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Management of Neurobehavioral Symptoms in Parkinson's Disease

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INTRODUCTION

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder that affects over 1 million individuals in the United States and Canada (1). It is considered a movement disorder based on the motor symptoms that herald its onset and dominate its early course. These motor symptoms are typically what bring patients to the doctor and are the target of most modern medical and surgical therapies. According to recent surveys that examined quality of life issues in PD, depression and other psychiatric symptoms have a higher impact on quality of life than the motor symptoms (2,3). Similarly, as the disease advances, it is the psychiatric symptoms, especially drug-induced hallucinations and delusions, that most contribute to the risk of nursing home placement (4).

The symptoms of PD are mediated by the progressive loss of aminergic neurons in the brainstem. These include dopaminergic, serotonergic, and noradrenergic neurons. Parkinsonian motor symptoms are due to the progressive loss of dopaminergic neurons in the substantia nigra that innervate the striatum. Dopamine denervation is by far the most severe, best

studied, and most closely associated with the motor symptoms of PD. In contrast, it appears that the less severe serotonergic and noradrenergic denervation may mediate the frequent psychiatric symptoms of PD such as depression and anxiety. Once present, these symptoms may become a source of major disability. Psychotic symptoms may be mediated by the chronic effects of dopaminomimetic therapy superimposed on slowly accumulating cortical Lewy body pathology (5,6).

COGNITIVE IMPAIRMENT

Mild to moderate cognitive dysfunction affects may nondemented patients with PD. Although this dysfunction has been termed bradyphrenia, the cognitive equivalent of bradykinesia, it is now clear that the dysfunction extends beyond a mere slowing of cognition to include aspects of working memory, attention, mental flexibility, visuospatial function, word fluency, and executive functions. The latter include anticipation, planning, initiation, and the monitoring of goal-directed behaviors. The biochemical basis for these deficits is thought to be, at least in part, due to denervation of the dopaminergic and noradrenergic inputs to the frontal lobes. Other factors include basal ganglia dysfunction, which can independently impair selected aspects of attention and mental flexibility.

Iatrogenic factors that can affect cognition in PD include the use of dopaminomimetic therapy to treat motor symptoms. This drug effect is complex and variable, with levodopa being unable to compensate for all the cognitive deficits observed in PD (7). It depends on the duration of illness, the severity of motor signs, the presence of dementia, sleep disturbances, and possibly depression. For instance, in the early stages of PD, levodopa treatment can improve executive functions normally regulated by the prefrontal cortex. However, this improvement is incomplete and task specific. As the disease advances, patients with a stable clinical response to levodopa fail to exhibit a notable improvement in vigilance and executive function, and patients who exhibit motor fluctuations tend to exhibit transient deterioration in these functions (8). Finally, the effect of these drugs in patients with PD and dementia is likely to be more notable and complex.

Other negative iatrogenic influences on cognitive function in PD include the use of drugs like anticholinergics and amantadine, often used to treat tremor and dyskinesias, and psychotropics used to treat sleep disturbances and affective symptoms. These drugs can negatively affect different aspects of memory and attention, particularly in already demented patients. Like these drug effects, many intercurrent medical illnesses and

depression can adversely yet reversibly affect cognitive function, thereby making their early recognition and treatment important.

DEMENTIA: THE PD/AD/LBD OVERLAP SYNDROMES

Dementia occurs in approximately 20–30% of PD patients. It represents a major risk factor for the development of many behavioral disturbances, including psychotic symptoms. Dementia appears to be associated with the combined effect of age and the severity of extrapyramidal symptoms (9). Pathologically, up to 40% of autopsy cases with a primary diagnosis of PD have comorbid findings consistent with senile dementia of the Alzheimer's type (SDAT) (10,11). Conversely, up to 30–40% of patients with SDAT have comorbid parkinsonian features and harbor Lewy body pathology that extends beyond the dopamine neurons in the brainstem to involve the frontal cortex, hippocampus, amygdala, and basal forebrain (12). These defects conspire with aminergic deficits to increase disability and the incidence of psychotropic-induced side effects. They also contribute to the progression of parkinsonian motor symptoms by narrowing the therapeutic window of all antiparkinsonian agents.

