

# Novel Antipsychotics in the Treatment of Behavioral Disturbances and Psychoses Associated With Neurodegenerative Disorders

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Behavioral disturbances and psychosis are common features of neurodegenerative disorders and may be drug induced, intrinsic to the underlying pathology, or both. These disturbances, including psychotic and mood symptoms, apathy, aggression and other behavioral symptoms, and superimposed delirium, cause a great amount of disability to the patient and stress on the caregiver. Conventional neuroleptics have been shown to be effective in the treatment of these symptoms, but unacceptable side effects may occur. However, the novel antipsychotics, with their lower risk of inducing extrapyramidal symptoms, have shown promise in the treatment of behavioral disturbances and psychosis associated with neurodegenerative disorders.

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**B**ehavioral disturbances and psychosis are common features of neurodegenerative disorders. The neurodegenerative disorders include extrapyramidal disturbances (e.g., Parkinson's disease, Huntington's disease), myelin disorders (e.g., multiple sclerosis [MS], amyotrophic lateral sclerosis [ALS], metachromic leukodystrophy), cortical disease (e.g., Alzheimer's disease [AD]), dementia with Lewy bodies, Niemann-Pick disease, and delirium. Several behavioral disturbances and psychotic symptoms that are common may be considered target symptoms for treatment with novel antipsychotic medications. These include psychotic and mood symptoms, apathy, aggression and other behavioral symptoms, and superimposed delirium.

These conditions mostly involve deterioration of cortical areas and neurochemical changes that are age-related and therefore most often diagnosed in the elderly. The elderly often have comorbid medical conditions, cognitive impairment, and sensory deficits such as visual and audi-

tory impairment. These factors may complicate diagnosis and treatment. Visual and auditory hallucinations due to poor vision and tinnitus, respectively, may occur, and delusions must be differentiated from misinterpretations due to sensory deficits or cognitive impairment. Further, comorbid illnesses lead to polypharmacy, whether with prescribed medications, over-the-counter products, or both. Thus, identification of behavioral disturbances and psychotic symptoms that may be obscured by multiple medical conditions, as well as age-related impairments in these patients, presents a challenge in diagnosis and treatment.

Once a neurodegenerative condition is identified, appropriate management of the primary medical condition is imperative. Treatment of concurrent behavioral disturbances or psychosis is also essential. A variety of psychotropic agents may be needed to stabilize these symptoms, including antipsychotics as well as antidepressants, psychostimulants, anxiolytic agents, and mood stabilizers. Two classes of antipsychotics are generally used in the treatment of these symptoms: conventional neuroleptics and novel antipsychotics. Conventional antipsychotics used for many years include haloperidol, chlorpromazine, thiothixene, and thioridazine. Recently, newer antipsychotics, the novel antipsychotics, have become available, including clozapine, risperidone, olanzapine, and quetiapine.<sup>1</sup>

The target behavioral disturbances and psychotic symptoms commonly encountered with these neurodegenerative diseases as well as published data on the use of novel antipsychotics to treat these disorders are reviewed below.

## TARGET SYMPTOMS

### Psychotic Symptoms

Delusions or hallucinations, or both, are the most common presenting symptoms reported in patients with neurodegenerative disease. Paranoid and persecutory delusions are experienced by patients with neurodegenerative disease, particularly those with AD.<sup>2</sup> These delusions have been reported to occur in 30% to 50% of AD patients.<sup>3</sup> Visual hallucinations are more common in patients with Parkinson's disease and are often related to medications prescribed for the motor components of the illness.

In patients with dementia, it is sometimes difficult to differentiate true psychotic symptoms from the patient's inability to organize thoughts because of cognitive impairment due to disease progression.<sup>4,5</sup> Furthermore, these psychoses can often lead to loss of touch with reality and behavioral disturbances such as agitation and aggression. Thus, the psychoses are some of the most debilitating of symptoms and cause increased stress on caregivers. Mild symptoms may be managed within a safe environment; however, moderate or severe delusions or hallucinations, particularly when complicated by agitation or aggression, may require pharmacologic intervention.

### Mood Disorders

Depression frequently occurs in patients with systemic illnesses involving the central nervous system and is commonly associated with the neurodegenerative conditions AD, Parkinson's disease, and MS.<sup>6,7</sup> Patients with cognitive dysfunction and concomitant chronic medical illness are at greatest risk for developing depression. Because of the often noted blunted or flat affect secondary to these neurologic conditions, depression may be misinterpreted as more severe or mild depending on the patients' ability to express themselves. It is also important to differentiate apathy from sadness since targeted pharmacotherapy may be different. A clinical pearl is asking the patient whether he or she feels the "blahs" or the "blues."

