

The Treatment of Psychosis in Late Life

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The authors emphasize the need for careful differential diagnosis when symptoms of psychosis arise in patients over the age of 65 years. Prevalence of psychotic disorders in the elderly ranges from 0.2%–4.7% in community-based samples to 10% in a nursing home population and as high as 63% in a study of Alzheimer's patients. Risk factors associated with the development of psychotic symptoms and common causes of delirium are reviewed. Because age-related changes affect the pharmacokinetics of neuroleptics, the authors' treatment recommendations, which include the use of traditional and novel antipsychotics, take into account the higher risk of side effects in the elderly.

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Psychotic symptoms can be found throughout the life cycle. Psychosis as defined by DSM-IV is restricted to "delusions or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature."¹ In this paper, we attempt to look at psychotic symptoms that arise in persons over the age of 65 years, how these symptoms are diagnosed and treated, and the side effects that arise from said treatments.

Kraepelin first coined the term *paraphrenia* to describe patients with a schizophrenic-like illness that developed after the age of 40.² Roth in 1955 modified the term to describe patients admitted to the hospital over the age of 65 who were diagnosed with delusions with or without auditory hallucinations.³ The following diagnoses are found in the literature to refer to psychotic symptoms that arise for the first time in patients over 65: late onset schizophrenia, late onset psychotic disorder, delusional disorders, dementia with psychotic symptoms, and psychotic disorders not otherwise specified.

EPIDEMIOLOGY

Geriatric data from the Epidemiologic Catchment Area study showed a 6-month prevalence for schizophrenia and schizophreniform disorders ranging from 0.2% to 0.9% at three sites; cognitive impairment including organic psy-

choses ranged from 16.8% to 23%.⁴ Grief and Eastwood⁵ found that 12% of all the cases reviewed of patients in different hospital settings diagnosed with psychotic symptoms met ICD-9 criteria for a paranoid diagnosis. Junginger et al.⁶ reported the prevalence of psychotic disorders to be 10% in a nursing home population diagnosed using the Structural Clinical Interview for DSM-III-R (SCID). In a community-based sample in Sweden, Skoog et al.⁷ found the prevalence of psychotic disorders to be 4.7%. Leuchter and Spar⁸ reported a prevalence of 8% in a retrospective study of patients admitted to a geropsychiatry unit. A study done by Ballard et al.⁹ found that, of 124 patients previously diagnosed with dementia, 67% had at least one psychotic symptom. In a study of 57 patients with Alzheimer's disease, Kotrla¹⁰ found that 63% developed psychotic symptoms.

RISK FACTORS

The risk factors that are described as being associated with the development of psychotic symptoms include the following: being cognitively impaired,^{4,11,12} having hearing or visual impairment, early life trauma or abuse,¹³ being female, single or never married, bedfast status,¹¹ and having a premorbid personality of paranoid or schizoid traits (Table 1).^{14,15} Furthermore, Roth¹⁶ in a review of the literature found that late-onset schizophrenia was frequently associated with long-standing severe bilateral deafness, most often caused by middle ear disease and cognitive impairment.

NEUROBIOLOGY OF LATE-LIFE PSYCHOSES

Brain structure abnormalities have been reported to be associated with psychotic symptoms in the elderly. Brown, in a review of the literature,¹⁷ reports that structural changes have included white matter hyperintensities,

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Table 1. Risk Factors Associated with Late-Onset Psychosis

Cognitive impairment
Hearing impairment
Visual impairment
Early life trauma or abuse
Female gender
Single or never married
Bedfast status
Premorbid paranoid personality
Premorbid schizoid personality

as assessed by magnetic resonance imaging of the brain, and focal brain disease of vascular origin. Flint et al.,¹⁸ in a study of 21 subjects with paraphrenia, found that 5 subjects showed evidence of clinically unsuspected cerebral infarctions. Most of the lesions were subcortical or in the frontal lobes. This was felt to be consistent with lesions affecting limbic and subcortical pathways in the genesis of psychosis. Lesser et al.¹⁹ found that two thirds of the subjects with late-onset psychotic disorders had abnormal brain imaging studies, and 50% of the subjects had white matter lesions greater than 5 cm² and/or lacunar infarctions. Miller et al.²⁰ found that when compared to healthy elderly subjects patients who developed their psychotic symptoms after the age of 45 were more likely to have cortical and subcortical white matter lesions and performed more poorly on neuropsychological tests, particularly on frontal lobe and memory abilities. Others report that functional studies show frontal and medial temporal lobe dysfunction.¹⁷ Almeida et al.²¹ found that late-life paraphrenics were more likely than controls to exhibit soft signs on neurologic examination.

