Management of Psychotic Aspects of Parkinson's Disease

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Psychotic symptoms have become increasingly common in patients with idiopathic Parkinson's disease and other parkinsonian syndromes. This increased prevalence of psychoses is in part a reflection of the greater longevity of people with Parkinson's disease and, to a certain extent, is a consequence of our success in treating the motor symptoms of these syndromes. The psychotic symptoms associated with Parkinson's disease can be as varied as the motor symptoms. They stem from interactions between the underlying neuropathologies of the syndromes and the adverse effects associated with chronic antiparkinsonian drug administration. In patients with advanced Parkinson's disease, there is also a high prevalence of affective comorbidity. This increase in affective symptoms and the relatively high incidence of cognitive and affective side effects of the antiparkinsonian medications contribute to the increase in psychoses observed in these older patients. The most significant risk factors for developing psychosis in Parkinson's disease are (1) coexistence of dementia, (2) protracted sleep disturbances, and (3) nighttime use of long-acting dopaminomimetics. This article reviews the phenomenology, pathophysiology, and treatment of psychosis associated with parkinsonism and discusses how atypical antipsychotic medications have revolutionized the management of the symptoms and improved the quality of life of those affected. *(J Clin Psychiatry 1999;60[suppl 8]:42–53)*

Idiopathic Parkinson's disease (IPD) is the most common cause of parkinsonian symptoms. It affects over 1 million adults in the United States or approximately 1% of those more than 55 years of age.[1] The prevalence of parkinsonian symptoms among residents of nursing homes who are 75 years of age and older is estimated to be as high as 35%.[2]

In addition to IPD, parkinsonism encompasses a host of extrapyramidal syndromes characterized by bradykinesia, rigidity, tremor, and abnormalities of posture and gait.[3] These syndromes include drug-induced parkinsonism and a host of progressive degenerative disorders such as multiple-systems atrophy (MSA), progressive supranuclear palsy (PSP), and dementias associated with parkinsonism.[4–7] Comorbid pathologies include Lewy body dementia (LBD), senile dementia of the Alzheimer's type (SDAT) with overlapping parkinsonian pathology, and, not infrequently, a combination of all three.[7–11]

Although there are significant differences among the parkinsonian syndromes and many varied presentations to the psychiatric aspects of the syndromes, management of the associated psychotic symptoms, unlike the motor symptoms, is fundamentally the same. The focus of this review will be on the psychotic aspects of IPD and related syndromes. For further information about the parkinsonian syndromes and related pathologies, the reader is directed to several recent reviews.[4–7,12]

Although the motor symptoms are what first call attention to parkinsonism, it is the associated neuropsychiatric symptoms that cause the greatest disability in advanced disease.[13,14] They affect 40% to 60% of patients and comprise a spectrum of psychosis and delirium, dementia, anxiety, and depression.[15] Some of these symptoms are drug-induced, others are intrinsic to the underlying pathologies, many are due to both. Drug-induced symptoms are treatable but not always avoidable given the nature of antiparkinsonian pharmacotherapy.[16,17]

PARKINSONISM AND NEUROPSYCHIATRIC DYSFUNCTION

Psychosis affects 6% to 40% of unselected parkinsonian patients and comprises a spectrum of visual hallucinations, delusion, dysphoria, mania, delirium, and altered sexual behaviors.[15,17,18] This relatively high incidence of psycho-

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sis ironically is due in part to the success in treating parkinsonian motor symptoms in the past 30 years.[19] As life expectancy has increased, so has the accrual of age-related neuropathologies, all of which lower the threshold for psychosis.[20,21] In our clinic, these symptoms account for the majority of parkinsonian-related admissions and, along with immobility and incontinence, represent the "final straw" that triggers placement in a nursing home.

PATHOPHYSIOLOGY OF PARKINSONISM IN RELATION TO PSYCHIATRIC DYSFUNCTION

Motor Symptoms

The motor signs and symptoms of parkinsonism can be attributed to a striatal dopamine deficiency due to the death of dopamine neurons in the midbrain, leading to postsynaptic striatal dopamine receptor hypersensitivity.[3] With advancing disease, this hypersensitivity contributes to levodopa-induced motor fluctuations and dyskinesias. The pathology of other parkinsonian syndromes extends beyond the midbrain dopaminergic neurons and represents additional risk factors for the development of psychosis, including intrinsic striatal and thalamic (e.g., MSA, PSP) and cortical pathology (e.g., SDAT, LBD).[22]

Psychiatric Symptoms

Anatomically, the frontal lobes and the limbic system connections to the basal ganglia have been associated with the regulation of emotions and the genesis of psychosis.[23] Physiologically, postsynaptic monoaminergic receptor hypersensitivity renders patients vulnerable to psychiatric comorbidity when affecting the nonmotor circuits that loop through the striatum and frontal cortex. Dysfunction in these cognitive and limbic pathways is analogous to the known dopamine receptor hypersensitivity of motor circuits in IPD.[24,25] Chronic stimulation of hypersensitive dopamine receptors with dopamine agonists may kindle psychotic symptoms.[26–28] Erratic stimulation of these receptors by orally administered dopamine agonists may contribute to mood fluctuations and paroxysms of anxiety.[29,30] Patients with IPD are equally sensitive to dopamine antagonists. For many, the psychotic symptoms respond well to minute doses of antipsychotics; however, the conventional antipsychotics and other dopamine blockers are poorly tolerated due to the predictable and, at times, profound worsening in parkinsonian motor symptoms brought about by these agents.[31]