Lewy body dementia (LBD) is an increasingly recognized syndrome in which dementia is accompanied by spontaneous parkinsonian features, depressive features, and apathy (5,13). Unlike SDAT, this form of dementia exhibits significant fluctuations in arousal ranging from "narcoleptic-like" sleep attacks to delirium in advanced cases. Sleep is often disrupted by sleep fragmentation due to rapid eye movement (REM)–related behavioral disorders. Patients have spontaneous features of PD and are extremely sensitive to drug-induced parkinsonism. Although parkinsonism associated with LBD can be indistinguishable from idiopathic PD, several clinical features tend to help differentiate the two. The course of LBD is more rapid than that of idiopathic PD (5–7 vs. 15–20 years); postural tremor is often more prominent than rest tremor, and the response to levodopa therapy tends to be short-lived. Compared to SDAT patients, LBD patients have spontaneous and drug-induced visual hallucinations early in the course of the illness and frequently exhibit fixed delusions. Although memory is clearly impaired in both conditions, visuospatial and frontal neuropsychological functions are more prominently affected in LBD than in SDAT.

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IN PARKINSONIAN SYNDROMES

Disturbances of behavior, mood, and perception are common in patients with dementia. These so-called behavioral psychological symptoms of

dementia (BPSD) are a major source of distress for patients and their caregivers. Clinically they include symptoms prominent in Alzheimer's disease including apathy, depression, delusional jealousy, paranoia, auditory hallucinations, screaming, and agitation (14). Before DSM-IV helped codify these symptoms as a defined clinical entity, they were thought to be secondary to the distress associated with the dementing process (15). The mechanisms mediating this heterogeneous group of symptoms are poorly understood, but in Alzheimer's disease and LBD, they appear to be linked to the accumulating cholinergic pathology (16). Clinical and research assessment methods are now being developed to assess these symptoms (17). The aim is to organize the complex array of symptoms of BPSD into logical and empiric clusters that can help guide research and, ultimately, treatment.

Several such symptom clusters have been identified: apathy, aggression and agitation, depression, psychosis, and possibly dementia-associated delirium. It should be apparent that these symptoms are not limited to demented patients, nor are they necessarily independent of each other. For instance, patients with PD can have drug-induced visual hallucinations without being demented, and patients with depression are often apathetic. BPSD-associated apathy and agitation are discussed in this section. Depression and psychosis are discussed under other psychiatric symptoms below.

It should be noted that most of the information above on BPSD comes from studies of patients with Alzheimer's disease and vascular dementia. Nonetheless, there is ample evidence that these symptoms may be as prominent and disabling in PD with dementia, particularly in LBD (18–20). The major difference between patients with Alzheimer's disease and PD-dementia syndromes is that, in the latter, these symptoms are as likely to be caused by the medications used to treat the motor symptoms as they are by the illness.

Apathy is characterized by lack of interest, diminished motivation, emotional indifference, flat affect, lack of concern, and social inactivity. Apathetic patients exhibit diminished overt behavioral, cognitive, and emotional components of goal-directed behavior, a change not attributable to level of consciousness or acute emotional distress. It is a major source of caregiver distress, as it is perceived as a personality change in the patient resulting in "no longer caring or appreciating the sacrifices being made on his or her behalf." Apathy can be the result of drug therapy (particularly antipsychotics), metabolic illnesses (e.g., hypothyroidism), and environmental factors such as institutionalization. Apathy can be a feature of depression but can be differentiated from it. For instance, most depressed patients exhibit increased emotional distress, whereas the typical apathetic patient exhibits decreased emotional distress and a lack of emotional

response to others. Apathy is also a major feature of dementia, particularly in LBD, where it is presumed to be related to the well-established frontal lobe dysfunction. In depressed patients apathy responds to antidepressants, and in demented patients it can respond to acetylcholinesterase inhibitors (21,22).

