Psychotic symptoms are common in patients suffering from Parkinson’s disease (PD). Visual hallucinations are the most common manifestation, occurring in approximately 30% of patients with PD. These hallucinations tend to appear suddenly, in one field of vision, several times a day. The hallucinations are usually composed of complex forms; they often appear to move and occur almost exclusively when the eyes are open. Auditory (10%) and tactile (8%) hallucinations may also occur with PD, but these usually exist in concert with visual hallucinations. Although PD patients with hallucinations typically have intact reality testing (benign hallucinosis), at least 5% of patients experience delusions and hallucinations unaccompanied by insight. In comparison to psychogenic psychoses, PD-related psychosis results in more visual hallucinations and sleep disturbances, but disruption of thought processes and delusions are less common. Unlike delirium, PD-related hallucinations occur in the setting of a clear sensorium. Socioeconomic sequelae of PD-related psychosis include higher caregiver stress, increased rates of nursing home placement, and dramatically worsened prognosis in extended care facilities. Unfortunately, hallucinations in PD tend to persist and, not uncommonly, may worsen over time.

Multiple risk factors for PD-related hallucinations have been identified. Psychotic symptoms usually occur in cases of advanced, chronically treated PD. In fact, early emergence of hallucinations or delusions often implies the presence of other Parkinsonian syndromes (eg, dementia with Lewy bodies) or a preexisting, unrevealed psychiatric disorder. Additionally, the use of all anti-PD medications, without exception, has been implicated in the development of hallucinations. Chronic exposure to multiple anti-PD medications appears to be a particularly potent risk factor for their occurrence. In Goetz et al’s longitudinal assessment of 89 PD patients, low Mini Mental State Examination (MMSE) scores and high Unified Parkinson’s Disease Rating Scale (UPDRS) scores were associated with the presence of hallucinations. A cross-sectional study of 172 PD patients found hallucinations to be independently associated with depression, particularly in the young and demented (odds ratios 76.0 and 10.2, respectively) patients. Vivid dreams and nightmares, which in some studies have been correlated with duration of levodopa therapy, may also be harbingers, if not epiphenomena, of PD-related hallucinations. Although Pappert et al found no relationship between sleep disturbances and hallucinations, they did describe a significant correlation between dream phenomena and psychotic symptoms. The relationship between sleep disturbances and PD-related hallucinations is described in more detail below.
PATHOPHYSIOLOGY

For decades, scientists have examined the relationship between dopamine (DA) and altered perceptions. Excessive dopaminergic activity, probably in mesocortical and mesolimbic systems, appears to play a role in the generation of hallucinations. This action may be mediated by DA's influence on glutamatergic systems. It is well recognized that dopaminergic agonists, such as cocaine and amphetamine, can induce psychotic states; conversely, dopamine antagonists such as haloperidol and pimozide are effective antipsychotics. There are experimental suggestions that chronic stimulation may cause persistent sensitization of dopamine receptors, thereby causing susceptibility to psychotic phenomena. Exogenous dopamine is clearly not the only factor in the pathophysiology of hallucinations. There were reports of hallucinations in PD patients before dopaminergic drugs became available, indicating that the illness itself may play some role in generating psychosis. A similar quality of psychosis is found in PD patients taking anticholinergic drugs, which, technically, do not have a direct effect on the dopaminergic system. Studies of hallucinating PD patients have also demonstrated that psychosis severity and medication doses are poorly correlated.

Serotonin (5-HT), another monoamine neurotransmitter, is also thought to play a role in producing psychotic symptoms. The body of evidence for 5-HT's involvement parallels that cited for dopamine—namely, that agonists at the 5-HT2 receptor (eg, lysergic acid diethylamide and 3,4-methylenedioxy-methamphetamine) can induce hallucinations, and blockade of 5-HT receptors (eg, with novel antipsychotics) can ameliorate psychosis. The relationship between serotonergic systems and PD-related psychosis remains unclear. The purported efficacy of atypical antipsychotic (AA) agents, such as clozapine and quetiapine, without worsening motor function, has been partly attributed to their affinity to 5-HT receptors.

