Neuropsychiatric Complications of Medical and Surgical Therapies for Parkinson’s Disease

David J. Burn, MD, FRCP, and Alexander I. Tröster, PhD

ABSTRACT

This review deals with the range of neuropsychiatric problems that may arise from the use of medical and surgical therapies in the treatment of Parkinson’s disease. As new approaches emerge, these problems are diversifying. Well-recognized drug-related complications include hallucinations and psychosis and the so-called dopamine-dysregulation syndrome. The etiology of these problems has not been fully established and is not clearly dose related, while the management can be difficult and needs to be tailored to the individual patient. Cholinergic and dopaminergic drugs may both influence cognitive function. The development of pharmacogenetics could improve the therapeutic ratio of medical approaches to PD in the future. The literature relating to the neuropsychiatric issues complicating the surgical treatment of Parkinson’s disease is more recent and frequently suffers from methodological problems, lack of a systematic approach, and adequate patient follow-up. The emergence of neuropsychiatric problems in association with surgery has shed new light upon the pathophysiological mechanisms underpinning these symptoms. Depression, hypomania, euphoria, mirth, and hypersexuality have all been described following deep brain stimulation procedures, although most studies have concentrated upon the depressive features. Anxiety has been described only rarely to date. Fortunately, permanent cognitive complications appear to be rare. The optimal management approach for surgically related neuropsychiatric problems is unknown at present. Prospective multicenter studies would contribute significantly to resolving this therapeutic uncertainty. (J Geriatr Psychiatry Neurol 2004; 17:172-180)

Keywords: Parkinson’s disease; medical and surgical therapies

Parkinson’s disease (PD) is classically thought of as a prototypic extrapyramidal motor disorder due to dopamine deficiency, resulting from catastrophic cell loss in the pars compacta of the substantia nigra. Even within the dopaminergic system, however, this is an oversimplification, and other, more variable, cell loss occurs within the medial nigra, retrorubral, and ventral tegmental areas. Projections from these structures modulate cognitive and affective function. Dopamine replacement therapy for the motor symptoms of PD could therefore alleviate or exacerbate neuropsychiatric features, depending on prevailing dopamine receptor stimulation within these systems. Furthermore, the subthalamic nucleus and globus pallidus, targeted for deep brain stimulation (DBS) treatment of PD, also have connections with limbic and cognitive cortical areas, making it difficult to restrict treatment purely on the motor syndrome.

Neuronal loss within other pigmented brainstem nuclei in parkinsonian patients leads to a variable and progressive loss of other neurotransmitters including acetylcholine, noradrenaline, and serotonin, rendering the individual increasingly susceptible to the psychotropic effects of dopaminergic and surgical treatments. There is likely to be a genetic predisposition toward this susceptibility, for example, via receptor polymorphisms, making it difficult to predict the neuropsychiatric complications of pharmacological and surgical interventions in a given PD patient. This review will consider neuropsychiatric problems related to the pharmacological and surgical therapies used to treat PD.
DRUG-RELATED NEUROPSYCHIATRIC ISSUES

Drug-related neuropsychiatric problems in PD may be mild and underrecognized, or be dose-limiting and a major management problem. An example of the former relates to fluctuation in mood that can occur with L-dopa medication. When “on,” the patient feels better and may report a sense of mild euphoria, while wearing off of the medication is associated with low mood and a feeling of helplessness and unease that may precede objective motor changes.

Hallucinations and Psychosis

Chronic treatment with virtually all antiparkinsonian agents, including dopaminergic drugs (L-dopa and dopamine agonists), monoamine oxidase type B inhibitors (selegiline), anticholinergics, and amantadine, can be associated with hallucinations, usually visual, in the susceptible PD patient. Visual hallucinations are common in PD and may be classified as either benign, with preserved insight, or malignant, whereupon insight is lost. In the latter instance, the patient is considered psychotic, and other features, including paranoid delusions, may also develop. Typical delusional symptoms in the PD patient are a belief that they are being targeted for death or that their spouse is having a sexual affair.

