

Introduction

Quetiapine: A 5-Year Update

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The treatment of schizophrenia changed in the 1950s with the discovery of conventional antipsychotics, such as chlorpromazine and haloperidol. In the ensuing decade, it became apparent that many patients would have an incomplete or partial response, with clinically significant positive symptoms remaining despite optimal dosing. It also became clear that typical antipsychotics were not effective against the most disabling aspects of schizophrenia, the negative symptoms and cognitive impairments. In addition, most patients would experience subjectively unpleasant and potentially disabling extrapyramidal side effects, including akathisia, dystonia, and parkinsonism. The extrapyramidal side effects often included negative symptoms, secondarily causing or further impairing motivation, drive, and emotional responsiveness.

The first of the atypical antipsychotics, clozapine, was patented in the 1960s and used in clinical trials in the 1960s and 1970s. Agranulocytosis, which occurred in 1% to 2% of patients taking clozapine, forced the removal of the drug from the market in 1975. It was reintroduced in 1990 for treatment-resistant schizophrenia because of continuing interest in this drug's pharmacologic effects and advancements in hematologic monitoring. Although many patients experience improvements in positive, negative, and cognitive symptoms with clozapine, its side effect profile, including the risk of potentially life-threatening side effects such as diabetes, seizures, agranulocytosis, myocarditis, and pancreatitis, has kept it from widespread use.

In the aftermath of clozapine's introduction, additional atypical antipsychotic drugs were developed and introduced throughout the world. Quetiapine was discovered in 1985 by scientists at AstraZeneca (formerly Zeneca) Pharmaceuticals who were searching for a drug that would have, like clozapine, enhanced efficacy, but with a better safety profile. Quetiapine was approved by the U.S. Food and Drug Administration (FDA) in September 1997 and is currently marketed to treat psychosis associated with schizophrenia in the United States, Canada, most of Europe, Japan, and 70 other countries. This supplement reviews the status of quetiapine 5 years after its approval by the FDA. Both published studies and preliminary results reported in abstracts and posters are summarized.

Charles B. Nemeroff, M.D., Ph.D., Becky Kinkead, Ph.D., and Jeffrey Goldstein, Ph.D., discuss preclinical studies, the pharmacokinetics of quetiapine, and issues of dosing. In animal models, the drug has a preclinical profile suggestive of antipsychotic efficacy with a very low tendency to cause extrapyramidal side effects. In clinical studies, the optimal dosing range for quetiapine was determined to be 150 to 750 mg/day, although recent usage patterns have gone above this range. Recent results suggest that once-daily dosing may be suitable for some patients.

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Henry A. Nasrallah, M.D., and Rajiv Tandon, M.D., summarize the results of clinical studies on the efficacy, safety, and tolerability of quetiapine in the treatment of psychotic symptoms in patients with schizophrenia. Antipsychotic efficacy for psychotic symptoms and potential beneficial effects on negative symptoms, cognition, mood, anxiety, and aggression have been reported in patients with schizophrenia. Furthermore, all studies have demonstrated the low propensity of quetiapine to produce extrapyramidal side effects or hyperprolactinemia.

The results of clinical studies on the use of quetiapine in elderly patients who have schizophrenia, Parkinson's disease with drug-induced psychosis, or Alzheimer's dementia with psychosis are highlighted by Pierre N. Tariot, M.D., and M. Saleem Ismail, M.D. Quetiapine is particularly advantageous in the treatment of these vulnerable elderly populations because its lack of anticholinergic activity does not exacerbate the symptoms of Alzheimer's dementia and its relatively low affinity for dopamine-2 (D_2) receptors appears to result in a decreased tendency to produce motor symptoms in patients with Parkinson's disease. Its propensity to cause fewer extrapyramidal side effects than conventional antipsychotics and its possible cognitive benefits make quetiapine a good agent for the treatment of psychotic symptoms in elderly patients.

Robert L. Findling, M.D., discusses the results of clinical studies on the use of quetiapine in children and adolescents with diverse psychiatric disorders. In studies with varying methodological rigor, quetiapine has shown good efficacy and tolerability in pediatric populations and has shown a low risk of weight gain and extrapyramidal side effects. Dr. Findling states that large-scale, prospective, randomized trials are lacking, and consequently, these results await confirmation from such clinical investigations.

The clinical use of quetiapine in disease states other than schizophrenia is reviewed by Adityanjee, M.D., and S. Charles Schulz, M.D. The most common psychiatric conditions have included mood and anxiety disorders, aggression, hostility, posttraumatic stress disorder, borderline personality disorder, delirium, and comorbid substance abuse. Considering its efficacy in a wide variety of neuropsychiatric conditions and its excellent tolerability profile, quetiapine could emerge as a broad-spectrum psychotropic medication that may be helpful in psychiatry across various diagnostic categories. Drs. Adityanjee and Schulz suggest that the clinical utility of quetiapine in psychiatric conditions other than schizophrenia has not been fully explored thus far.

In the evolution of treatments for schizophrenia and related psychotic disorders, quetiapine has proven to be one of the second generation of antipsychotic drugs and a bona fide atypical agent. Its pharmacology has aspects that are consistent with the atypical pharmacologic profile and, at the same time, novel and distinct in its low D_2 binding affinity and fast dissociation from the receptor. Similarly, its clinical applications are both as a first-line antipsychotic and as an agent uniquely suited to specific clinical indications. Quetiapine represents an important addition to the psychotropic pharmacopeia.