Antipsychotic Treatment of Psychosis and Agitation in the Elderly

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Agitated, aggressive behavior and psychosis are common manifestations of Alzheimer's disease that frequently lead to institutionalization. The usefulness of conventional neuroleptic treatment in this population is limited by narrow therapeutic windows because of limited efficacy and high sensitivity to side effects. More recently, investigational clinical trials have suggested potential utility for atypical antipsychotics such as risperidone, olanzapine, and quetiapine in treatment of behaviorally disturbed individuals and for the psychotic manifestations of dementia.

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The diagnostic evaluation and treatment of psychosis and agitation in the elderly require special considerations. The elderly brain provides a different substrate for both the therapeutic and potentially toxic effects of antipsychotic medication. In elderly patients with degenerative brain disorders, the normal redundancy, interdependence, and checks and balances of neuronal networks and neurotransmitters may be disturbed or deficient. Institutionalized, demented, and acutely medically ill elderly populations, particularly those taking multiple medications, are at risk for psychosis and behavioral disturbances. Patients with long-standing schizophrenia-like disorders or with bipolar or agitated depression may become increasingly antipsychotic resistant or intolerant with aging. Recently, there has been increasing activity in systematic study of the behavioral effects of antipsychotic medications, mood stabilizers, and cholinergic agents in elderly populations with Alzheimer's and vascular dementia. In contrast, systematic, controlled trials of the therapeutic effects of antipsychotic agents in elderly populations with schizophrenia or psychotic affective disorders remain relatively sparse.

DIAGNOSTIC CONSIDERATIONS

The primary consideration in evaluating psychotic or agitated symptoms in the elderly is to rule out medically reversible etiologies, especially delirium. Delirium may be reversible if the underlying medical causes are addressed promptly, or fatal if overlooked or untreated. Delirium in the elderly is protean in its clinical picture, with both activated and quiet forms and a broad continuum of intensities of behavioral disturbances. Delirium frequently piggybacks as a "double-diagnosis" imposed on any other disorder that inculcates increased fragility of the brain's usual homeostatic mechanisms. The prevalence of delirium in the elderly may be surprisingly high. Levkoff and colleagues[1] found that 64% and 24% of hospital admissions from a nursing home and the community, respectively, were delirious. Common medical causes of confusion and agitation in the elderly include infections (e.g., respiratory, urinary, integument); endocrine, fluid, and electrolyte imbalances; and even constipation. The elderly are frequently taking multiple medications. They may be more vulnerable to the cognitive effects of drug interactions or to what may be considered therapeutic blood drug levels in the nonelderly. Medications with anticholinergic effects may be particularly toxic.

BEHAVIORAL AND PSYCHOTIC DISTURBANCES IN DEMENTIA

Psychopathology and behavioral disturbances in dementia are often more disturbing to caregivers than cognitive loss per se and often engender the initial consultation with the medical/psychiatric community.[2,3] In Alzheimer's disease, psychosis and behavioral disturbances are the leading causes for use of more restrictive, supervised environments including institutionalization.[4] Psychotic symptoms are highly prevalent in dementia, with delusions noted in 10% to 73% of patients and hallucinations in 3% to 49%.[5] Delusions may be associated with relatively rapid clinical deterioration.[6–8] Persecutory delusions are seen in

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approximately 21% of patients with Alzheimer's disease.[9] In dementia, delusions and hallucinations may coexist and increase the risk of violence and other behavioral problems.[10–14] Psychotic and behavioral symptoms may respond to similar therapies.[10–14]

CONVENTIONAL NEUROLEPTIC TREATMENT OF PSYCHOSIS AND BEHAVIORAL DISTURBANCES IN DEMENTIA

In contrast to schizophrenia, no medications have been specifically approved for either the psychotic or behavioral manifestations of dementia. Conventional antipsychotics have been extensively studied in elderly demented populations with overall disappointing results.[3,12,14,15] Effect size and response rates have been modest, with no consistent evidence that any conventional neuroleptic is more effective than another. Adverse events occur frequently relative to efficacy, especially motor side effects, sedation, cognitive impairment, orthostatic hypotension, constipation, and urinary hesitancy. This has led to increasing reluctance and some statutory obstacles to use of these agents in the elderly, particularly in institutional settings.