DIFFERENTIAL DIAGNOSIS (FIGURE 1)

When older patients present with new onset psychotic disorders, it is essential that the patient be evaluated for possible reversible causes of their symptoms. A thorough psychiatric history should be obtained to determine if this is truly a new onset psychotic disorder. One should assess the patients for the presence of any other psychiatric illness currently or in the past, for example, the presence of a mood disorder or cognitive disorder.²² Patients should be evaluated for the presence of organic causes of their symptoms.

Delirium presents with acute mental status changes, which can be accompanied by psychotic symptoms. These may consist of hallucinations often of the visual type, and frequently with paranoid delusions. Common causes of delirium in the elderly include infections, especially urinary tract and upper respiratory; drugs, especially anticholinergics; electrolyte imbalance; arrhythmias and myocardial infarctions.²² One should also evaluate for the presence of transient ischemic attacks, cerebral vascular accidents, and structural brain lesions such as tumors

or subdural hematomas. Critically important in delirium is to evaluate the patient's medications as well as to look for the presence of withdrawal symptoms both from prescribed medications such as benzodiazepines and substances of potential abuse such as alcohol.

TREATMENT OF PSYCHOSIS

The Omnibus Budget Reconciliation Act (OBRA 1987)²³ regulates the prescribing of neuroleptics in the nursing home. Prescribing recommendations include: (1) patients should be free of unnecessary drugs; (2) they should not be prescribed an antipsychotic unless a specific condition is documented; (3) attempts at dose reductions should be made every 6 months; (4) there should be drug holidays when possible; (5) behavioral programming should exist as an alternative. Prior to the implementation of OBRA, about 50% of nursing home residents were receiving neuroleptics.²⁴ Harrington²⁵ in a review of the literature found that, prior to the implementation of OBRA, the percentage of nursing home residents on antipsychotic therapy ranged from 22% to 86%. Currently, studies have shown that approximately 25% of patients on antipsychotic therapy in the nursing home can have their antipsychotics safely discontinued.²⁶ When nursing home staff are educated about neuroleptics and their appropriate use, Ray²⁷ found that the use of neuroleptics decreased by 72% in the study home compared to the control home.

