The Efficacy, Safety, and Tolerability of Antipsychotics in the Elderly

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Antipsychotic medications are among the most widely prescribed class of medications for elderly patients. Despite their high use, few studies document the efficacy, safety, and tolerability of these agents in this patient population. This is unfortunate because, as a group, the elderly are exceptionally sensitive to the adverse effects associated with antipsychotics, in particular, the extrapyramidal side effects (EPS). The atypical antipsychotics with their lower propensity to cause EPS and lower need for augmenting anticholinergic medication have introduced new options for elderly patients who need antipsychotic therapy for a number of psychiatric and neurologic disorders with psychotic manifestations. This review covers the pharmacologic, clinical, and regulatory issues involving antipsychotic use in elderly patients that warrant consideration by the practicing psychiatrist.

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The increasing proportion of the elderly in our population and their disproportionately greater use of health care resources have led to renewed attention to elderly patients' unique health needs. Although only 12% of the population in the United States are older than 65 years of age, they use 31% of all medications consumed.[1] Antipsychotics are among the most widely prescribed psychotropic drugs for the elderly population, particularly among the 5% to 8% of patients who are institutionalized.[2] It is estimated that nursing home patients receive antipsychotics for 17 of every 100 resident days.[3] Antipsychotics are primarily used for treating psychotic disorders, including schizophrenia, delusional disorder, psychotic symptoms in a psychotic mood disorder, and for a number of organic psychoses. In addition, it is increasingly common to use antipsychotics for treating behavioral disturbances (particularly agitation and aggression) that are associated with dementia. Although several factors unique to elderly patients impact the optimal use of antipsychotic agents in this population, there is a relative paucity of high-quality data about the use of these drugs in the elderly.

In this review, we summarize pharmacologic, clinical, and regulatory issues involving antipsychotic use in elderly patients that warrant consideration by the practicing psychiatrist. After a brief general comparison of atypical to conventional antipsychotics, we review studies of various atypical antipsychotics in the elderly. We conclude with some general recommendations.

ISSUES OF ANTIPSYCHOTIC USE IN THE ELDERLY

The disproportionate use of total medications in the United States by patients over 65 is not unique; in the United Kingdom, the elderly are dispensed twice as many medications as the national average.[1,4] Drug interactions are more common because of the frequent use of multiple medications. Physical changes that are part of the aging process also affect how medications are metabolized (e.g., liver function and kidney function often become compromised). Chronic illnesses further complicate the use of antipsychotics in the elderly. Eighty percent of elderly patients have at least one chronic disease; consequently, concurrent medical problems and their treatments must be considered when antipsychotic medications are prescribed. In addition, the elderly are more susceptible to extrapyramidal side effects (EPS) and tardive dyskinesia (TD) than younger patients.[5] Falls resulting from orthostatic hypotension may have devastating consequences because of substantial risk of bone fractures, head injury, and other fall-related consequences. Cardiovascular reserve is diminished, making the elderly more susceptible to cardiovascular side effects. Sexual functioning may be impaired. Cognitive function can decline (and is clearly impaired in patients with dementia), making the elderly particularly vulnerable to medications that adversely affect cognition. Complicating care, the use of antipsychot-

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Table 1. Antipsychotics in the Elderly: Issues to Consider[a]

Pharmacokinetics
EPS
Tardive dyskinesia
Falls and orthostasis
Hyperprolactinemia and osteoporosis
Anticholinergic effects and cognition
Weight gain and associated effects
Cardiac effects
Ocular effects
Sexual dysfunction
Regulatory issues (eg, OBRA)
Economic issues

[a]Abbreviations: EPS = extrapyramidal symptoms, OBRA = Omnibus Budget Reconciliation Act.

ics and other psychotropic medications in nursing home settings is regulated under the Omnibus Budget Reconciliation Act (OBRA), and clinicians and facilities must follow special guidelines.[6] Further, special economic questions must be considered, both on an individual and national level.

Each of these factors warrants consideration as decisions about antipsychotic use in the elderly are made. These factors are briefly reviewed (Table 1).

Pharmacokinetics

All relevant pharmacokinetic parameters (i.e., absorption, distribution, metabolism, and clearance) can be affected by the aging process. For example, reductions in gastric acidity and splanchnic blood flow that occur with aging modify absorption. With aging, lean body mass decreases as does total body size. Fat-soluble drugs, including antipsychotics, distribute more widely and may take longer to clear (in view of the general increase in body fat relative to total body weight). Hepatic function and renal function decline because of decreased blood flow, reduced metabolic enzyme activity, decreased rate of glomerular filtration, and decreased tubular function. The aging process slows the elimination of many medications because hepatic and renal mechanisms predominantly control the clearance of medications. For many psychoactive drugs, decreased phase I oxidative transformation accompanying aging prolongs the half-life.[7,8] In addition, differences in body mass composition, effects from smoking, dosage forms (i.e., by mouth vs. parenteral), and concurrent medications may affect the plasma concentrations of drugs. There are wide variations in plasma concentrations of psychotropic drugs between patients receiving the same dose. This variability is much greater in the elderly than in younger patients and makes generalizations about optimal dosages difficult based on pharmacokinetic principles alone.[8]

Sweet and Pollock reviewed the function of cytochrome P450 (CYP) isoenzymes relative to the metabolism of antipsychotics in elderly patients and found no uniform age-associated decline in liver metabolism via the CYP isoenzymes.[8] In particular, no age-related changes were noted with the CYP2D6 isoenzyme, which is responsible for the metabolism of perphenazine, thioridazine, and risperidone. A possible age-related decline in function was noted for the CYP3A4 isoenzyme, the predominant metabolizer of quetiapine.[8] Although not systematically studied, some evidence of a decline with the CYP1A2 isoenzyme, a primary metabolizer of clozapine and olanzapine, was found by Sweet and Pollock.[8] Such declines in function would imply a lower clearance of the drug metabolized by these enzymes, necessitating a decrease in dosage. Specific pharmacokinetic properties of conventional and atypical antipsychotic agents are reviewed elsewhere.[9]

Side Effects

Antipsychotic drugs are associated with a variety of adverse effects, which are related to the specific pharmacologic attributes of the particular drug (see Tandon et al., this issue). The elderly are more susceptible to a variety of side effects because of reduced functional reserve, decreased adaptive ability, and other physiologic changes that accompany the aging process.