Postsynaptic serotonergic receptor hypersensitivity due to the partial loss of serotonergic projections from the raphe nuclei in the brain stem to the striatum and cortex may also contribute to the genesis of psychosis in patients with IPD. In patients with IPD, serotonergic mechanisms have been implicated in the genesis of dopamine agonist–induced hallucinations and psychosis through still unclear mechanisms.[17,32] The efficacy of the atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine), compared to conventional antipsychotics, has been attributed in part to their relative high affinity for 5-HT_2 compared to D_2 receptors.[33]

RISK FACTORS FOR PSYCHOSIS

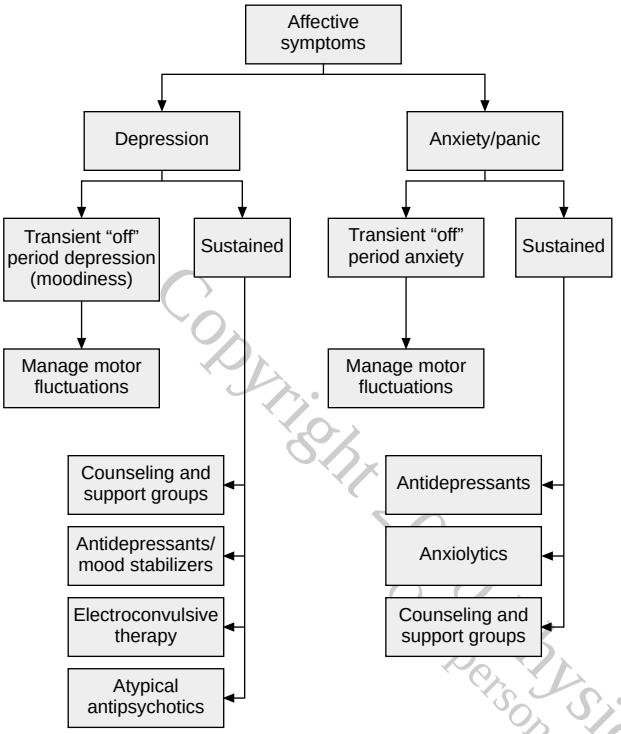
Most patients with parkinsonism exhibit some degree of subcortical cognitive impairment, but these deficits are seldom sufficient to warrant a diagnosis of dementia. Typically, a general slowing of mental processes occurs similar to what is observed in individuals with depression.[34] Cognitive slowing, or bradyphrenia, is presumed to be the cognitive equivalent of parkinsonian bradykinesia. Memory impairment is characterized by good encoding with faulty retrieval. In contrast, language and calculation skills are relatively preserved. Subcortical cognitive impairment is relevant to IPD because, when severe, it may increase the risk of drug-induced confusion and psychosis.[35]

DEMENTIA

Eighteen to 37% of patients with IPD exhibit a clinical dementia.[35–37] In addition to subcortical cognitive impairment, patients with IPD and dementia exhibit profound cortical memory defects that affect encoding, priming, and retrieval. These patients also exhibit language, visuospatial, and calculation defects not typical of uncomplicated IPD. The spectrum of dementia in IPD is highly variable, ranging from typical SDAT with minor parkinsonian features to LBD, to vascular dementia, to various overlap syndromes (e.g., SDAT/parkinsonism and SDAT/LBD). For example, more than 70% of pathologically verified cases of SDAT have overlapping clinical and pathologic features with LBD.[7,8,38–42] In addition to the above dopamine and striatal cell loss, these heterogeneous parkinsonian-dementia syndromes exhibit extensive cortical, hippocampal, and subcortical pathology.[7,40,41] This neuropathologic burden probably lowers the psychosis threshold far more than any other risk factor.[43,44]

Among the dementias, LBD deserves special mention in that it is often misdiagnosed as IPD, and LBD represents a major risk factor for psychosis. Affected patients frequently exhibit systematized delusions and hallucinations (visual and nonvisual), even in the absence of antiparkinsonian therapy.[43–47] Parkinsonian features are common and may precede or follow the dementia.[48,49] Attentional and executive function deficits present early and, initially, are out of proportion to memory deficits.[40,41,50] Bradyphrenia is accompanied by difficulties with concentration and arousal, the latter sometimes bordering on narcolepsy. The dementia is rapidly progressive and severely limits the treatment of motor symptoms due to an exquisite sensitivity to the side effects associated with antiparkinsonian therapy.[10,39,40,51,52] Patients are equally sensitive to the side effects of the conventional

Figure 1. Algorithm for Minimizing Affective Symptoms in Patients Treated With Antiparkinsonian Drugs[a]



[a]Modified from Olanow and Koller,[19] with permission.

antipsychotics, which often worsen motor symptoms even in small doses.[53] A few reports suggest that in LBD patients, atypical antipsychotics may be better tolerated than conventional antipsychotics.[54,55]

Figure 1 illustrates a consensus approach among neurologists to maximize cognition by minimizing affective symptoms in patients treated with antiparkinsonian drug therapy. Attempts at improving cognition using acetylcholinesterase inhibitors have been hampered by the tendency of these agents to induce tremor.[56,57] In our experience, demented parkinsonian patients may tolerate small doses of tacrine (20 mg q.i.d.) or donepezil (5 mg/day) for short periods, but the long-term safety and efficacy of these agents in this population are unknown.