The role of acetylcholine (ACh) is also under investigation. Some neuropathological specimens of patients with dementia with Lewy bodies indicate that levels of choline acetyltransferase (ChAT) were lower and the ratio of 5-hydroxyindoleacetic acid to ChAT was higher in hallucinating than in nonhallucinating patients. Marked degeneration of cholinergic neurons is evident in the brains of PD patients, possibly to a greater degree than that seen in patients with Alzheimer's dementia. Goetz et al, after effectively treating hallucinations by reducing anticholinergic and/or dopaminergic agents, postulated that acetylcholine blockade might induce PD-related hallucinations. The mechanism they suggested was acetylcholine's reciprocal relationship with dopamine in limbic cortex. PD causes degeneration of cholinergic pedunculopontine neurons, which control rapid eye movement (REM) sleep, leading some authors to hypothesize that hallucinations may be fragments of dreams that are released from the usual cholinergic inhibition.

The relationship between sleep disturbances and hallucinations is another fertile area of study. In Moskovitz et al’s retrospective study of 88 patients being treated for PD, 30.7% of the patients experienced vivid dreams and 29.5% had hallucinations attributable to their treatment. Vivid dreams preceded or accompanied 61.3% of the hallucinations experienced by subjects. The investigators argued that vivid dreams and nightmares were precursor or subsyndromal forms of frank psychosis. Many in the PD community accept that view today. Arnulf et al reported that all 10 of the hallucinating PD patients they studied had clinical histories consistent with a sleep disorder, in contrast to only 4 of the 10 nonhallucinating PD patients. Polysomnography revealed abnormal muscle activity during REM sleep in 7 of the hallucinating patients, compared to 5 of the nonhallucinating patients. In another study of 20 PD patients with visual hallucinations, 8 of the patients' 24 hallucinations were temporally related to sleep, occurring within 40 seconds of the last polysomnographically confirmed sleep epoch. One potential explanation why certain AA drugs work better for drug-induced psychosis in PD compared to other antipsychotics may be related to differential effects on sleep architecture. Studies on how AA agents modify sleep architecture in PD are currently under way.

Abnormalities of visual processing may also contribute to PD-related hallucinations. Visual dopaminergic systems, even at the level of the retina, are impaired in PD patients, but no definite functional correlate of this pathology has been identified. Various other abnormalities have been discovered in visual networks of PD patients, including dysfunction of visual processing and categorization. In a study of 35 PD patients (14 with hallucinations) with normal visual acuity and no dementia, testing revealed impairments of color vision and contrast sensitivity in all patients; those with hallucinations fared significantly worse. In patients with PD, deficits in color discrimination and contrast sensitivity also progressed over time, particularly in patients with compromised psychiatric functioning. In addition to their difficulty with perceiving basic visual stimuli, Barnes et al's cohort of hallucinating PD patients appeared to have difficulty distinguishing between images they saw and images created in their own minds. They also had a greater tendency than nonhallucinating patients to report having seen or imagined a visual stimulus that they did not see.

Despite the lack of histopathological studies and a unifying hypothesis for the pathogenesis of hallucinations in PD, there has been some recent further evidence for a role of the visual system. Goetz and Stebbins studied fMRI in both hallucinators and nonhallucinators with PD. Both groups activated posterior areas and the occipital lobes to visual stimuli, but the hallucinators also activated...
the frontal lobes. Their evidence is supportive of the notion that nonhallucinators process visual information in the occipital/temporal and posterior parietal areas, whereas hallucinators use frontal activation.43 Future studies may help us to elucidate the role of the frontal cortices in hallucinations and to develop a unifying pathophysiologic hypothesis.

