Duodopa and apomorphine infusions, remains to be performed. Studies are examining additional DBS targets that might benefit gait dysfunction, depression, and cognitive impairment in PD patients.

EXPERIMENTAL THERAPIES FOR PD

There has been considerable scientific and public interest in a number of novel interventions that are being investigated as possible treatments for PD. These include cell-based therapies (such as transplantation of fetal nigral dopamine cells or dopamine neurons derived from stem cells), gene therapies, and trophic factors. Transplant strategies are based on the concept of implanting dopaminergic cells into the striatum to replace degenerating SNc dopamine neurons. Fetal nigral mesencephalic cells have been demonstrated to survive implantation, re-innervate the striatum in an organotypic manner, and restore motor function in PD models. However, two double-blind studies failed to show significant benefit of fetal nigral transplantation in comparison to a sham operation with respect to their primary endpoints. Additionally, grafting of fetal nigral cells is associated with a previously unrecognized form of dyskinesia that persists after lowering or even stopping levodopa. This has been postulated to be related to unregulated release of dopamine from serotonin neurons. In addition, there is evidence that after many years, transplanted healthy embryonic dopamine neurons from unrelated donors develop PD pathology and become dysfunctional, suggesting transfer of α-synuclein from affected to unaffected neurons in a prion-like manner (see discussion above). Perhaps most importantly, it is not clear how replacing dopamine cells alone will improve nondopaminergic features such as falling and dementia, which are the major sources of disability for patients with advanced disease. These same concerns apply to dopamine neurons derived from stem cells, which have not yet been properly tested in PD patients and bear the additional concern of tumors and unanticipated side effects. The short-term future for this technology as a treatment for PD, at least in its current state, is therefore not promising, and there is no scientific basis to warrant routine treatment with stem cells as is being marketed in some countries.

Trophic factors are a series of proteins that enhance neuronal growth and restore function to damaged neurons. There are several different trophic factors that have been demonstrated to have beneficial effects on dopamine neurons in laboratory studies. Glial-derived neurotrophic factor (GDNF) and neurturin have attracted particular attention as possible therapies for PD. However, double-blind trials of intraventricular and intraputaminal infusions of GDNF failed to show benefits compared to placebo in PD patients, possibly because of inadequate delivery of the trophic molecule throughout the target region.

Gene delivery offers the potential of providing widespread delivery throughout a target region and long-term expression of a therapeutic protein with a single procedure. Gene therapy involves placing the DNA of a therapeutic protein into a viral vector that can then be delivered to specific target regions. The DNA of the therapeutic protein is then incorporated into the genome of the host cells and released on a continual basis. The AAV2 virus has been most often used as the viral vector because it does not promote an inflammatory response, is not incorporated into the host genome, and is associated with long-lasting transgene expression. Clinical trials of AAV2 delivery of the trophic factor neurturin showed promising results in open label trials but failed in double-blind trials, possibly because axonal damage in PD prevented retrograde transport of the protein to dopamine neurons in the SNc where it is required to induce upregulation of repair genes required for the trophic response. However, a subsequent double-blind trial of AAV2-neurturin delivered into both the putamen and SNc also failed.

Gene delivery is also being explored as a means of delivering aromatic amino acid decarboxylase with or without tyrosine hydroxylase to the striatum to facilitate dopamine production and glutamic acid decarboxylase to the STN to inhibit overactive neuronal firing. None of these procedures has been established to be effective in PD patients. Furthermore, although gene delivery technology has great potential, this approach also carries the risk of unanticipated side effects, and current approaches directed at the nigrostriatal system do not address the nondopaminergic features of the illness.

MANAGEMENT OF THE NONMOTOR AND NONDOPAMINERGIC FEATURES OF PD

Although PD management has primarily focused on the dopaminergic features of the disease, management of the nondopaminergic features should not be ignored. Some nonmotor features, although not thought to reflect dopaminergic pathology, nonetheless benefit from dopaminergic drugs. For example, problems such as anxiety, panic attacks, depression, sweating, sensory problems, freezing, and constipation all tend to be worse during "off" periods and may improve with better dopaminergic control. Approximately 50% of PD patients suffer depression during the course of the disease, and depression is frequently underdiagnosed and undertreated. Antidepressants should not be withheld, particularly for patients with major depression. Serotonin syndromes have been a theoretical concern with the combined use of SSRIs and MAO-B inhibitors but are rarely encountered. Anxiety can be treated with short-acting benzodiazepines.

Psychosis can be a problem for some PD patients. In contrast to AD, hallucinations are typically visual, formed, and nonthreatening. Importantly, they can limit the use of dopaminergic agents to obtain satisfactory motor control. Psychosis in PD often responds to low doses of atypical neuroleptics and permits higher doses of levodopa to be tolerated. Clozapine is the most effective drug, but it can be associated with agranulocytosis, and regular monitoring is required. For this reason, many physicians start with quetiapine even though it has not been established to be effective in placebo-controlled trials. Hallucinations in PD patients are often a harbinger of a developing dementia.

Dementia in PD (PDD) is common, ultimately affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to AD, primarily affects executive functions and attention, with relative sparing of language, memory, and calculations. When dementia precedes, or develops within 1 year after, the onset of motor dysfunction, it is by convention referred to as dementia with Lewy bodies (DLB; **Chap. 448**). These patients are particularly prone to have hallucinations and diurnal fluctuations. Pathologically, DLB is characterized by Lewy bodies distributed throughout the cerebral cortex (especially the hippocampus and amygdala) and is often also associated with AD pathology. It is likely that DLB and PDD represent a PD spectrum rather than separate disease entities. Mild cognitive impairment (MCI) frequently precedes the onset of dementia and is a more reliable index of impending dementia in PD than in the general population. Dopaminergic drugs can worsen cognitive function in demented patients and should be stopped or reduced to try and provide a compromise between antiparkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the following sequence: anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Eventually, patients with cognitive impairment should be managed with the lowest dose of standard levodopa that provides meaningful antiparkinsonian effects and does not worsen mental function. Anticholinesterase agents such as rivastigmine and donepezil reduce the rate of deterioration of measures of cognitive function and can improve attention, but do not typically improve cognitive function in any meaningful way.

Autonomic disturbances are common and frequently require attention. Orthostatic hypotension can be problematic and contribute to falling. Initial treatment should include adding salt to the diet and elevating the head of the bed to prevent overnight sodium natriuresis. Low doses of fludrocortisone (Florinef) or midodrine provide control for most cases. Vasopressin, erythropoietin, and the norepinephrine precursor 3-0-methylDOPS can be used in more severe or refractory cases. If orthostatic hypotension is prominent in early disease, MSA should be considered. Sexual dysfunction can be helped with sildenafil or tadalafil. Urinary problems, especially in males, should be treated in consultation with a urologist to exclude