AFFECTIVE DISORDERS

As would be expected, mania and major depression are significant risk factors for the onset of psychosis in parkinsonism. In several surveys, 40% to 70% of patients with IPD were found to exhibit a variety of affective symptoms ranging from anxiety, to dysthymia, to mania and major depression.[34,58–61] Despite its prevalence, depression is especially difficult to detect in this population due to the substantial overlap between parkinsonian and depressive symptoms.[62,63]

Table 1. Signs and Symptoms That May Herald the Onset of Psychosis in Patients With Parkinsonism

Progressive Cognition Impairment
Pervasive Sleep Dysfunction
Insomnia
Daytime somnolence
REM-related behavioral disorder
Nocturnal myoclonus
Conceptual disorganization
Recurrent befuddlement
Mild intermittent systematized delusions
Spontaneous or drug-induced hallucinations with retained insight
Intermittent confusion

Depression in parkinsonism is the product of a complex, nonlinear interaction between the underlying neuropathologies, their treatments, and the psychosocial and disability considerations that accompany the illness.[62–65] In these patients, motor disability correlates poorly with the severity of depression.[60,62,66] Depression may antedate the onset of motor symptoms,[65,67,68] or, in our experience, present as a sudden, otherwise unexplained failure of antiparkinsonian therapy. When the depression is severe, it is not uncommon for the patients to exhibit panic attacks that mirror the motor fluctuations.[29,69] Accordingly, diagnosing depression in patients with IPD requires a high level of suspicion and acuity for unexplained signs of distress.

Recognizing and treating depression early may prevent more advanced psychiatric symptoms from developing, including psychosis. As illustrated in Figure 1, treatments of affective symptoms in parkinsonism include (1) optimization and simplification of antiparkinsonian therapy, (2) amelioration of the motor symptoms (particularly pain), (3) use of psychosocial support such as involvement in support groups and individual psychotherapy, and (4) introduction of antidepressants or electroconvulsive therapy. Since it has been reported that dopaminomimetic therapy may induce or aggravate depression,[67,70–72] atypical antipsychotics with their lower incidence and severity of extrapyramidal side effects and recently reported effectiveness for affective symptoms should be considered for patients with Parkinson's disease and depression.[17,73,74]

SPECTRUM OF HALLUCINATIONS AND PSYCHOSIS IN PARKINSONISM

Much of what is referred to as psychotic symptomatology in patients with IPD includes a spectrum of nonpsychotic signs, which in the view of Emory's Movement Disorders Group represents a risk factor for, or a prelude to, psychosis and delirium in this population. Of the early symptoms, visual hallucinations are the most easily recognized, but there are other common and subtle signs and symptoms that often herald the onset of more advanced symptoms (Table 1). Unlike patients with true psychosis, those with early psychiatric symptoms retain insight and

the ability to test reality. Advanced psychiatric symptomatology refers to psychosis and delirium in which, by definition, patients have lost touch with reality or have severe disturbances of arousal or both.

In patients with IPD on dopaminomimetic therapy (e.g., levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors), these nonpsychotic symptoms present a continuum of drug-induced symptomatology, the progression of which seems to be kindled by the ongoing therapy. The natural history of psychosis among parkinsonian patients who are also demented or have an underlying major affective illness is less predictable, probably resulting from an interaction between the evolving neuropathology(ies) and the chronic and often changing antiparkinsonian regimens.

Psychotic reactions to drugs like amantadine and anticholinergic medications may occur abruptly without the kindling effect suggested for other dopaminomimetic agents. Our group at Emory, however, has the impression that many patients with IPD who exhibit these severe idiosyncratic psychotic reactions to any of these agents will, in time, exhibit other signs of dementia.

EARLY BEHAVIORAL CHANGES: A PRELUDE TO PSYCHOSIS?

Psychotic symptoms in nondemented patients with IPD chronically treated with dopaminomimetics evolve in a setting of mild conceptual disorganization, and a stepwise progression of sleep disruption, subtle personality changes, and mild delusional thinking (see Table 1). Although it is unknown what percentage of patients with IPD with these prodromes go on to develop true psychosis and delirium, it is our view that these otherwise "benign symptoms" represent an ongoing risk of developing more advanced psychiatric symptomatology.

Sleep Disruption and Related Abnormalities

Dopaminomimetic psychosis starts with sleep disruption and abnormal dreaming. As early as 1982, Nausieda and colleagues reported that almost 98% of patients with levodopa-induced psychiatric symptoms experienced sleep disruption in the form of insomnia, sleep fragmentation, excessive daytime sleepiness, altered dreams, and parasomnias.[75] They noted that 39% of patients with sleep disturbances had hallucinations compared to only 4% of those with normal sleep patterns.[75] Comella and colleagues have reported that any significant disruption of sleep increases a patient's vulnerability to psychotic symptoms.[76]

