

Treatment of Older Patients with Schizophrenia

In contrast to the large number of studies in younger adults with schizophrenia, there have been only a handful of well controlled, large-scale double-blind trials of the effects of antipsychotic medication on elderly patients with schizophrenia. Hence, one has to rely on studies in middle-aged adults with schizophrenia as well as those in elderly dementia patients with psychosis in order to make recommendations for treating elderly patients with schizophrenia. The term “elderly” refers to people aged 65 and older. As the data on the treatment of schizophrenia patients in that age group are very limited, the term “older” is used here to refer to middle-aged (45-64 years) and elderly (≥ 65 years) patients.

It will be useful to briefly describe the nosology of schizophrenia in late life. Of the middle-aged and elderly patients, approximately 20% have late-onset schizophrenia – with onset of illness in the fifth, sixth, or seventh decade of life. (Onset during or after the eighth decade is more aptly called “Very Late-Onset Schizophrenia-like Psychosis”). Thus, a majority of older patients with schizophrenia are those with early-onset schizophrenia, and have had a very long duration of illness. The course of schizophrenia in late life varies considerably. While a small minority experiences complete or nearly complete remission of symptoms, and a small minority worsens to the level of dementia, a majority of the patients have a relatively stable course, with significant improvement in positive symptoms (8). The rate of aging-associated cognitive decline in older schizophrenia patients living in the community is similar to that in age-comparable normal individuals. (Of course, patients with schizophrenia generally start out with a greater degree of cognitive deficits than normal subjects.) In contrast to younger adults, illicit substance use disorders are less of a problem than physical comorbidity in older patients with schizophrenia. Late-onset schizophrenia is more common in women, is generally of paranoid subtype, and is associated with less severe negative symptoms as well as less severe cognitive impairment than early-onset schizophrenia.

As in younger adults, antipsychotics form the backbone of treatment of older patients with schizophrenia. Until the introduction of the atypical antipsychotic medications, the primary pharmacologic treatment for schizophrenia in the elderly involved the use of conventional neuroleptics. Although there is a dearth of literature on the effects of conventional neuroleptics in elderly patients, these drugs were shown to be at least moderately effective in the management of psychotic patients (6). Several important considerations now limit the use of conventional neuroleptics in the elderly. These agents carry a significant risk of undesirable side effects, particularly extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). The risk of EPS is higher in elderly patients than in younger adults. Furthermore, the cumulative annual incidence of TD with conventional neuroleptics has been found to be higher by six fold-- i.e., about 30% (4)--in later life.

Other side effects of particular concern in elderly patients include sedation, anticholinergic effects, and postural hypotension.

The atypical antipsychotic medications such as risperidone, olanzapine, and quetiapine have become the treatments of choice for schizophrenia in older patients, due to a lower risk of both EPS and TD. Available data support the use of risperidone or olanzapine as a first-line pharmacologic treatment for schizophrenia and related disorders in older patients (7). Olanzapine has also demonstrated overall efficacy and tolerability in

geriatric schizophrenia patients at an average daily dose of 12.4 mg (Street et al., 2000b). In the only large-scale, double-blind comparative study of atypical antipsychotics in elderly patients with schizophrenia, risperidone at a mean dose of 2 mg/day was found to be as effective as olanzapine at a mean dose of 10 mg/day (3). Both the drugs produced significant improvement in psychopathology from baseline. The incidence of EPS was low in both the groups in this 8-week trial. There were no significant differences between the two drugs in therapeutic or adverse effects except that clinically significant weight gain (greater than 7% of baseline weight) occurred in 14% of olanzapine-treated patients compared to 5% of risperidone-treated patients ($p < .05$). The published data on clozapine and quetiapine in this population are limited to open label studies (10). No large-scale studies of ziprasidone or aripiprazole in elderly patients with schizophrenia have yet been published.

While the atypical agents are generally well tolerated by older individuals, recommended dose ranges are considerably lower than for younger patients. Dose titration should also be carried out more gradually in older patients. For patients with late-onset schizophrenia, the dose is lower than that in similarly aged early-onset patients. The starting dose in late-onset patients should generally be one-quarter to one-half of the usual adult starting dose; for patients with very-late-onset schizophrenia-like psychosis, even lower doses may be effective. There are several factors related to a need for low doses in older patients. These include aging-associated liver and kidney damage leading to pharmacokinetic changes, degenerative brain changes resulting in pharmacodynamic alterations, and reduced level of psychopathology possibly secondary to reduced dopaminergic activity.