The multiple neurochemical and neuropsychological abnormalities that are associated with psychosis in PD suggest that no single brain structure accounts for the PD-related hallucinations. Areas other than the substantia nigra that undergo degeneration in PD include the nucleus basalis of Meynert. Interestingly, Diederich et al reported a case of reversible visual hallucinations resulting from deep brain stimulation of the region of the subthalamic nucleus in a PD patient. The hallucinations occurred in the absence of pharmacological treatment and were extinguished by clozapine.44 It is unclear whether part of a circuit relevant to psychosis was stimulated or whether the stimulation unmasked an underlying tendency toward hallucinations. This finding has not since been reported, but future study of this region will be important to clarify the findings. Other potentially relevant sites include the thalamus and occipital and temporal cortices.

TREATMENT

General Considerations
As in any geriatric and/or neurological patient, urinary and pulmonary infections, metabolic and endocrine derangements, cerebral hypoperfusion states, and even social stressors such as changes in the environment are potential precipitating factors for delirium and psychosis in PD. A search for these correctable causes is always required. Resolution of the underlying medical illness may completely reverse psychosis.1,7,45,46

Another easily ignored etiology is the addition of medications with central nervous system effects such as narcotics, hypnotics, antidepressants, anxiolytics, and any pharmacologic agent that crosses the blood-brain barrier, including anti-PD medications.

Decreasing Dopaminergic Stimulation
If psychotic symptoms persist despite the withdrawal of psychotropic medications, anti-PD medications are then gradually reduced or, if possible, discontinued. When a PD patient is on multiple medications, most authorities slowly “peel off” anti-PD drugs in the following order: anticholinergic agents, selegiline, amantadine, dopamine agonists, then catechol-O-methyltransferase (COMT) inhibitors, and finally, levodopa.47,48 Often, reliance on the regular/short-acting formulation of levodopa is preferred over the sustained-release formulation because its pharmacokinetics are more predictable and the shorter half-life means less potential for the cumulative side effects of repeated dosing. If psychosis improves, the patient is then maintained on the lowest possible dose of anti-PD medications. However, withdrawal of anti-PD drugs usually worsens parkinsonism and may not be tolerated. The use of an AA agent is then recommended.

Atypical Antipsychotic Drugs
The choice of an AA agent is based largely on its ease of use and side effect profile, as most antipsychotic reports, with few exceptions, have comparable efficacy in improving psychosis. The main difference in the antipsychotic agents lies in their propensity to worsen motor functioning in this frail and already vulnerable population. Thus far, 6 drugs have been marketed in the United States as “atypical”: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. In general, the use of an AA agent allows the clinician to control psychosis with fewer motor side effects and, in some cases, without the need for cutting back on anti-PD medications.

It remains unclear whether antipsychotic medications should be continued once they are initiated. While there are some data that show persistence of hallucinations in PD patients with drug-induced psychosis after their initial occurrence, there is little direct evidence that confirms the need for lifelong use of antipsychotic agents.11,12 Moreover, antipsychotic drugs are not completely benign.49,50 To determine if psychosis-free PD patients could be successfully weaned off their antipsychotic medication, one study prospectively followed PD patients on successful long-term treatment with quetiapine or clozapine as these drugs were withdrawn.51 The study was aborted after enrollment of only 6 patients due to an unacceptable rate of psychosis recurrence (5 patients, 83%). Patients were weaned off their antipsychotic medication over an average of 4 weeks. Psychosis recurred within 2 months of the end of each taper. In 3 patients, the “rebound psychosis” was worse than the original psychotic episode that prompted AA use, and it required higher AA doses to control the acute symptoms. All 3 patients had a history of benign visual hallucinations. Upon discontinuation, in addition to the recurrence of their visual hallucinations, 2 of the 3 patients developed paranoid delusions and 1 patient developed threatening auditory hallucinations.