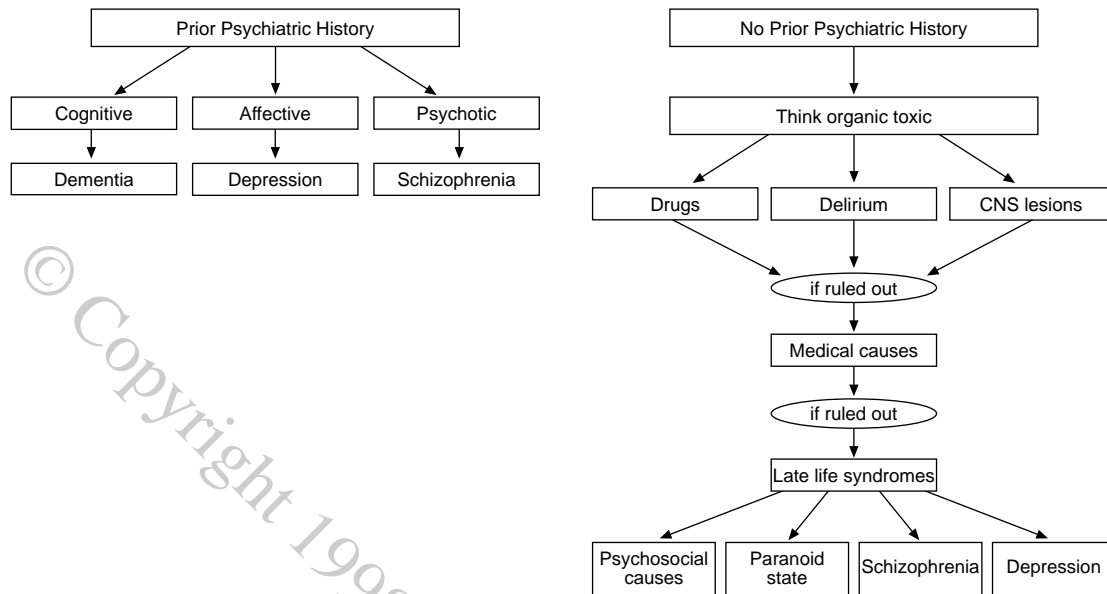
PHARMACOKINETICS

Age-related changes can affect the pharmacokinetics of neuroleptics. Absorption can be altered by changes in gastric acidity, gastric emptying, splanchnic blood flow, and changes in absorption rate.²⁸ Antacids, and some compounds with huge absorbing surfaces like Metamucil, may delay absorption and delay the onset of action of some drugs.^{24,29} Body composition changes in the elderly include a decrease in lean body mass and a decrease in total body water accompanied by an increase in total body fat.^{28,29} There are decreases in liver mass, liver blood flow, and renal blood flow and function. The hepatic cytochrome p450 does not appear to undergo age-associated decline.³⁰

Phenothiazines are lipophilic, well absorbed, and have extensive first-pass metabolism in the liver.²⁸ Lipid soluble substances are distributed in body fat. In the elderly, the volume of distribution is increased, because of the increase in total body fat. This results in an increase in the half-life of lipophilic substances.

The half-life of a drug is directly proportional to the volume of distribution divided by the clearance of said drug;²⁴ for this reason elderly patients should be given lower doses of lipophilic drugs. The antidopaminergic effects of estrogen may contribute to the need for lower doses of neuroleptics in women.³¹

Figure 1. Late-Life Psychosis: Diagnostic Tree*



*Adapted from reference 22.

Rabin et al.³² reported that the response rate of patients with late-onset schizophrenia treated with neuroleptics was 57%. Pearson et al.³³ reported a response rate of 75% in a similar group. Jeste and colleagues¹⁴ found that treatment is more effective on positive than negative symptoms in both early- and late-onset schizophrenia. Rockwell and associates³⁴ found that patients with schizophrenia responded better to treatment than patients with somatic delusional disorders. In contrast, Flint and colleagues³⁵ reported that patients with somatic delusions and schizophrenia responded better to treatment with neuroleptics.

The most frequently prescribed medications for the treatment of psychosis are neuroleptics. Neuroleptics can be classified as high, intermediate, and low potency. High-potency neuroleptics are, for example, haloperidol, fluphenazine, and thiothixene; intermediate-potency neuroleptics are perphenazine, loxapine, and molindone; and low-potency agents are chlorpromazine and thioridazine. Newer antipsychotics include risperidone and clozapine.²⁴

High-potency neuroleptics have higher affinity for the dopamine receptors and less affinity for the alpha and muscarinic receptors. The high-potency neuroleptics tend to cause extrapyramidal or parkinsonian symptoms, akathisia, acute dyskinesia, and acute dystonic reactions. Akathisia can be misdiagnosed as anxiety or agitation in the elderly.

The lower potency neuroleptics have greater affinity for the histaminic, α_1 -adrenergic, and muscarinic receptors. Their muscarinic activity may cause urinary retention, dry mouth, and constipation. They should be used with precaution in patients with closed-angle glaucoma. Their activity on histaminic receptors can cause sedation and hypoten-

sion. Their affinity for the α -adrenergic receptors causes orthostatic hypotension. Elderly patients are very sensitive to all of the above-mentioned side effects. This must be considered prior to the administration of a neuroleptic. Pollack and Mulsant²⁴ recommend the use of intermediate-potency neuroleptics in the elderly, for example, perphenazine, loxapine, or molindone. In a review, he also reports a prescribed average dose of 200 mg/day of chlorpromazine equivalents. Mulsant et al.³⁶ in their review of the literature recommend the use of intermediate-potency neuroleptics and advocate starting at half the initial neuroleptic dose used in younger patients. Titration should be based on response and monitoring for side effects.

