Pharmacologic Management of Psychosis in Dementia

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Significant consequences of untreated psychosis in patients with dementia have led clinicians to seek improved therapeutic options. This review presents the scope of the problem, discusses some of the underlying neurobiology, and highlights the evidence for appropriate therapies. A range of potentially effective pharmacologic therapies is available and is discussed. *(J Clin Psychiatry 1999;60[suppl 8]:54–60)*

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In this article, the treatment of patients with dementia who also have signs and symptoms of psychosis is discussed. The epidemiology and clinical characteristics of this condition will be described, as well as its differential diagnosis and underlying neurobiological mechanisms. In addition, evidence-based behavioral and pharmacologic approaches to the management of patients with psychosis that accompanies dementia are reviewed.

DESCRIPTION AND EPIDEMIOLOGY

Psychotic signs associated with dementia include delusions, hallucinations, and misperceptions. The vast majority of patients with dementia are likely to develop psychosis, agitation, aggression, or disruptive behavior over the course of their illness. In a number of studies of patients with dementia, the prevalence of delusions has varied from 10% to 73%, with an overall median of 34%.[1] It is uncommon for patients with dementia to have a typical, sustained, and well-developed delusional syndrome. More often, delusions tend to be variable, evanescent, and relapsing, and, sometimes, chronic. In patients with Alzheimer's disease, delusions do not necessarily portend disease progression or indicate the severity of the cognitive impairment. Rather, delusions may occur at any stage of the illness. Common examples of delusions include beliefs of theft, that one's house is not one's home, that a caregiver will abandon the person, that a caregiver is an impostor, or that one's mate is unfaithful.

Hallucinations are also common in patients with dementia. The prevalence of hallucinations among these patients has varied between 21% and 49% in different studies; the median is approximately 28%. Visual and auditory hallucinations are most common. Patients with dementia show variable reactions to their hallucinations. Some are disturbed by the hallucinations and respond to their perceptions. Often, however, patients do not seem to change their behavior as a result of the hallucinations or to act against them.

Nearly 25% of patients with dementia have misperceptions, although the prevalence varies greatly depending on the population studied, ranging from 1% to nearly 50% in different studies. Examples of such misperceptions are the inability to recognize one's self in the mirror, the belief that T.V. characters appear real, and the misidentification of objects. Misperceptions are often not viewed as psychotic features and do not disrupt behavior; hence, they are often not treated. In general, both hallucinations and misperceptions are transient or episodic, sometimes occurring at particular times of the day.

Although delusions and hallucinations can be understood within the context of a patient's cognitive impairment (e.g., that impaired memory leads to forgetting where something is kept and hence to the belief that it has been stolen), there are also neurobiological correlates of delusions and hallucinations, suggesting that some of these phenomena are a direct result of the disease process (see "Neurobiology of Psychosis in Dementia").

CONSEQUENCES OF PSYCHOSIS IN DEMENTIA

Hallucinations and delusions both may lead to subjective distress on the part of the patient and adverse effects on caregivers. Patients under the influence of delusions or hallucinations may be disruptive and troubled, responding to the internal stimuli and not to the environment. This condition may lead to unsafe and violent situations where the patient is acting on his or her hallucinations. These patients are at risk for being overmedicated or restrained.

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Those living at home are at increased risk for institutionalization. Indeed, behavioral disruption is among the most common immediate causes for nursing home placement of dementia patients.[2]

Caring for a patient with psychosis and dementia can cause considerable adverse effects on the caregivers, including the physical demands of constantly needing to tend to the patient and the emotional stress of caring for a loved one who is "out of touch" and unable to respond.

Although there is only a modest relationship of delusions or hallucinations with the severity of cognitive impairment, a consistent observation is that patients with delusions or hallucinations show an increased rate of cognitive decline independent of their current degree of cognitive impairment and, hence, a likelihood of an earlier placement.[3,4]

Lastly, the appearance of psychotic symptoms in patients with dementia has significant consequences on the health care system, including outpatient and long-term care settings. Psychotic behaviors often require both pharmacologic and behavioral management approaches.