### Behavioral Symptoms

The most common behavioral symptoms noted in neurodegenerative diseases are aggression, agitation, sleep disturbances, apathy, hypersexuality, and confusion. These behaviors are often disruptive, resulting in patient distress and increased caregiver burden. Behavioral disturbances, particularly aggression, are the most commonly cited factors leading to institutionalization of patients. Agitation and verbal and physical aggression frequently coexist in demented patients and are generally the dominant behavioral symptoms in patients with AD. Drug-induced sleep disturbances and related behaviors such as insomnia and altered dreams occur in almost 98% of patients with Parkinson's disease.<sup>8</sup> In these patients, sleep disturbances increase the risk for the development of psychotic symptoms.<sup>9</sup>

## ALZHEIMER'S DISEASE

Dementia is estimated to affect 5% to 8% of the population over age 65, 15% to 20% over age 70, and 25% to 50% over age 85, with AD being the most common form of dementia, representing 50% to 75% of the total.<sup>10</sup> In the early stages of AD, deficits in memory retrieval are often noted and sometimes accompanied by personality changes or increased irritability. Psychosis and behavioral disturbances generally emerge during the middle and later

stages. Periodic and fragmentary delusions are often noted in patients with AD, particularly persecutory or paranoid delusions.<sup>4</sup> Hallucinations are also common in demented patients, with prevalence ranging from 21% to 49%.<sup>11</sup> Both auditory and visual hallucinations have been reported. In the elderly, it is important to distinguish hallucinations resulting from loss of hearing or poor vision from those resulting from a medical condition or medications.

Delusions and hallucinations can cause considerable distress to the patient and may lead to behavioral disturbances, particularly agitation and aggression. Violent behavior may arise if the patient acts on his or her hallucinations. Caregivers often cite these behaviors as the precipitating factors leading to institutionalization. Pharmacologic management of these patients is generally required. However, the complete medical presentation of the patient, including comorbid medical conditions and concomitant medications, must be considered before antipsychotics are introduced.

Once psychotic symptoms associated with AD are identified, the specific signs and symptoms need to be characterized. Mild delusions and hallucinations may be managed by nonpharmacologic methods such as providing appropriate sensory input and regulated environment, and routines should be maintained. It is essential that caregivers communicate clearly and be able to redirect the patient as necessary. Unfortunately, these methods alone are often not effective in patients who have more advanced psychosis or who are agitated or aggressive. For these patients, antipsychotics are the drugs of choice for delusions and hallucinations.

Conventional neuroleptics have been commonly used to treat behavioral disorders associated with dementia and have shown some reduction of behavioral symptoms.<sup>12,13</sup> Undesirable adverse events, however, limit use of these agents. Neurologic adverse effects such as extrapyramidal symptoms (EPS) and tardive dyskinesia are of most concern. The risk of tardive dyskinesia is much higher in elderly than younger patients treated with conventional antipsychotics.<sup>14</sup> The newer antipsychotics may offer a better risk:benefit ratio with reduced risk for the development of these adverse events that can be further minimized when these agents are administered at low doses.

### Risperidone

Early case reports of elderly patients with dementia first suggested that risperidone may reduce delusions and behavioral symptoms of aggression and agitation without substantial EPS or sedation.<sup>15,16</sup> In an open-label study of 109 nursing home patients, the authors reported that risperidone at 0.25 to 1 mg twice daily was safe and effective in the treatment of behavioral symptoms (agitation, aggression, verbal outbursts).<sup>17</sup>

More recently, the efficacy of low-dose risperidone in the treatment of psychotic and behavioral symptoms in

elderly patients with severe dementia was evaluated in 2 large, randomized, double-blind, placebo-controlled studies.<sup>18,19</sup> Most of the patients in both studies had AD (73% and 67%), and all had significant psychotic and behavioral symptoms. More than 90% were at Functional Assessment Staging 6A or higher. Baseline assessments of the patients included in these studies indicated aggression was the dominant symptom, particularly physical aggression.

In the first study, 625 elderly patients were randomly assigned to receive placebo or 0.5 mg/day, 1.0 mg/day, or 2 mg/day of risperidone for 12 weeks.<sup>18</sup> At endpoint, greater reductions in the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) total scores and psychosis and aggressiveness subscale scores were noted in patients receiving 1 and 2 mg/day of risperidone than in patients receiving placebo (all comparisons,  $p < .01$ ). In a subanalysis of patients who demonstrated overt violent behavior at baseline, approximately 70% of the patients receiving 1 or 2 mg/day of risperidone showed substantial reduction in aggressive behavior. The severity of EPS did not differ significantly between patients receiving 0.5 or 1 mg/day of risperidone and placebo; however, differences between 2 mg/day and placebo were significant ( $p < .001$ ).

