers have identified these symptoms as targets for treatment and are interested in elucidating mechanisms by which these symptoms are produced.<sup>25,26</sup>

The relevant outcome domains for treatment of BPSD include relief of symptoms and patient distress, decline in functional status, effects on safety and well-being, and treatment-related adverse effects. BPSD also has implications for quality of life and costs of care, which are part of the rationale for treatment.

For any particular target, outcome measures must be identified. For each outcome measure, thresholds for treatment response, remission, or other treatment benefits also need to be defined.

### Government Regulatory Agency Perspective

**United States Regulatory Criteria.** Prior to March 2000, the United States Food and Drug Administration (FDA) did not recognize psychosis of dementia as an indication for drug treatment. Agitation was not considered a specific symptom of Alzheimer's disease or dementia. The



**Figure 2.** Aripiprazole for psychosis of Alzheimer's disease (nursing home): Mean change in Neuropsychiatric Inventory-Nursing Home (NPI-NH) total score.<sup>18</sup>  
\*  $P < 0.05$ .

FDA has indicated that, in order to expand the claim for use of a particular antipsychotic drug, a clinical entity must be defined that is accepted by the clinical and scientific community, that is operationally definable, and that identifies a homogenous patient group.

In 2000, Jeste and Finkel<sup>3</sup> proposed diagnostic criteria for psychosis of Alzheimer's disease. In addition to a diagnosis of Alzheimer's disease, patients need to exhibit characteristic hallucinations or delusions presenting intermittently for more than 1 month, with onset after the diagnosis of dementia. These hallucinations or delusions must be disruptive to functioning, and may be associated with agitation, negative symptoms, and depression. Schizophrenia, delirium, and other causes of psychotic symptoms should be ruled out.

Using the above definition, the FDA has identified two potential avenues for approval of antipsychotic use for extended indications like psychosis of Alzheimer's disease. One avenue is to show efficacy in two definitive placebo-controlled trials, which is the pathway most often used by industry when designing clinical trials and filing for a new treatment indication. A more daunting avenue is to establish that agitation can be responsive to treatment across at least three different or distinct clinical disorders.<sup>27,28</sup>

**European Regulatory Criteria.** Guidelines approved by the European Committee for Proprietary Medicinal Products (CPMP) in 1997 have focused on the as-

assessment of symptomatic improvement in three domains—cognitive, functional, and global—for the treatment of Alzheimer’s disease.

The BPSD were only briefly mentioned in the guidelines. Efficacy for a claim for BPSD would require a specific trial design and behavioral symptoms as a primary variable, which would be measured by specific and validated scales. The CPMP does not actually recognize an established tool for the purpose of measuring outcomes in this area.

**Regulatory Criteria in Other Countries.** Other countries have established limited guidance on this topic. In Japan, there is emphasis on improving cognition and slowing disease progression in Alzheimer’s disease, but the value of treatment for BPSD in Japan is still unclear from a regulatory perspective.

In Canada, Health Canada has gone further than perhaps any other regulatory body by acknowledging the need to assess behavior as a central part of Alzheimer’s disease. For example, disturbed thinking, disruption of the sleep-wake cycle, pacing, and wandering have been established as appropriate targets for treatment of Alzheimer’s disease. Health Canada recognizes and recommends the Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD) scale as a well-validated measurement instrument, but other study requirements are less clearly specified.<sup>29</sup>

### Industry Perspective

Pharmaceutical companies depend on regulatory approval for marketing. Especially in the United States, pharmaceutical companies are not permitted to advertise without an approved indication for use. The focus, therefore, has been on efficacy studies that involve treatment of some of these target BPSD.

Health care insurers or payors are interested not only in efficacy but also in cost. While function and quality of life studies are not required for regulatory approval, they are relevant to the decisions about formulary choices and health care costs that insurers must face.

### Consumer Perspective

The consumer perspective is one of the most important considerations. Symptom relief, improved

functional status, reduced caregiver burden, risk reduction, and improved quality of life are all valued treatment benefits for patients, families, and caregivers.

Karlawish and Lantos<sup>30,31</sup> proposed the concept of *equipoise* in designing research, which asks what patients (or their surrogates) consider an acceptable level of risk or cost that they are willing to incur to obtain a given level of treatment benefit. If that question can be answered, it can help to define treatment outcomes that are truly of clinical value.

