New Atypical Antipsychotics
Experience and Utility in the Elderly

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Summary

The atypical antipsychotics are a new class of agents with great promise for use in the elderly because of their reduced propensity to cause acute extrapyramidal adverse effects. Treatment of older patients with these agents, however, needs to take into consideration age-related changes in pharmacokinetics and the risks of drug-drug interactions. Additionally, current evidence of their efficacy in late-life psychoses is derived largely from case series and from the extrapolation of results obtained in studies of younger patients with schizophrenia. Controlled clinical studies of atypical antipsychotics in elderly patients are urgently needed.

Antipsychotic drugs are among the most frequently prescribed medications in elderly patients.[1,2] Both psychotic mood disorders and schizophrenia occur in the elderly and are indications for antipsychotic treatment.[3,4] The widespread use of these agents, however, largely reflects the exponential increase in the prevalence of dementia that occurs with advancing age.[5] Behavioural syndromes such as agitation, aggression and psychosis occur at some point in over 80% of patients with Alzheimer’s disease (AD).[6-10] When present, these syndromes are highly distressing to both patients and caregivers, and can be the ‘last straw’ leading to the institutionalisation of the patient.[9,11,12]

Currently, the classical antipsychotics remain the only established mode of pharmacotherapy for psychosis and agitation complicating dementia.[13-15] Estimates of the efficacy of classical antipsychotic drugs in the treatment of behavioural syndromes complicating dementia are, however, relatively modest. Only 8 randomised, parallel-group, placebo-controlled studies, comprising 285 patients who received classical antipsychotics for the treatment of behavioural symptoms associated with dementia,
have been reported. Four of these studies used methodologically adequate standardised outcome assessments. These 4 studies showed that antipsychotic treatment resulted in an average of only 46% of patients being categorised as moderate-to-marked responders, with a corresponding placebo response rate of 18%. In contrast, when classical antipsychotics are used in the acute treatment of schizophrenia, approximately 75% of patients demonstrate a moderate-to-marked response, with a placebo response rate of <25%.

The reduced antipsychotic response rate in patients with dementia might be explainable if, in the context of AD, psychosis and agitation are not associated with pathophysiological changes in dopaminergic neurotransmission. An increasing body of evidence suggests, however, that dopaminergic neurotransmission is involved in the pathogenesis of these syndromes. Alternatively, if the concentration-effect curve for antipsychotic effects on motor function was shifted to the left (i.e. signs of parkinsonism were increased at a given concentration of an antipsychotic agent) of the corresponding curve for effects on behavioural symptoms, antipsychotic-induced parkinsonism would interrupt therapeutic trials before effective antipsychotic dosages could be reached. A shift to the left is consistent with the observation of an age-related decline in brain dopamine levels. It is also consistent with several lines of clinical evidence suggesting that the elderly are more sensitive than middle-aged patients to the extrapyramidal adverse effects of classical antipsychotics.

Thus, Schneider et al. have noted that the dosages of antipsychotics used in studies of patients with dementia have been low compared with effective dosages in younger patients. In fact, the mean antipsychotic dosage for the 4 studies cited previously was 148mg chlorpromazine equivalents (CPZE) per day (range 66 to 262mg CPZE/day), compared with the usual effective dosage of ≥300mg CPZE/day in younger patients with schizophrenia. Moreover, even at these lower dosages, antipsychotic drug–induced parkinsonism occurs more often in elderly than in younger patients. Among elderly patients, those diagnosed with AD or with dementia with Lewy bodies appear to be particularly sensitive to developing antipsychotic drug–induced parkinsonism.

In contrast to younger patients, concerns about antipsychotic-induced parkinsonism in the elderly go beyond the issues of compliance or cosmetic considerations. Older patients with antipsychotic drug–induced parkinsonism have an increased risk of falls and urinary incontinence. There are additional concerns about the use of anticholinergic agents for the prevention or treatment of antipsychotic drug–induced parkinsonism, or the use of low potency antipsychotics with significant anticholinergic effects, in elderly patients. As a group, the elderly are more sensitive to the cognitive adverse effects, including delirium, that can result from the use of anticholinergic agents.

The elderly are also at greater risk for the development of tardive dyskinesia (TD) compared with younger patients. In elderly patients, the incidence of TD increases linearly with the total lifetime duration of antipsychotic drug treatment; the risk of TD is significantly increased after a total antipsychotic drug exposure of as little as 3 months. Nonetheless, after allowing for the contribution of the duration of antipsychotic drug treatment in elderly patients, neither age alone nor the diagnosis of an organic disorder (primarily AD) independently contributes to the risk of TD.

Clearly, elderly patients, and particularly those with dementia, have much to gain from the development of antipsychotic drugs with broader efficacy and a reduced propensity to induce extrapyramidal syndromes. In younger patients with schizophrenia, the advent of atypical antipsychotics with such properties has revolutionised treatment. In these patients, atypical agents have been demonstrated to have an equal or greater efficacy compared with the classical antipsychotics, provide a greater reduction in negative symptoms, and cause significantly lower rates of parkinsonian adverse effects and TD.

Psychiatrists and primary care physicians were quick to extrapolate from the observed benefits of