Agitation and aggression are perhaps the most distressing BPSD symptoms and a critical factor in the decision to institutionalize patients with LBD or PD-SDAT. Clinically the behaviors can take the form of motor restlessness, verbal outbursts, and verbal or physical aggression. These symptoms are often comorbid with psychosis and depression, yet psychosis and depression are surprisingly uncommon predictors of aggressive behaviors (23). Although more prominent in patients with advanced dementia, in patients chronically treated with dopaminomimetic agents, they can appear in the early stages of dementia.

Agitation and aggression require careful interpretation of the semiology and individualized treatment approaches, particularly in patients who can no longer effectively communicate their needs. For instance many patients become agitated because they are in pain that they cannot explain or localize; they may be uncomfortable due to severe constipation or urinary retention, or because they have developed an acute medical illness like a urinary tract infection. Also important are psychosocial factors, which include caregiver exhaustion and stress, or for those in chronic care facilities, possible institutional mistreatment. Management consists of eliminating or treating acute medical conditions and modifying the triggering psychosocial factor whenever possible. Treatment of depression and psychosis as appropriate are also important. These treatments are discussed below.

In patients not responding to these approaches, anticonvulsants are being used with increasing frequency but variable success (24). In a 6-week, placebo-controlled study of divalproex sodium (mean dose 826 ± 126 mg/day titrated over weeks) for agitation in dementia (mostly SDAT), 68% of 56 nursing home patients showed reduced agitation compared to 52% in the placebo group ($p = 0.06$) (25). However, side effects occurred in 68% of the divalproex group compared to 33% of the placebo group. This high rate of side effects is of particular concern given the fact that valproic acid can cause reversible tremor and other parkinsonian features in demented patients without PD (26,27). It remains an open question whether these doses are effective in patients receiving ongoing treatment with dopaminomimetics and how long it can be tolerated. Experience with using alternative anticonvulsants like carbamazepine, lamotrigine, and topiramate in this population is virtually nonexistent.

There is little evidence to support the long-term use of benzodiazepines in the treatment of BPSD-associated agitation. In the acute setting, short-

acting benzodiazepines with few active metabolites, like lorazepam, may be helpful in controlling agitated behaviors until more definitive measures can be taken. Because many of the patients with agitation in the setting of PD and LBD are probably already taking an atypical antipsychotic and several antiparkinsonian agents, it is important to anticipate the profound effects on blood pressure and arousal that may result from the combination.

PSYCHIATRIC SYMPTOMS

Depression

Depression affects up to 50% of patients and may be present at any stage of the illness or even precede the onset of motor symptoms (28,29). Although depression correlates poorly with the severity of motor symptoms (30), it is probably the single most important contributor to poor quality of life in PD (2,3). Depression can also have a negative impact on cognition and motor function even in the face of optimally treated motor symptoms (31–34). A common etiology for the subacute (i.e., days to weeks) loss of response to antiparkinsonian drug therapy is the development of depression. Depression in PD may be difficult to recognize because many of its symptoms overlap those of PD. This overlap includes psychomotor retardation, loss of energy, decreased motivation, social withdrawal, poor sleep, and somatic complaints (29). Personality changes in the form of apathy, lack of assertiveness, and indecisiveness are also common, further obscuring the differential. It is important to rule out other medical conditions like hypothyroidism, vitamin deficiencies (e.g., B_{12}), or cerebrovascular disease, which may contribute to negative symptoms and depression. Testosterone deficiency can be associated with otherwise refractory depression, loss of libido, fatigue, and other nonmotor symptoms (35).

Various lines of evidence suggest that depression in PD is an intrinsic part of the illness rather than a reaction to disability. Nonetheless, the psychosocial stressors that result from the illness often trigger or compound already existing depression. Depression in PD seldom reaches suicidal proportions except in cases with preexisting affective illness. On the other hand, even *subclinical or mild depression* can affect quality of life and impair cognition and motor function. There is no consensus on whether treating minor depression is warranted in PD, but if there is any doubt that the symptoms are interfering with quality of life, depression should be treated.