Sleep problems attributable to antiparkinsonian therapy include insomnia, vivid dreams, night terrors, nocturnal myoclonus, and rapid eye movement (REM)-related behavioral disturbances.[77,78] In the latter, patients have paroxysmal nocturnal vocalizations and may both thrash in bed and sleepwalk. Nocturnal myoclonus is a separate problem often aggravated by dopaminomimetics and selective serotonin reuptake inhibitors (SSRIs). This disorder is characterized by sudden and sometimes violent jerking of the legs or whole body, a situation that tends to disturb the spouse more than the patient. Selegiline, anticholinergic medications, and amantadine can produce or aggravate insomnia and should be reduced or eliminated in patients with otherwise refractory sleep symptoms. Idiopathic insomnia is more common and chronic in patients with IPD than in the general population and can often be managed with a program of sleep hygiene, sparing use of hypnotics, or use of a tricyclic antidepressant, trazodone, or melatonin.[77,79] Restless legs syndrome is a frequent parkinsonian symptom that can further disrupt sleep.[80–82] These symptoms often improve with the addition of nocturnal doses of levodopa or dopamine agonists. However, this strategy may increase the risk of psychosis in already demented patients. Other agents used in the treatment of restless legs syndrome are clonazepam, gabapentin, or propoxyphene.[19]

Depression and chronic anxiety commonly cause sleep disruption and need to be treated appropriately with antidepressants or anxiolytics.[83] Patients who are demented and experience sundowning may need small doses of atypical antipsychotics at night to promote sleep. In refractory cases, or in those suspected of having restless legs syndrome or nocturnal myoclonus, a sleep study should be considered to rule out sleep apnea and other sleep disorders common among the elderly.[82] Although the above nocturnal events do not always lead to a complete awakening, when chronic, they take a toll on the daytime motor and mental functioning. Indeed, anything that causes protracted sleep fragmentation in patients with IPD can increase the risk of psychosis and worsen parkinsonian motor signs.

Hypersexuality

Some patients on increasing antiparkinsonian drug therapy exhibit increased libido, in part due to improved mobility and a sense of well-being.[84] Of interest is that the increased libido may not be constrained by erectile dysfunction or impotence, a common finding in advanced parkinsonism.[15] This resurgence of sexual interest may be a healthy response in some patients. In others, it emerges as an inappropriate sexual disinhibition including paraphilias.[85,86] Although recurrent, each incident tends to be short-lived, suggesting an element of drug-induced impulsivity. These behaviors may also represent an early sign of conceptual disorganization and thus decreased self-control. For example, when such patients are confronted, they appear embarrassed and try to rationalize the inappropriate behaviors. However, the explanations tend to lack insight and come across as befuddled. Fortunately, because the pathological behaviors are almost always drug-induced and dose-dependent, they can be corrected with a judicious reduction in dopaminomimetic therapy.

Personality Changes and Conceptual Disorganization

The above behaviors coexist or are heralded by other less well understood and often subtle nonpsychotic symptoms best characterized as early conceptual organization.[87,88] To a casual observer, the patient appears to be undergoing mild personality changes. For instance, a patient may become more demanding toward his partner or caregiver, acting at times unreasonable and selfish. At the slightest provocation, they may even act aggressively toward family members. With time, patients seem to lose sight of the increasing burden their disability places on their families. This development represents an alarming departure from the typical premorbid personality of patients with IPD who, as a group, tend to be noted for their industrious, punctual, reserved, and selfless nature.[89,90]

Intermediate Behavioral Changes and Psychiatric Symptomatology

As psychiatric morbidity progresses, it is characterized by drug-induced hallucinations with preserved arousal and insight. This stage of the illness is often preceded by visual illusions consisting of misinterpretation of shadows or figures in the peripheral visual field. Spontaneous hallucinations that develop before or shortly after initiation of dopaminomimetic therapy are suggestive of LBD or SDAT with parkinsonian pathology.[44] This suspicion is heightened when spontaneous auditory and tactile hallucinations develop, symptoms that are rarely seen in the setting of uncomplicated IPD.

Initially, hallucinations tend to occur during the twilight hours, often fusing with the vivid dreams mentioned above. Visual hallucinations include stereotyped "lilliputian" images of children, animals, or otherwise familiar or unfamiliar faces that roam in and out of the patient's room. The figures often chat among themselves but seldom address the patient; thus, the patient rarely hears "the conversation." Although patients concede these phenomena are imaginary, they may proceed to describe how they tried to get rid of "those people" in the room.

With ongoing antiparkinsonian therapy, the hallucinations may also appear during the daytime, lasting seconds to an hour or more, depending on their severity. By this stage, most patients are befuddled by the symptoms and are reluctant to discuss them. When asked directly, patients may rationalize or minimize the phenomena in a futile attempt to keep their mentation in check. Patients with mild hallucinosis may respond to reassurance, at least initially. At our clinic at Emory, it has been our practice to minimize or eliminate these symptoms, using the strategies outlined below and in Figure 1.

A common but seldom-mentioned spectrum of psychiatric symptoms at this stage consists of mild delusion or intermittent confusion with preserved arousal and insight.[88] When persistent, this cluster of symptoms typically heralds other signs of dementia, particularly LBD dementia. The phenomenon can be spontaneous or drug-induced and can linger for months before developing into more advanced psychiatric symptomatology.

Advanced Psychiatric Symptomatology

Advanced psychiatric symptoms can be subdivided into those associated with clear sensorium and those occurring in the setting of a clouded sensorium or delirium. Those occurring in the setting of a clear sensorium include schizophreniform psychoses. The manifestations of these psychoses are not unlike those in a general psychiatric population. Spontaneous symptoms are suggestive of either comorbid dementing pathology, a major affective illness, or independent schizophreniform processes rarely reported among unselected parkinsonian patients. Drug-induced psychotic reactions are well recognized and can emerge with or without delirium.