In the second study,<sup>19</sup> 344 elderly patients were randomly assigned to receive placebo or flexible doses of risperidone or haloperidol (0.5 to 4 mg/day) for 12 weeks. The mean doses at endpoint were 1.1 mg/day of risperidone and 1.2 mg/day of haloperidol. Greater improvements in BEHAVE-AD aggressiveness scores and Cohen-Mansfield Agitation Inventory (CMAI) aggressiveness scores were noted with risperidone than with haloperidol or placebo (all comparisons,  $p < .05$ ). The severity of EPS with risperidone did not differ from placebo and was less than that noted with haloperidol.

The authors of both studies recommend low doses of risperidone (1 mg/day) and initiation of risperidone at low doses (0.25 mg twice daily) and with slow increments until symptoms improve.

### Olanzapine

There are 2 abstracts of unpublished reports of olanzapine in the treatment of psychosis and behavioral disturbances in nursing home patients with moderate to severe dementia.<sup>20,21</sup> In the first,<sup>20</sup> 238 elderly patients with psychotic and behavioral manifestations associated with AD were randomly assigned to receive 1 to 8 mg/day of olanzapine or placebo. In both efficacy and safety, olanzapine was not different from placebo in this trial. In a second multicenter, double-blind, placebo-controlled study,<sup>21</sup> 206 patients were randomly assigned to receive fixed-dose olanzapine (5 mg, 10 mg, or 15 mg/day) or placebo for 6 weeks. A 50% or greater improvement in symptoms (Neuropsychiatric Inventory-Nursing Home scale sum of agitation, delusions, and hallucinations) was seen in significantly more patients receiving 5 mg/day (56%) or 10

mg/day (57%) of olanzapine than placebo (36%;  $p < .05$ ). Severity of EPS was similar in patients treated with olanzapine and placebo. Adverse events at the 2 higher olanzapine doses included somnolence and accidental injury, each in 31%, and constipation in 7%.

## PARKINSON'S DISEASE

Parkinson's disease often becomes evident in persons over age 50 years and affects approximately 1% of those over age 65. Degeneration of dopamine neurons leads to abnormally low levels of dopamine in several areas of the brain. Abnormal motor symptoms such as bradykinesia, hypokinesia, rigidity, and tremor are the classic signs and symptoms of early Parkinson's disease. Treatment with dopamine agonists such as carbidopa-levodopa helps to restore dopamine levels. Most patients, however, require long-term therapy that generally results in overstimulation of the mesolimbic dopamine systems. These changes lead to dyskinesias and response fluctuations as well as psychotic symptoms. Risk factors in patients with Parkinson's disease for developing psychosis include coexistence of dementia, progressive sleep disturbances, and nighttime use of long-acting dopaminomimetics.<sup>22</sup>

Neuropsychiatric symptoms can include anxiety, depression, dementia, and psychoses. Approximately 20% of patients with Parkinson's disease receiving antiparkinsonian treatment will develop drug-induced psychosis, mainly hallucinations and delusions.<sup>23</sup> In Parkinson's disease patients, hallucinations are more common than delusions. Hallucinations are mostly visual, and delusions are most often paranoid in nature. Early signs and symptoms of psychosis in patients with Parkinson's disease include progressive impairment of cognition, alterations in sleep-wake cycle, conceptual disorganization, spontaneous or drug-induced hallucinations with retained insight, and intermittent confusion.<sup>22</sup>

Initial steps to address mild-to-moderate drug-induced psychosis in patients with Parkinson's disease should include the reduction of polypharmacy (if possible), correction of sleep disorder, and treatment of cognitive and affective symptoms as needed. Drug-induced hallucinations and delusions in Parkinson's disease patients may remit within a few days of discontinuing or reducing the doses of drugs most likely to be associated with psychotic symptoms, namely dopamine agonists. For about 50% of patients, however, dopaminomimetic medications can be reduced only so far before motor symptoms recur, causing concern.<sup>22</sup> Thus, additional reduction of antiparkinsonian drugs may not be helpful. For Parkinson's disease patients with psychosis, antipsychotic agents should then be considered.