Although visual hallucinations were reported in PD before the introduction of L-dopa, this phenomenon has become a frequent complication only since dopaminergic drugs were introduced. Between 8% and 40% of patients receiving long-term treatment are reported to experience visual hallucinations. Many of these figures have been derived from hospital-based patient samples. From a community-based study of 245 PD patients, Aarsland and colleagues determined 10% of patients to have hallucinations with retained insight and a further 6% with more severe degrees of thought disorder. These figures were, however, derived using the Unified Parkinson’s Disease Rating Scale (UPDRS) part I, which may not be the most sensitive instrument to detect such problems. The problem is not confined to patients with advanced disease, and up to 16% of PD patients with early disease, treated with a variable combination of L-dopa and dopamine agonists, develop features compatible with a drug-induced psychosis. Age, cognitive impairment, daytime somnolence, and disease duration, as well as possibly depressed mood and ocular pathology, have been identified as risk factors predictive of visual hallucinations in some studies. The patient will commonly describe realistic images of people (familiar or strangers), animals, or insects. The images are often in miniature, blurred, and may be moving. The content may vary and can be in either color or monochromatic.

The relationship between the use of dopaminergic drugs and the induction of psychosis is complex and does not relate simply to the dose of medication used. In 2 recent surveys of visual hallucinations in PD, the dose of dopaminergic therapy was not predictive of the occurrence of hallucinations. Furthermore, the administration of intravenous L-dopa to PD patients with a prior history of hallucinosis does not reliably precipitate this symptom. It may be postulated that other factors, such as an interaction between dopaminergic and cholinergic neurotransmission, are more critical in precipitating drug-induced psychosis. Relative dopaminergic overactivity in the mesocorticolimbic system combined with cholinergic underactivity secondary to subcortical neuronal loss could therefore provide a more permissive environment for drug-induced psychosis. Such a hypothesis would be supported by the poor prognosis attached to the occurrence of early drug-induced visual hallucinations in parkinsonian syndromes, and the later development of dementia in such patients. Once hallucinations develop in PD, they are likely to be persistent and progressively more intrusive.

The management of presumed drug-induced psychosis in PD is discussed in more detail elsewhere. In brief, if the sensorium is clouded with the psychotic symptoms, then other causes of delirium should be sought and excluded. Subdural hematoma, infection, “silent” myocardial ischemia, and other nonparkinsonian medications may all be responsible for a delirious state, particularly in elderly PD patients. Thereafter, the antiparkinsonian medication regimen should be reviewed and a tapered, gradual withdrawal undertaken in the following suggested order: anticholinergics, selegiline, dopamine agonists, catechol-O-methyltransferase inhibitors. The patient is thus managed on L-dopa monotherapy, in the lowest possible dose necessary to maintain motor function. If psychotic symptoms persist, and cognition is otherwise preserved, a low dose of an atypical antipsychotic agent (quetiapine, olanzapine, clozapine, or risperidone) should be introduced and the patient carefully monitored for deterioration in his or her extrapyramidal signs. Cholinesterase inhibitors may offer an alternative therapeutic approach in this situation, although robust trial data are currently lacking and no clear recommendation can be given.

Cognitive Impairment

Anticholinergic Drugs

Anticholinergic drugs and amantadine have a particular propensity to cause psychosis in the PD patient, often in association with delirium. Anticholinergic treatment is also associated with chronic cognitive impairments, even when used early in the disease course in previously drug-naive patients. Executive functions, mediated by subcortico-frontal connections, seem to be particularly susceptible to anticholinergics. Chronic exposure to these drugs may be an independent clinical risk factor for dementia in PD. A recent study of pathologically confirmed and clinically nondemented PD cases demonstrated increased amyloid plaque and neurofibrillary tangle counts (though below those sufficient to warrant a diagnosis of Alzheimer’s disease) in patients chronically (ie, more than
2 years) exposed to anticholinergic drugs, indicating that these agents may directly influence disease processes mediating cognitive decline, and in particular, amyloid processing and tangle formation.¹⁶

**Dopaminergic Drugs**

The effect of dopaminergic treatments on cognition in PD is complex and is influenced by the stage of the disease and also the extent of extranigral dopaminergic cell loss. In early PD, subtle cognitive deficits may be elicited, reminiscent of those found in patients with lesions of the prefrontal cortex.¹⁷ Skills required for anticipation, planning, initiation, and monitoring of goal-directed behaviors are thus impaired, collectively termed a *dysexecutive syndrome*. Spatial working memory is also affected in early PD.¹⁸ The dorsolateral prefrontal cortex has been implicated as the critical locus for dopaminergic effects on these high-level cognitive functions. Functional imaging studies suggest that executive deficits result from reduced dopaminergic innervation of the dorsolateral prefrontal cortex, mediated via the loss of mesocortical projections from the ventral tegmental area.¹⁹,²⁰