Severe spontaneous disturbances of arousal are highly suggestive of LBD dementia. Even early drug-induced disturbances of arousal, in retrospect, often mark the first recognizable sign of a dementing process. These organic states can also be accompanied by psychotic symptomatology not unlike the schizophreniform psychoses alluded to above.

Agitation and aggression are the most disruptive forms of psychotic behaviors seen in patients with IPD. They may start with sundowning, which when left untreated can carry over to daytime behaviors and affect the quality of life of the entire family. Agitation is commonly associated with paranoid delusions involving alleged spousal infidelity or suspicious behaviors toward other family members. Agitation may also be secondary to dysphoria, depression, or mania.

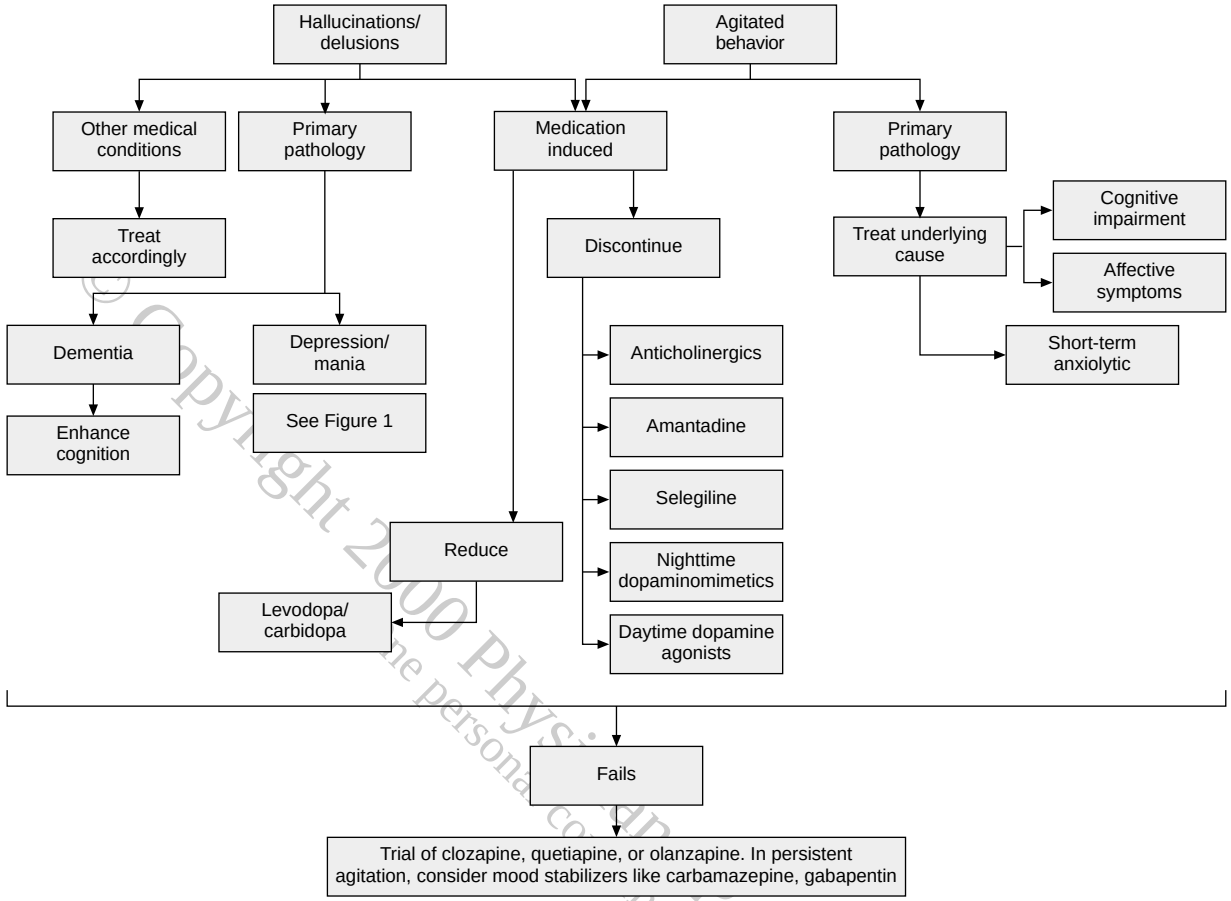
Not surprisingly, psychosis and agitation tend to make the parkinsonian motor symptoms relatively refractory to therapy in a manner similar to depression.[91] Psychosis and agitation are first managed by removing as many potentially offending agents as possible (Figures 1 and 2). The next step is to control the psychosis itself. When appropriate, antidepressants and mood stabilizers should be considered. In patients with IPD, mood stabilizers like lithium carbonate and valproate are poorly tolerated due to their tendency to aggravate tremor. Anticonvulsants like carbamazepine, gabapentin, and lamotrigine may be better tolerated but have not yet been carefully studied in this population.