We recommend the use of high-potency neuroleptics at low doses, for example, haloperidol at a starting dose of 0.25 mg a.m. and h.s., and titrating to a maximum dose of 2 mg/day (Table 2). For an intermediate-potency neuroleptic, we recommend starting perphenazine at a dose of 2 mg/day, and titrating to a maximum dose of 12 mg/day. We tend not to recommend the use of low-potency neuroleptics as these can cause both peripheral as well as central anticholinergic side effects. They may produce confusion as well as increase the risk of falls in the elderly secondary to their side effects of sedation and orthostasis.

CLOZAPINE

Clozapine is an atypical antipsychotic. Compared with the typical neuroleptics, it has a greater affinity for D_2 receptors and is more selective for mesolimbic and mesocortical pathways. Clozapine is reported to have the

following side effects: drowsiness, salivation, tachycardia, dizziness, constipation, nausea/vomiting, hypotension, sweating, dry mouth, tremor, seizure, and agranulocytosis. It is required that patients prescribed clozapine have their cellular blood count monitored weekly, and physicians must monitor total white count as well as neutrophil counts. Clozapine should be used after patients have been treated and have failed two trials of conventional neuroleptics. Failure can be defined as a lack of symptom response on a therapeutic dose and/or the emergence of side effects such as parkinsonism or tardive dyskinesia.

Pitner et al.³⁷ reported their experience with clozapine in four elderly patients with psychotic symptoms. Two of the patients did have relief of their psychotic symptoms. Falls, symptomatic bradycardia, and delirium were reported, and the patients with moderate-to-severe dementia experienced these symptoms after the first dose. The authors recommended a starting dose of 6.25 mg/day, with weekly titration. Oberholzer et al.,³⁸ in their study of 18 psychogeriatric patients with dementia, reported that four patients had to discontinue the drug because of side effects. They found no leukopenia, and the mean daily dose was 53.2 mg. In a study done by Chengappa et al.³⁹ looking at the use of clozapine in elderly women, the side effects more frequently seen were postural hypotension, excessive salivation, and sedation. One patient developed agranulocytosis. They reported that two patients had a better response to clozapine than to conventional neuroleptics. In a prospective open-label trial, Factor and colleagues⁴⁰ treated 17 patients with Parkinson's disease complicated by psychosis with doses of clozapine ranging from 6.25 to 150 mg/day and reported improvement in psychotic and motor symptoms.

RISPERIDONE

Risperidone, a benzisoxazole, is a novel antipsychotic. It is a potent antagonist of the 5-HT receptor as well as having D₂ blocking action. It is thought to cause fewer extrapyramidal symptoms than older high-potency antipsychotics.⁴¹ It is also reported to have efficacy for both the positive and negative symptoms of schizophrenia. Side effects include orthostatic hypotension, sedation, fatigue, and palpitations. We often recommend starting at 0.25 mg a.m. and h.s. and titrating the dose slowly to a ceiling of 2 mg/day in two divided doses.⁴² Elderly psychotic patients who are naive to neuroleptics will do best with low doses of risperidone (2 mg/day or less). Those who have been taking neuroleptics may require higher dosing.

Raheja and colleagues⁴³ reported on two elderly subjects treated with a dose of 3 mg/day of risperidone who had no side effects and no changes in their ECG or laboratory findings. Jeanblanc and Davis⁴⁴ reported using risperidone in five elderly patients at a starting dose of 0.5 mg b.i.d. and noticing antipsychotic effects in 10 days.

Table 2. Geriatric Dosing of Representative Neuroleptics*

Generic Name	Dosage (mg/d)
Haloperidol	0.25–2
Thiothixene	1–5
Loxapine	2.5–15
Clozapine	6.5–150
Risperidone	0.5–2

*Adapted from reference 42.

Madhusoodanan et al.⁴⁵ reported having used risperidone to treat 11 geriatric patients with psychotic symptoms; 8 patients responded, 1 did not, and 2 had to discontinue treatment because of hypotension and dizziness. Of the 8 patients who responded, 7 had improvement in both positive and negative symptoms. Four of the patients had decreases in their extrapyramidal symptoms and symptoms of tardive dyskinesia.

