Parkinson disease

Changing concepts and treatments

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Since the disease was identified by James Parkinson in 1817, treatment for Parkinson disease (PD) has emphasized reducing motor symptoms, which were eventually shown to be the result of a lack of dopamine in specific areas of the brain. It was not until the mid-1960s that dopamine replacement became a practical reality with the introduction of levodopa.

Several closely related parkinsonian syndromes have been identified; not all conditions that initially look like PD will be confirmed at autopsy to have been PD. In this issue, Frank and colleagues (**page 862**) review criteria that help improve diagnostic accuracy. They also review other disorders that might be mistaken for PD. It is important to differentiate PD from the parkinsonian syndromes, as this helps predict response to available medications. Indeed, poor response to levodopa raises the possibility of a misdiagnosis.

Patients and their families might also seek advice about what they can reasonably expect over the next several years following a diagnosis of PD. Prognosis for PD is often different from that of the parkinsonian syndromes. It is also necessary to identify whether patients have diffuse Lewy body disease, which can overlap with PD and which might require treatment with a cholinesterase inhibitor. These agents are currently accepted as standard care for diffuse Lewy body disease, although more controlled clinical trials are needed.

Also in this issue, Dr Gordon Hardacre (**page 850**) describes the journey that our patients take in reaching some degree of acceptance when they are faced with diagnosis of a progressive neurologic disease. Although curing the disease is impossible at this time, Dr Hardacre attests that symptoms of PD are often ameliorable, and treatment can improve patients' quality of life.

Changes in thinking

The way we think about PD is changing. Increasingly recognized as more than a motor disorder, PD might be associated with cognitive and psychiatric disorders as well. There might be changes not only in the dopaminergic system, but also in the cholinergic system (leading to dementia), in the serotonergic system (resulting in depression), and in the noradrenergic system (perhaps contributing to changes in concentration). Dementia is now thought to occur in up to 30% of PD patients.

Other complications include bowel and bladder problems, sexual dysfunction, and autonomic dysregulation leading to orthostatic hypotension. Recognition of these common problems in PD patients is an important part of management, and primary care physicians will be expected to deal with them. Patients with PD who are treated with dopaminergic drugs might also develop frank psychoses. Hallucinations are the most common reason for placing PD patients in nursing homes. Early recognition and treatment of these symptoms is important and can improve quality of life for these seriously impaired patients.

Innovative treatments

Innovative treatments are increasing our ability to improve symptoms and reduce complications of PD. Most of the drugs currently on the market enhance the dopaminergic system, acting either as dopamine precursors, as levodopa does, or as dopamine receptor agonists. Newer drugs that act as dopamine reuptake inhibitors are in development. Agents that do not directly target the dopaminergic system are also likely to be part of our armamentarium—drugs that modulate the adenosine receptors, for example. Such agents will eventually help to treat specific symptoms, such as motor fluctuations.

Nonmotor fluctuations are increasingly being acknowledged as important complications of long-standing PD. Such fluctuations might account for mood changes and other nonspecific physical symptoms that occur during "off" periods, when drug effects wear off. When it comes to treating off-period symptoms, such as panic attacks or dysphoria, it might be prudent to start with therapies that reduce fluctuations, rather than using mood-altering drugs, such as antidepressants.

Surgical interventions, such as deep brain stimulation, have been used increasingly to treat patients with advanced PD in whom drug therapies are no longer effective. Stem cell research is raising the possibility of a more permanent solution to the problems of PD. As these options increase the expectations of patients and their families, it is important to realize their limitations. Deep brain stimulation is effective only in patients who have exhibited some response to dopaminergic therapy, and will not reverse the condition of all parkinsonian patients, again illustrating the importance of differentiating PD from the parkinsonian syndromes.

Regenerative or reparative medicine is becoming relevant to PD, as stem cell research progresses and offers

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the possibility of introducing dopamine-producing cells into the brain that might serve to replace those lost to neurodegeneration. Several technical hurdles remain before this becomes a practical reality. Neuroprotective agents are also being developed to slow down the rate of decline once the neurodegenerative process is in effect. Several putative neuroprotective agents are being evaluated in clinical trials.

Challenges

Research is progressing at an unprecedented rate, and novel approaches are being developed. With many of these highly publicized experimental approaches, however, there are technical obstacles that remain to be overcome, and as clinicians we are often faced with patients with false hopes of a cure around the corner. Many of the interventions being researched focus on dopaminergic replacement in one form or another. Parkinson disease, however, brings with it nonmotor problems, such as dementia and psychiatric complications, which do not respond to a single approach. Family physicians as well as specialists in this field need to be sensitive to the complexities of this disorder, to be able to identify complications of PD, and to initiate other treatments when appropriate.

Despite the many challenges in treating PD, we have reason to be optimistic about the future. Primary care physicians will have a greater role in the multidisciplinary team required to treat patients with PD and parkinsonian syndromes.

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