Management of bipolar illness in PD is complicated by the fact that dopamine agonists are capable of triggering a manic episode. These patients are best managed with mood stabilizers, appropriate antidepressants, and occasionally atypical antipsychotics. With these provisions, the judicious use

of small doses of dopamine agonists may be possible in some cases. Among the mood stabilizers, lithium carbonate is poorly tolerated, as are large doses of valproic acid due to their potential to aggravate tremor and possibly other parkinsonian symptoms (24,27). Other potential mood stabilizers not formally tested in PD for which there are few data in PD include carbamazepine, lamotrigine, and topiramate.

Anxiety

Generalized anxiety disorders are also associated with PD. As in many other conditions, anxiety can appear in isolation or as an accompaniment to depression in PD (36). Unlike other conditions, in PD, anxiety can be due to an *akathesia equivalent* mediated by "dopamine hunger" (i.e., under-medication of motor symptoms) rather than dopamine blockade. This is compounded by the advent of motor fluctuation, which can precipitate panic attacks during the "off" periods (37,38). During the "off" periods associated anxiety is the most disabling to the patients. Patients describe a feeling of "doom" reminiscent of a drug withdrawal reaction. Anxiety increases as patients become demented, and it can be particularly severe in patients with LBD and delusions.

PSYCHOTIC SYMPTOMS

Hallucination and Delusions

The incidence of psychotic symptoms in PD varies greatly, ranging from 6 to 40%, depending on the age group of the population surveyed and the number of demented patients in the survey (39,40). Leading up to the first psychotic symptom, many patients exhibit behavioral changes, becoming erratic, temperamental, unreasonable, demanding, and seemingly self-centered, with apparent disregard for the needs of others. These personality changes can be multifactorial due to, for instance, emerging depression, conceptual disorganization due to emerging dementia, or mild delusional thinking due to drug-induced psychosis. The relation between the drugs, particularly dopamine agonists, and the psychotic symptoms is complex. In the absence of dementia, this behavior is typically drug-induced and equivalent to the BPSD psychosis mentioned above for demented patients.

Patients with LBD may experience all of the above even before being exposed to dopaminomimetic agents. For patients exhibiting the above mild and insidious nonpsychotic symptoms, the risk and the time course for developing psychotic symptoms remains unclear. When these symptoms are combined with sleep disturbances, the risk is significant.

Early drug-induced psychotic symptoms in PD are typified by formed visual hallucinations (usually people and animals) with retention of insight. The presence of auditory hallucinations suggests coexisting psychotic depression or dementia, or it may be a side effect of anticholinergic medications (41). In many instances, disturbing cognitive and psychiatric symptoms will cease with elimination of anticholinergics and amantadine. Although chronic dopaminomimetic therapy is associated with drug-induced hallucinations and possibly other psychotic symptoms, the mechanisms of this association are unclear. In one study acute elevation of plasma levodopa levels failed to trigger hallucinations in patients with a history of hallucinations, suggesting the effect is not simply a function of plasma levodopa levels or its pharmacokinetics (42). The phenomena of hallucinations depend on the chronic pharmacodynamic changes that take place downstream from the striatal dopamine receptor (43). In a clinicopathological study there was an association between the hallucinatory symptoms in demented PD patients and the presence of Lewy body (and presumably cholinergic) pathology in the amygdala and hippocampus (12). In a cerebral blood flow study, hallucinatory patients exhibited significantly lower blood flow in the left temporal regions than nonhallucinatory patients (44).

In hallucinating patients an attempt should be made to reduce the overall impact of the dopaminomimetic strategy. This is done in a systematic stepwise manner eliminating first the less effective drugs and, as necessary, eliminating longer-acting drugs before shorter-acting drugs before deciding on what to do with levodopa. Until the patient shows signs of improvement, sequentially eliminate selegiline, nocturnal doses of dopamine agonists or controlled release carbidopa-levodopa, reduce daytime doses of dopamine agonists, eliminate catechol-O-methyl transferase inhibitors, and finally reduce the dose of immediate release carbidopa-levodopa. If a significant reduction in antiparkinsonian therapy is required, the resulting aggravation of motor symptoms may be intolerable, requiring the introduction of selective atypical antipsychotics (41).

