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Atypical Antipsychotics for Older Adults: Are They Safe and Effective As We Once Thought?

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Summary

The initial enthusiasm for atypical antipsychotics as being safe and effective for treating older adults with psychotic disorders has diminished. Despite multiple short-term double-blind trials, these drugs have not been approved by the FDA for the most common form of psychosis in this population – i.e., psychosis associated with dementia. On the contrary, these drugs have received FDA warnings for adverse cerebrovascular events and mortality in these patients. Our pragmatic clinical trial failed to show evidence of either safety or effectiveness of the four most commonly prescribed atypical antipsychotics in middle-aged and older patients with different psychotic disorders – schizophrenia as well as psychosis associated with mood disorders, dementia or PTSD. A reconsideration of the common use of these medications, especially off-label use, in older patients is warranted. Unfortunately, there are no evidence-based alternatives to these agents in the target population. Wider employment of psychosocial interventions, cautious and limited use of medications, shared decision making, and greater research on developing better treatments are the order of the day.

Keywords

Antipsychotics; Dementia; Psychosis; Cognitive Behavioral Therapy; Pragmatic Trials

Introduction

Psychotic disorders are serious mental illnesses at any age, including late life. Whereas schizophrenia and psychotic mood disorders are important causes of psychosis in younger adults, a much more common form of psychosis in older adults is that associated with dementia. Psychotic symptoms in older adults result in considerable distress for patients and their families, and lead to adverse outcomes such as decreased quality of life [1,2], impaired functioning [3], increased caregiver distress [4], greater risk for placement in long-term care facilities [5,6], and higher health care costs [7]. At present, atypical antipsychotic medications are commonly used, frequently off label, to treat psychosis in older adults. With the aging of the general population, numbers of older adults with psychiatric disorders including psychosis are growing rapidly [8]. Learning about the long-term safety and

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effectiveness of atypical antipsychotics to treat FDA-approved or off-label psychotic disorders in older adults has, therefore, become an important public health imperative. We recently conducted a pragmatic clinical trial of four commonly prescribed atypical antipsychotics in middle-aged and older adults with different types of psychotic disorders [9]. The results were sobering. Below, we review the background history of antipsychotics followed by a discussion of our study, and conclude with clinical recommendations for treating these patients.

Background

The first antipsychotic medication, chlorpromazine, was introduced in the early 1950s, dramatically changing the landscape for treatment of schizophrenia and other psychotic illnesses, making it possible for many individuals with these disorders to be treated outside of state hospitals. Frequently reported side effects associated with chlorpromazine and other first generation (“typical” or “conventional”) antipsychotics included parkinsonism, akathisia, dystonic reactions, and tardive dyskinesia, along with sedation, postural hypotension, and anticholinergic effects. The most serious of these was tardive dyskinesia because of its propensity for persistence and even irreversibility in some cases. The use of typical antipsychotics was especially problematic for older adults. Age-related pharmacokinetic and pharmacodynamic changes result in an increased risk for motor side-effects, falls, sedation, and metabolic disturbances [10–12]. Yet, there were no safe and effective alternatives to the typical antipsychotic agents for three decades.

Subsequent introduction of the second generation or “atypical”, antipsychotics, starting with the FDA approval of clozapine for treatment-resistant schizophrenia in 1989, followed by risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone has expanded the available therapeutic options for the treatment of psychosis. Because atypical antipsychotic medications were generally associated with a much lower risk for parkinsonism and tardive dyskinesia, they were widely hailed as safer alternatives to their “conventional” predecessors [13] and became the agents of choice, especially in older adults who are more sensitive to these side effects [14,15]. Currently atypical antipsychotic medications have been approved by the FDA primarily for treatment of schizophrenia and bipolar disorder.

Atypical antipsychotics have also come to be widely used “off label” in the treatment of psychosis related to a variety of other psychiatric diagnoses [16] including dementia and post-traumatic stress disorder (PTSD) [10,11,14]. This is due, in part, to the frequently severe nature of these symptoms and their adverse effects on the patients and their families along with a lack of safe and effective pharmacological alternatives to treat psychosis. During the past decade, numerous studies have documented an elevated risk of metabolic side effects of atypical antipsychotics in youth and in younger adults [12]. A number of short-term double-blind controlled trials of risperidone, olanzapine, quetiapine, and aripiprazole have been conducted in older dementia patients with psychosis or agitation. Combining data from these trials, the FDA issued warnings regarding increased risk for cerebrovascular adverse events (strokes and transient ischemic attacks) and mortality in older patients with dementia treated with atypical antipsychotics. Consequently, there is a

clinical dilemma regarding the use of atypical antipsychotics in older adults, especially their off label use.