TREATMENT OF PSYCHOSIS IN PARKINSONISM

General Measures

The management of psychiatric problems in IPD involves a minimization of polypharmacy, correction of sleep disturbances, and treatment of cognitive and affec-

Figure 2. Algorithm for Management of Psychosis and Agitation in Patients With Parkinson's Disease[a]



[a]Modified from Olanow and Koller,[19] with permission.

tive symptoms as needed and as summarized in the article by Tariot, this issue. Our preferred strategy is a modification of an algorithm developed by Olanow and Koller and is illustrated in Figure 1.[19]

Simplifying Antiparkinsonian Therapy

Patients experiencing mild-to-moderate drug-induced hallucinations and delusions can benefit from a simplification of their antiparkinsonian medications, with or without the concurrent use of antipsychotics. We first discontinue or reduce the agents that are most likely to induce psychiatric symptoms—anticholinergics, selegiline, and amantadine (see Figure 2). When this strategy is successful, hallucinations and psychosis generally begin to remit within a matter of a few days. The first sign of progress is typically an improvement in sleep.

If this strategy fails, we eliminate all long-acting nighttime dopaminomimetics beginning with dopamine agonists followed by controlled-release carbidopa/levodopa. In patients who experience a severe recurrence of their motor symptoms during the night, we introduce small doses of the regular carbidopa/levodopa formulation. We base our strategy on our observations that hallucinations and other psychotic symptoms increase with a nighttime infusion of any dopamine agonist (e.g., levodopa, apomorphine, and lisuride).[92] The next step involves reducing daytime doses of the dopaminomimetics. We gradually substitute the controlled-release carbidopa/levodopa for the evening dose of the regular carbidopa/levodopa. If necessary, we reduce or eliminate doses of controlled-release product after mid-to-late afternoon. Next, we reduce daytime dopamine agonists while adjusting the dose of the regular carbidopa/levodopa so that the anticipated increase in parkinsonian motor symptoms is mitigated.

Drug holidays or the complete elimination of all dopaminomimetic therapy, although popular a decade ago, is no longer recommended due to the significant risk of medical complications following a total withdrawal of antiparkinsonian medications.[93–95] Sudden withdrawal of dopaminomimetic therapy in parkinsonian patients has been linked to a neuroleptic malignant syndrome–like state with hyperpyrexia, rhabdomyolysis, stupor, coma, and death.[96,97] The risk of this complication is highest in patients on high doses of dopamine agonist therapy who have

the on-off phenomenon. Drug holidays also fell into disfavor when it became apparent that most patients had to resume dopaminomimetic therapy within weeks of a drug holiday because of a recurrence of severe motor symptoms.

At Emory, we have found that approximately 50% of our patients with IPD who develop psychotic symptoms initially respond to treatment with the above strategy. The limiting factor appears to be how well the patients tolerate the inherent exacerbation of motor function. Accordingly, the extent to which dopaminomimetic therapy can be reduced in a given patient remains a matter of clinical judgment. Once psychotic symptoms reappear, it is unlikely that further reductions in antiparkinsonian therapy will be beneficial and antipsychotic therapy will need to be considered.

ANTIPSYCHOTIC THERAPY

Conventional Antipsychotics

The alternative to the often unacceptable reduction strategies is to treat psychosis directly using dopamine and serotonin receptor blockers. The challenge is to do so without aggravating parkinsonian motor signs and symptoms. High-potency conventional antipsychotics like haloperidol should be avoided because of their rapid and often profound aggravation of parkinsonian symptoms.[98] The risk of tardive dyskinesia (TD) and acute extrapyramidal symptoms in this neurologically impaired population is also higher than in a comparable elderly population, and drugs that are less likely to induce these adverse events are better candidates. Further, the potential for conventional antipsychotics to cause cognitive impairment makes these medications unsuitable for patients with parkinsonism, especially if cognitively impaired. Low-potency neuroleptics such as molindone and thioridazine were considered acceptable short-term solutions for the management of psychosis in IPD a few years ago[99]; however, subsequent experience and the advent of atypical antipsychotics have led to the conclusion that conventional antipsychotics are no longer viable alternatives.[19]

Atypical Antipsychotics

The standards of care for the treatment of psychosis among patients with IPD have improved since the introduction of atypical antipsychotics. These agents can treat the positive symptoms of psychosis at doses comparable to those of conventional antipsychotics without the same burden of adverse effects.[100,101] In a recent review by Keck and McElroy, it is suggested that these agents can treat negative symptoms and improve cognition at lower doses than those that would have been required of conventional antipsychotics.[101] This property may reflect their high ratio of serotonin-2 (5-HT_2) to dopamine-2 (D_2) receptor blockade compared to the receptor affinity profile for conventional antipsychotics.[100] Further, the low incidence of EPS associated with the atypical antipsychotics may be mediated by their selectivity for mesolimbic rather than nigrostriatal dopamine receptors.[102]

Clozapine. Scholz and Dichgans were the first to report beneficial effects with clozapine in the treatment of patients with IPD and drug-induced psychosis.[103] Since then, a large number of open-label trials have supported this earlier observation.[104–111] Factor and Friedman reviewed these studies and found that, of the 136 patients with IPD and drug-induced psychosis reported, 82% responded favorably to clozapine with complete or partial resolution of their psychosis, while 18% withdrew because of an absence of response or, more commonly, because of adverse effects.[112] The most common side effects associated with clozapine are delirium, sedation, sialorrhea, orthostasis, and dizziness.[112,113] Reports of a worsening of parkinsonian motor symptoms and the development of EPS are extremely rare.

