Role of Atypical Antipsychotics in the Treatment of Psychosis and Agitation Associated with Dementia

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Abstract

The drug treatment of elderly patients is challenging because of the various pharmacokinetic and pharmacodynamic changes associated with increasing age, and the frequent comorbid medical conditions found in and multiple concurrent medications used by this population.

Behavioural symptoms, such as agitation and psychosis, commonly occur with dementia. Until recently, conventional antipsychotics were the mainstay of treatment, but their use in geriatric patients is limited because of serious adverse events. Compared with conventional antipsychotic agents, risperidone, olanzapine and quetiapine appear to be generally well tolerated in the elderly population (the use of clozapine is limited by its adverse effects). However, only 1 large controlled trial of one of these atypical antipsychotics (risperidone) in the treatment of behavioural symptoms of dementia has been published. While data indicate that risperidone may be the drug of choice, head-to-head, double-blind, controlled, comparative studies assessing the efficacy, tolerability and pharmacoeconomics of atypical antipsychotics in patients exhibiting behavioural symptoms associated with dementia are warranted to clarify the most appropriate choice of treatment.

The most common behavioural symptoms of dementia include agitation and psychosis. Agitation may present as aggression, combativeness, shouting, hyperactivity and disinhibition. Psychotic symptoms include paranoia, delusions and hallucinations. Symptoms of agitation, aggression and wandering are seen in at least 75% of patients with Alzheimer’s-type dementia, and symptoms of frank psychosis...
occur at some point in the course of the illness in at least 50% of patients with Alzheimer’s disease.\textsuperscript{[1,2]} Furthermore, progression of the dementia syndrome may be more rapid in patients with psychosis.\textsuperscript{[3,4]} Behavioural symptoms often lead to institutionalisation and are the most frustrating symptoms for caregivers.

Until recently, conventional antipsychotic agents have been the mainstay of pharmacotherapy for behavioural symptoms of dementia.\textsuperscript{[5-7]} Results of a meta-analysis of controlled trials of antipsychotic treatment in dementia indicated that antipsychotics were significantly more effective than placebo.\textsuperscript{[8]} However, the use of conventional antipsychotics in geriatric patients is limited because of their serious adverse events. Older patients are more prone than younger patients to the extrapyramidal and anticholinergic adverse events of antipsychotic agents. The risk of acute extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) is about 50% in patients 65 years or older who are taking conventional antipsychotics.\textsuperscript{[9-11]}

In recent years, the introduction of atypical antipsychotics has provided new options in the treatment of behavioural disturbances associated with dementia. Whereas the conventional antipsychotics act by blocking dopamine D\textsubscript{2} receptors in the brain, the atypical antipsychotics act by binding to both serotonin (5-hydroxytryptamine; 5-HT) and dopamine receptors. Moreover, the greater affinity of the atypical agents for serotonin 5-HT\textsubscript{2}, rather than dopamine, receptors and, in the case of certain drugs such as olanzapine, the mesolimbic specificity of action, are thought to account for the lower incidence of EPS with these agents.\textsuperscript{[9-11]}

The atypical antipsychotics currently marketed in the US include clozapine, risperidone, olanzapine and quetiapine. These agents are also available in a number of other countries worldwide. Ziprasidone is still undergoing clinical trials in the US and Japan and is approved in Sweden, and there are no published reports regarding the use of this drug in patients with dementia.

In this article we review the published literature and selected poster presentations on the use of these atypical antipsychotics in the treatment of behavioural symptoms (psychosis and agitation) associated with dementia. Most of the published literature, with the exception of a recently published controlled trial of risperidone (see section 2), comprises nonblind trials, case reports and retrospective chart reviews. The inherent limitations of these studies should be considered when analysing the results and conclusions.

The receptor binding profiles and the pharmacokinetic properties and implications for the use of clozapine, risperidone, olanzapine and quetiapine in the geriatric population are presented in tables I and II.\textsuperscript{[12-16]}

1. Clozapine

Clozapine was the first atypical antipsychotic marketed in the US, in 1990. The advantage of clozapine is that it is associated with few EPS. Disadvantages of its use in the elderly include such adverse events as sedation, postural hypotension, elevated seizure potential, and the risk of agranulo-

![Table I. Receptor binding profiles of atypical antipsychotic agents. Symbols indicate the relative affinity of the agents for each receptor subtype (K\textsubscript{i} and IC\textsubscript{50} values will vary within the indicated range).\textsuperscript{[12-15]}](image-url)