NEUROBIOLOGY OF PSYCHOSIS IN DEMENTIA

There are substantial neurobiological correlates to psychosis in dementia. These correlates include observations that psychosis is associated with decreased serotonin in the cerebral cortex,[5,6] that decreases in acetylcholine function are correlated with increases in thought disorders,[7] and that cholinergic agents decrease the emergence of psychotic features.[8–11] There are also observations of greater cholinergic loss (deficiency) in the frontal temporal cortex of demented patients with delusions than in patients with dementia without delusions matched for age, years of education, duration of illness, and severity of illness.[12–14]

Increased levels of norepinephrine[5] and increased levels of α-adrenergic receptors[15] have also been observed in multiple brain regions in psychotic Alzheimer patients compared to patients with Alzheimer's disease without psychosis. Furthermore, a relationship has been observed between an enhanced norepinephrine responsiveness and increased psychosis.[16,17]

DEMENTIA WITH LEWY BODIES

Alzheimer's disease associated with diffuse cortical Lewy bodies has been increasingly recognized as possibly the second or third most common form of dementia.[18] Lewy bodies are found in the brainstem, subcortical nuclei, limbic region, or neocortex in 15% to 25% of all dementia patients.[19] These neuronal bodies are cytoplasmic, spherical, and eosinophilic. Patients with Lewy body dementia present with a dementia syndrome that is similar to Alzheimer's disease. In addition, these patients may have a fluctuating cognition with recurrent visual hallucinations that are typically detailed and contain formed elements; they also show subtle parkinsonian signs. Patients with Lewy body dementia may be more subject to falls and syncope, may be particularly sensitive to neuroleptic medications, and may have well-systematized delusions.[19]

DIFFERENTIAL DIAGNOSIS OF HALLUCINATIONS AND DELUSIONS IN THE ELDERLY

Hallucinations and delusions can be associated with several types of dementia, including Alzheimer's disease, vascular dementia, dementia related to alcohol, Lewy body–related dementias, frontotemporal dementias, and dementias that are secondary to medication or medical conditions. Hallucinations and delusions also occur in schizophrenia and mood disorder. Approximately 5% to 10% of patients with major depressive disorder also have delusions or so-called delusional depression. Among the elderly, a delusional disorder is characterized by a well-developed delusional system in the absence of major depression, schizophrenia, or dementia.[20] Visual hallucinations also occur in patients with Parkinson's disease, often as a result of both the disease and the use of dopaminergic and anticholinergic parkinsonian medications. Lastly, hallucinations or delusions can be associated with delirium or medication use.

Patients presenting with hallucinations and delusions should be assessed for the concurrent presence of a cognitive or mood disorder. Conversely, elderly patients presenting with dementia should be assessed for the presence of hallucinations or delusions. A high index of suspicion should be maintained, especially since patients and their caregivers may not readily report these symptoms.

A number of medications may cause delusions and hallucinations in the elderly, including anticholinergics, dopaminergics, serotonergic antidepressants, antidepressants with anticholinergic effects, bupropion, nonsteroidal anti-inflammatory drugs, and prednisone.

TREATMENT APPROACHES TO SYMPTOMS OF PSYCHOSIS IN DEMENTIA

The first step in developing a treatment plan for demented patients with psychosis is to perform a medical evaluation to identify any concomitant medical disorders, intercurrent illnesses, or medications that might be causing or exacerbating the symptoms. The next step is to perform a psychiatric evaluation and to make a differential diagnosis. If the evaluation indicates that delusions or hallucinations may be secondary to a medical disorder or medication, and if symptoms are minor or tolerable, then it may be prudent to treat the medical disorder and adjust or discontinue the offending medications, if indicated. However, even when the psychosis seems to be caused by the medication, discontinuing it often does not improve the psychosis.

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After determining the diagnosis and concluding that the psychotic symptoms are associated with a primary dementia such as Alzheimer's disease or vascular dementia, the next step is to characterize the signs and symptoms to be treated. For example, the excessive suspiciousness of someone with paranoid delusions should be noted. It is important to ascertain whether the patient becomes frightened or aggressive when approached or confronted and to determine if the delusions are bizarre or incomprehensible rather than paranoid in nature. An accurate characterization of the signs and symptoms before treatment, if initiated, allows for an effective means of monitoring target symptoms and assessing improvements.

Nonpharmacologic Management of Psychosis

The nonpharmacologic management of psychosis involves a number of general principles and a number of specific tasks. In general, with a patient who is both cognitively impaired and psychotic, caregivers and health care professionals need to ensure that there is adequate sensory input and that the patient is in an enhanced and regulated environment. There should be increased light during the day and decreased light at night. General environmental cues should be maintained and noise should be kept to a minimum. Psychosocial interaction should be optimized and routines and social contacts should be maintained. Objects familiar to the patient should be available, and adequate support and reassurance from staff and loved ones should be given.