Due to a 50% dropout rate in a small double-blind study of clozapine in IPD, Wolters and colleagues were not able to confirm the earlier favorable findings.[114] This unexpectedly high incidence of side effects may have resulted from a relatively rapid titration schedule and high target dose (up to 250 mg/day over a 10-day period).[114] In a second, carefully designed, multicenter trial in 60 patients treated for 4 weeks (29 in the treatment arm), Friedman and colleagues reported a significant improvement in psychosis with a minimum of side effects.[115] In this case, the initial dose was 6.75 mg/day and the maximum dose was 50 mg/day. Antiparkinsonian drug therapy was kept constant and parkinsonian motor symptoms did not change.

The median dose of clozapine for the treatment of psychosis in IPD is between 75 and 100 mg/day administered at night or twice daily (range, 12.5–400 mg/day).[105,106,111,112] As with many other medications, clozapine must be introduced slowly in elderly patients.

The first and clearest benefit from the use of clozapine is an immediate improvement in sleep even if it is at the expense of some transient daytime sedation. Friedman's group and others have also noted that there is a significant antitremor benefit with clozapine.[116–118] Other benefits with clozapine in patients with IPD include a reduction in symptoms such as painful dystonia, dyskinesias, and nocturnal akathisia.[112,119–123] Clozapine may even benefit patients with LBD and MSA who experience psychotic symptoms.[22,54] In some studies, treatment with clozapine has made it possible to increase the dose of dopaminomimetics in previously psychotic patients resulting in better motor responses.[124]

Although the antipsychotic response to clozapine in IPD is clearly superior and better documented than other alternatives, use of the drug has been slowed by the risk of agranulocytosis, the inconvenience and expense of weekly blood tests, and the rare reports of agranulocytosis. Other issues include the reported and still controversial risk of

TD, acute dystonia, and, in association with lithium, the rare risk of neuroleptic malignant syndrome.[125–129] The risk of adverse events notwithstanding, clozapine remains an attractive option for the treatment of psychosis in parkinsonian patients who have not responded to the more conservative measures outlined above.[109]

Risperidone. Risperidone has a relatively high affinity for both 5-HT_2 and D_2 receptors.[100] Its efficacy is comparable to that of older high-potency antipsychotics but with fewer EPS.[130] This profile has been demonstrated in schizophrenic patients as well as in elderly psychotic patients.[131–134]

Reports on the use of risperidone for psychotic aspects of IPD have been mixed. In an open trial, Meco and colleagues reported a satisfactory antipsychotic response with little effect on parkinsonian motor symptoms in 6 patients treated with doses between 0.25 and 1.25 mg/day for 7–35 weeks.[135] Allen and coworkers reported similar findings in 3 patients with LBD.[55] In contrast, Ford and colleagues and Rich and colleagues have reported an intolerable worsening in parkinsonian motor symptoms in all but 1 of their 10 combined IPD patients and in 2 LBD patients.[136,137] Although the doses used in the Rich et al. study were slightly higher than those used in the other 2 studies (1.25 mg/day vs. 4 mg/day), the doses were slowly titrated to minimal efficacy.[137] Despite this cautious approach, risperidone was not a suitable option for the management of parkinsonian psychosis.

At Emory, we have had similar experiences to that of Rich and Ford in over 20 patients with parkinsonism treated with risperidone. However, by slowly titrating the dose to no more than 0.25–0.5 mg/day, and giving only 1 dose at night, our patients have exhibited short-term, beneficial effects. As with all antipsychotics, limiting the dose to nighttime minimizes daytime sedation and postural hypotension. In nonagitated patients with psychoses, dosing regimens as described above may prove useful, although in our experience, patients with an initial response ultimately succumbed to a gradual worsening of their parkinsonian motor symptoms. In our center, few patients with IPD have been able to stay on risperidone longer than 4 months.

Olanzapine. Olanzapine is another atypical antipsychotic that is highly effective in schizophrenia.[101,138,139] It has a pharmacologic profile similar to that of clozapine, but unlike clozapine, it has no reported risk of agranulocytosis.[100,140,141] Its risk of EPS is well within the atypical antipsychotic range. The risk of EPS with olanzapine is less than with risperidone but more than with clozapine and quetiapine, particularly at higher doses.[100,140,141] In schizophrenia, effective doses range between 5–30 mg/day with the majority of patients taking between 10 and 20 mg/day.[102,142–144] In elderly patients with psychosis, the mean dose range is likely to be lower, on the order of 5–10 mg/day. Unlike other atypical antipsychotics, olanzapine has the advantage that it can be administered once daily.[143]

In an open-label study, Wolters and colleagues found that olanzapine was effective in reducing psychoses and was well tolerated in 15 nondemented patients with IPD who had drug-induced psychosis.[145] In this study, the titration period ranged from 8 to 50 days with doses of 1 mg/day up to a maximum of 15 mg/day while maintaining the usual dosage of the antiparkinsonian medication. Brief Psychiatric Rating Scale (BPRS) total scores improved by 65% within 2–5 weeks of treatment initiation, and there was a significant improvement in the patients' ability to sleep. There was no significant change in scores for the Unified Parkinson's Disease Rating Scale (UPDRS), the gold standard for assessing motor and functional disability in IPD.[146] During the latter part of the study (days 50–64), patients were given increased doses of dopaminomimetics, which improved parkinsonian motor symptoms without significantly changing the BPRS scores in all but 1 patient.[145]

Uncontrolled observations in our center in 20 patients with IPD and psychosis suggest that patients with parkinsonism and dementia may be relatively intolerant of olanzapine's central nervous system side effects. In this heterogeneous mix of patients with LBD, IPD/SDAT, and LBD/SDAT, almost 50% experienced confusion and delirium when olanzapine was first introduced, and this was only partially tempered by the careful titration schedule suggested by Wolters et al.[145] Although the incidence of sedation was less than reported with clozapine,[107,115,147] the incidence of EPS was clearly higher than with clozapine, particularly at doses at or above 10 mg/day.