Extrapyramidal side effects. Elderly patients are exceptionally sensitive to EPS, particularly akathisia, TD, and pseudoparkinsonism (akinesia, slowing of movement, masked faces, cogwheeling, rigidity, resting tremor, and hypersalivation). The presence of EPS can contribute to medication intolerance, medication noncompliance, falls, and other adverse effects. Fewer EPS occur with low-potency conventional antipsychotics compared with the high-potency agents. However, with the atypical antipsychotics, it is possible to have therapeutic effects at doses devoid of associated EPS (see Tandon et al., this issue); in fact, lack of extrapyramidal adverse effects is the principal characteristic distinguishing atypical from conventional antipsychotics.

Tardive dyskinesia. Tardive dyskinesia is significant because it can lead to unintelligible speech, respiratory distress with diaphragmatic involvement, falls, and psychosocial stigmata of shame, guilt, anger, and depression. Increased morbidity and mortality accompany its occurrence. Age is an independent risk factor for TD; increasing age substantially increases both the risk of developing TD and its severity.[5,10–13] Patients over 40 years of age are 3 times more likely to develop TD.[13,14] According to Jeste and colleagues, the cumulative incidence of TD in elderly patients is 26%, 52%, and 60% after 1, 2, and 3 years of antipsychotic exposure, respectively,[10] in contrast to corresponding values of 4%, 8%, and 11% in younger patients. Once TD develops, it appears relatively stable in older psychiatric patients and does not always progress.[15]

Development of EPS is a significant risk factor for TD.[16,17] With typical antipsychotics, there is a narrow therapeutic-to-toxic index. This index is wider for atypical antipsychotics, meaning fewer EPS at therapeutic doses

Table 2. Side Effect Profile of Available Antipsychotic Agents[a]

Side Effect	Neuroleptics	Clozapine	Risperidone	Olanzapine	Quetiapine
Anticholinergic	± to +++	+++	±	+	±
EPS	± to +++	0 to ±	0 to +	0 to ±	0 to ±
Orthostatic hypotension	+ to +++	+++	++	+	+ to ++
Prolactin elevation	++ to +++	0	++	0 to ±	0 to ±
Sedation	+ to +++	+++	+	++	+ to ++
Seizures	± to ++	++	±	±	±
Weight gain	+ to ++	+++	++	++ to +++	++

[a]Data from reference 9, Tandon et al. (this issue), and based on clinical trials data and clinical experience. Symbols: 0 = absent; ± = minimal; + = mild; ++ = moderate; +++ = severe.

and a theoretically decreased risk for TD.[16] The lower EPS risk associated with atypical rather than conventional antipsychotic treatment is likely to translate into a lower TD risk (see Tandon et al., this issue); clinical trials are necessary to confirm this expectation. Although extensive data with clozapine and emerging data with risperidone and olanzapine provide support for this contention, confirmatory, long-term, systematic studies are needed.

Since few treatments exist for TD, the best strategy is its prevention by minimizing a patient's exposure to antipsychotics, limiting long-term use to well-defined indications, using the lowest effective doses, preferentially using an atypical antipsychotic, and frequently monitoring for TD.[14]

Falls and orthostasis. In geriatric populations, the prevalence of orthostatic hypotension is estimated to be 5% to 33% and increases with age.[18] Orthostatic hypotension is a common side effect of a number of medications, including the antipsychotics, and a major contributing factor to the occurrence of falls. The elderly are more prone to adverse consequences from falls, such as bone fractures, injuries, functional decline, dependency, and death.[19,20] Risks for falls in the elderly include mental impairment, restricted mobility, congestive heart failure, use of long-acting benzodiazepines, and the use of 3 or more psychoactive agents.[21] Combining drugs that have a potential to cause orthostasis increases the risk of orthostatic hypotension (e.g., antihypertensives, nitrates, antiparkinsonian medications, and antidepressants). For an extensive review of drug-induced orthostatic changes see Verhaeverbeke and Mets.[18]

The extent to which antipsychotics cause hypotension differs (Table 2). Low-potency typical antipsychotics and some of the atypical antipsychotics, especially clozapine, cause a significant drop in orthostatic blood pressure.[18]

Hyperprolactinemia and osteoporosis. All conventional antipsychotics and risperidone cause an elevation in the secretion of prolactin. Prolactin elevation can potentially diminish levels of gonadotropins and gonadal hormones, causing hypogonadism and potentially leading to a decrease in bone-mineral density and osteoporosis.[22–25] Coupled with the postmenopausal risk of osteoporosis due to declining estrogen levels, the risk of incurring fractures is theoretically greatly increased in elderly women who take antipsychotics. One study in younger psychiatric inpatients demonstrated that both male and female patients taking antipsychotics had significant decreases in their bone-mineral density when compared with age-matched normal data.[26] However, no systematic study of the effects of antipsychotics on bone-mineral density in the elderly has been published.