The administration of dopaminergic therapy can ameliorate these deficits, improving cognitive inflexibility, but also increasing impulsivity.²¹ In contrast, PD patients with more advanced disease and motor problems such as wearing off tend to deteriorate cognitively on acute L-dopa challenge, suggesting that a relative “hyper-dopaminergic” state may have adverse effects.²²

**Dopamine Dysregulation Syndrome and Other Behavioral Disturbances**

A number of behavioral phenomena have been associated with chronic use of dopaminergic drugs, mainly relating to L-dopa and dopamine agonists (Table 1), although there have been reports of selegiline-inducing hypomania, compulsive spending and transvestic fetishism.²²,²³ Hypersexuality, punding (repetitive purposeless motor acts not distressing to the patient), compulsive gambling and shopping, and other obsessive behaviors may be consequent to drug use in some patients. Reducing dopaminergic therapy can lead to cessation or improvement in symptoms. It is unknown why only some individuals develop these disorders, although susceptibility via dopamine receptor polymorphisms has been suggested.

Dopamine dysregulation syndrome (DDS) is a compulsive and dysregulated drug use beyond that needed to achieve relief of motor symptoms, resulting in harmful consequences. It is recommended that terms such as *substance dependence or addiction* should be avoided for this disorder, as they may stigmatize the patient and are probably inappropriate for a problem occurring in the context of a progressive neurodegenerative disorder.²⁴ A number of theories relating to psychostimulant addiction have been applied to DDS, and each may partly explain the phenomenon, although it is unlikely that any one theory can account for all the observed features.²⁴ Changes in dopaminergic neurotransmission in the nucleus accumbens and related circuitry have been proposed to play a key role in the pathogenesis of DDS through aberrant activation related circuitry have been proposed to play a key role in the pathogenesis of DDS through aberrant activation and/or maladaptive processing in a “reward pathway.” Dopamine plays a key role in the positive-reinforcing effects of drugs of abuse, via the mesocorticolimbic system. Dopamine D₁, D₂, and D₃ receptors have all been shown to mediate this effect in animal models.²⁵ Current working diagnostic criteria for DDS are outlined in Table 2.

DDS has been reported in approximately 4% of PD patients attending a specialist referral clinic.²⁶ The typical case scenario for DDS is a male PD patient with early onset disease. There may be a premorbid history of depression, although this is not invariable. The patient will perceive the need for increasing doses of dopaminergic therapy, in excess of those required to control the extrapyramidal symptoms. The preoccupation and anticipation involved in taking the dopaminergic medication leads to abnormal behavior and impairment in social and occupational functioning. Hoarding, aggression, and unwillingness to reduce treatment despite severe and continuous dyskinesias are all characteristic features of this state.²⁶ A spiraling misuse of dopaminergic drugs may lead to hypomania and frank psychosis. Although the psychosis responds readily to reduction in medication, the patient then develops a withdrawal negative affect, characterized by depression, irritability, and anxiety.²⁷

The primary prevention of DDS, through anticipation and minimization of risk factors, is preferred since the established syndrome is extremely difficult to manage. Subcutaneous “bolus” apomorphine should be avoided in patients known or suspected to have these problems because the “high” induced by the parenteral administration may precipitate or exacerbate DDS.²⁵,²⁶ Atypical antipsychotics to block the induction of psychomotor sensitization and treat episodes of psychosis may be considered, whereas

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**Table 1. Behavioral Phenomena Associated With Overuse of Dopaminergic Drugs**

- Euphoria and hypomania: may be associated with feelings similar to mania but without indiscriminate enthusiasm for interpersonal interactions
- Heightened aggression: includes irritability and angry outbursts but violence uncommon
- Pathological gambling and shopping: the compulsive need to gamble (“until it hurts”) or shop may lead to financial ruin
- Hypersexuality: increased libido, not necessarily associated with increased erectile frequency, may lead to repeated masturbation and repeated demands for sexual intercourse and be associated with paraphilias
- Altered appetite: compulsive eating is seen during “on” phases, sometimes associated with uncontrollable food cravings
- Punding: an intense preoccupation with complex, repetitive manipulations of technical equipment, examining and sorting through common objects, hoarding and handling that may be associated with motor restlessness and hyperactivity (“walkabouts”)

Modified from reference 24.
there is commonly a need for antidepressants in the postpsychotic stage. Drugs may need to be dispensed under strict supervision via the physician and/or pharmacist, whereas psychosocial support and psychotherapy are essential in severe cases. The prognosis for established DDS is poor with a tendency to relapse.