Quetiapine. Quetiapine fumarate is the most recently approved atypical antipsychotic. In controlled clinical trials, it has proven to be safe and effective in the treatment of schizophrenia.[148–151] It is a dibenzothiazepine derivative that has been associated with a very low incidence of EPS.[149,151,152] Its antipsychotic potency is comparable to that of chlorpromazine.[150] Like clozapine, it has high affinity for 5-HT_2 receptors and a low affinity for D_2 receptors.[140,153] Compared to clozapine, it has a low affinity for the dopamine-4 (D_4) receptor and less muscarinic receptor affinity than clozapine or olanzapine.[144] Unlike clozapine, it has not been associated with agranulocytosis or other significant laboratory abnormalities.[154] In preclinical studies, lenticular changes were noted in one (beagle dogs) and not other species (e.g., rodents and primates), nor in several studies in man (data on file, Zeneca Pharmaceuticals). For a more detailed review of ophthalmic considerations in the use of typical and atypical antipsychotics, see Maixner et al.[155] and Tandon et al.[156] this issue and others.[157]

According to a recent large multicenter open-label study, quetiapine is safe and effective in the treatment of elderly patients with psychosis.[158] Side effects included somnolence (30%), dizziness (13%), postural hypotension (12%), and agitation (11%). The median effective dose in

this open-label study was 100 mg/day, compared to the 300–750-mg/day dose range for younger patients with schizophrenia.[149–151,158]

In patients with advanced parkinsonism and drug-induced psychosis, quetiapine was found to be safe and effective in 15 patients with psychosis.[159] This heterogeneous group included patients with IPD, PSP, LBD, and overlapping syndromes of IPD/Alzheimer's disease and SDAT/LBD. Improvement in psychosis was dramatic and sustained despite a gradual progression of the underlying dementing processes. Parkinsonian motor symptoms improved during the first 6 months and, at 1 year, approached those observed at baseline; there were no detectable EPS in the patients in this study.[159] The median antipsychotic dose was 70 mg/day with a range of 12.5–200 mg/day. Side effects included transient sedation during the 4–8 week dose titration (all patients), agitation in 1, and dose-limiting tachycardia in another. Using slightly higher doses (200–400 mg/day) and a 12–16 week dose titration schedule, Parsa and Bastani reported similar findings in 2 elderly patients with IPD who also had drug-induced hallucinations and delusions.[160] Although preliminary and uncontrolled, the above findings suggest quetiapine is an effective and well-tolerated alternative treatment for psychosis in most parkinsonian syndromes.

Rosenfeld and colleagues, in an 8-week, open-label study, also evaluated quetiapine for the control of psychotic symptoms caused by antiparkinsonian medications.[161] Twenty of 24 patients with IPD not previously treated with antipsychotics reported marked subjective improvement of psychotic symptoms without any objective decline in motor function, as measured by the UPDRS. In addition, using the BPRS, 10 of these patients demonstrated significant improvement in psychotic symptoms during a 4-week follow-up survey.

CONCLUSIONS

The risk of psychosis among elderly patients on chronic antiparkinsonian polypharmacy is high, although it can be significantly reduced through the measures outlined in Figures 1 and 2. Shortcomings of these measures include a tendency to aggravate parkinsonian motor symptoms and their inherent risk of medical complications. More importantly, these measures are often not enough to control psychosis and leave the patients with a high level of physical disability. In such instances, low-dose atypical antipsychotics are a more effective and humane alternative. When carefully titrated, they are clearly more effective and better tolerated than typical antipsychotics in parkinsonism regardless of etiology.

Among the atypical antipsychotics, clozapine has the most extensively documented beneficial effects in parkinsonism with psychosis, its low risk of agranulocytosis notwithstanding. Among these studies, preliminary uncontrolled studies suggest quetiapine and olanzapine may offer a ratio of antipsychotic efficacy to EPS that is comparable but not superior to clozapine, but without the risk of agranulocytosis. However, in one uncontrolled study of olanzapine in patients with IPD, it appeared that 50% of the patients experienced confusion and delirium when the drug was first introduced, so a slow and careful titration period is recommended. Risperidone appears to have a greater potential for aggravating parkinsonism than the other atypicals, thus it should be avoided or limited to short-term situations.

Drug names: amantadine (Symmetrel), carbidopa-levodopa (Sinemet), carbamazepine (Tegretol), chlorpromazine (Thorazine), clonazepam (Klonopin), clozapine (Clozaril), donepezil (Aricept), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levodopa (Larodopa), molindone (Moban), olanzapine (Zyprexa), propoxyphene (Darvon and others), quetiapine (Seroquel), risperidone (Risperdal), selegiline (Eldepryl), tacrine (Cognex), thioridazine (Mellaril), trazodone (Desyrel).

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