Anticholinergic effects and cognition. The elderly are particularly susceptible to anticholinergic side effects such as constipation, dry mouth, urinary retention, and cognitive impairment. Constipation causes abdominal discomfort, impaction, anorexia, early satiety, gastric reflux, and at times circulatory changes during straining on the stool, fever, and confusion.[27–30] The use of laxatives is particularly high in nursing homes especially among patients taking highly anticholinergic antidepressants and antipsychotics.[27]

Urinary retention can cause great discomfort and worry, especially for men with prostatic hypertrophy. Dry mouth can lead to dental caries and possible systemic infections. Cognitive impairment may also occur, which may lead to decreased independence. In fact, a recent study suggested a more rapid decline in cognitive function associated with antipsychotic treatment in a sample of patients with dementia.[31] Anticholinergic and sedative effects associated with antipsychotic treatment are of greatest relevance in terms of worsening cognition; unfortunately, the cognitive effects of antipsychotic agents in an elderly population have not been carefully assessed. Of interest is a double-blind study of risperidone and haloperidol in elderly schizophrenic patients.[32] Mini-Mental State Examination (MMSE) scores significantly improved in patients taking risperidone but not in patients taking haloperidol; however, other cognitive tests did not significantly change from baseline. Similarly, Street and colleagues have shown in a double-blind, placebo-controlled study in patients with Alzheimer's disease that the MMSE scores for patients treated with a 5-mg dose of olanzapine improved, while scores for the 10- and 15-mg-treated patients did not differ from placebo.[33] Additional studies are warranted to further evaluate the effects of olanzapine on cognition.

Weight gain and associated effects. Obesity is associated with type II diabetes mellitus, hypertension, elevated triglyceride and cholesterol levels, and mechanical stress on joints.[34] Social consequences are also significant. Weight gain is a common side effect with antipsychotic use, and the above complications of obesity coupled with coexisting medical conditions could increase the elderly person's risk of morbidity and mortality. Stanton, in a re-

view of weight gain with antipsychotic agents, observed that increased weight appeared to be associated with an increase in appetite; but the precise mechanism has not been delineated.[35] Further, fat distribution from these drug-induced weight gains appears to be more central than peripheral, which may increase the morbidity resulting from obesity.[35–38]

Low-potency conventional antipsychotics such as chlorpromazine are associated with more weight gain than high-potency antipsychotics. Few data about weight gain among the atypical agents in elderly populations have been published. In younger patients, clozapine is associated with the most weight gain, olanzapine with high-to-moderate weight gain, and risperidone and quetiapine with moderate weight gain (approximated to the level of chlorpromazine).[39]

Cardiac effects. Cardiovascular side effects of antipsychotic agents include postural hypotension (discussed above), tachycardia, conduction disturbances (increased PR and QT intervals), and arrhythmias including torsades de pointes (polymorphic ventricular tachycardia) and ventricular fibrillation. The normal heart rate–corrected interval (QTc) is ≤ 440 milliseconds. The mean increase in QT interval seen with haloperidol, clozapine, risperidone, olanzapine, and quetiapine is about 2.5–4 milliseconds, while the mean increase with thioridazine and pimozide is 8–14 milliseconds. The effect of many but not all antipsychotics on the QT interval appears to be dose-related. Limited data are available on cardiac effects of antipsychotics in geriatric populations, but with many patients having a cardiac history, this bears consideration.

Extra caution must be taken when prescribing antipsychotics to patients receiving cardiac medications such as calcium channel blockers or diuretics that may deplete potassium or magnesium and predispose a patient to QT prolongation or other arrhythmia. A pre- and during-treatment ECG may be considered for patients with cardiac vulnerability.

Ocular effects. With traditional antipsychotics, a dose-related corneal, conjunctival, and lenticular pigmentation and pigmentary retinopathy occur, but do not generally lead to severe visual disturbances.[40] With thioridazine, pigmentation of the retina has been noted on dosages exceeding 800 mg/day. A microscopic study of schizophrenia patients on long-term antipsychotics did not support a close relationship between corneal endothelial changes and antipsychotic use.[40] Anticholinergic effects may cause reversible vision changes. Patients with glaucoma are sensitive to anticholinergic effects and should avoid antipsychotics or any other agent with significant anticholinergic effects.

Lenticular changes have been noted with some atypical antipsychotics. For example, in chronic dog studies at 4 times the typical human dosage, evidence of lens opacities were noted with quetiapine; however, there were no specific associations with other species (e.g., rats, primates, etc.) or in several human studies. Although a substantial specific increased risk of cataracts with quetiapine appears unlikely, the Food and Drug Association (FDA) has encouraged the manufacturer to recommend routine eye examinations at the initiation of treatment and every 6 months.[41] As clinical experience with quetiapine increases, this recommendation may need to be reconsidered. Scattered punctate cortical lens opacities as well as conjunctivitis have been reported with carbamazepine, an anticonvulsant often used in psychiatry.[42]

Sexual functioning. Although sexual functioning declines with aging, sexuality is a vital part of life in the geriatric population.[1] Many medications, including antipsychotics, can adversely affect sexual functioning.[43] Other agents causing decreased sexual functioning include antidepressants, antihypertensives, cardiac medications, H_2 blockers, metoclopramide, anticonvulsants, opiates, alcohol, and tobacco—agents which geriatric patients frequently take.[1] Thus, because of high polypharmacy among this population, selecting an antipsychotic with a low potential for adverse sexual consequences should be considered. The rate of sexual dysfunction among patients taking an antipsychotic can be as high as 25%, depending on the agent.[1,44] Both sexes may experience decreased libido, thought to be due to increased circulating prolactin levels. Thioridazine, fluphenazine, and trifluoperazine have been associated with female anorgasmia. Antipsychotics with high anticholinergic potential and high α-adrenergic activity (i.e., chlorpromazine and thioridazine) have been associated with erectile dysfunction and ejaculatory impairment.[1]