Conventional antipsychotics should not be initiated because they often profoundly worsen parkinsonian symptoms. In addition, elderly patients with neurologic impair-

ments such as Parkinson's disease have a higher risk for tardive dyskinesia and acute EPS, common adverse effects associated with conventional neuroleptics.<sup>22</sup> Until recently, low-potency neuroleptics such as molindone and thioridazine were thought acceptable alternatives for the higher-potency haloperidol; however, experience with novel antipsychotics suggests that treatment with conventional antipsychotics is no longer recommended. Treatment of psychosis associated with Parkinson's disease has greatly improved with the advent of the novel agents.

### Clozapine

The benefit of clozapine treatment in patients with Parkinson's disease was first reported in 1985.<sup>24</sup> Many open-label trials have since supported this initial finding. A review of the literature revealed that, of more than 200 patients with Parkinson's disease and drug-induced psychosis, 90% had complete or partial resolution of their psychoses without worsening of EPS.<sup>25</sup> For the most part, clozapine was initiated at low doses (12.5 mg/day), which were slowly increased until resolution of psychotic symptoms; overall doses ranged from 6.25 mg every other day to 275 mg/day, with most patients receiving less than 125 mg/day. Adverse effects included sedation, sialorrhea, orthostasis, dizziness, and weight gain. These adverse effects generally resolved when clozapine doses were reduced. A few reports of psychotic aggravation have been published.

A chart review<sup>26</sup> of 49 psychotic patients with Parkinson's disease reported improved psychotic symptoms in 76% of the patients within 3 months and 71% to 80% of patients within 1 year. Significant improvement in psychosis has recently been reported with clozapine in 29 Parkinson's disease patients who received an initial dose of 6.75 mg/day of clozapine, which was increased to a maximum of 50 mg/day; parkinsonian motor symptoms did not change.<sup>27</sup> In another controlled study of clozapine in 6 Parkinson's disease patients,<sup>28</sup> psychotic symptoms were significantly improved, but 3 of the 6 patients dropped out of the study because of side effects (sedation and toxic confusional state); these were attributed to a rapid titration schedule and high target dose (up to 250 mg/day over a 10-day period).

It is recommended that treatment with clozapine be initiated at low doses (6.25 mg/day), with slow increases to induce the best response in Parkinson's disease patients. Interestingly, clozapine appears to benefit Parkinson's disease patients by reducing tremor, improving sleep, and relieving anxiety, depression, and hypersexuality. The most serious risk of clozapine is agranulocytosis, necessitating periodic white blood cell screening. Elderly patients are at higher risk for agranulocytosis than younger patients.

### Risperidone

The first use of risperidone to treat hallucinations in 6 patients with Parkinson's disease was reported in an open-

label trial: hallucinations were eliminated in 3 patients and were decreased significantly in 3.<sup>29</sup> Adverse effects were mild. In other open-label trials,<sup>30,31</sup> 0.5 to 2.5 mg/day of risperidone effectively controlled psychosis in patients with Parkinson's disease, although some experienced worsening of EPS or confusion. In 6 elderly Parkinson's disease patients (aged 66–79 years) with akinetic-rigid syndrome and psychosis, risperidone at 1 to 4 mg/day was associated with intolerable exacerbation of parkinsonism in 5 of the patients.<sup>32</sup> Four of the 5 improved when switched to clozapine. Only 1 patient, the youngest, did well on risperidone treatment. Workman et al.<sup>33</sup> reported significant improvement in agitation and psychotic symptoms in 9 patients with Parkinson's disease given risperidone (mean discharge dose = 1.9 mg/day) without worsening of EPS or further cognitive impairment. Risperidone was both efficacious and well tolerated in a recent open-label study, in which 17 Parkinson's disease patients aged 57–79 years with dopamine-induced psychosis received 0.5 to 3.0 mg/day (mean = 1.1 mg/day) of risperidone for 12 weeks.<sup>34</sup> Positive and Negative Syndrome Scale (PANSS) positive symptom scores decreased significantly during treatment, with a 60% improvement from baseline at endpoint. Clinical Global Impressions (CGI)-Severity scores also improved significantly. Moreover, parkinsonian symptoms, as measured by the Unified Parkinson's Disease Rating Scale, were unchanged.

Results of these studies indicate that starting doses of risperidone should be low (0.125–0.25 mg/day) with subsequent gradual dose titration. Most patients with Parkinson's disease will need between 0.25 mg/day and 0.5 mg/day.