Clozapine
Clozapine is a dibenzodiazepine derivative. It causes neither catalepsy in rodents nor parkinsonism in humans, even at high doses.52 The cumulative experience of all open-label reports on clozapine in parkinsonism involving more than 400 patients has been surprisingly consistent.48 First, low doses are required. While the usual dose in schizophrenia is 300-900 mg/d, PD patients with psychosis required an average of 25 mg/d given as a single bedtime dose, with some patients requiring only 6.25 mg/d.42 Another obser-
vation was the speed and consistency of response. Many patients enjoyed complete resolution of psychosis in 1 day, and most improved significantly in a week or two. A meta-analysis of all large clozapine reports on psychosis in PD showed an 85% improvement rate with acceptable tolerance.42,53 Most important, clozapine did not worsen motor symptoms. In some reports, it actually improved tremor.54-59

The lone negative report was also the first double-blind placebo-controlled trial.60 It used a small number of patients at a single site and reported worsened parkinsonism and poor drug tolerance. However, this trial was undermined by the lack of experience with clozapine in the PD population at that time. The authors treated the patients as if they were young schizophrenia patients, beginning with clozapine 25 mg per day and increasing by 25 mg each day. This resulted in severe sedation, partly manifested as worsened parkinsonism.

It was not until 1999 that 2 well-designed, placebo-controlled double-blinded positive trials were published, making clozapine the gold standard AA for the treatment of psychosis in PD.61,62 In the US trial, 60 patients were enrolled at 6 sites and treated with clozapine, starting at 6.25 mg/d and increased to a ceiling dose of 50 mg/d. Motor function was rated using the UPDRS. Clozapine, at a mean dose of 25 mg/d, improved psychosis, as measured on each of 4 different neuropsychiatric scales. The overall motor function improved slightly, but tremor improved significantly. Only 1 patient required study termination after suffering a decline in white blood cell (WBC) count, which recovered in 1 week.61 The French study also involved 60 patients and a very similar protocol. Published in letter form, the results are less detailed than the US study but almost identical.62

Despite clozapine’s freedom from motor worsening in PD, it has been difficult to use because of its potential for inducing agranulocytosis. The problem is idiosyncratic, so that even the small doses used in PD do not exempt patients from this side effect. Nonetheless, leukopenia is usually transient, as was the agranulocytosis in both reported PD cases.63,64 The small numbers involved, along with the variability of reporting, suggests that there is a lack of evidence to indicate whether PD patients are more likely than age-matched controls to suffer clinically significant abnormalities of WBC count. As far as we are aware, no deaths due to agranulocytosis have occurred in PD. In the United States, for the first 6 months, each patient on clozapine undergoes a weekly WBC count, verified by the pharmacy, and can receive only 1 week’s supply of the drug at a time. After 6 months, the process becomes biweekly. Thus, with the cumbersome requirement to maintain a patient on clozapine, each newly released AA agent has been tried in PD in the hope of reducing clozapine to being a secondary agent, rather than the drug of choice.

In 2002, a Movement Disorders Society task force that considered all well-designed peer-reviewed reports on clozapine in PD concluded that low-dose clozapine is efficacious in short-term improvement or clearing of hallucinosis/psychosis in PD with “acceptable risk with specialized monitoring,” but there is insufficient evidence for its long-term efficacy.65

In support of its long-term efficacy and safety, a retrospective analysis of 39 parkinsonian patients on clozapine for a mean duration of 60 months showed 85% with continued partial/good response and 13% with complete resolution of psychosis on clozapine.66 Thirteen of the 39 patients (33%) were eventually admitted to nursing homes. Six of them (46%) died over a period of 5 years—a significant improvement over previously reported 2-year mortality rates approaching 100% among nursing home residents with PD and psychosis.11 The overall 5-year mortality rate in this cohort was 44% (17/39).

In summary, there are strong data to support the use of low-dose clozapine in PD patients with psychosis. However, clozapine still requires onerous monitoring, making its use problematic and the search for a practical and “low-maintenance” first-line treatment for psychosis in PD an important goal.