Adverse Drug Interactions

The elderly are more susceptible to adverse drug reactions. It is estimated that approximately 11% to 22% of hospital admissions are related to adverse drug reactions.[45–47] In a nursing home population, the 2 most frequent organ systems affected by medications are the cardiovascular and central nervous systems. Antipsychotics cause the most adverse effects of any of the psychotropic medications and are second only to diuretics with respect to adverse drug reactions in general.[48]

Several factors contribute to the increased relevance of adverse drug interactions in the elderly. Geriatric patients often have coexisting physical illness, necessitating polypharmacy. Both drug-drug and drug-illness interactions are possible. With aging, homeostatic mechanisms such as postural control, orthostatic circulatory responses, thermoregulatory systems, visceral muscle function, and higher cognitive functions are more sensitive to environmental changes.[49] Elderly patients are also more sensitive to psychoactive medications, which can result in EPS, hypotension, cardiac effects, constipation, sedation, and confusion. Further, agents that decrease renal clearance may lead to an increase in drug concentrations. Pharmacodynamic changes also promote sensitivity to medications. For ex-

ample, oversedation can be misinterpreted as depression because of social withdrawal and apathy. The sedation may be due to a highly sedating drug or an additive effect from multiple agents.[50] Analgesics or anxiolytics given concomitantly may also exacerbate sedation from an antipsychotic.

Regulatory Issues—OBRA 87

Prior to the introduction of the OBRA guidelines in the United States, antipsychotic medications were extensively used in institutionalized elderly patients. The overutilization was not limited to the United States; Barton and Hurst in the United Kingdom reported a "high use of unnecessary tranquilizers," noting that approximately 80% of demented patients were so medicated.[51] Because of the perception that antipsychotic use in nursing homes was excessive and unregulated, consumer groups in the United States influenced Congress to investigate the situation.[6] Congress called on the Institute of Medicine for the investigation and, thus, set into motion the process that lead to the introduction of OBRA. Their report addressed a number of quality-of-care issues for nursing home facilities.[52] To implement OBRA and the Nursing Home Reform Amendments, Congress, through the Health Care Financing Administration (HCFA), developed guidelines that applied to all Medicaid- and Medicare-certified nursing homes.[53,54] The government developed specific standards for allowable dosages for individual drugs in regular and p.r.n. use, required dose-reduction trials, and encouraged the use of sedative-hypnotics rather than neuroleptic drugs. These regulations restricted the use of psychotropic agents to situations for which there were definite diagnostic indications, with the objective of preventing overmedication and iatrogenic psychotropic-related medical morbidity.[55] Table 3 briefly describes the OBRA 87 guidelines for antipsychotic use in nursing home facilities that are currently in effect.

Since the implementation of OBRA 87, numerous studies have recorded the change in prescribing patterns[56–59]; predictably, the use of antipsychotics has declined. Despite the plethora of studies investigating the impact of OBRA, there have been no broad investigations of the effects of the new psychotropics in the frail elderly population. Because of the ever increasing use of atypical antipsychotics, stemming from their greater safety and tolerability, such studies are needed to bring OBRA regulations into harmony with current medical and clinical practice.[59]

Pharmacoeconomics

Pharmacoeconomic studies in younger patients with diagnoses of schizophrenia and bipolar disorder have demonstrated that clozapine- and risperidone-treated patients use fewer medical resources.[60,61] These savings in hospital and clinic expenses have resulted in lower overall costs. Studies with olanzapine and quetiapine are ongoing but suggest a similar pattern of reduced medical service utilization.[62,63] In some studies, societal costs from loss of productivity and quality-of-life issues are considered and the savings are even greater. For elderly patients residing in the community or nursing home facilities, economic data regarding typical versus atypical antipsychotics are scarce. However, economic data reflecting the effects of antipsychotic use for treating behavioral consequences of illnesses are available.

Many elderly patients are on a limited income, and the costs of the new agents may be prohibitive and thus contribute to noncompliance. Similarly, Medicare and health maintenance organization (HMO) regulations may place yearly caps on reimbursable drug costs. Having to cover a few expensive medications could mean an entire budget would be spent in a few months since drug costs for Medicaid-eligible patients residing in nursing homes are covered by the Medicaid program.

Although quality-of-life issues are difficult to assess, studies are needed to investigate all of the pharmacoeconomic issues of antipsychotic use in the elderly.

Table 3. OBRA-87 Guidelines for Antipsychotic Use[a]

- Patient's Clinical Record Must Document One or More "Specific Conditions"
  - Primary Psychosis
    - Schizophrenia
    - Schizoaffective disorder
    - Delusional disorder
    - Psychotic mood disorder
    - Acute psychotic episodes
    - Brief reactive psychosis
    - Schizophreniform disorder
    - Atypical psychosis
    - Tourette's disorder
    - Huntington's disease
  - Psychosis or Agitation in an Organic Condition
    - Document quantitatively
    - Document objectively
    - Not due to preventable reason
    - Resident is danger to self or others
    - Continuous crying, yelling, screaming functionally impairing patient
    - Psychotic symptoms cause distress or functional impairment
  - Medical Reasons (limited to 7 days)
    - Nausea
    - Hiccups
    - Vomiting
    - Pruritus
- Cannot Be Used for Indications Below
  - Wandering
  - Poor self-care
  - Restlessness
  - Memory impairment
  - Anxiety
  - Depression (no psychosis)
  - Insomnia
  - Unsociability
  - Indifference to surroundings
  - Fidgeting
  - Nervousness
  - Uncooperativeness
  - Agitation NOT causing danger to self/others

[a]Adapted from Stoudemire and Smith,[55] with permission.