### Olanzapine

In an open-label trial,<sup>35</sup> 15 psychotic Parkinson's disease patients without dementia were treated with olanzapine. Psychotic symptoms decreased significantly within 2 to 5 weeks of treatment, with no worsening of EPS. One patient discontinued treatment because of drowsiness. The initial dose was 1 mg/day, up to a maximum of 15 mg/day. Aarsland et al.<sup>36</sup> treated 14 elderly Parkinson's disease patients with psychosis (mean age = 77 years) with olanzapine (final dose of 3.9 mg/day) for 8 weeks. Seven discontinued treatment because of adverse events (sedation or confusion in 5); 6 of these also had dementia. Psychosis improved in the other 7 patients with no worsening of parkinsonian symptoms. Worsened motor function has been reported with olanzapine,<sup>37</sup> although the patient population in this study was more heterogeneous than in the original open-label study.<sup>38</sup> Severe akinetic-rigid EPS accompanied by paranoid symptoms were recently reported in a patient with Parkinson's disease given olanzapine for drug-induced psychosis.<sup>39</sup> Graham et al.<sup>40</sup> reported an increase in motor disability, noting that the starting dose, 5 mg/day, may have been too high for pa-

tients with Parkinson's disease. In a retrospective review<sup>41</sup> of 12 Parkinson's disease patients with psychosis treated with olanzapine, the authors reported that, while psychotic symptoms improved in 9 patients, all experienced a worsening of motor function, which was considered severe in 6.

Because of the blood monitoring required with clozapine, attempts to switch previously psychiatrically stable patients with Parkinson's disease to olanzapine have been reported. Worsening of parkinsonism, however, has been noted in 2 published reports.<sup>42,43</sup> In an open-label study,<sup>42</sup> 12 patients with idiopathic Parkinson's disease, 7 of whom were moderately demented and psychiatrically stable on clozapine treatment, were switched to olanzapine (2.5 mg/day). Parkinsonism worsened in 9 of the 12 subjects, who were switched back to clozapine. It is unclear whether this intolerance resulted from the administration of olanzapine or from the withdrawal phenomenon as a consequence of the abrupt discontinuation of clozapine. In another report, 2 Parkinson's disease patients previously treated with clozapine for visual hallucinations experienced worsening akinesia, rigidity, and psychiatric symptoms after switching to olanzapine (5 mg/day).<sup>43</sup> Both patients returned to their previous clinical states after discontinuation of olanzapine and restitution of clozapine.

### Quetiapine

In an open-label, long-term trial of 15 patients with advanced parkinsonism and related conditions, such as AD or dementia with Lewy bodies, as well as drug-induced psychosis, patients' psychoses improved markedly with quetiapine (median dose = 70 mg/day), despite progressing dementia.<sup>44</sup> There were no detectable EPS and little anticholinergic or prolactin-raising activity. Adverse effects included transient sedation, agitation, and dose-limiting tachycardia. In another study,<sup>45</sup> 35 Parkinson's disease patients with drug-induced psychosis received quetiapine, starting at 12.5 mg/day (mean dose after titration was 40.6 mg/day). Of the 24 neuroleptic-naïve patients, 20 had a marked improvement in psychosis without decline in motor function, while 3 discontinued quetiapine because of adverse events (orthostatic hypotension, headache, nausea, and persistent hallucinations). When 11 patients were switched to quetiapine from clozapine or olanzapine, 5 made the transition without loss of effect (Brief Psychiatric Rating Scale [BPRS] and Mini-Mental State Examination [MMSE] scores), but in 6 the change in medication was associated with confusion, erratic behavior, and increased hallucinations. In a 24-week study<sup>46</sup> of 9 Parkinson's disease patients with psychosis and dementia with Lewy bodies who received flexible doses of quetiapine (25–300 mg/day), all patients showed a marked improvement in psychosis with no significant worsening of motor function or cognition. Menza et al.<sup>47</sup> recently re-

ported on 3 Parkinson's disease patients with drug-induced psychosis previously managed with clozapine who were successfully switched to quetiapine (12.5 to 150 mg/day) with no worsening of parkinsonian symptoms.

Forty patients were included in a 1-year trial of quetiapine in elderly psychotic patients with Parkinson's disease.<sup>48</sup> Patients received 25 to 800 mg/day, depending on clinical response and tolerability (mean dose = 75 mg/day). Significant improvement in psychotic symptoms (BPRS and CGI scores) was noted after 12 weeks of treatment with quetiapine and was maintained throughout the 52-week trial. Overall, no worsening in motor symptoms was noted. In fact, a short-term (week 12) initial improvement in motor symptoms was noted, but the symptoms returned to baseline levels by the end of the trial. Additional controlled clinical trials are needed to further explore the potential clinical benefits of quetiapine in Parkinson's disease patients with psychosis.

### DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies is probably the second most common dementia after AD, and its clinical, pathologic, and genetic features overlap with those of AD and Parkinson's disease. Clinically, dementia with Lewy bodies is characterized by progressive cognitive impairment progressing to dementia, spontaneous parkinsonism, and psychosis with recurrent visual hallucinations.<sup>49</sup> Visual hallucinations occur in about 80% of patients.

Some patients with dementia with Lewy bodies are supersensitive to antipsychotics and thus use of these agents for behavioral and psychotic symptoms common in this disease can be difficult. In 20 cases of autopsy-confirmed dementia with Lewy bodies, 13 of the 16 patients treated with conventional antipsychotics developed neuroleptic sensitivity syndrome (with severe reactions in 7), resulting in increased morbidity and mortality.<sup>50</sup> Sensitivity to risperidone has also been reported in 3 patients aged 63, 88, and 91 years who met clinical diagnostic criteria for dementia with Lewy bodies.<sup>51</sup> Two cases of extreme sensitivity to clozapine in patients with dementia with Lewy bodies have been reported, with an increase in confusion and behavioral symptoms.<sup>52</sup>

Several case histories have been published on the use of risperidone to treat psychotic and behavioral symptoms associated with dementia with Lewy bodies. One case report<sup>53</sup> suggested that risperidone combined with an acetylcholinesterase inhibitor such as donepezil might be useful for patients with the disease. A 74-year-old psychotic man had been treated with 5 mg/day of loxapine before hospital admission, but his parkinsonism worsened. On hospital admission, he was diagnosed with dementia with Lewy bodies, loxapine treatment was discontinued, and a low dose of risperidone (0.25 mg) was initiated. The frequency of his psychotic experiences decreased, and he

acted less frequently on his psychotic experiences. However, his subjective distress continued. Because of a previous report of successful treatment of dementia with Lewy bodies with an acetylcholinesterase inhibitor, 5 mg of donepezil was added. Significant subjective and objective improvement occurred within 2 weeks. His psychosis was eliminated, and his sleep, expressive aphasia, and constructional apraxia all improved. He was discharged and remained symptom-free for at least 2 months. The authors suggested that a controlled trial of donepezil and small doses of risperidone be conducted in patients with dementia with Lewy bodies. In another case report,<sup>54</sup> hallucinations and delusions resolved in a 74-year-old woman with dementia with Lewy bodies treated with risperidone. Risperidone was titrated to 5 mg/day over 10 days; however, the patient developed increased drowsiness and confusion. After the dose had been reduced to 1.0 mg/day, her mental and cognitive state improved and her psychosis remained in remission. Allen et al.<sup>55</sup> treated behavioral and psychotic symptoms of dementia with Lewy bodies in 3 patients with risperidone (0.5 to 1.0 mg/day). Improvements in both behavioral and psychotic symptoms were noted in all 3 patients. With conventional neuroleptic treatment, cognitive decline in such patients is common, but no decline was observed in these patients while receiving risperidone.

In the section on Parkinson's disease above, a 24-week study<sup>46</sup> is cited in which 9 patients with Parkinson's disease, psychosis, and dementia with Lewy bodies showed a marked improvement when treated with quetiapine. In an open-label trial, 2 of 8 patients with dementia with Lewy bodies with psychosis and behavioral disturbances showed improvement when treated with olanzapine (2.5 to 7.5 mg/day).<sup>56</sup> Three other patients gained only minimal benefit, and the other 3 patients had to discontinue treatment because of adverse effects.

### HUNTINGTON'S DISEASE

Huntington's disease is an autosomal dominant hereditary movement disorder characterized by chorea, dementia, and psychiatric features. Age at onset is variable, and approximately half of the patients experience psychiatric symptoms, including depression, apathy, irritability, and mania. The psychotic symptoms generally occur early in the illness and may even occur before the movement disturbances.

Risperidone has been successfully used to treat the psychotic symptoms in patients with Huntington's disease.<sup>57-61</sup> In one report,<sup>60</sup> a woman with a strong family history of Huntington's disease presented with psychotic symptoms, cognitive deficits, personality problems, gradual deterioration of her level of functioning, and genetically confirmed Huntington's disease. She received 4 mg/day of risperidone during 2 weeks of hospitalization. On discharge,

her psychotic symptoms associated with Huntington's disease were effectively controlled without any significant adverse effects.<sup>60</sup> Four patients with Huntington's disease (1 genetically confirmed, 3 with a positive family history) and various degrees of motor disabilities but no psychotic symptoms had been unsuccessfully treated with haloperidol and benzodiazepines.<sup>61</sup> Risperidone was started at 3 mg/day with no significant improvement in the involuntary movements. Twenty-five days after the dose had been increased to 6 mg/day, substantial reductions in abnormal movements were noted together with general improvement in usual daily activities.<sup>61</sup> A fifth Huntington's disease patient with psychosis but no movement or cognitive disorders showed marked reduction in psychotic symptoms when treated with 3 mg/day of risperidone.