Risperidone

The second AA drug released in the United States was readily discovered to be less atypical than clozapine.67,68 Risperidone causes dose-related problems typical of conventional neuroleptics, such as prolactin elevation and acute dystonic reactions. Almost all reports concerning risperidone in PD have involved open-label studies. Unfortunately, the studies showed mixed results. A meta-analysis of 82 PD patients treated with risperidone revealed that 23 (33%) experienced motor worsening.69

The only double-blinded study of risperidone in PD was a small trial comparing low-dose clozapine to low-dose risperidone in 12 patients.70 Two patients on clozapine and 1 on risperidone dropped out. Parkinsonism worsened in 1 clozapine-treated patient and 3 risperidone patients. Although the mean UPDRS improved in the clozapine group and worsened in the risperidone group, this was not statistically significant. The mean improvement in the Brief Psychiatric Rating Scale (BPRS) psychosis score was similar between the groups.

One article casting doubt on the “atypicality” of risperidone compared the development of various extrapyramidal symptoms in young neuroleptic-naïve patients with primary psychoses receiving either risperidone (mean dose 3.2 mg/d) or haloperidol (mean dose 3.7 mg/d).71 There were no significant differences in the incidence of parkinsonism (59% versus 52%) or akathisia (50% versus 39%). Another study found that in human patients with schizophrenia under the age of 65, risperidone induced more prolactin elevation than higher haloperidol doses.72

It is unclear why the results of open-label risperidone studies in PD vary so widely. It is likely that the conflicting results reflect the open-label nature of the studies, vari-
able sophistication of the authors’ ability to recognize and assess parkinsonism, the speed of titration, and duration of the observations. At the time of the 2002 Movement Disorders Society Task Force report, studies performed on risperidone were of inadequate quality or size to make any conclusion regarding its efficacy or safety in the PD population. Nonetheless, there are enough data to suggest that risperidone behaves more like a low- to medium-potency conventional neuroleptic than an AA even among schizophrenia patients. Its effect on motor function in PD has been mixed.

**Olanzapine**

Olanzapine is a thiobenzodiazepine of similar chemical structure to clozapine. It offered more promise than risperidone for being atypical. If it elevates prolactin in humans, it does so only transiently. In animal models, only very high doses induce catalepsy or block amphetamine-induced stereotypy, but it has been reported to induce acute dystonic reactions and tardive dyskinesia.

As with risperidone, the first publication of olanzapine in PD was very positive. Psychosis improved in 15 nondemented PD patients without motor worsening. Shortly thereafter, Jimenez-Jimenez et al published the first of several negative reports to follow. A meta-analysis of these studies shows motor worsening in about 40% of PD patients.

Only 2 olanzapine studies reported no patients with worsened motor function. Fortunately, there have been double-blinded trials on olanzapine in PD. A single-site double-blinded trial comparing olanzapine to low-dose clozapine for psychosis in PD enrolled only 15 patients before the safety monitoring committee aborted the study due to worsened motor function in 6 of 7 olanzapine-treated patients. No worsening occurred in the clozapine group. The mean olanzapine dose was 11.2 mg/d.

In another double-blind, placebo-controlled trial, olanzapine was tested in nonpsychotic PD patients with levodopa-induced dyskinesias based on similar reports using clozapine. Every patient randomized to olanzapine suffered intolerable motor effects.

The task force on evidence-based review on the treatment of psychosis in PD fittingly concluded that there is insufficient evidence to demonstrate efficacy of olanzapine in drug-induced psychosis, and it carries an “unacceptable risk of motor deterioration,” even at low conventional doses.

**Quetiapine**

Quetiapine is a dibenzothiazepine with the closest pharmacologic resemblance to clozapine but without the risk of agranulocytosis. It is a strong 5-HT2 receptor antagonist and a moderate D2 receptor antagonist, does not block apomorphine-induced stereotypy, and does not alter prolactin levels. It has not yet been cited as a cause of any acute dystonic reaction among previously neurolepticaive individuals.

Unfortunately, quetiapine has been subject to only one small single-center, double-blinded trial, the results of which have been presented only in abstract form. Due to the lack of double-blinded trials, the 2002 Movement Disorder Society Task Force resolved that there is insufficient evidence to conclude on the efficacy or safety of quetiapine in treating drug-induced psychosis in patients with PD. However, several open-label reports involving more than 200 PD patients give a fairly solid positive impression on the drug’s standing as an AA.