To be truly effective, caregivers must be both educated about their task and supported for their efforts. For example, they should be instructed to provide simple and clear communication to the psychotic patients under their care. When a patient is particularly delusional or hallucinatory, distracting and redirecting them to another task or object may prove useful. Direct confrontational or argumentative behavior should be avoided.

A behavioral management plan is necessary for each specific behavioral approach. In such a plan, it is important to determine the antecedents of the behavior, the troublesome behavior itself, and the consequences of the behavior, commonly referred to as the "ABCs." For example, a caregiver or professional might notice that there are certain antecedents or environmental stimuli that tend to be associated with the onset of delusions or hallucinations. If these antecedents can be changed or modified, then the delusions might also be mitigated.

Pharmacotherapeutic Approaches

In many instances, nonpharmacologic approaches in the treatment of demented patients with psychoses will have only limited benefit. Psychotic patients, who are distressed and agitated to the extent that they or others are in danger, need psychopharmacologic treatment. The use of pharmacotherapeutic agents is intended to decrease psychotic symptoms, thereby increasing the patients' ability to interact with others and the environment with the goal of improving quality of life and safety for both patients and their caregivers.

The general principles of psychopharmacologic treatment include (1) assessing target symptoms, (2) choosing a medication that is most likely to be appropriate for the symptoms, and (3) starting with a low dosage but adjusting and individualizing dosages until there is clinical benefit or toxicity. If the treatment is effective, then it should be continued for a period of weeks to months and gradually reduced after a patient has been asymptomatic for a period of time, perhaps 2 to 4 months. The maintenance dosage of a medication is usually considered to be the dosage that was effective in the acute setting. If treatment is ineffective, then medication should be gradually discontinued, followed by a reevaluation and consideration of another agent. Or, when a patient's behavior is particularly severe, such that medication cannot be withdrawn, a second, noninteracting medication should be introduced.

Neuroleptics are the drugs of choice for treating delusions and hallucinations. They can be divided into 2 main classes: the conventional neuroleptics and the newer atypical neuroleptics. Other medications, such as selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, anticonvulsants, and benzodiazepines, have been used to treat the associated agitation and aggression; however, these classes of drugs are generally not considered first line or truly effective in treating psychosis. Recently, evidence has been presented that cholinergic medications may mitigate hallucinations and delusions or their development, but this topic is the subject of ongoing research.[8–10]

The distinction between a conventional neuroleptic and an atypical neuroleptic involves the specificity with which they block dopamine receptors. Both types of neuroleptics block dopamine D_2 receptors, but atypical neuroleptics also block an array of serotonin receptors. In addition, the atypical neuroleptics have effects on other dopamine receptor subtypes.

Conventional neuroleptics. The specific signs or symptoms that tend to improve with neuroleptics include hallucinations, delusions, excessive suspiciousness, paranoia, and jealousy and may be considered "target" symptoms. Other symptoms, such as agitation and aggression, are also frequently reduced with these drugs. However, cognitive function, apathy, and emotional withdrawal often do not improve with neuroleptic treatment and may sometimes become worse. Alternatively, cognitive symptoms may occasionally improve, possibly related to improvements in behavior.

The magnitude of the treatment effect varies, with some patients improving substantially and others only minimally. The efficacy of a drug does not seem to be influenced so much by the class of neuroleptic used as by the specific agent and dose used. In general, low doses of neu-

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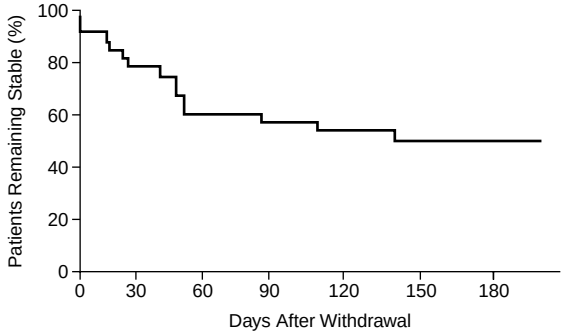
Table 1. Range of Dosages for the Conventional Neuroleptics[a]

Drug Name	Approximate Dose (mg/day)
Phenothiazines	
Thioridazine	10–75
Perphenazine	4–24
Butyrophenones	
Haloperidol	0.25–2
Loxapine	10–50
Thiothixene	1–10
Molindone	5–20

[a]Clinicians should be aware that these values, which are cited in the literature or in common use, cannot be used to predict efficacy or safety in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in clinical studies or are used by others. The values are guides and are not to be construed as recommendations, and, indeed, the higher doses in the range may be associated with significant side effects.