Safety and effectiveness of atypical antipsychotics in older adults

We recently compared the safety and effectiveness of four most commonly prescribed atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in a group of 332 outpatients over the age of 40 years, with psychotic symptoms related to schizophrenia, mood disorders, PTSD, or dementia, over 2 years or treatment [9]. The study, funded by the National Institute of Mental Health, employed a pragmatic trial design including an equipoise-stratified randomization strategy in which the patient and his/her treating clinician could exclude one or two of the four study medications because of past experience or anticipated risks. As long as the participants had at least two medications on their acceptable list (equipoise stratum), they were randomized with equal probability to one of them. This design has the advantages allowing for randomization and, therefore, direct comparison of different medications, while closely mimicking clinical practice in which treating clinicians exclude consideration of some drugs because of their potential for side effects or poor efficacy in a given patient. (In a trial with traditional randomization, each subject must agree to be randomized to *any* of the study medications; otherwise, s/he would have to refuse participation.) In our study only 16.6% of the participants agreed to be randomized to all 4 medications; therefore 83.4% of the patients would probably not have participated if we had employed traditional randomization, thereby markedly reducing generalizability of the results. Thirty-nine percent of the participants had a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder whereas 61% had other diagnoses - i.e., psychosis associated with PTSD, depression, or dementia) for which these drugs are not approved by the FDA. To mimic clinical practice and to give each medication the maximum chance to succeed in an individual patient, we asked each patient's treating clinician to choose the dose of the randomized drug, to change the dose any time, and to discontinue the agent as and when needed. There was no placebo group.

The results were disappointing. Over half of the participants discontinued their assigned antipsychotic medication within 6 months, with a median time of only 26 weeks to discontinuation. The two most common reasons for discontinuation were side effects (51.6%) followed by a lack of efficacy (26%). A majority of these patients were switched by their treating clinician to another atypical antipsychotic, suggesting that the randomized drug had not been helpful and that a different drug was needed. The cumulative one-year incidence of metabolic syndrome among those who did not meet criteria for it at baseline was 36.5%. Overall, the rates of serious adverse events such as hospitalizations, deaths, and emergency room visits for life threatening conditions were also high (23.7%) as were the rates of non-serious adverse events (50.8%). Age was a significant risk factor for the development of all of these categories of side effects whereas diagnosis was not. Quetiapine had to be discontinued midway through the trial because the incidence of serious adverse events was twice that with other atypical antipsychotics [17]. There was no significant improvement in psychopathology as measured by the Brief Psychiatric Rating Scale [9].

Thus the overall results of our study suggested that the commonly used atypical antipsychotics were neither safe nor effective in the treatment of psychotic disorders in middle-aged and older adults. This finding is similar to that of several recent shorter-term studies comparing the use of atypical antipsychotics with placebo for the treatment of psychosis related to Alzheimer's disease, suggesting that the adverse events with these drugs tend to offset any clinical benefit from the use of the atypical antipsychotics in this population [18].

Alternative Treatment Options

There are no FDA-approved treatments for psychosis associated with PTSD or dementia. Several psychosocial interventions have been used to treat middle-aged and older patients with psychosis in combination with antipsychotic medications. In older adults with schizophrenia for example, in whom positive symptoms (which tend to be most responsive to antipsychotic medications) have become less severe over time, manualized interventions targeting everyday functioning (arguably a more important outcome for many patients with schizophrenia) are now available. There has been considerable interest in using psychosocial interventions for behavioral disturbances associated with dementia in older adults. Studies suggest that one-to-one social interaction, support groups, simulated family presence, music therapy, dance therapy, aromatherapy, bed baths, person-centered bathing, and muscle relaxation therapy could be potentially useful, although many of these trials are limited by small sample sizes, lack of appropriate control groups, and suboptimal outcome measures. More research is clearly needed in this area including better-powered, well designed randomized controlled trials [19]. Notably, placebo-controlled trials of pharmacological interventions for behavioral symptoms in dementia typically have a high placebo response rate (30%–50%), suggesting that some patients seem to benefit from the increased attention and better care they receive as a result of participating in a research study [19,20].

At present, given the lack of safe and effective evidence-supported pharmacological alternatives, atypical antipsychotics will continue to have a limited role in the treatment of some patients with psychosis in older adults, particularly when the symptoms are severe (with potential for harm to self or others) requiring aggressive treatment. However, these drugs may not be effective or safe for many older patients. Wider employment of psychosocial interventions, cautious and limited use of medications, shared decision making, and greater research on developing better treatments are the order of the day.

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