Of the larger, long-term PD studies on quetiapine, Reddy et al reported on 43 consecutive quetiapine-treated PD patients for a mean duration of 9.7 months. Eighty-one percent had improved psychosis. Five patients (13%) experienced mild worsening of motor symptoms, but none were sufficient to stop the drug. Only demented patients had motor worsening on quetiapine.

Similarly, Fernandez et al reported on 106 parkinsonian patients treated at a single PD center with quetiapine. Seventy-eight of 106 patients (74%) remained on quetiapine for a mean duration of 15 months at an average dose of 60 mg/d. Eighty-seven (82%) patients had partial or complete resolution of their psychosis, whereas 19 (18%) patients had no improvement on quetiapine. Motor worsening was noted in 34 (32%) patients but was rarely sufficient to warrant study discontinuation. Demented subjects had a 12-fold increased risk of nonresponse to quetiapine. Similar to Reddy et al’s report, patients who developed motor worsening tended to be more demented.

The only double-blind, placebo-controlled study of quetiapine use in PD psychosis, presented in abstract form, involved 20 patients placed on quetiapine and 10 patients on placebo. Although quetiapine doses of up to 200 mg per day were well tolerated and did not worsen the UPDRS scores compared to placebo, there was no significant difference in the BPRS psychosis scores between the 2 groups. It may be that the sample size was too small to detect any difference.

Taking into consideration all open-label reports, quetiapine appears to be slightly less effective than clozapine against psychosis. However, one open-label trial comparing the efficacy of quetiapine or clozapine in 20 PD patients with psychosis showed no difference in the BPRS and Clinical Global Impression Scale improvement scores between the 2 groups. There was also no worsening in the UPDRS motor scores of either group.

Quetiapine, unlike clozapine, does not improve tremor and may induce mild motor worsening. But, unlike olanzapine and risperidone, no reported motor worsening on quetiapine has precipitated hospitalization. The majority of motor decline, especially in long-term trials, was mild or could be attributed to PD progression. The mean daily dose was generally below 75 mg/d.
Ondansetron was tested for treatment of schizophrenia and has a higher affinity for 5-HT2 than D2 receptors. There has been no report on its use in the PD population. With the historically lower dose requirement of antipsychotic drugs in PD compared to schizophrenia patients, the inability to cut ziprasidone in half (it comes in a capsule) makes it a difficult and perhaps a riskier drug to initiate in PD. A panel of expert psychiatrists reviewing all available data on ziprasidone use in schizophrenia concluded that its extrapyramidal symptoms profile is “better than risperidone, the same as olanzapine but not quite as good as quetiapine or clozapine.”

### Ziprasidone
Ziprasidone was the fifth marketed antipsychotic with a partial agonist at the D2 and 5-HT1a receptors and an antagonist at 5-HT2a receptors. It also has a high 5-HT2/D2 ratio and may therefore carry a low risk of extrapyramidal side effects while effectively alleviating psychosis in Parkinson-vulnerable populations. Our preliminary experience with aripiprazole, however, is mixed but not very encouraging. Eight PD patients were treated with aripiprazole for drug-induced psychosis. Two patients were neuroleptic-naïve, 5 patients were “quetiapine failures,” and 1 patient was switched from olanzapine to aripiprazole. Aripiprazole was initiated at 5-10 mg/day and slowly titrated over 3-7 days until side effects or improvement of psychosis occurred. Only 2 out of 8 patients experienced near-complete resolution of their psychotic symptoms with aripiprazole. The other 6 patients discontinued aripiprazole within 40 days, 2 owing to motor worsening. Controlled studies are currently under way to definitively evaluate the safety and tolerability of aripiprazole use in parkinsonian patients.