**NEUropsychiatric Issues related to the Surgical Treatment of Parkinson’s disease**

Neurosurgical therapies for PD, none curative, fall into 3 categories: ablative, deep brain stimulation (DBS), and transplantation. Ablative and DBS therapies have 3 anatomical targets: ventrointermediate (Vim) nucleus of the thalamus, internal globus pallidus (GPi), and subthalamic nucleus (STN). In general, DBS is currently preferred over ablation given the adjustability of stimulation parameters and potential reversibility of adverse effects, lack of interference with benefit from possible future drug therapies, and putatively lesser morbidity, especially in cases of bilateral surgery. Note must be taken, however, that cost of DBS and lack of readily available expertise in implanting, programming, and adjusting devices hinders adoption of DBS in many geographic regions, especially in rural areas in developed countries and in developing regions. Similarly, ethical and technological issues may preclude widespread adoption of transplantation techniques, including autographs and xenografts. Transplantation of adrenal medullary tissue, which was associated with significant psychiatric morbidity, has been virtually abandoned, and recent placebo-controlled trials of fetal mesencephalic tissue transplantation have noted more frequent confusion, hallucinations, and psychosis in the transplant than the sham surgery group.

Ablative surgical treatments date back to the late 1930s and 1940s (with stereotactic [as opposed to “open”] procedures being carried out in the 1950s). Widespread availability of levodopa in the late 1960s was associated with a virtual abandonment of surgical treatments, although realizations of the limitation of medical therapies led to their renaissance in the 1980s. The 1980s and 1990s also saw the development and refinement of alternatives to ablative neurosurgical therapies, such as DBS and various forms of tissue transplantation. Although neurobehavioral issues were often ignored in early series, reviews of those studies make it evident that significant cognitive and psychiatric complications could attend thalamotomy and pallidotomy, and especially bilateral interventions. Although the neurobehavioral outcomes of early and recent ablative procedures are difficult to compare given differences in patient selection criteria, surgical targets, and procedures, it is generally believed that modern ablative procedures are relatively safer (but see Laitinen for a dissenting view).

Modern studies of surgical interventions usually suffer from methodological limitations, given their relatively brief history. Foremost among these limitations is a lack of systematic attention to neurobehavioral morbidity. Given these methodological issues, estimates of the incidence of neuropsychiatric complications following surgical interventions are highly preliminary.

**Psychosis**

Although psychosis has been observed after fetal mesencephalic tissue transplantation and was commented on in earlier ablative studies, it is rarely commented on in modern ablation and DBS studies. Herzog et al. observed psychosis in a small number of STN DBS cases, in some instances, in the context of mania. Visual hallucinations were clearly evoked by stimulation in one STN DBS case with apparently properly placed electrodes.

**Depression**

In evaluating morbidity, it must be borne in mind that changes in scores on symptom inventories and casesness (how many persons had a condition of interest before and after surgery) do not always go hand in hand. This is well illustrated by the findings of Lagrange et al. and Berney et al. Whereas depression symptom inventory scores either improved or did not change, several patients developed depression after DBS, sufficiently severe in some cases to precipitate suicidal ideation or attempts.

Depression has rarely been observed in early studies of thalamotomy, and symptom inventories revealed either no change in, or an elevation of, mood. Recent studies of unilateral and bilateral pallidotomy using formal measures of mood state have similarly observed either an improvement or no change in mood. Two other studies, however, reported noteworthy frequencies of depression: Bezerra et al. in 5 (12%) of 41 unilateral pallidotomy patients and Ghika et al. in 2 (50%) of 4 bilateral operates. Depression has not been reported in subthalamotomy studies.
Whereas thalamic DBS was associated with small improvements in depressive symptoms 4 to 10 days after surgery,59 studies have generally reported unchanged levels of depressive symptoms after pallidal (GPi) DBS.48,60-62 Given the predominant lack of depression after ablations and thalamic and pallidal DBS, it is striking that numerous cases of depression and attempted or completed suicide are reported subsequent to bilateral subthalamic (STN) DBS. In the largest STN DBS series to date, Benabid et al 63 reported depression in 16 of 137 patients (12%). Others have reported similar rates of depression after STN DBS, ranging from 6% to 30%.35,64-69 In contrast, one study using symptom inventories found reductions in depressive symptoms.70

