disassembly or collection and sorting of objects. This is known as punding, a term taken from the Swedish description of the meaningless behaviors seen in chronic amphetamine users. Hypersexuality and other impulse-control disorders are occasionally encountered with levodopa, although these are more commonly seen with dopamine agonists.

DOPAMINE AGONISTS

Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors. Unlike levodopa, they do not require metabolism to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g., bromocriptine, pergolide, cabergoline) and were associated with ergot-related side effects, including cardiac valvular damage. They have largely been replaced by a second generation of nonergot dopamine agonists (e.g., pramipexole, ropinirole, rotigotine). In general, dopamine agonists do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and reduce "off" time in fluctuating patients. Subsequently, it was shown that dopamine agonists, possibly because they are relatively long-acting, are less prone than levodopa to induce dyskinesia. For this reason, many physicians initiate therapy with a dopamine agonist, although supplemental levodopa is eventually required in virtually all patients. Both ropinirole and pramipexole are available as orally administered immediate (tid) and extended-release (qd) formulations. Rotigotine is administered as a once-daily transdermal patch. Apomorphine is a dopamine agonist with efficacy comparable to levodopa, but it must be administered parenterally and has a very short half-life and duration of activity (45 min). It is generally administered by injection as a rescue agent for the treatment of severe "off" episodes. Apomorphine can also be administered by continuous subcutaneous infusion and has been demonstrated to reduce both "off" time and dyskinesia in advanced patients. However, this approach has not been approved in the United States.

Dopamine agonist use is associated with a variety of side effects. Acute side effects are primarily dopaminergic and include nausea, vomiting, and orthostatic hypotension. As with levodopa, these can usually be avoided by slow titration. Side effects associated with chronic use include hallucinations and cognitive impairment. Sedation with sudden unintended episodes of falling asleep while driving a motor vehicle have been reported. Patients should be informed about this potential problem and should not drive when tired. Dopamine agonists can also be associated with impulse-control disorders, including pathologic gambling, hypersexuality, and compulsive eating and shopping. The precise cause of these problems, and why they appear to occur more frequently with dopamine agonists than levodopa, remains to be resolved, but reward systems associated with dopamine and alterations in the ventral striatum and orbitofrontal regions have been implicated. In general, chronic side effects are dose-related and can be avoided or minimized with lower doses. Injections of apomorphine and patch delivery of rotigotine can be complicated by development of skin lesions at sites of administration.

MAO-B INHIBITORS

Inhibitors of monoamine oxidase type B (MAO-B) block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter. Selegiline and rasagiline are relatively selective suicide inhibitors of the MAO-B enzyme. Clinically, MAO-B inhibitors provide antiparkinsonian benefits when used as monotherapy in early disease and reduced "off" time when used as an adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors are generally safe and well tolerated. They may increase dyskinesia in levodopa-treated patients, but this can usually be controlled by down-titrating the dose of levodopa. Inhibition of the MAO-A isoform prevents metabolism of tyramine in the gut, leading to a potentially fatal hypertensive reaction known as a "cheese effect" because it can be precipitated by foods rich in tyramine such as some cheeses, aged meats, and red wine. Selegiline and rasagiline do not functionally inhibit MAO-A and are not associated with a cheese effect with doses typically used in clinical practice. There are theoretical risks of a serotonin reaction in patients receiving concomitant selective serotonin reuptake inhibitor (SSRI) antidepressants, but these are rarely encountered.

Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects. MPTP toxicity can be prevented experimentally by coadministration of an MAO-B inhibitor that blocks its conversion to the toxic pyridinium ion MPP^+. MAO-B inhibitors also have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress. In addition, both selegiline and rasagiline incorporate a propargyl ring within their molecular structure that provides antiapoptotic effects in laboratory models. The DATATOP study showed that selegiline significantly delayed the time until the emergence of disability, necessitating the introduction of levodopa, in untreated PD patients. However, it could not be determined whether this was due to a neuroprotective effect that slowed disease progression or a symptomatic effect that merely masked ongoing neurodegeneration. More recently, the ADAGIO study demonstrated that early treatment with rasagiline 1 mg/d, but not 2 mg/d, provided benefits that could not be achieved when treatment with the same drug was initiated at a later time point, consistent with a disease-modifying effect; however, the long-term significance of these findings is uncertain.

COMT INHIBITORS

When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized in the periphery by COMT. Inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces "off" time and prolongs "on" time in fluctuating patients while enhancing motor scores. Two COMT inhibitors have been approved, tolcapone and entacapone. There is also a combination tablet of levodopa, carbidopa, and entacapone (Stalevo).

Side effects of COMT inhibitors are primarily dopaminergic (nausea, vomiting, increased dyskinesia) and can usually be controlled by down-titrating the dose of levodopa by 20–30%. Severe diarrhea has been described with tolcapone, and to a lesser degree with entacapone, and necessitates stopping the medication in 5–10% of individuals. Cases of fatal hepatic toxicity have been reported with tolcapone, and periodic monitoring of liver function is required. This problem has not been encountered with entacapone. Discoloration of urine can be seen with both COMT inhibitors due to accumulation of a metabolite, but it is of no clinical concern.

It has been proposed that initiating levodopa in combination with a COMT inhibitor to enhance its elimination half-life could provide more continuous levodopa delivery if administered at frequent intervals and reduce the risk of motor complications. While this result has been demonstrated in a preclinical MPTP model, and continuous infusion reduces both "off" time and dyskinesia in advanced PD patients, no benefit of initiating levodopa with a COMT inhibitor compared to levodopa alone was detected in early PD patients in the STRIDE-PD study. This may have been because the combination was not administered at frequent enough intervals to provide continuous levodopa availability. For now, the main value of COMT inhibitors continues to be in patients who experience motor fluctuations.

OTHER MEDICAL THERAPIES

Centrally acting anticholinergic drugs such as trihexyphenidyl and benztropine were used historically for the treatment of PD, but they lost favor with the introduction of dopaminergic agents. Their major clinical effect is on tremor, although it is not certain that this benefit is superior to what can be obtained with agents such as levodopa and dopamine agonists. Still, they can be helpful in individual patients with severe tremor. Their use is limited particularly in the elderly, due to their propensity to induce a variety of side effects including urinary dysfunction, glaucoma, and particularly cognitive impairment.