COMPARISON OF CONVENTIONAL AND ATYPICAL ANTIPSYCHOTICS

Conventional antipsychotics or "neuroleptics" were the first truly effective treatments for controlling psychotic symptomatology. They revolutionized the management of psychotic disorders when introduced in the 1950s. Unfortunately, their use was marked by several shortcomings, including limited efficacy in treating the negative and cognitive symptoms of schizophrenia and the development of significant EPS, TD, and a host of other side effects. Elderly patients are particularly susceptible to many of their associated adverse effects, including hypotension, peripheral and central anticholinergic toxicity, cardiac arrhythmias, sedation, EPS, and TD. Whereas low-potency conventional antipsychotics such as chlorpromazine and thioridazine are less likely than high-potency agents such as haloperidol and fluphenazine to cause EPS, they are more likely to cause sedation, hypotension, and anticholinergic toxicity (manifested by constipation, urinary retention, cognitive impairment, confusion). Both groups of conventional antipsychotics are associated with a similarly high risk of TD. Thus, in elderly patients, thioridazine and haloperidol (the 2 conventional antipsychotics most commonly prescribed) are both associated with unique sets of problems.

How is the newer class of atypical antipsychotics different? The fundamental characteristic that distinguishes atypical from conventional antipsychotics is that the atypicals are at least as effective as conventional antipsychotics in treating psychotic symptomatology but have a significantly lower propensity to cause EPS. This benefit of EPS reduction extends far beyond the absence of rigidity, tremor, dystonia, and akathisia; in fact, EPS reduction is associated with a notable cognitive benefit, a mood advantage, and a reduced risk of TD.

Cognitive impairment is a cardinal feature of dementia, and often accompanies psychotic disorders, including schizophrenia.[64] Antipsychotics have only minor effects on most aspects of cognition in the context of treating psychotic disorders.[65] There is some beneficial effect of antipsychotic treatment on measures of attention and distractibility associated with reduction in psychotic symptomatology.[66] This improvement in attention is associated with a broad, although modest, improvement in a number of neuropsychological measures. EPS, on the other hand, results in a slower response in certain timed neuropsychological tests and adversely impacts aspects of cognitive function. Of greater significance, anticholinergic activity (either intrinsic to the antipsychotic agent or due to the addition of an anticholinergic antiparkinsonian agent such as trihexyphenidyl or benztropine to treat EPS) adversely affects memory, learning, and other cognitive functions.[67,68] Since atypical agents are less likely than conventional antipsychotics to cause EPS or require the addition of adjunctive anticholinergics, modest cognitive advantages are expected. In fact, several studies suggest that atypical antipsychotics have a small but better effect on cognitive function than conventional antipsychotics in psychotic patients.[69,70]

Early expression of EPS significantly increases the likelihood of subsequently developing TD.[71] Further, both EPS and TD add to the stigma associated with psychotic disorders, are disfiguring, and may hasten the patient's decline in social functioning. The lower propensity of atypical antipsychotics to cause EPS is predicted to result in a lower risk of TD; in fact, clozapine is not associated with TD, and preliminary findings with risperidone and olanzapine also suggest they have a substantially lower risk of TD compared with the older neuroleptics.[33,72,73] Given the exceptionally low rate of EPS with quetiapine, it too is predicted to have a favorable TD profile.

For patients in whom EPS are a major concern, these side effects can be significantly reduced or completely eliminated with the newer atypical drugs. This EPS advantage has many potential ramifications for patients, including improvement in negative symptoms, less cognitive impairment, better mood, fewer motor problems, better compliance, and reduced risk of TD.

It should be emphasized that while atypical antipsychotics share these clinical attributes, there are also substantial clinical differences between them, particularly with regard to their adverse effect profiles (Table 2). Given the unique drug profiles with respect to side effects, it may be possible to tailor treatment to a patient's individual needs. Further refinement of our understanding of the clinical utility of these drugs awaits their widespread use in mainstream clinical settings. Controlled studies comparing them to one another should be of particular interest.

CLINICAL TRIALS OF ANTIPSYCHOTIC MEDICATIONS IN THE ELDERLY

When we critically review the clinical trials conducted in elderly patients, a number of questions need to be considered:

1. While antipsychotics are widely used in the elderly, how effective and safe are they?[59,74–79]
2. How extensive is the scientific database about the use of these agents in the elderly?
3. How do patients with various psychotic disorders and dementia respond?
4. What symptoms respond best to antipsychotics in dementia and other psychiatric disorders?
5. How well are these agents tolerated in elderly patients?
6. Are there differences in the efficacy and tolerability among antipsychotic agents?

Conventional antipsychotics have undergone more studies than any other group of agents for managing be-

havioral disturbances in dementia. However, despite the relatively large number of scientific publications, few of the reports have been from controlled studies. Many are case reports or case series. Several studies lack randomization, placebo control, or blinding of investigators. Given the tendency toward high rates of placebo response, findings without the benefit of placebo are difficult to interpret. Further, many studies used poor assessment methods or included subjects with widely varying diagnoses. Since many of these studies were conducted in inpatient settings, generalizing findings to other settings could be problematic.