The shortcomings of traditional neuroleptics in this population have engendered increasing interest in the potential of atypical antipsychotics. In a psychotic, behaviorally disturbed elderly population, an ideal agent might have rapid onset, sustained action, and minimal somatic or cognitive side effects. The most commonly used atypical antipsychotics in the United States share a relatively high ratio of affinity at serotonin-2A ($5\text{-}HT_{2A}$) receptors compared with dopamine D_2 receptors. They differ, however, in their relative affinities at central muscarinic M_1 and M_4, dopamine D_1, and adrenergic α_1 and α_2 receptors. Substantial preclinical and clinical evidence suggests that relative affinity at these receptors may affect multiple aspects of cognition, including memory and executive functions. Modulation of multiple somatic functions may also be disturbed, such as the gastrointestinal, urinary, and cardiovascular systems.

THEORETICAL CONSIDERATIONS FOR AN IDEAL ATYPICAL AGENT

There is a rational basis for prediction of cognitive sensitivity of patients with Alzheimer's disease to the central muscarinic effects of medication. Evidence of a critical role for cholinergic mechanisms in Alzheimer's disease includes the following:

1. Cholinergic mechanisms modulate learning and memory in humans.[16]
2. Lesions of the central cholinergic system in animals create learning and memory deficits that may be reversed with cholinomimetic administration.[16]
3. Postmortem studies of Alzheimer's disease indicate cholinergic cell loss, decreased concentrations of choline acetyltransferase and acetylcholinesterase, and a correlation between these changes and cognitive impairment.[16]
4. Centrally active cholinesterase inhibitors may enhance cognitive function in Alzheimer's disease.[16]
5. Anticholinergic agents may impair memory in the young and elderly.[17–19]
6. Elderly patients with Alzheimer's disease may be exquisitely sensitive to memory and other cognitive deficits when exposed to anticholinergic agents such as scopolamine.[20,21]

The anticholinergic effects of available antipsychotics vary widely. Many conventional neuroleptics appear to possess strong antagonism for central muscarinic receptors. Among the antipsychotics with atypical motor properties, olanzapine exhibits significant anticholinergic receptor affinity as evidenced by (1) inhibition of oxotremorine-induced behavior in rodents[22] and (2) affinity for muscarinic, primarily M_1 but also M_2, M_3, M_4, and M_5, subtypes.[23] Clozapine also has a relatively strong muscarinic affinity. Despite these in vitro findings, ex vivo and in vivo functional studies have raised doubt as to the extent of potent functional anticholinergic activity. Evidence that clozapine and olanzapine possess some muscarinic *agonist* properties exists as well. For example, clozapine and to a lesser extent olanzapine produce concentration-dependent, atropine-sensitive inhibition of cAMP (cyclic adenosine monophosphate) formation at human muscarinic M_4 receptors.[23] The extent, if any, to which such muscarinic affinities could affect cognition in Alzheimer's disease or modify the effect of concomitant cholinesterase inhibitor treatment has not been systematically studied. Other antipsychotic medications with atypical motor profiles such as risperidone and quetiapine lack significant muscarinic affinity. Antiparkinsonian agents and tricyclic antidepressants with strong anticholinergic properties should be utilized in Alzheimer's disease with caution. Anticholinergic delirium is a significant cause of morbidity in the elderly.

CLINICAL TRIALS OF ATYPICAL AGENTS

Katz et al.[24] conducted one of the first multicenter, double-blind, randomized, placebo-controlled studies of an atypical antipsychotic in treatment of psychosis and behavioral disturbances in an elderly demented population.[24] Six hundred twenty-five patients with DSM-IV diagnoses of Alzheimer's disease (73%) or vascular (15%) or mixed dementia (12%) were randomly assigned to receive either placebo or 0.5 mg, 1 mg, or 2 mg of risperidone each day. The mean baseline Mini-Mental State Examination (MMSE)[25] score was 6.6, indicating a mostly severely demented population. At endpoint, significantly greater reductions were

seen on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[26] total score and psychosis and aggressiveness subscale scores in patients who took risperidone, 1 or 2 mg/day, than in those taking placebo. The most common adverse events were motor symptoms, sedation, and mild peripheral edema. Risperidone, 1 mg/day, was statistically indistinguishable from placebo in production of motor side effects. Risperidone, 2 mg/day, was associated with more adverse events than the 1-mg/day dose.

Brecher and colleagues[27] performed an interim analysis of the frequency of tardive dyskinesia in 330 patients who participated in an open-label extension of up to 1 year's duration following the double-blind trial described above. Among patients without dyskinetic movements at baseline, persistent tardive dyskinesia was seen in 2.4%. The mean change in the clinician's global impression dyskinetic movement score from baseline was –1.2 and –1.4 at endpoint and 12 months, respectively.