Delirium

Delirium refers to confusional states characterized by severe and fluctuating disturbances of arousal. In PD they are most often seen in patients with dementia and an intercurrent medical illness. These illnesses can be varied but commonly include infections, dehydration, metabolic disturbances, congestive heart failure, or analgesic use associated with chronic pain (45). Other common etiologies include use of anticholinergics, amantadine, selegiline, and dopamine agonists. Other agents include benzodiazepines,

narcotic analgesics, and a host of drugs with anticholinergic side effects ranging from tricyclic antidepressants to bladder antispasmodics. Delirium may be due to underlying dementia. Before making this assumption it is important to first rule out the above medical causes, which are not only common, but equally likely to aggravate dementia-associated delirium and far easier to treat than the dementia itself. The treatment of dementia-induced delirium is far more complicated and may involve the use of dopamine antagonist doses higher than those used to treat hallucinations in PD, the introduction of acetyl-cholinesterase inhibitors, or a combination of both (46).

TREATMENT OF PSYCHIATRIC SYMPTOMS

Depression and Anxiety

Depression can be managed with drugs as well as changes in daily routine. Correcting abnormal sleep patterns, daily exercise, and behavioral approaches are recommended. Patients with depression may respond as well to conventional antidepressants [e.g., tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs)]. Short-acting rather than long-acting SSRIs are preferred. Although all SSRIs are probably effective in PD, citalopram (10–30 mg/day), sertraline (50–150 mg/day), and paroxetine (10–30 mg/day) are particularly well tolerated (47). Buproprion (50–200 mg/day) and venlafaxin SR (37.5–150 mg/day) are less sedating. Concerns about the potential for hyperserotonergic reaction (delirium with myoclonus and hyperpyrexia) stemming from the combination of selegiline and SSRIs appear to be exaggerated (48). Finally, electroconvulsive therapy (ECT) is recommended for patients with PD who suffer from refractory or severe psychotic depression and are intolerant of oral antidepressants (49).

Antipsychotic Therapy

Given the pivotal role of dopaminomimetic agents in the genesis of psychotic symptoms in PD, in past years the treatment of motor symptoms was sacrificed in order to improve psychiatric symptoms. As was the case with ''drug holidays,'' cognitive improvement was negated by the resulting worsening in motor symptoms. Since then, ''drug holidays'' have been largely abandoned due to their associated morbidity (50).

Conventional antipsychotics are poorly tolerated due to their associated tendency to aggravate parkinsonian symptoms in the elderly due to D_2 dopamine receptor blockade (51). The newer, selective, atypical

antipsychotics have a lower incidence of extrapyramidal symptoms (e.g., parkinsonism) compared to conventional antipsychotics (52). This low tendency to generate extrapyramidal symptoms has been attributed to the high in vitro affinity for serotonin (5HT2a) receptors and the relatively low affinity for dopamine D_2 receptors of these compounds compared to typical antipsychotics. Not all atypical antipsychotics behave the same way. Using positron emission tomography, radioligand displacement studies have shown that the atypical antipsychotics clozapine and quetiapine tend to dissociate from striatal D_2 receptors faster (in less than 2 hours) than other atypicals (i.e., risperidone and olanzapine) and typical antipsychotics (53–55). This fast dissociation appears not to compromise the antipsychotic effect of these agents while reducing the risk of extrapyramidal symptoms. In other words, high affinity for and extended association with D_2 dopamine receptors is a better predictor of drug-induced parkinsonism than of antipsychotic response (56).