Figure 1. Percentage of Patients Remaining Stable After Withdrawal of Antipsychotic Medication[a]



[a]From Horwitz et al.,[21] with permission.

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roleptics tend to be effective. Doses above 2 mg/day of haloperidol or 75 mg/day of thioridazine tend to be less effective and are associated with greater side effects. Side effects with the conventional neuroleptics are common but are dose-related. Table 1 lists the currently prescribed conventional neuroleptics and their suggested dosages.

The optimal duration of antipsychotic therapy for demented patients with psychosis is unknown. Withdrawal studies show variable rates of relapse, and there are few long-term studies. In one example, nursing home patients who had been maintained on long-term antipsychotic treatment and who had no current behavioral symptoms were gradually withdrawn from antipsychotic therapy.[21] Over the course of 3 to 6 months, approximately 50% of the patients experienced recurrence of delusions and hallucinations (Figure 1).

Adverse events associated with conventional neuroleptics in dementia. Adverse events associated with conventional neuroleptics can be grouped into 4 main categories: neurologic, cardiovascular, anticholinergic, and miscellaneous.

The neurologic side effects are listed in Table 2 and can be subdivided into 3 main groups: extrapyramidal reactions, tardive dyskinesia, and miscellaneous neurologic effects. Extrapyramidal reactions tend to have an acute onset. They include neuroleptic-induced parkinsonian signs, acute dystonic reactions, and akathisia. Parkinsonian signs and symptoms include bradykinesia or akathisia, markedly diminished motor movements, rigidity, tremor, and gait disturbances. Associated with the bradykinesia may be a masked face. There may also be drooling and decreased postural reflexes.

Tardive dyskinesia tends to occur later in the course of neuroleptic treatment, generally after several months to a year. It is more common in elderly patients, especially in people with dementia.

Other neurologic effects of conventional neuroleptics include seizures, catatonia, temperature dysregulation, and neuroleptic malignant syndrome. Cardiovascular side effects can include orthostatic hypotension—especially with the less potent neuroleptics that tend to block α-adrenergic receptors—tachycardia, and electrical conduction delays. Patients with dementia who take conventional neuroleptics have an increased risk of falls. This effect may be due to sedation or to the α-adrenergic blockade produced by the lower potency medications.

The anticholinergic effects include both peripheral and central manifestations. The peripheral manifestations include dry mouth, constipation, urinary retention, blurred vision, and glaucoma. Central effects include confusion, delirium, impaired memory, visual hallucination, and possibly irritability and agitation.

In addition, because conventional neuroleptics block dopamine receptors, they cause an elevation of plasma prolactin concentrations, weight gain, and a slightly increased risk for inappropriate secretion of antidiuretic hormone. Uncommonly, agranulocytosis and rashes have been associated with the phenothiazines.

Atypical neuroleptics. As mentioned above, atypical neuroleptics are characterized by their ability to affect serotonergic as well as dopaminergic systems. The atypical neuroleptics currently available include risperidone, clozapine, olanzapine, and quetiapine. There are marked differences among the atypical neuroleptics with respect to their selectivity for dopamine receptor subtypes and to their effects on serotonergic receptors. As a group, these medications are relatively potent at blocking α_1- and α_2-adrenergic receptors as well as histaminergic receptors.

Adverse events associated with atypical neuroleptics in dementia. In general, atypical neuroleptics are associated with a lower risk of extrapyramidal symptoms (EPS), than the conventional neuroleptics, and they show an ability to improve the so-called negative symptoms of schizophrenia.[22–24] This may be because atypical neuroleptics show relatively greater selectivity for mesolimbic compared to nigrostriatal dopamine receptors.