De Deyn and colleagues[28] conducted an international, randomized, double-blind, flexible-dosing trial of risperidone (0.5–4 mg/day, N = 155), haloperidol (0.5–4 mg/day, N = 155), or placebo (N = 144) in patients with Alzheimer's disease (72%) or vascular (18%) or mixed (10%) dementia. The mean BEHAVE-AD total score at baseline was approximately 16.5. At endpoint, patients receiving risperidone had significantly greater reductions than the placebo group in BEHAVE-AD aggressiveness scores and Cohen-Mansfield Agitation Inventory aggressive cluster scores. At week 12, at least 30% reduction in the BEHAVE-AD total score was observed in 72%, 69%, and 61% of patients receiving risperidone, haloperidol, or placebo, respectively, and in 54%, 63%, and 47%, respectively, at endpoint. The most common adverse events seenin the risperidone and haloperidol groups were somnolence and falls. Haloperidol was associated with higher motor side effect scores than risperidone at both 12 weeks and endpoint.

The Expert Consensus Guideline Series for Treatment of Agitation in Older Persons With Dementia[29] recommends a starting dose of 0.25 to 0.5 mg/day of risperidone, with a mean target dose of 0.5 to 1.5 mg/day and a ceiling of 2 to 3 mg/day.

Olanzapine, 5 mg (N = 56), 10 mg (N = 50), or 15 mg (N = 53), and placebo (N = 47) were compared in nursing home facility patients with Alzheimer's dementia with psychosis or behavioral disturbances.[30] Approximately 70% of the patients had MMSE scores of 10 or less, and inclusion criteria required the exhibition of significant hallucinations, delusions, agitation, or aggression on the primary rating instrument, the Neuropsychiatric Inventory, Nursing Home version (NPI/NH).[31] Statistically significant improvement from baseline was seen on the NPI/NH: with the 5- and 10-mg/day dosages on the core total score even when controlled for somnolence, with the 5-mg dose on the hallucinations/delusions subscale, and with the 10-mg dose on the agitation/aggression subscale. The NPI/NH total and Brief Psychiatric Rating Scale[32] (BPRS) total scores significantly improved from baseline compared with placebo in the 5-mg/day group. There was no significant change from baseline compared with placebo in the total MMSE score for any of the dosage groups; however, modest numeric improvement was seen in the 5-mg/day group and modest decline in the 10-mg and 15-mg/day groups. Measures of akathisia and parkinsonian side effects did not differ from placebo in any dose group. Somnolence occurred more frequently in all 3 olanzapine dose groups than with placebo. Abnormal gait occurred more frequently in the 5- and 15-mg/day groups than with placebo. Vital signs, laboratory measures, and electrocardiogram measures were unchanged in each dosage group compared with placebo.

A 52-week, open-label, multicenter trial of quetiapine, 25 to 800 mg/day, was performed in a mixed diagnostic group of 184 elderly psychotic patients.[33] The median total daily dose was 100 mg, and the median duration of treatment was 350 days. Statistically significant improvement from baseline was seen in the BPRS total and Clinical Global Impressions-Severity of Illness scores at all timepoints from week 2 onward. Mean parkinsonian and dyskinetic side effect scores declined from baseline, and quetiapine was generally relatively well tolerated.

SUMMARY

The evolution of antipsychotic treatment in the elderly appears to be providing more efficacious treatments with wider therapeutic safety/tolerability windows. Elderly patients for whom antipsychotic treatment is appropriate may anticipate improved relief from psychotic symptoms, agitated mood states, and disturbing behaviors. There is a growing empirical basis for optimism that this will be accomplished with fewer acute motor side effects, less tardive dyskinesia in the long term, and less cognitive toxicity. Titration speed and target dosage are substantially reduced in the elderly. Aside from fewer motor side effects, the mechanisms for the apparent advantages of the atypical antipsychotics over conventional neuroleptics in the demented elderly are poorly understood. Although the pathophysiology and substrate for psychosis in Alzheimer's disease and other dementias may differ from that in younger patients with schizophrenia, some of the final common pathways of dopaminergic dysregulation may be shared. The treatment of elderly patients with schizophrenia and bipolar disorder with psychotic features will ultimately benefit from the kind of systematic randomized controlled trials currently being applied to Alzheimer's and vascular dementia.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, clozapine, haloperidol, olanzapine, quetiapine, and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of psychosis in elderly patients with dementia.

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