many other countries, it is combined with benserazide (Madopar). Levodopa is also available in controlled-release formulations as well as in combination with a catechol-*O*-methyltransferase (COMT) inhibitor (see below). Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. No current medical or surgical treatment provides antiparkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Almost all PD patients experience improvement, and failure to respond to an adequate trial should cause the diagnosis to be questioned.

There are, however, important limitations of levodopa therapy. Acute dopaminergic side effects include nausea, vomiting, and orthostatic hypotension. These are usually transient and can generally be avoided by gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa) or a peripheral dopamine-blocking agent such as domperidone (not available in the United States). More important are motor complications (see below) that develop in the majority of patients treated long-term with levodopa. In addition, the disease continues to progress, and features such as falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge with disease progression that are not adequately controlled by levodopa. Indeed, these nondopaminergic features (especially falling and dementia) are the primary source of disability and the main reason for nursing home placement for patients with advanced PD

Levodopa-induced motor complications consist of fluctuations in motor response ("on" episodes when the drug is working and "off" episodes when parkinsonian features return) and involuntary movements known as dyskinesias **(Fig. 449-6)**. When patients initially take levodopa, benefits are long-lasting (many hours) even though the drug has a relatively short half-life (60–90 min). With continued treatment, however, the duration of benefit following an individual dose becomes progressively shorter until it approaches the half-life of the drug. This loss of benefit is known as the *wearing-off effect*. In more severe cases, patients may experience a delay in turning on (delayed-on) or no response at all to a given dose (no-on). Dyskinesias tend to occur at the time of levodopa peak plasma concentration and maximal clinical benefit (peak-dose dyskinesia). They are usually choreiform in nature but can manifest as dystonic movements, myoclonus, or other movement disorders. They are not troublesome when mild, but can be disabling when severe, and can limit the ability to fully use levodopa to control PD features. In more advanced states, patients may cycle between "on" periods complicated by disabling dyskinesias and "off" periods in which they suffer from severe parkinsonism and painful dystonic postures. Patients may also experience "diphasic dyskinesias," which occur as the levodopa dose begins to take effect and again as it wears off. These dyskinesias typically consist of transient, stereotypic, rhythmic movements that predominantly involve the lower extremities and are frequently associated with parkinsonism in other body regions. They can be relieved by increasing the dose of levodopa, although higher doses may induce more severe peak-dose dyskinesia.

The cause of levodopa-induced motor complications is not precisely known. They are more likely to occur in females, younger individuals with more severe disease, and with the use of higher doses (mg/kg) of levodopa. The classic model of the basal ganglia has been useful for understanding the origin of motor features in PD, but has proved less valuable for understanding levodopa-induced dyskinesias (Fig. 449-5). The model predicts that dopamine replacement might excessively inhibit the pallidal output system, thereby leading to increased thalamocortical activity, enhanced stimulation of cortical motor regions, and the development of dyskinesia. However, lesions of the pallidum that completely destroy its output are associated with amelioration rather than induction of dyskinesia as suggested by the classic model. It is now thought that dyskinesia results from levodopa-induced alterations in the GPi neuronal firing pattern (pauses, bursts, synchrony, etc.) and oscillatory activity, and not simply the firing frequency alone. This in turn leads to the transmission of misinformation from pallidum to thalamus/cortex, resulting in dyskinesia. Surgical lesions or high-frequency stimulation might ameliorate dyskinesia by interfering with (blocking or masking) this abnormal neuronal activity and preventing the transfer of misinformation to motor systems.

Current information suggests that altered neuronal firing patterns and motor complications relate to nonphysiologic levodopa replacement. Striatal dopamine levels are normally maintained at a relatively constant level. In PD, dopamine neurons degenerate and striatal dopamine is dependent on the peripheral availability of levodopa. Intermittent doses of short-acting levodopa result in fluctuating plasma levels because of variability in transit of the drug from the stomach to the duodenum where it is absorbed and the short half-life of the drug. This variability results in exposure of dopamine receptors to pathologically high and low concentrations of dopamine. It has been hypothesized that more continuous delivery of levodopa might prevent the development of motor complications. Indeed, a recent controlled study demonstrated that continuous intraintestinal infusion of levodopa/carbidopa intestinal gel (Duodopa) is associated with significant improvement in "off" time and in "on" time without dyskinesia in advanced PD patients compared with optimized standard oral levodopa.

Behavioral alterations can also be encountered in levodopa-treated patients. A dopamine dysregulation syndrome has been described where patients have a craving for levodopa and take frequent and unnecessary doses of the drug in an addictive manner. PD patients taking high doses of levodopa can develop purposeless, stereotyped behaviors such as the meaningless assembly and

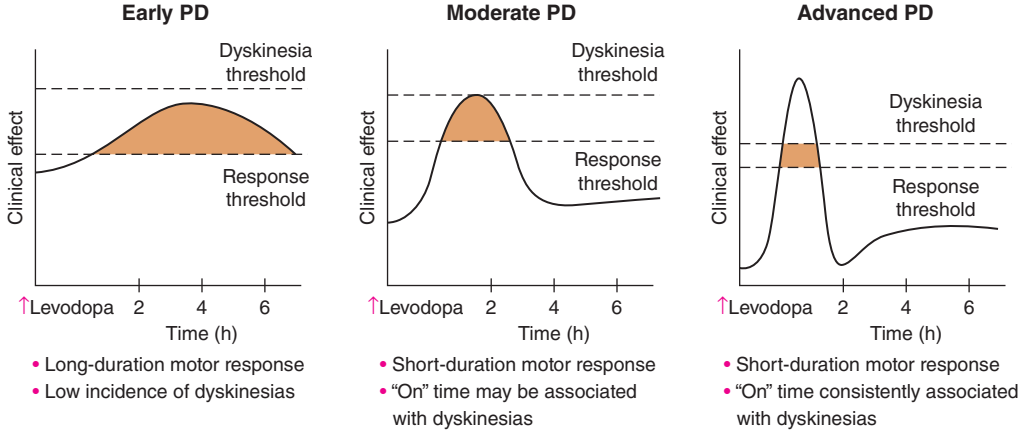

FIGURE 449-6 Changes in motor response associated with chronic levodopa treatment. Levodopa-induced motor complications. Schematic illustration of the gradual shortening of the duration of a beneficial motor response to levodopa (wearing off) and the appearance of dyskinesias complicating "on" time. PD, Parkinson's disease.