Risperidone appears to be a safe and effective treatment for psychotic symptoms in the elderly. It may be particularly suited for those who have not responded to traditional neuroleptics, those who could not tolerate older agents secondary to side effects, and older patients with preexisting parkinsonism with psychosis. Risperidone is currently being studied in the behavioral disturbances of dementia, namely psychosis as well as agitation.

SIDE EFFECTS OF NEUROLEPTICS (TABLE 3)

Parkinsonism is a frequent neuroleptic side effect that has a triad of symptoms: resting tremor, rigidity, and bradykinesia. The elderly are particularly vulnerable to developing parkinsonism.⁴⁶ As well, patients with Lewy body dementia are also exquisitely sensitive to the side effects of neuroleptics.⁴⁷ Geriatric patients, while being treated with neuroleptics, were 5.4 times more likely to begin on an antiparkinsonian medication for the above side effects.⁴⁸ This side effect may be treated by reducing the neuroleptic dosage, and/or using anticholinergics such as benztropine at a dose of 0.5 mg to 1 mg/day. One should be careful when using antiparkinsonian agents as they can cause confusion and delirium in the elderly as well as a variety of annoying peripheral anticholinergic side effects.

Akathisia is characterized by increased restlessness, psychomotor activity, and agitation and an inability to sit still.²⁸ This is a frequent side effect that can be mistaken for increasing agitation and or worsening agitation especially in the demented elderly.²⁹ Akathisia can be treated with β -blockers, benzodiazepines, and anticholinergics.²⁸ Perhaps the most efficacious are the β -blockers, with a recommended dose of propranolol being 30–80 mg/day.⁴⁹

Tardive dyskinesia consists of abnormal involuntary choreiform movements. This movement disorder is more frequently observed in the peribuccal, periocular areas, but

Table 3. Side Effects of Neuroleptics

Receptors	Side Effects
Dopaminergic	Parkinsonism Akathisia Dystonias Tardive dyskinesia
Histaminic	Sedation Weight gain
Alpha-Adrenergic	Orthostatic hypotension
Muscarinic	Sedation Delirium Falls Constipation Urinary retention
Quinidine-like	Arrhythmias Torsades de pointes

can be seen in the hands, legs, torso, and feet. A significant risk factor is advanced age. Other associated risk factors are previous history of drug-induced parkinsonism, organic brain disease, and female sex. Jeste et al. in a prospective longitudinal study of 266 patients who were over the age of 45 found the cumulative incidence of tardive dyskinesia to be 26%, 52%, and 60% after 1, 2, and 3 years, respectively.⁵⁰ The principal risk factors for the development of tardive dyskinesia were the duration of prior neuroleptic use at baseline, cumulative amount of high-potency neuroleptics, history of alcohol abuse/dependence, and the presence of borderline or minimal dyskinesia on initial assessment.

Other side effects may be secondary to the muscarinic or quinidine-like effects of neuroleptics. These include sedation, delirium, falls, and cardiac conduction abnormalities. Sedation can lead to confusion and falls. Orthostasis can also cause falls, placing the elderly patient at a higher risk for hip fractures. Falls that lead to hip fractures are a leading cause of hospitalization and death in the elderly⁵¹; 14% of hip fractures in the elderly have been attributed to the use of psychotropics.²⁵ Neuroleptics can cause the emergence of cardiac arrhythmias. Haloperidol is reported to cause QTc prolongation and torsades de pointes. Recent cases in the literature have reported on the association between high-dose intravenous haloperidol and the occurrence of QTc prolongation and torsades de pointes.^{52,53}

CONCLUSION

This article has attempted to review psychotic disorders that occur in older patients. Psychosis is a symptom that is sometimes difficult to diagnose and treat. We have reviewed current treatment strategies, which include the use of traditional and novel antipsychotics, and have given some dosing guidelines. One must keep in mind the differential diagnosis, treatment strategies, and potential side effects that these drugs can cause in the elderly, so as to maximize benefits of treatment while minimizing side effects.

Drug names: benzotropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane), molindone (Moban), perphenazine (Trilafon), propranolol (Inderal and others), risperidone (Risperdal), thioridazine (mellaril and others), thiothixene (Navane).

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