Studies of Conventional Antipsychotics

There have been multiple reviews based on studies of the use of conventional antipsychotics in elderly patients with psychosis or dementia.[80–85] Sunderland and Silver[81] reviewed 34 published studies and noted that 60% demonstrated a positive clinical response to neuroleptics. Only 6.6% of patients in these studies discontinued antipsychotics due to intolerable side effects. Common side effects included sedation, orthostasis, EPS, and anticholinergic symptoms. The authors concluded that antipsychotics are safe and effective in persons with dementia when used for specific purposes and at low doses. Helms concluded that while results of adequately designed studies are mixed, judicious use of antipsychotics in patients with behavioral disturbance and dementia may be justified[82]; in contrast, Devanand and colleagues reviewed 15 double-blind trials of conventional antipsychotics for treating behavioral disturbances of dementia and reported only limited evidence of efficacy.[86]

Schneider and coworkers conducted a meta-analysis of controlled trials that attempted to quantify the efficacy of conventional antipsychotics in the treatment of behavioral disturbances in dementia; they observed that neuroleptics were significantly more effective than placebo, but only approximately 18% of the dementia patients were better while taking antipsychotics compared with placebo.[80] In this analysis, studies comparing thioridazine or haloperidol to another antipsychotic did not demonstrate significant differences in efficacy. Patients who failed to complete the studies were not accounted for in this analysis, and side effects were not discussed.

Many studies have reported overall improvement but few, including the reviews, have characterized the types of symptoms that respond to antipsychotic treatment. Studies discussing the efficacy, safety, and tolerability of neuroleptics in the treatment of elderly patients are summarized in Table 4. Responsive symptoms seen in more than one study are also reported in Table 4. Additionally, safety and tolerability data from the studies are also summarized. For medications with only a small number of published studies, the most common effects reported in each study are listed. Negative studies are also included. This table does not take into account the efficacy of antipsychotics in treating psychosis associated with Parkinson's disease (see Juncos, this issue).[87] In the last column of Table 4, our opinion about the adequacy of data and its application to the use of the agent in the elderly is summarized.

As is evident from Table 4, psychotic symptoms and behavioral agitation were the symptoms generally found to be most responsive to neuroleptic treatment. The few studies that measured cognition by the MMSE did not demonstrate a change. Frequently reported adverse effects include orthostasis/hypotension, EPS/parkinsonism, falls, anticholinergic effects, and sedation. No conventional agent is generally found to be superior in efficacy to another, yet usually a difference of intensity of adverse effects is noted. In general, low-potency agents such as chlorpromazine and thioridazine are more likely to be associated with cardiovascular and anticholinergic side effects, whereas high-potency agents such as haloperidol are more likely to be associated with EPS. Based on a relatively better tolerability, high-potency neuroleptics such as haloperidol are generally the drugs of choice,[88] although low-potency agents such as thioridazine are sometimes preferred for their sedating effects and for patients highly susceptible to EPS.

Studies of Atypical Antipsychotics

Due to the more benign side effect profile of atypical antipsychotics, these agents would seem to be an attractive choice for treating psychotic disorders and dementia-related behavioral disturbances in the elderly. Currently 4 atypical agents are available for use in the United States: clozapine, risperidone, olanzapine, and quetiapine. As with conventional antipsychotics, few randomized, placebo-controlled studies have been conducted in older patients with the atypical agents. These studies are summarized in Table 5.

Clozapine. No placebo-controlled, randomized studies of clozapine in the treatment of behavioral disturbances in the elderly were found in the literature. Only 1 retrospective study focused on elderly dementia patients.[89] In this study, symptoms responsive to clozapine included antisocial behavior, irritability, social competence, and social interest.[89] Leukopenia was not reported (N = 18). Four (22%) of 18 patients discontinued clozapine due to delirium, somnolence, and restlessness. When all studies pertaining to the use of clozapine in the elderly are considered, most focus on primary psychotic illness. The primary responsive symptoms are reported to be psychosis, auditory hallucinations, irritability, antisocial behavior, violence, and self-care. The most common side effects are delirium, somnolence, orthostasis/falls, agranulocytosis/leukopenia, and cardiac effects. In different studies, differing percentages of patients were reported to be intolerant of clozapine. In a long-term study of clozapine in an elderly population, no patients discontinued clozapine because of side effects after the initial 6 months of treatment.[90] The

Table 4. Conventional Antipsychotics in the Elderly: Summary of Controlled Studies[a]

Agent	Efficacy	Responsive Symptoms	Safety/Tolerability	Summary
Chlorpromazine Terman, 1955[100] Robinson, 1959[101] Abse et al, 1960[102] Barton and Hurst, 1966[51] Howanitz et al, 1999[140]	None to moderate	"Manageability" Self-care Organization of thoughts/ speech Sleep	Hypotension Jaundice Drowsiness EPS Dizziness Gait disturbance	Modest efficacy Side effects limit use
Fluphenazine depot Raskind et al, 1979[104] Gottlieb et al, 1988[103]	Moderate	Not specified	EPS	Insufficient data
Haloperidol Sugarman et al, 1964[105] Tobin et al, 1970[106] Tsuang et al, 1971[110] Smith et al, 1974[107] Cowley and Glen, 1979[111] Rosen, 1979[112] Petrie et al, 1982[113] Steele et al, 1986[114] Devanand et al, 1989[108] Tune et al, 1991[84] Carlyle et al, 1993[109] Sultzer et al, 1997[115]	Moderate (similar to loxapine and thioridazine)	Hallucinations/delusions/ suspiciousness Restlessness/overactivity/ agitation Aggression/hostility/irritability Confusion/uncooperativeness/ anxiety/depression/lability	EPS Orthostasis Weight loss Drowsiness Unsteadiness	Moderate efficacy Side effects will limit use High EPS Low sedation
Loxapine Petrie et al, 1982[113] Barnes et al, 1982[116] Carlyle et al, 1993[109]	Moderate	Suspiciousness/hallucinations Excitement/thought disturbance/anxiety/lability/ uncooperativeness	Sedation EPS	Modest efficacy Moderate side effects
Thioridazine Jackson, 1961[117] Kral, 1961[118] Cavero, 1966[119] Lehmann and Ban, 1967[120] Tsuang et al, 1971[110] Birkett and Boltuch, 1972[121] Altman et al, 1973[122] Branchey et al, 1978[88] Cowley and Glen, 1979[111] Rosen, 1979[112] Barnes et al, 1982[116] Stotsky, 1984[123] Steele et al, 1986[114] Phanjoo and Link, 1990[124] Tune et al, 1991[84]	Moderate (equal to other antipsychotics)	Agitation/uncooperativeness/ confusion/anxiety/ depression/lability	Falls Orthostasis Drowsiness Body sweat early in treatment	Moderate efficacy Side effects may limit use Low EPS High sedation High anticholinergic side effects
Thiothixene Rada and Kellner, 1976[125] Finkel et al, 1995 [126]	None to moderate	Agitation Verbal agitation Evening physical aggression No effect on MMSE, ADL	Parkinsonism Sedation	Insufficient data Conflicting data
Trifluoperazine Hamilton and Bennett, 1962[127]	Moderate	Alertness/responsiveness	Lethargy EPS Edema	Insufficient data Side effects may limit use