Among the atypical neuroleptics, risperidone is the most likely to cause EPS, particularly at higher doses, but

Table 2. Side Effects Associated With Conventional Neuroleptics[a]

Extrapyramidal reactions
Neuroleptic-induced parkinsonian signs
Bradykinesia
Rigidity
Tremor
Gait disturbance
Decreased postural reflexes
Masked faces
Drooling
Acute dystonic reaction
Akathisia
Tardive dyskinesia
Miscellaneous neurologic effects
Seizures
Catatonia
Neuroleptic malignant syndrome
Hypo- or hyperthermia
Anticholinergic effects
Peripheral
Dry mouth
Urinary retention
Glaucoma
Constipation
Blurry vision
Central
Confusion
Impaired memory
Irritability
Delirium
Visual hallucinations
Agitation
Cardiovascular
Orthostatic hypotension
Tachycardia
Conduction delays
Sedation
Falls/fractures
Miscellaneous
Agranulocytosis (uncommon, but associated with phenothiazines)
Weight gain
Rashes and other dermatologic signs
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

[a]From Schneider et al.,[33] with permission.

the incidence of EPS is relatively low.[25] During the clinical evaluation trials for drug approval, the percentages of patients developing EPS for olanzapine, clozapine, and quetiapine were low, often no different than placebo.[26–28] The patient populations in these trials were largely younger adults with chronic schizophrenia. Recent evidence with quetiapine and low-dose risperidone (≤ 2 mg/day) suggests that the rate of EPS with these drugs is also low among elderly patients.[29,30] In these studies, elderly patients with a variety of diagnoses associated with psychotic symptoms were included. However, unlike the randomized trials, which were controlled, the quetiapine trial was open label[29] and the risperidone study was a chart review.[30]

As with conventional agents, atypical neuroleptics are generally associated with weight gain, although with differences between agents. For example, in the study of quetiapine in the elderly, the mean weight gain was modest (+0.78 kg).[29] Weight gain is not reported in the risperidone study in the elderly.[30] Specific weight gain with olanzapine in elderly patients has not been published; however, in younger patients olanzapine has been associated with significant weight gain (56% gained > 7% of their baseline weight in long-term studies).[31,32]

EVIDENCE-BASED USE OF NEUROLEPTIC AGENTS IN DEMENTIA

Neuroleptic medications have been extensively studied for the treatment of psychosis in patients with dementia. For example, a 1990 meta-analysis identified 33 clinical trials in dementia patients.[33] Of the 17 placebo-controlled trials, however, only 7 used a double-blind, placebo-controlled, parallel-group design to assess dementia patients (Alzheimer's disease or vascular dementia); these 7 trials included 252 patients treated for 3–8 weeks (Table 3).

The results from this meta-analysis indicate that antipsychotic treatment was associated with a modest improvement in behavioral symptoms (Figure 2A), as assessed by clinicians. The bimodal effect size indicates improvement in 59% of agitated dementia patients taking antipsychotics compared to 41% of patients taking placebo (Figure 2B). The relatively high placebo response can also be appreciated. Unfortunately, these are rather short-term trials, and the duration of effect is not known.

Atypical Neuroleptics

Because these drugs are newer, they have been used to a far lesser extent in patients with dementia who have hallucinations and delusions.

The limited data with clozapine are mainly case series and reports suggesting efficacy with respect to hallucinations and delusions and occasional reports of improved cognition.[34,35] The usual starting dose for clozapine is 12.5 mg/day, which can be adjusted up to about 75 mg/day. These doses are far less than the 300 to 400 mg used in young schizophrenic patients. Side effects are of particular concern with clozapine. Side effects include seizures, anticholinergic effects, sedation, and confusion. Of greatest concern are the rare episodes of agranulocytosis, which has necessitated that blood tests be done every 2 weeks to assess leukocyte count.[27,36] If not caught early, the agranulocytosis may become irreversible and fatal.

Risperidone is the most widely studied atypical antipsychotic for the control of hallucinations and delusions. The data include several case reports and series[37–39] and the results of a large multicenter placebo-controlled nursing home clinical trial.[40] In this trial involving 40 sites and 625 patients, 73% had a diagnosis of Alzheimer's disease, and 15% had vascular dementia. The mean age was 83 years, hence the study comprised a very old population; 68% were women. These patients were at the most severe stages of dementia. Although patients were not necessarily

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Table 3. Double-Blind, Placebo-Controlled Studies of Neuroleptics in Dementia[a]