### Acetycholinesterase Inhibitors
The neurotransmitter ACh is catabolized by acetylcholinesterase (AChE). Cholinesterase inhibitors, which increase ACh levels in the brain, have been approved for the treatment of Alzheimer’s dementia. A case study and a case series (N = 9) also reported efficacy in reducing hallucinations in patients with Lewy body dementia. Given the substantial loss of cholinergic neurons in PD, AChE inhibitors might prove useful in PD as well. In an open-label study, 5 of 7 demented PD patients had complete resolution of their hallucinations when treated with tacrine, the oldest AChE inhibitor; the other patients showed improvement. None of the patients had worsening of his or her UPDRS motor score. One case report has indicated worsening of preexisting parkinsonian signs in a patient with Alzheimer’s dementia who was treated with tacrine. In that case, the patient improved with the addition of levodopa.

In addition to being an AChE inhibitor, galantamine also potentiates nicotinic ACh neurotransmission. In an open-label trial in patients with PD and dementia, 3 of the 16 patients withdrew because of intolerable side effects (2 with vomiting, 1 with worsening tremor). Seven of the 9 patients with hallucinations experienced amelioration of their hallucinations with galantamine. Three of the hallucinating patients had complete disappearance of their hallucinations. On the other hand, 1 patient who did not hallucinate at baseline began hallucinating with galantamine. Worsening of tremor was noted in 3 patients, but 6 had improvement of their parkinsonism.

Rivastigmine is an AChE inhibitor that also inhibits the activity of butryrylcholinesterase. One open-label study of rivastigmine for PD-related psychosis and cognitive impairment involved 15 patients. In the 12 patients who completed the study, hallucinations, sleep disturbance, and caregiver stress were improved. Motor scores did not worsen. Although side effects limited 9 of the patients to submaximal doses, only 1 patient withdrew from the trial because of intolerable nausea. Another small case series found that rivastigmine improved psychosis in 10 patients with PD, without worsening motor function. There are also indications from its effect in dementia with Lewy bodies that rivastigmine may have some utility in PD-related psychosis. It appears that effective use of this agent may require slow and flexible dose titration.

Donepezil, perhaps the most popular AChE inhibitor, has not been extensively studied for treating PD-related hallucinations. However, reports about successful treatment of psychosis in Lewy body dementia suggest that this agent might be helpful in PD. Fabbriini et al followed 8 PD patients on 5 mg of donepezil per night and reported significant improvement of psychotic symptoms in all patients. Unfortunately, 2 of the patients experienced declines in motor function. Another open study of donepezil observed 3 patients with visual hallucinations that persisted after withdrawal of anti-PD medications. Each

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### Aripiprazole
Aripiprazole is the latest AA drug to be marketed in the United States. It is the only AA that is a partial agonist at the D2 and 5-HT1a receptors and an antagonist at 5-HT2a receptors. It also has a high 5-HT2/D2 ratio and may therefore carry a low risk of extrapyramidal side effects while effectively alleviating psychosis in Parkinson-vulnerable populations. Our preliminary experience with aripiprazole, however, is mixed but not very encouraging. Eight PD patients were treated with aripiprazole for drug-induced psychosis. Two patients were neuroleptic-naïve, 5 patients were “quetiapine failures,” and 1 patient was switched from olanzapine to aripiprazole. Aripiprazole was initiated at 5-10 mg/day and slowly titrated over 3-7 days until side effects or improvement of psychosis occurred. Only 2 out of 8 patients experienced near-complete resolution of their psychotic symptoms with aripiprazole. The other 6 patients discontinued aripiprazole within 40 days, 2 owing to motor worsening. Controlled studies are currently under way to definitively evaluate the safety and tolerability of aripiprazole use in parkinsonian patients.