[a]Abbreviations: ADL = activities of daily living, MMSE = Mini-Mental State Examination.

response rate in the maintenance phase of treatment was 93%. Patients with schizophrenia were found to need higher doses than patients with mood disorders; patients with organic psychoses required the smallest dose.[90]

Although clozapine is very effective in the treatment of psychoses and moderately effective in the management of behavioral disturbances in the elderly, adverse events are common and necessitate cautious use. Suggested starting doses are 6.25–12.5 mg/day, with a slow titration of 6.25–12.5 mg every 3 days. Patients must be closely monitored for usual and unusual side effects. For dementia patients, the dose is typically less than 100 mg/day (average of 41.1 mg in 1 study); patients with a primary psychotic disorder may need up to 400 mg/day.[89,91–94]

Risperidone. Many open-label and retrospective trials of the use of risperidone in the elderly have been published. However, there are only 2 double-blind, placebo-controlled studies.[95] In the first study, which compared risperidone, haloperidol, and placebo, improvements were noted with risperidone on the global psychopathology scale, psychosis subscale, aggression subscale and for paranoia and delusion items. Risperidone significantly decreased aggression compared with placebo, whereas haloperidol did not.

Table 5. Atypical Antipsychotics in the Elderly: Summary of Studies

Agent	Efficacy	Responsive Symptoms	Safety/Tolerability	Summary
Clozapine Oberholzer et al, 1992[89] Frankenburg and Kalunian, 1994[94] Chengappa et al, 1995[93] Pitner et al, 1995[92] Richards et al, 1996[90] Sajatovic et al, 1997[91] Shulman et al, 1997[129] Howanitz et al, 1999[140]	Moderate to marked	Delusions/auditory hallucinations Disruptive behavior/ violence	Delirium Somnolence Orthostasis/falls Agranulocytosis/leukopenia Cardiac effects Varied proportion of patient discontinuation rates due to side effects	Moderate-to-good efficacy Very low EPS Significant other side effects Begin at 6.25–12.5 mg/day Use low doses Titrate very slowly
Risperidone Reyntjens et al, 1988[130] Borison et al, 1994[97] Goldberg et al, 1995[131] Marciniak and Guay, 1995[132] Madhusoodanan et al, 1995[133] Gierz et al, 1996[134] Berman et al, 1996[135] Jeste et al, 1996[136] Sajatovic et al, 1996[96] Kopala et al, 1997[137] Madhusoodanan et al, 1997[138] Zarate et al, 1997[139] Katz et al, 1999[95]	Moderate to marked 1–2 mg produce significant improvement in psychotic subscales	General psychopathology Positive symptoms Negative symptoms Aggression/behavioral disturbance Perseverative vocalizations Paranoid/delusional ideation	Varied reports of adverse effects Few need to discontinue medication Sedation/EPS (up to 21%), dose related Dizziness/orthostasis	Moderate-to-good efficacy Greatest symptom reduction at 2 mg, but more side effects at this dose Recommended dose in dementia is 1 mg/day, but start at 0.25–0.5 mg/day
Olanzapine Satterlee et al, 1995[98] Street et al, 1998[99]	Mild to marked	None in 1 study Delusions/hallucinations Agitation/aggression	Somnolence and abnormal gait appear to be dose related No changes in laboratory values, vital signs No significant difference found between olanzapine and placebo for discontinuation rates	Conflicting findings Although moderate efficacy suggested more data needed 5–10 mg is best according to data (effect of 2.5 mg not known)
Quetiapine McManus et al, 1999[39]	Moderate	Psychosis Positive symptoms Negative symptoms	Somnolence Dizziness Orthostasis	Moderate efficacy although more data needed No fixed-dose studies Range in studies 25–800 mg/day Due to lower clearance, begin at 25 mg qd/bid Average dose 100–150 mg/day Because of low EPS, consider use in movement disorder patients

In the second study, 3 dosages of risperidone (0.5, 1, and 2 mg/day) were compared with placebo.[95] The 2-mg/day dose was most effective in reducing symptoms, but was associated with a higher dropout rate due to side effects and a greater incidence of adverse effects. The 1-mg/day treatment group had the best reduction in symptom severity and tolerability. A high placebo response rate was noted in BEHAVE-AD scores at 12 weeks, which was not significantly different from the 0.5- and 1-mg/day dose groups. Patients receiving 1 mg/day of risperidone additionally showed significant reduction in psychosis, paranoid/delusional ideation, and aggression. As shown in Table 5, a high percentage of patients with behavioral disturbances associated with dementia improved with risperidone therapy. Although a significant number of subjects experienced some adverse events, few needed to discontinue medications. The most common adverse effects were sedation, dizziness, orthostasis, agitation/restlessness, constipation, insomnia, and confusion. EPS was reported in up to 21% of elderly patients on mean doses of 2 to 4 mg/day.[95,96] Some improvement in cognition has been noted with risperidone.[32,97]