### Conclusions

The majority of studies have been designed and outcome measures have been chosen with heavy influence from regulatory pressures. However, there needs to be a shift toward evaluating ethical principles. The regulatory requirements and study designs should place more emphasis on outcomes that are valued by consumers, taking into consideration the balance of costs, risks, and benefits of treatment.

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### STUDYING MEDICATION EFFECTIVENESS IN THE “REAL WORLD”: THE NIMH CATIE MODEL

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Dr. Ryan described the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), a large research project funded by the National Institute of Mental Health (NIMH).<sup>32</sup> The trial was developed to study medication effectiveness in the real world. Dr. Ryan discussed the rationale and implications of this innovative approach.

### Rationale for CATIE

Most clinical trials of antipsychotics have focused on short-term efficacy and are conducted under close to ideal conditions with regard to patient selection, monitoring, and adherence to treatment. There is concern about whether outcome measures, such as changes in scores on symptom rating scales, really translate into meaningful results for patients and families. The CATIE study was developed to address the limitations often associated with clinical trials of antipsychotic drugs.

CATIE is a large, multicenter, clinical trial designed to evaluate the effectiveness of antipsychotic medications in broad patient populations and “real world”

settings. The trial includes an arm for schizophrenia and another arm for Alzheimer's disease patients with psychosis or agitation.

### *CATIE Alzheimer's Disease Trial*

The CATIE Alzheimer's disease trial will enroll 450 outpatients with Alzheimer's disease, who do not live in skilled nursing facilities, and who have a caregiver who lives with or visits the patient at least 8 hours per week. The study duration is 36 weeks. There are at least 30 study sites, comprised of both academic and community-based settings.

CATIE is a controlled, randomized efficacy trial merged with features from health services or effectiveness research studies. Assessments of overall effectiveness of antipsychotic drugs are made using not just psychopathology scales, but by incorporating a wide variety of assessment measures in order to determine the real-world consequences of treating patients with Alzheimer's disease with these medications.

This trial is unique in that physicians may adjust, switch, or discontinue medications as they might do in a clinical setting. Patients are followed over the course of the trial whether or not they are complying with the protocol, which will provide further follow-up and outcomes information and will allow intent-to-treat analyses.

In phase 1 of this trial, patients are randomized to either flexible-dose olanzapine (2.5-10 mg per day), flexible-dose quetiapine (25-100 mg per day), flexible-dose risperidone (0.5-2 mg per day), or placebo. Investigators can adjust the dosage up or down as necessary. Patients are kept in phase 1 for a minimum of 2 weeks to determine whether the drug is having an effect. Patients who respond to treatment in phase 1 are maintained in this phase for the duration of the study.

Patients who respond inadequately to phase 1 treatment proceed to phase 2, where they are randomized to one of the other treatment drugs or citalopram. Citalopram, a selective serotonin reuptake inhibitor (SSRI), was included in phase 2 because there has been research showing the association between SSRIs and reduction of agitation. Responders in phase 2 remain in this phase for the duration of the study.

Patients who do not respond well in phase 2 or who

do not wish to continue in a blinded trial any longer can proceed into phase 3 of the trial, in which they are randomly assigned to one of the study medications that they have not yet taken in an open-label fashion.

There is also a phase 4, in which the clinician treats the patient open-label with whichever psychotropic drug they feel is necessary. The clinician can also choose to discontinue psychotropic medication entirely and monitor symptoms.

The CATIE trial will analyze efficacy outcomes using the CGI, BPRS, and NPI. The trial will evaluate tolerability and compliance, quality of life, functional activities, caregiver indices, service utilization, and costs. There will be careful neuropsychological testing to determine whether these drugs help or worsen cognition and to identify the domains that are affected.

### *Summary*

Large effectiveness trials are feasible but complex. Outcomes must assess the impact on patients, families, and caregivers. CATIE aims to mirror clinical practice and study the effectiveness of antipsychotic medications in the real world. It is hoped that this study design can also be applied to the long-term care setting.

