TABLE 449-5 DRUGS COMMONLY USED FOR TREATMENT OF PARKINSON'S DISEASE[a]

Agent	Available Dosages	Typical Dosing
Levodopa[a]		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/d 2–4 times/d
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250	
Carbidopa/levodopa/entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC		2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid
Rasagiline	0.5, 1.0 mg	1.0 mg QAM

[a]Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Abbreviations: COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

Amantadine also has historical importance. Originally introduced as an antiviral agent, it was appreciated to also have antiparkinsonian effects that are now thought to be due to *N*-methyl-D-aspartate (NMDA) receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an antidyskinesia agent in patients with advanced PD. Indeed, it is the only oral agent that has been demonstrated in controlled studies to reduce dyskinesia without worsening parkinsonian features, although benefits may be relatively transient. Cognitive impairment is a major concern. Other side effects include livido reticularis and weight gain. Amantadine should always be discontinued gradually because patients can experience withdrawal-like symptoms.

Several new classes of drug are currently being investigated in an attempt to enhance antiparkinsonian effects, reduce off time, and treat or prevent dyskinesia. These include adenosine A_{2A} antagonists, nicotinic agonists, glutamate antagonists, and 5-HT_{1A} agonists.

A list of the major drugs and available dosage strengths is provided in Table 449-5.

NEUROPROTECTION

Despite the many therapeutic agents available for the treatment of PD, patients continue to experience disease progression with intolerable disability. A neuroprotective therapy that slows or stops disease progression remains the major unmet therapeutic need in PD. As noted above, trials of certain drugs (e.g., selegiline and rasagiline) have provided positive results consistent with a disease-modifying effect. However, it is not possible to determine if the positive results were due to neuroprotection with slowing of disease progression or confounding symptomatic effects that mask ongoing progression. CoQ10, a mitochondrial bioenhancer and antioxidant, attracted attention with a positive preliminary trial, but this was not replicated in larger double-blind studies.

SURGICAL TREATMENT

Surgical treatments for PD have been used for more than a century. Lesions placed in the motor cortex improved tremor but were associated with motor deficits, and this approach was abandoned. Subsequently, it was appreciated that lesions placed into the ventral intermediate (VIM) nucleus of the thalamus reduced contralateral tremor without inducing hemiparesis, but these lesions did not meaningfully help other more disabling features of PD. In the 1990s, it was shown that lesions placed in the posteroventral portion of the GPi (motor territory) improved rigidity and bradykinesia as well as tremor. Importantly, pallidotomy was also associated with marked improvement in contralateral dyskinesia. This procedure gained favor with greater understanding of the pathophysiology of PD (see above). However, this procedure is not optimal for patients with bilateral disease, because bilateral lesions are associated with side effects such as dysphagia, dysarthria, and impaired cognition, and has largely been replaced by deep brain stimulation (DBS). Unilateral lesions of the STN are associated with a larger antiparkinsonian benefit and reduced levodopa requirement, but there is a concern about the risk of hemiballismus, and this procedure is not commonly performed.

Most surgical procedures for PD performed today use DBS. Here, an electrode is placed into the target area and connected to a stimulator inserted SC over the chest wall. DBS simulates the effects of a lesion without necessitating making a brain lesion. The precise mechanism whereby DBS works is not fully resolved but may act by disrupting the abnormal signal associated with PD and motor complications. The stimulation variables can be adjusted with respect to electrode configuration, voltage, frequency, and pulse duration in order to maximize benefit and minimize adverse side effects. In cases with intolerable side effects, stimulation can be stopped and the system removed. The procedure does not require making a lesion in the brain and is thus suitable for performing bilateral procedures with relative safety.

DBS for PD primarily targets the STN or the GPi. It provides dramatic results, particularly with respect to reducing "off" time and dyskinesias, but does not improve or prevent the development of features that fail to respond to levodopa such as freezing, falling, and dementia. The procedure is thus primarily indicated for patients who suffer disability resulting from severe tremor, or levodopa-induced motor complications that cannot be satisfactorily controlled with drug manipulation. In such patients, DBS has been shown to improve quality of life in comparison to best medical therapy. Side effects can be seen with respect to the surgical procedure (hemorrhage, infarction, infection), the DBS system (infection, lead break, lead displacement, skin ulceration), or the stimulation itself (ocular and speech abnormalities, muscle twitches, paresthesias, depression, and rarely suicide). Recent studies indicate that benefits following DBS of the STN and GPi are comparable, but that GPi stimulation may be associated with a reduced frequency of depression. Although not all PD patients are candidates, the procedure is profoundly beneficial for many. Studies of DBS in early PD patients show benefits in comparison to medical therapy, but this must be weighed against the cost of the procedure and the risk of side effects. Long-term studies demonstrate continued benefits with respect to the classical motor features of PD, but DBS does not prevent the development of nondopaminergic features, which continue to be a source of disability. Studies continue to evaluate the optimal way to use DBS (low- vs high-frequency stimulation, closed systems, etc.). Comparison of DBS to other therapies aimed at improving motor function without causing dyskinesia, such as