Olanzapine. Only 2 studies have investigated olanzapine in the elderly.[98,99] A double-blind, placebo-controlled study of patients with schizophrenia and patients with dementia of the Alzheimer's type (DAT) noted that olanzapine- and placebo-treated groups did not differ in efficacy.[98] The olanzapine dose ranged from 1–8 mg/day. There were no significant differences between the placebo and olanzapine groups in relation to tolerability and safety. It is not known if higher olanzapine dosages would have been more effective.[8]

The second study is a larger double-blind, placebo-controlled study in nursing home patients with severe

dementia and behavioral disturbances.[99] Patients (N = 206) received placebo or olanzapine at 5 mg, 10 mg, or 15 mg/day. Despite a high placebo-response rate (36%), patients receiving olanzapine 5 mg and 10 mg/day had a significantly higher response rate (65% and 57%, respectively), with significant improvements noted in measures of agitation, delusions, and hallucinations. No EPS were noted. Significant side effects included somnolence and abnormal gait, both of which were dose-related.[99] The recommended dose of olanzapine for elderly patients is 5–10 mg/day. A 2.5-mg dose has not been systematically studied.

Quetiapine. A 52-week, open-label study of quetiapine was conducted in 151 patients with psychosis due to a primary psychotic disorder or dementia; patients received 25–800 mg/day of quetiapine.[39] At the interim analysis at 3 months, quetiapine was equally effective in both primary psychotic illness and dementias. The mean dosages were 75 mg and 150 mg for idiopathic psychosis and organic psychosis, respectively. Positive and negative symptoms were reduced. Somnolence, dizziness, and postural hypotension were the most common adverse effects. No laboratory, ECG, or vital sign changes were noted. As measured both directly (clinical measures) and indirectly (low use of anticholinergic drugs), few patients reported any EPS. Based on the positive findings in this open-label study, further blinded and placebo controlled studies are warranted. A placebo- and haloperidol-controlled, multicenter trial in nursing home patients is underway to study the efficacy of quetiapine in controlling psychotic symptoms in long-term care settings.

Summary

Atypical antipsychotics appear to have a similar profile of efficacy and better tolerability than conventional antipsychotics in elderly patients. Although there is a marked paucity of controlled studies comparing conventional with atypical antipsychotics in this population, it appears that the expected benefits secondary to the EPS advantage of atypicals are borne out. Cognitive effects of these agents are not well defined, but are obviously important for patients already experiencing a cognitive decline; emerging data do indicate that atypical agents may be better than conventional antipsychotics from the standpoint of cognitive function. More double-blind studies need to be done, as well as head-to-head comparisons of the antipsychotics to resolve which agents are most efficacious and best tolerated in the elderly. When atypical antipsychotics are used, initial doses should be low, and titration should occur gradually. Vigilant monitoring for adverse effects must occur, both initially and long term.

CONCLUSIONS

The recent introduction of atypical antipsychotics warrants a reassessment of the optimal use of antipsychotics in the elderly. There are important differences between the young adult and the elderly with regard to pharmacology, clinical application, and regulatory aspects governing use of antipsychotic medications; consequently, lessons learned from clinical trials of these agents in the young are not readily extrapolated to the elderly. Antipsychotics are more difficult to use in the elderly, and a careful ongoing assessment of the trade-off between efficacy and adverse effects is essential. Some general guidelines for clinical use of antipsychotics in the elderly are summarized in Table 6.

Table 6. Guidelines for Using Antipsychotic Medications in the Elderly

Careful diagnostic evaluation
Clear delineation of target symptom
Careful review of systems and physical examination
Laboratory assessment of cardiac, hepatic, and renal functions
Preferentially use atypical antipsychotic because of generally better tolerability
Select agent principally based on adverse effect profile of agent and specific patient needs
Hypotension, sedation, EPS, and anticholinergic side effects should be avoided to extent possible
"Start low and go slow" in terms of dosing; generally use 25% of young adult dose
Watch very closely for adverse effects
Monitor risk-benefit in terms of efficacy and adverse effects on an ongoing basis

Before initiating antipsychotic treatment, a careful diagnostic evaluation and definition of specific target symptoms are necessary. Once these target symptoms are identified, they should be serially monitored during the course of antipsychotic treatment to see if treatment is beneficial and to what extent. The patient should undergo a thorough review of systems, clinical examination, and laboratory investigations of cardiac, renal, and hepatic functions along with other tests that may be indicated in the particular patient. Age-dependent changes in pharmacokinetics and tolerability of side effects need to be considered. Potential drug interactions must be factored into the decision-making process. The choice of antipsychotic is primarily based on likely adverse effects rather than efficacy. The adage of "start low and go slow" is appropriate, although there is considerable intersubject variation in optimal dose. Typically, the dose in the elderly should be approximately 25% of that in the young adult. Existing data, although limited, suggest that atypical antipsychotics are better tolerated than conventional agents, and consequently should be preferentially used. While atypical antipsychotics share many attributes, there are important differences between them as well that can guide choosing a particular agent for a particular patient. Monitoring of the effect of the antipsychotic in terms of the balance between efficacy and side effects on an ongoing basis is essential. Additional clinical trials comparing the various atypical and conventional antipsychotics for different clinical indications in the elderly are warranted.

Drug names: benztropine (Cogentin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane), metoclopramide (Reglan and others), olanzapine (Zyprexa), perphenazine (Trilafon), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine), trihexyphenidyl (Artane and others).

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