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## CME Accreditation

### Atypical Antipsychotics for the Management of Patients With Dementia and Psychotic Symptoms

This activity was developed for primary care physicians and geriatric psychiatrists.

#### ACCREDITATION

- The American Association for Geriatric Psychiatry (AAGP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.
- AAGP designates this continuing educational activity for a maximum of one Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

- This CME activity was planned and produced in accordance with the ACCME Essentials.
- Based upon trials, the estimated time to complete this program is 1 hour.

#### EDUCATIONAL OBJECTIVES

- Identify the differences between antipsychotic agents, with particular emphasis on efficacy, safety, and tolerability.
- Describe novel antipsychotic mechanisms of action and associated clinical implications.
- Discuss factors that influence the choice of outcome measures in clinical trial design, and distinguish the design and outcome measures of large clinical trials of antipsychotics.

# CME EXAMINATION & INSTRUCTIONS

## Atypical Antipsychotics for the Management of Patients With Dementia and Psychotic Symptoms

A certificate of completion will be awarded to physicians completing the post-test and evaluation form. Please complete the post-test and program evaluation and mail to:

**Association for Geriatric Psychiatry**

**7910 Woodmont Ave**

**Suite 1050**

**Bethesda, MD 20814-3004**

Please allow three weeks for processing. Program expiration date is December 2004. Please phone (301) 654-7850 or fax (301) 654-4137 with any questions.

1. Psychosis of Alzheimer's disease occurs before the onset of Alzheimer's disease.
  - a. True
  - b. False
2. Second-generation antipsychotics are associated with:
  - a. Lower liability for tardive dyskinesia compared with first-generation agents
  - b. Higher incidence of somnolence (with some agents) compared with placebo
  - c. Improvement in cognition with some agents
  - d. All of the above
3. The partial agonist properties of aripiprazole may explain improvement of positive symptoms, minimal extrapyramidal symptoms, and lack of hyperprolactinemia.
  - a. True
  - b. False
4. In Jeste and Finkel's diagnostic criteria for psychosis of Alzheimer's disease, which of the following criteria is true?
  - a. Hallucinations and delusions have onset before the diagnosis of Alzheimer's disease.
  - b. Schizophrenia and other causes of psychotic symptoms may also be present.
  - c. Hallucinations or delusions may be associated with agitation, negative symptoms, and depression.
  - d. All of the above
5. Achieving equipoise in designing research requires that we ask what patients (or their surrogates) consider an acceptable level of cost or risk that they are willing to incur to obtain a given level of treatment benefit.
  - a. True
  - b. False
6. The Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) will enroll 450 outpatients with Alzheimer's disease from at least 30 study sites.
  - a. True
  - b. False
7. Which of the following statements is false?
  - a. Extrapyramidal symptoms and tardive dyskinesia are associated with incoordination, disfigurement, falls, and fractures.
  - b. Postural hypotension can lead to falls and fractures.
  - c. Central anticholinergic effects can lead to blurred vision, urinary retention, constipation, and dry mouth.
  - d. None of the above
8. In nursing home patients, treatment with aripiprazole was associated with significantly greater improvements on the NPI-NH and BPRS total scores compared to placebo.
  - a. True
  - b. False
9. In outpatients, treatment with aripiprazole was associated with significantly greater improvements on the NPI psychosis subscale compared with placebo.
  - a. True
  - b. False
10. There are multiple stakeholders to whom the treatment outcomes of antipsychotic drugs are important. These include:
  - a. Consumers
  - b. Health care professionals
  - c. Regulatory agencies
  - d. All of the above

## CME EVALUATION

Please circle the number that best reflects your opinions on the following statements, using the following rating scale:

1 = Strongly Agree; 2 = Agree; 3 = Disagree; 4 = Strongly Disagree.

- |                                      |   |   |   |   |
|--------------------------------------|---|---|---|---|
| 1. The program objectives were met.  | 1 | 2 | 3 | 4 |
| 2. The program content was useful.   | 1 | 2 | 3 | 4 |
| 3. The program content was relevant. | 1 | 2 | 3 | 4 |
| 4. The program was educational.      | 1 | 2 | 3 | 4 |
| 5. The program was not promotional.  | 1 | 2 | 3 | 4 |

Additional Comments: \_\_\_\_\_

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