Clozapine has been shown to be highly effective in the treatment of drug-induced hallucinations in PD and may have additional beneficial effects on tremor, dystonia, and dyskinesias (57–60). Doses effective in the management of drug-induced hallucinations in non-demented PD patients are between 25–50 mg/day, typically administered at night before bedtime to help induce sleep and reduce the risk of early morning orthostatic hypotension. Higher doses may be needed to control behavioral symptoms in patients with LBD, PD/SDAT complex, or cases of dementia-associated delirium. Associated side effects include dizziness, orthostatic hypotension, sialorrhea, and confusion. Doses higher than 75–100 mg/day are not well tolerated in this population. It is widely accepted that the use of clozapine is tempered by the 1% risk of agranulocytosis, which requires frequent monitoring of the leukocyte count (61), and, more recently, by rare reported cases of myocarditis.

Quetiapine is now the first-line drug for the treatment of all psychotic symptoms in PD (62). It is not associated with serious toxicity and has a low incidence of drug-induced parkinsonism (63–67). In PD with drug-induced hallucinations, the median doses are 25–75 mg/day, with most of the dose administered at night. Daytime doses can be administered at noon or later. As with clozapine, the doses required to treat behavioral symptoms in LBD or dementia-associated delirium have not been well studied but may be higher. Side effects included sedation, orthostasis, dizziness, and, in demented patients, possible increased confusion. If the symptoms are not well controlled with quetiapine, the patient may be switched to clozapine (68).

Risperidone is the second oldest atypical antipsychotic. In small doses (0.25–1 mg/day) it is an effective antipsychotic in PD patients with drug-

induced hallucinations. In some patients, a worsening of parkinsonian signs may occur (62). In fact in one study investigators failed to find a difference between the neurological effects of low-dose risperidone and haloperidol in PD patients being treated for psychotic symptoms (69). Olanzapine does not appear to be well tolerated by patients with PD (70–74).

Acetylcholinesterase Inhibitors

A novel strategy for the treatment of psychotic symptoms in LBD, and possibly PD, is the use of acetylcholinesterase inhibitors (22). In a 20-week, double-blind, placebo-controlled study, the acetylcholinesterase inhibitor rivastigmine in doses of 6–12 mg/day significantly improved hallucinations, delusions, anxiety, and apathy in patients with LBD (75). The improvement in psychotic symptoms was in the order of 30%, which is comparable to that typically obtained with the atypical antipsychotics. Patients did not experience increased tremor or a worsening of parkinsonian features, which had been previously reported with other acetylcholinesterase inhibitors (76,77). Similar findings were reported in patients with PD (with and without dementia) treated with donepezil for psychotic symptoms over the course of 6–26 weeks. In these small studies donepezil 5–10 mg/day produced a significant improvement in psychotic symptoms without worsening parkinsonian motor symptoms (78,79). Although the safety and efficacy of this approach needs further study, it may be worth considering in patients with PD and dementia who continue to experience apathy and delusions after an adequate trial of atypical antipsychotics.

SLEEP DISTURBANCES

General

Sleep disturbances are a common and underrecognized feature of PD (80). They can be part of a primary sleep disorder or be secondary to advancing PD or comorbid depression or dementia (81). Specific types of sleep disturbances in PD may even be linked to the pathophysiology of psychotic symptoms.

Sleep problems in PD range from delayed sleep onset and sleep fragmentation to periodic leg movements (PLMS), restless leg syndrome (RLS), and REM-related behavioral disorders (REM-BD). Recognizing these important elements of nonmotor dysfunction in PD is important due to the increasing evidence that they are critically linked to disability and emerging evidence that some sleep disorders may be linked to psychiatric symptomatology (2,82,83). Factors intrinsic to the illness or its treatment

that may disrupt sleep include the dopaminergic pathology itself (84,85), the dopaminomimetic treatment strategies (86), and the diurnal fluctuations associated with the treatment. Nighttime reemergence of parkinsonian motor signs presents with reemergence of tremor, pain, and urinary urgency that forces the patient to get up (82). In addition, some patients experience sleep apnea, which may indirectly contribute to daytime somnolence and cognitive decline. Sleep apnea has been linked to cases of otherwise unexplained daytime fatigue (87). Untreated depression is also a major factor contributing to the high incidence of sleep disturbances in PD.