Several explanations might account for the apparently greater incidence of depression after STN DBS: (a) greater awareness of neuropsychiatric side effects since the earlier non-STN procedures; (b) STN DBS is typically done bilaterally, whereas Vim and GPi DBS are more often unilateral; and (c) the STN is a small target, and the electrode is more likely to be inaccurately placed (or inappropriate contacts are activated or stimulation is more likely to spread to adjacent nonmotor circuits). That electrode placement and contact selection are critical factors is supported by reports that depression is reversible by altering contact selection66 and that depression occurred after activation of a misplaced contact, 2 mm below the STN, in the substantia nigra.71 Stefurak et al72 described a patient in whom right, but not left, STN DBS reliably produced depressive dysphoria. The right electrode was superior and lateral to the intended target. Another elegant pilot study that asked patients to rate moods on a visual analog scale during stimulation of different electrode contacts also suggests that stimulation dorsal or ventral to the site of optimal motor benefit may be associated with mood changes (and more so with STN than GPi stimulation).73

Disease progression and medications may contribute to depression, particularly relevant to STN DBS since dopaminergic drugs are frequently dramatically reduced after electrode implantation, and because the acute psychotropic effects of levodopa and STN DBS may be similar.74 Depression often occurs well after electrode implantation and may not be responsive to manipulation of stimulation parameters. Krack et al75 reported that within the first 3 months after surgery, only 1 of 49 patients (2%) showed depression. In contrast, between 3 months and 5 years after surgery, 7 of 42 patients (17%) demonstrated significant depression. In the absence of a control group, it is unclear whether depression distant from surgery reflects the high prevalence of depression in PD,76,77 a point reinforced by the similar frequency of depression noted in fetal tissue transplantation and placebo treatment groups.78

Depression after surgery may also reflect exacerbation or recurrence of preexisting illness, changes in medications, or long-term stimulation effects. Houeto and colleagues’ findings suggest that preexisting depression may be a risk factor for postoperative depression.86 Among 5 patients with postsurgical major depression episodes, 4 had a history of such episodes prior to surgery. Nonetheless, it is also clear that mood disturbance can occur after surgery in the

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**Table 3. Possible Neurobehavioral Effects of Modern Surgical Interventions for Parkinson’s Disease (PD)**

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Target</th>
<th>Possible Adverse Effects in PD</th>
<th>Possible Beneficial Effects in PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation</td>
<td>Globus pallidus interna</td>
<td>Confusion</td>
<td>Reduction in obsessive-compulsive symptoms</td>
</tr>
<tr>
<td></td>
<td>Ventricle intermediate nucleus of thalamus</td>
<td>Rare cognitive impairment</td>
<td>Mildly improved performance on some memory tests (probably not a true memory improvement)</td>
</tr>
<tr>
<td>Deep brain</td>
<td>Subthalamic nucleus (modern target)</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>stimulation</td>
<td>Globus pallidus interna</td>
<td>Hypomania</td>
<td>Reduced anxiety and depressive symptoms</td>
</tr>
<tr>
<td>Ventricle intermediate nucleus of thalamus</td>
<td>Apathy</td>
<td>Depression (incl suicidality)</td>
<td>Mild naming improvement</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>Depression</td>
<td>(Hypo)mania</td>
<td>Reduction in depressive and anxiety symptoms</td>
</tr>
<tr>
<td>Transplantation</td>
<td>Putamen and/or caudate</td>
<td>Psychosis</td>
<td>Transient memory improvement</td>
</tr>
</tbody>
</table>

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absence of a preoperative history of such neuropsychiatric disturbance. Depression may resolve spontaneously in some cases. In others, symptoms may respond to antidepressants such as fluoxetine and, especially if occurring in the context of dopaminergic medication withdrawal, to increases in the dosage of dopaminergic medications. In some cases, both antidepressants and dopaminergic medication dosage adjustments may be needed.

Finally, from the psychosocial perspective, when the patient or caregiver expectations of surgical results are not met or maintained, or functional independence does not increase despite symptom amelioration, familial discord accompanied by depression may arise. A condition separate from depression, heightened emotionality may also occur after STN DBS.