In a double-blind trial,<sup>62</sup> 33 patients with Huntington's disease were randomly assigned to receive clozapine (up to 150 mg/day) or placebo for 31 days. Improvement in abnormal involuntary movements was noted only in the neuroleptic-naive patients, with no effect noted in patients who were receiving neuroleptics. A high proportion of the clozapine-treated patients experienced adverse effects, including drowsiness, fatigue, anticholinergic symptoms, and walking difficulties.

### MULTIPLE SCLEROSIS

Multiple sclerosis is a demyelinating disorder characterized by motor and ocular symptoms. It usually becomes evident in patients in their 20s or 30s. Depression, mania, and psychotic symptoms are common neuropsychiatric sequelae<sup>63-65</sup> and may result from the interruption of the integrity of frontotemporal circuits by demyelinating lesions. Psychoses can occur in patients with MS, and treatment of these psychoses is probably warranted.

Clozapine was reported to be effective in the treatment of a 43-year-old psychotic patient with MS who presented with paranoid delusions, thought disorder, and deterioration of self-care.<sup>66</sup> She had been treated successively with trifluoperazine, thioridazine, a single trial of intramuscular fluphenazine decanoate, and sulpiride, but all resulted in severe EPS without any improvement of her psychosis. Concurrent trihexyphenidyl was associated with severe constipation and urine retention. All medications were withdrawn, and clozapine was initiated and gradually increased to 125 mg/day. Her psychosis steadily improved, and her score on the BPRS fell from 71 to 43 after 4 months of treatment with clozapine. Improvement in psychosis continued after 12 months of treatment (BPRS score = 34). No EPS were reported with clozapine.

Drug-induced priapism has been reported with phenothiazines, butyrophenones, clozapine, and olanzapine.<sup>67</sup> In one recent report, a 68-year-old man with a 40-year history of MS experienced priapism after receiving 2 daily 5-mg doses of olanzapine on the 5th day of a hospital stay.

The patient was receiving polypharmacy with doxazosin, furosemide, benazepril, lansoprazole, gabapentin, and perphenazine for other medical conditions.

## DELIRIUM

Delirium, an acute confusional state characterized by fluctuating levels of consciousness and global impairment of cognitive functioning, is particularly common among elderly medical and surgical patients.<sup>68</sup>

A report<sup>69</sup> of 2 patients with delirium treated with risperidone has been published. One was a 60-year-old man admitted to the hospital for the treatment of sepsis and pneumonia who suffered a cardiac arrest and was resuscitated for 46 minutes, after which he was withdrawn, apathetic, and disoriented. Delirium due to multiple etiologies, including hypoxic brain injury and hyponatremia and a combination of medications, was diagnosed on the 23rd day of his hospital stay. The other patient was a 14-year-old boy admitted to the hospital after a suicide attempt. He was apathetic and withdrawn, laughing inappropriately at times as though responding to internal stimuli. His gait was unsteady, and he had shifting levels of consciousness and concentration and was disoriented to place and time. The diagnosis was delirium due to hypoxic brain injury. In both cases the delirium was successfully treated with risperidone, 1 mg twice daily. In a further report,<sup>70</sup> 9 additional patients with delirium were treated with risperidone. Their medical diagnoses included sepsis with hypoxic encephalopathy, acquired immunodeficiency syndrome (AIDS), lung cancer with brain metastases, diabetes, traumatic brain injury, and urinary tract infection. After a mean duration of 9 days of risperidone treatment (mean dose = 1.6 mg/day), improvement was marked in 4 patients, moderate in 1, and minimal in 1, and 3 patients showed no improvement. Extrapyramidal symptoms were noted in 1 patient at 3 mg/day of risperidone, but these resolved when the dose was reduced to 2 mg/day.