Drug-induced sleep disruption includes vivid dreams and hallucinations, as well as daytime somnolence with resulting nocturnal insomnia (83). When sleep abnormalities are successfully treated, improved daytime functional capability is realized (''sleep benefit'') (88).

REM-Related Behavioral Disorder and a Possible Link to Psychotic Symptoms

REM-BD is yet another form of sleep disturbance that, although not specific to PD, may facilitate the development of psychotic symptoms (89,90). REM-BD is characterized by nocturnal vocalizations and bursts of motor activity during which the subject appears to be acting out his dreams (91). Polysomnographically, normal REM sleep appears during stages III and IV of sleep and is characterized by ''awake-appearing'' cortical desynchronization. REM sleep is normally accompanied by cardiorespiratory irregularities, muscle atonia, and dreaming, whereas REM-BD is associated with REM intrusions into stage I and II of sleep, sleep fragmentation, and motor and vocal phenomena (91). In addition to PD, REM-BD has been described in LBD, in multiple system atrophy (MSA), and in other conditions unrelated to PD (92).

A pathophysiological link between REM-BD and psychotic symptoms has been suggested by numerous observations and by a recent study in which 10 of 10 nondemented PD patients with hallucinations were found to have REM-BD (90). The finding is not specific since similar findings have been noted in LBD (92), and not all patients with REM-BD suffer from hallucinations (90). Nonetheless, daytime hallucinations coincident with REM intrusions during wakefulness were reported by all 10 and by none of the nonhallucinating patients, again suggesting a pathophysiological link between this phenomenon and the ''dream-like state' of hallucinatory symptoms in PD (92).

Treatment of Sleep Disturbances

Treatment of sleep disorders in PD starts with the implementation of a sensible program of sleep hygiene (93). General principles include setting a regular time for rising and going to bed, providing bright lights during the daytime and darkness and a cool environment to sleep at night. Other suggestions include the use of satin sheets to facilitate moving in bed, avoiding liquids after supper, emptying the bladder before retiring for bed, and careful attention to bladder dysfunction. Parkinson-specific maneuvers include improving nocturnal akinesia and reemergence of tremor through the judicious use of controlled-release carbidopa/levodopa or dopamine agonists. Specific adjustments in other anti-PD medications include the discontinuation of the noon dose, or all doses of selegiline, which has a notable incidence of insomnia, or the use of nighttime doses of dopaminomimetics. In patients already experiencing hallucinations, this approach may lead to a worsening of psychotic symptoms, perhaps mediated by a ''kindling effect'' these drugs may have on psychiatric symptoms, particularly when administered at night (94). It is known that nighttime dopaminomimetics tend to block normal REM sleep, perhaps facilitating the REM shift from stages III and IV to stage I and II (95). Paradoxically, in patients with daytime sleepiness, the use of daytime stimulants like methylphenidate and modafinil may improve daytime arousal while improving nighttime sleep (96).

Other strategies to improve sleep in PD include ruling out or treating conditions like sleep apnea, PLMS and RLS. Trazadone or the judicious short-term use of hypnotics or benzodiazepines like clonazepam are viable alternatives. Other alternatives include the use of melatonin, small doses of tricyclic antidepressants like nortriptyline, or nighttime doses of a sedating antidepressant like mirtazapine. Treatment of REM-BD is more complex and may not work in all patients (97). The most effective treatment has been small doses of clonazepam (0.25–0.5 mg one hour before sleep). Dopamine agonists may help REM-BD but aggravate nightmares and possibly daytime psychotic symptoms (81). Atypical antipsychotics like clozapine and quetiapine have not been studied adequately. The effect of dopamine agonists is more variable, with some patients reporting improvement and others worsening. The reasons for this apparent heterogeneity to dopaminomimetic response is unknown but may have to do with clinical co-variants such as the presence of PLMS, RLS, and dementia.

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