Since the introduction of the atypical antipsychotics, a frequent dilemma facing clinicians involves whether and how best to switch patients from a conventional to an atypical agent. Because of the high risk of relapse when antipsychotic drugs are withdrawn, the dose of the conventional neuroleptic should be slowly titrated down while the atypical is slowly titrated up (7). The lowest effective maintenance dose should be used once the patient is clinically stable.

Side effects of atypical antipsychotic medications that occur with clinically significant frequency include sedation (particularly with clozapine, olanzapine, and quetiapine), orthostatic hypotension, and, at higher dose ranges, EPS (especially with risperidone). The risk of developing TD is likely to be much lower for patients taking atypical antipsychotics than for patients taking typical antipsychotic medications. In one study, Jeste et al. (5) found that the cumulative annual incidence of TD in older patients was five times lower with risperidone than with haloperidol; the average doses of both the drugs in this flexible-dose study were 1 mg/day. In a recent trial, Dolder and Jeste (1) reported that the incidence of definitive TD in a very high-risk population (older patients with borderline TD at baseline) was significantly lower with atypical (risperidone, olanzapine, or quetiapine) compared to typical antipsychotics. The long-term side effects that are of increasing concern with the atypical agents in older patients include weight gain and new onset diabetes mellitus, especially with clozapine and olanzapine.

A number of other, non-antipsychotic pharmacologic options have been used with varying success in older patients with psychosis, although there are no published controlled studies. Such agents include antidepressants such as citalopram, trazodone, and sertraline; mood stabilizers such as valproic acid and carbamazepine; and anxiolytics

such as benzodiazepines and buspirone. Further research will be needed to clarify the potential roles of these treatments in the management of older patients with schizophrenia.

Nonpharmacologic Treatment

Nonpharmacologic treatment for schizophrenia is also indicated in a majority of cases. Recent work has evaluated the benefits of a novel, integrated Cognitive Behavioral, Social Skills Training (CBSST) intervention in groups of older patients with primarily early-onset schizophrenia (2). As the name suggests, CBSST combines the Social Skills Training (SST) elements of problem-solving and role-playing with the Cognitive Behavior Therapy (CBT) techniques of thought identification and challenging. Results of a small, randomized controlled pilot study comparing CBSST plus pharmacotherapy to pharmacotherapy alone demonstrated the feasibility of the regimen, acceptability by patients, and psychopathological improvement with CBSST in older patients with schizophrenia (2). Another pilot study showed the usefulness of Functional Adaptation Skills Training (9) in improving daily functioning in older patients with schizophrenia.

Treatment Algorithm

The published controlled data on the treatment of elderly patients with schizophrenia are very limited. Hence, it is not possible to present a definitive treatment algorithm. One may, however, make some recommendations based on the available information.

- A. Choice of Class of Antipsychotics: Atypical antipsychotics are to be preferred to conventional ones given the high risk of EPS and TD in older persons. One exception to this rule is a patient who has been on a conventional neuroleptic for many years, is stable, does not have distressing side effects, and does not wish to risk switching to another antipsychotic.
- B. Choice of Specific Atypical Antipsychotic: The only comparative study of atypical antipsychotics in elderly patients suggests that risperidone and olanzapine are comparable in their therapeutic efficacy and most side effects (except for greater weight gain with olanzapine). There are no published large-scale data on the other agents in this population. Clozapine should be used in patients who are resistant to other atypical antipsychotics.
- C. Dosing: All the atypical agents need to be used in much lower doses in older patients. The recommended doses for elderly patients are as follows:

<u>Drug</u>	<u>Initial(mg/day)</u>	<u>Maintenance(mg/day)</u>
Risperidone	0.5-1	1.5-3
Olanzapine	5-7.5	10-15
Quetiapine	25-50	100-250
Clozapine	12.5	75-200

- D. Treatment Trials: The length of treatment trial in an elderly patient should be longer (6-10 weeks) than in a younger adult, with slower dose increase.

- E. Switching Medications: Switching antipsychotics should be done gradually and over a much longer period than in younger adults (barring life-threatening adverse events). Generally, the dose should be reduced by no more than 25% at a time, with further dose reductions staggered over a period of several weeks. During the time of dose reduction of an older drug, the new drug should be started at a low dose and increased slowly.

Addition of other psychotropic drugs: If the patient has significant depressive symptoms, an antidepressant may be added. No comparative trials of antidepressants in this population have yet been published, but citalopram has been found to be useful and relatively safe in small studies of older psychotic patients.

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