Apathy
Apathy, which occurs less frequently than depression in PD (for review, see Tröster and Letsch), may also be less common than depression after surgical interventions for PD. It has been particularly reported after STN DBS. Krack and coworkers observed apathy unresponsive to medication in 1 of 49 patients within 3 months of bilateral STN DBS. Between 3 months and 5 years after surgery, 7 of 42 patients (17%) developed apathy, and in only 2 (5% of all patients) was the apathy responsive to dopaminergic and/or antidepressant therapy. Houeto et al also described 1 patient among 24 who experienced lack of motivation and initiative in the absence of sadness, guilt, or suicidal ideation. Although paroxetine (20 mg per day) was ineffective in alleviating this condition, treatment with bromocriptine (30 mg per day) was. Daniele and colleagues described a case of “psychic akinesia” after STN DBS. The pathophysiology of apathy after DBS is unknown but may reflect the STN DBS–associated anterior cingulate and medial frontal metabolic changes reported in one study (though apathy was not reported to be associated with these changes).

Mania, Hypomania, Euphoria, Mirth, and Hypersexuality
Mania may occur after pallidotomy. Hypomania has also been reported after GPI DBS, but this may have related to medication overuse since the episodes could not be reproduced under a variety of stimulation conditions when drugs were carefully controlled. Instances of possible DDS were observed in 2 of Houeto and colleagues’ 24 patients undergoing STN DBS. This proved refractory to medical management with clozapine and lithium in 1 case. Hypomania and mania (with or without psychotic features) is one of the more common neuropsychiatric complications described among PD patients having undergone STN DBS. Krack et al reported hypomania in 5 of 49 patients (10%) within 3 months of surgery (4 transient, 1 permanent) but no new cases (except “hilarity”) between 3 months and 5 years following intervention. Herzog et al observed hypomanic behavior in 2 of 48 cases (4%), though the 2 other patients with “psychotic symptoms” may also have had mania since the same group described a case of a patient with mania and psychosis. Houeto et al described hypomania in only 1 of 24 cases (4%), whereas Romito et al reported that 3 of 30 patients (10%) experienced manic episodes. Kulisevsky and colleagues described manic behavior in 3 of 15 patients (20%). Manic behavior may, like depression, be related to stimulation caudal to the STN target as evidenced by reversibility of the behaviors by altering stimulation parameters. Unlike depression, however, hypomania is often seen soon after surgery, suggesting a possible interaction between dopaminergic medication and stimulation (or a hypersensitivity to medications under stimulation conditions) as causal. In cases refractory to adjustment of stimulation parameters, medication with antipsychotics (eg, clozapine) and/or mood stabilizers (eg, carbamazepine) may control symptoms.

Anxiety
Anxiety has rarely been commented on in studies of surgical treatments of PD. Higginson et al and Fields et al reported reductions in anxiety inventory scores after pallidotomy or GPI DBS and Daniele et al after STN DBS, and Junqué et al observed reductions in obsessive and compulsive symptoms after pallidotomy. Reductions in obsessive symptoms were also reported in an older study of thalamotomy. In contrast, Houeto et al diagnosed anxiety disorders in a large proportion of their 24 patients after STN DBS: agoraphobia (17%), obsessive-compulsive disorder (4%), posttraumatic stress disorder (4%), and general anxiety (75%). However, these conditions are unlikely to be related to STN DBS per se (though they could have been rekindled by DBS or the surgical procedure or medication changes) because with the exception of 1 instance of general anxiety, all conditions were observed in the patients at some point before surgery.

Cognition
A detailed discussion of the cognitive consequences of surgery for PD is beyond the scope of this article, and the interested reader is referred to recent reviews by Tröster and Fields, Woods et al, and de Bie et al. Although perioperative, transient confusion is common (occurring in
18% of patients undergoing STN DBS\(^9\) and permanent cognitive complications are rare. Thalamic and GPi DBS are considered to be generally safe, with few, if any, cognitive changes noted. Like pallidotomy, STN DBS most commonly affects verbal fluency (see Woods et al\(^9\)). This is unlikely to represent motor speech dysfunction or bradyphrenia. Instead, the cognitive mechanisms underlying efficient word retrieval may be altered.\(^9\) Others have observed more widespread and severe cognitive compromise in their DBS and pallidotomy series,\(^4,8\) impacting episodic and working memory, executive functions, and attention.

**CONCLUSION**

The advent of modern drugs and renaissance of neurosurgery have undoubtedly led to refinements in the treatment of complex motor problems in advanced PD. This review has considered the range of neuropsychiatric problems that may, however, arise from these therapies. Some problems occur more commonly than others, and many are difficult, if not impossible, to predict. Effective control of neuropsychiatric complications in PD can be extremely difficult and may ultimately lead to compromise in motor control. Future challenges in the management of PD include an improved understanding of the pathophysiology of these nonmotor symptoms and a sharper therapeutic focus, thereby avoiding iatrogenic problems as far as possible.

**References**