Medication	Dose (mg/day)	Duration (weeks)	N	Age (y)	Improvement[b] (%)	p Value	Reference
Chlorpromazine	75	8	16/16	75	. . .	. . .	Abse et al, 1960[42]
Trifluoperazine	8	8	18/9	71	22, 0	.12	Hamilton and Bennett, 1962[43]
Acetophenazine	40	3–8	14/5	71	64, 20	.09	Hamilton and Bennett, 1962[44]
Haloperidol	3.75	6	9/9	72	89, 67	.26	Sugarman et al, 1964[45]
Thiothixene	10.5	4	22/20	76	59, 55	.79	Rada and Kellner, 1976[46]
Haloperidol	4.6	8	20/22	73	65, 36	.06	Petrie et al, 1982[47]
Loxapine	22		19/22		58, 36		
Thioridazine	62.5	8	17/17	83	59, 47	.25	Barnes et al, 1982[48]
Loxapine	10.5		19/17		68, 47		

[a]Modified from Schneider et al.[33] (see citation for details on selection, dosage calculation, rates of improvement, and p values).
[b]The last number is the percentage of patients improving in the placebo group.

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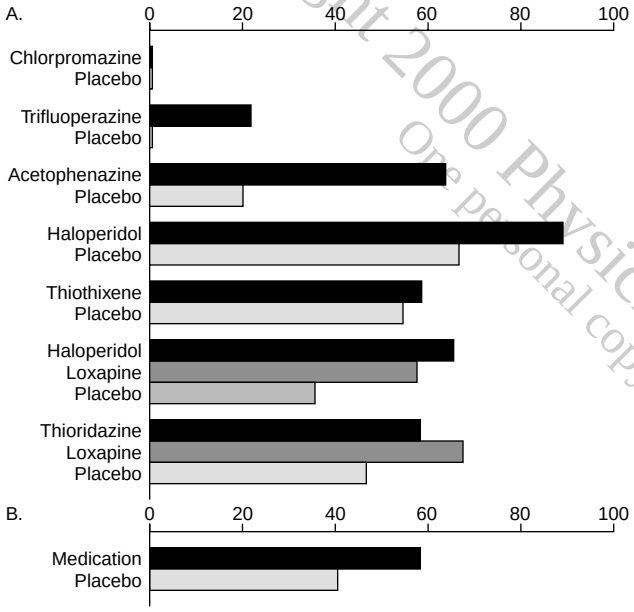
Figure 2. Percentage of Dementia Patients Responding to Antipsychotics[a]



[a]Data are from a meta-analysis of double-blind, placebo-controlled trials of neuroleptics in patients with psychosis in dementia conducted by Schneider et al.[33] (A) Percentage of patients responding to various neuroleptics and to placebo. Details can be found in Table 3. (B) The results of the meta-analysis reported as the binomial effect size display, an estimate of the change in effect size between medication and placebo groups (see the citation for details on the calculations).

selected because of the presence of psychotic features, low doses of risperidone were associated with significant improvement in psychosis scores on a behavioral rating scale. The effective doses were 0.5 or 1.0 mg b.i.d. It should be noted that although 60% and 65% of the risperidone-treated patients improved, so did 52% of the patients treated with placebo, a finding consistent with the clinical trials of conventional neuroleptics (see meta-analysis by the author[33]). Although risperidone was clearly efficacious, the high response rate in the patients treated with placebo indicates the waxing and waning and evanescence of disruptive behavior among elderly patients with dementia and the tendency for improvement when patients are entered into studies.

A large open-label study of quetiapine for the control of psychosis in elderly patients has recently been reported.[29] Among 152 elderly patients with idiopathic and organic psychoses (50% with Alzheimer's disease), quetiapine in doses from 12.5 to 450 mg/day was associated with a reduction of psychotic symptoms with few adverse effects. As with other medications, individualization of quetiapine doses is important. The broad range of effective quetiapine dosages makes such individualization feasible.[41]

PSYCHOSIS IN DEMENTIA: TREATMENT SUMMARY

Most randomized clinical trial evidence favors the use of low-dose, conventional neuroleptics or risperidone for the treatment of delusions and hallucinations. For both haloperidol and risperidone, starting doses should be 0.25 or 0.5 mg b.i.d, with maximum doses of 1 mg b.i.d.

Side effects and sensitivity to side effects often determine medication choice. Patients with Lewy body dementia may be particularly sensitive to extrapyramidal side effects. Atypical neuroleptics may hold considerable promise because of low liability for extrapyramidal side effects. However, they have not yet been adequately evaluated in both nursing home and outpatient populations in efficacy trials.

Drug names: acetophenazine (Tindal), bupropion (Wellbutrin), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), loxapine (Loxitane), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon), prednisone (Delta-Dome and others), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine).

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