### Other Agents and Treatments

#### Ondansetron
Ondansetron is a 5-HT3 receptor antagonist best known for its use as an antiemetic in cancer patients. Because of possible antipsychotic effects of 5-HT3 blockade, ondansetron was tested for treatment of schizophrenia but has not been found effective. However, because of its remarkable selectivity for 5-HT3 receptors, PD investigators thought it might be an ideal agent to ameliorate psychosis without worsening parkinsonian motor symptoms. Zoldan et al tested this hypothesis in an open-label trial with 16 patients. They found marked improvement in the areas of visual hallucinations, confusion, and functional impairment, with no effect on UPDRS scores. Only 1 patient showed no improvement. Unfortunately, the open design and small size of this trial limit the conclusions that can be drawn about ondansetron in PD-related psychosis. Moreover, these positive findings have not been universally reproduced.
patient was treated with 5 mg per day of donepezil. Visual hallucinations were improved in all patients, but 1 patient experienced treatment-emergent delusions that disappeared when donepezil was discontinued. Although some controlled studies of donepezil in PD exist, none evaluates psychotic symptoms as a primary endpoint. One placebo-controlled study followed 14 patients with PD and dementia for 20 weeks (crossover design, 10 weeks on active drug and 10 on placebo). Two patients left the study because of intolerable side dizziness, nausea, and diarrhea from donepezil. There were no significant differences in UPDRS scores when patients switched between placebo and donepezil. Because scores on the neuropsychiatric inventory were low at baseline, donepezil’s effect on psychotic symptoms was impossible to assess. Nevertheless, the minimal change in motor function is encouraging for future studies in patients with psychosis. Caveats regarding the use of donepezil include avoiding abrupt withdrawal and careful monitoring for motor worsening.

**Electroconvulsive Therapy**

Electroconvulsive therapy (ECT) is most commonly used for treatment-resistant psychiatric disorders. It has also been reported to improve motor symptoms of PD. In general, ECT’s effects are short lived, and repeated treatments and/or pharmacological augmentation are required to maintain any benefits. ECT has not been formally studied in PD-related psychosis, perhaps because of the associated cost and stigma. However, there have been some scattered reports of success. In general, ECT should probably be reserved for patients who are unresponsive to, or intolerant of, other treatments, especially if psychosis is associated with severe depression.

**Supportive Treatment**

Once present, hallucinations in PD rarely resolve without treatment. Even with pharmacological treatment, the majority of patients may not experience complete resolution of their hallucinations. Thus, nonpharmacological methods of managing hallucinations, although under-studied, are an important aspect of treatment. In fact, many PD patients invent their own “coping strategies” to deal with hallucinations. A study of 46 patients with PD-related visual hallucinations demonstrated that 36 (78%) of them had developed their own approaches for dealing with disruptive perceptual phenomena. Techniques included focusing on the false object, looking away, interacting with others, or self-assurance. The authors did not measure success rates; however, patients who used coping strategies found the hallucinations “bothersome or depressing” only 39% of the time, compared to 60% for those who did not use any strategy (a nonsignificant result, perhaps because of small sample size). Use of group therapy for other forms of psychosis suggests that strategies for coping with hallucinations might also be shared among patients. Clinicians should make patients with PD-related hallucinations aware of these tactics and the possible beneficial impact on their lives.

**CONCLUSION**

Psychosis in PD is common. The pathophysiological changes underpinning psychosis in PD remain unknown, although there is emerging research implicating multiple neurochemicals (dopamine, serotonin, acetylcholine, etc), as well as changes in sleep and visual perception. It is important for the practitioner to recognize premonitory symptoms as well as symptoms of overt psychosis so that treatment strategies can be implemented immediately. Underlying medical causes should be considered before medication adjustments are made. If reduction of anti-parkinsonian medications results in worsening of parkinsonism, then the addition of an atypical agent is warranted. The addition of an AA often allows the treating physician the latitude to give the PD medications necessary to effectively maintain his or her current motor state without causing psychosis.

Although quetiapine and clozapine seem to be the most efficacious drugs for the treatment of PD-related psychosis, there is still a need for better and more selective AA agents, and for better designed, larger placebo-controlled studies that meaningfully assess their efficacy and tolerability in this vulnerable population. Likewise, as we come closer to unlocking the complex interrelationship of various hypothesized mechanisms in PD psychosis, future studies will be needed to evaluate the role of AChE inhibitors, ECT, and other novel behavioral approaches to the treatment of psychosis in PD.

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