In another report,<sup>71</sup> 11 hospitalized patients with delirium were treated with olanzapine (mean dose = 8.2 mg/day) and 11 were treated with haloperidol (mean dose = 5.1 mg/day) for a mean of 16 days (range, 2–74 days). Moderate-to-marked improvements (according to scores on the Delirium Rating Scale) were noted in 8 of the 11 patients in each treatment group. No adverse events were noted in the olanzapine patients; however, 3 patients in the haloperidol group had EPS, and 2 were excessively sedated. Olanzapine has also been used to treat complicated delirium in a 59-year-old cancer patient who had been treated unsuccessfully with low doses of haloperidol (0.5–2 mg/day) and had developed EPS.<sup>72</sup> Olanzapine treatment was initiated at 5 mg daily, which was then increased to 10 mg nightly with 2.5 mg as needed during the day. After 3 days, the patient's mental status was normal, and she was discharged.

One report<sup>73</sup> of quetiapine in the treatment of delirium has been published. In a retrospective review, charts of 2 matched groups of patients with delirium were evaluated: quetiapine (mean dose = 211.4 mg/day) was received by 11 patients and haloperidol (mean dose = 3.4 mg/day) by 11. A reduction of > 50% in scores on the Delirium Rating Scale was seen in equal numbers of quetiapine patients (10 of 11) and haloperidol patients (10 of 11). The time to peak response was similar in the 2 groups (6.5 days in the quetiapine group and 7.6 days in the haloperidol group). EPS were reported by 2 of the haloperidol patients and by none of the quetiapine patients. Quetiapine was discontinued in 1 patient because of sedation.

## CONCLUSION

Psychosis and behavioral disturbances associated with neurodegenerative diseases may be drug induced or intrinsic to the underlying pathology and are often the result of both. These symptoms cause the greatest disability and increase the stress on caregivers. Nonpharmacologic methods of treatment may be effective for mild symptoms. Drug-induced psychosis, particularly with antiparkinsonian therapy, can sometimes be eliminated when doses are reduced. However, reduction in medication may aggravate motor symptoms and may not reduce the psychosis. Because psychosis and behavioral disturbances often leave caregivers no alternative but institutionalization, it is imperative that other measures such as antipsychotic therapy be initiated.

Although conventional neuroleptics have been shown to be effective in the treatment of these behaviors, unacceptable adverse effects such as EPS and tardive dyskinesia may occur. Recent experience with the novel antipsychotic agents has shown promise in the treatment of psychosis and behavioral disturbances associated with neurodegenerative disorders. Furthermore, the novel antipsychotics appear to offer a better risk:benefit ratio with reduced risk for development of these adverse effects.

In AD, risperidone has the largest body of evidence from controlled clinical trials. In the reported trials to date, risperidone ameliorated behavioral symptoms, particularly aggression and agitation. Limited data with olanzapine also indicate that it may be efficacious. In patients with Parkinson's disease, clozapine has been shown to be an efficacious agent in the treatment of psychotic symptoms. Because clozapine requires routine white cell monitoring, its use may be limited in particular settings and in those at high risk for agranulocytosis, such as the elderly. Both risperidone and olanzapine appear to be efficacious and well tolerated; however, adverse events and exacerbation of parkinsonism have been noted, particularly in the very elderly and at higher doses. Quetiapine appears to be as efficacious as the previously discussed novel antipsychotics with a better safety record than either risperidone

or olanzapine and without the blood monitoring required with clozapine treatment.

There appears to be a high risk for the neuroleptic sensitivity syndrome with conventional antipsychotics in the treatment of dementia with Lewy bodies. Current experience with risperidone (perhaps combined with an acetylcholinesterase inhibitor) and quetiapine has shown these agents to be generally safe and efficacious in dementia with Lewy bodies. At the present time, no information on the use of olanzapine in this disease is available. Risperidone has shown some promise in the treatment of movement disorders and psychotic symptoms associated with Huntington's disease. No other information on the use of the other novel antipsychotics for Huntington's disease patients is available. Psychotic symptoms were controlled in a patient with MS who was given clozapine. Finally, risperidone, olanzapine, and quetiapine have been reported to be efficacious in patients with delirium.

The experience reported here suggests that the novel antipsychotics hold considerable promise for patients suffering from psychosis and behavioral disturbances associated with neurodegenerative diseases, especially with their low risk for inducing EPS. However, it is evident that these agents need to be further evaluated in controlled trials in the treatment of these disorders to confirm these results.

*Drug names:* benazepril (Lotrel), carbidopa-levodopa (Sinemet), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), donepezil (Aricept), doxazosin (Cardura), furosemide (Lasix and others), gabapentin (Neurontin), haloperidol (Haldol and others), lansoprazole (Prevacid), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine), trihexyphenidyl (Artane and others).

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