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# Parkinson's Disease Management: Towards a New Paradigm

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**ABSTRACT:** Over the past decade, management of Parkinson's disease has changed significantly due to the expansion of medical and surgical treatment modalities. Neurologists now have the ability (and the challenge) of choosing from multiple medications to devise an individual management strategy for each patient depending on his/her clinical symptoms and needs. Several different surgical therapies are also available. The topics covered in this supplement have highlighted the new options that are now available, as well as the treatments that have been in clinical usage. This review attempts to synthesize the information that is currently available in an attempt to help clinical neurologists make the appropriate choice for their patients.

**R SUM : Traitement de la maladie de Parkinson: vers un nouveau paradigme.** Dans la dernière décennie, le traitement de la maladie de Parkinson a changé beaucoup à cause des nouveaux modes de traitements médicaux et chirurgicaux. Les neurologues ont maintenant la capacité (et le défi) de choisir parmi de nombreux médicaments pour définir une stratégie de traitement individualisée pour chaque patient selon ses symptômes cliniques et ses besoins. Plusieurs traitements chirurgicaux sont également disponibles. Les sujets couverts dans ce supplément ont illustré les nouvelles options maintenant disponibles ainsi que les traitements d'usage courant dans le but d'aider les neurologues à faire des choix appropriés pour leurs patients en clinique.

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Coming into the Millenium, physicians treating Parkinson's disease patients are faced with many challenges. There is a renewed sense of hope and excitement that with the current explosion in neuroscience research, a cause, followed closely by a cure for this devastating neurodegenerative disorder will soon be found. With this increase in knowledge, clinicians must keep current with the new advances for their own information and to respond to the intense pressure by patients and their families to be informed. The lay press and the internet provide easy access to new advances, but may unfortunately be taken out of context, and used to serve other interests. Clinicians must be able to respond to questions about these new findings to best serve the interests of their patients.

In spite of increased knowledge about brain function, and long standing appreciation that PD is caused by nigro-striatal degeneration resulting in dopamine deficiency, the cause of Parkinson's disease is still unknown. The diagnosis remains a clinical one, without a readily available test to provide an objective assessment of this condition. On the other hand, the high level of understanding of the biochemical alterations that occur in the nigro-striatal pathway has led to the availability of rational pharmaco-therapy. Available therapies are beneficial to most patients, as they improve patient symptoms and enhance quality of life. None however, have been proven to alter the natural history of the disease and there is no evidence to date of effective neuroprotective strategies.

Recently, we were fortunate to have a number of new med-

ications approved in Canada for the treatment of Parkinson's disease. In addition, new neurosurgical techniques can be performed to ameliorate some of the signs and symptoms of this condition. How do these new strategies fit into our approach to patients? This article will attempt to put into perspective the new options and help develop a new paradigm for the management of Parkinson's disease.

## PREVIOUSLY AVAILABLE TREATMENTS

Although new treatments are becoming available, it is inappropriate to discount the drugs that we have become accustomed to over the years. Experience in clinical practise, sometimes over a number of decades, provides a level of confidence that is hard to put aside for new options that have not yet withstood the test of time.

Levodopa is still the gold standard treatment, and in Canada is available in many different formulations including Sinemet, Sinemet CR, generic levodopa/carbidopa, and Prolopa (levodopa/benserazide). Levodopa remains the most efficacious treatment, and all options should still be compared to it for efficacy data. With generics now available, the cost has been

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reduced which is also an important consideration. Controlled release Sinemet may offer an added benefit, in patients experiencing response fluctuations and nocturnal “wearing off”. The debate concerning levodopa toxicity, with the development of response fluctuations as well as dyskinesias is ongoing.<sup>1,2</sup> At this time, as there is no convincing evidence for neurotoxicity, levodopa is recommended in patients who are developing significant disability. Essentially all PD patients will require a levodopa preparation at some point in their disease.

Other older drugs continue to have a place in therapy. Anticholinergics may be beneficial for the treatment of mild Parkinson’s disease, particularly in younger, tremor predominant patients. Amantadine may be helpful in similar circumstances. Recently, experience has shown that amantadine may improve dyskinesias in more advanced patients.<sup>3</sup> Use of anti-cholinergics and amantadine is limited in the elderly due to side effects as confusion, and hallucinations.

Selegiline has been shown to help patients with response fluctuations in advanced disease. In early patients, it delays the need for levodopa therapy by approximately one year most likely due to its mild symptomatic effect.<sup>4</sup>

Dopamine agonists have been used as an adjunctive treatment for almost twenty-five years to levodopa.<sup>1</sup> Bromocriptine and pergolide are effective drugs for advanced Parkinson’s disease but their role in early Parkinson’s disease before levodopa treatment is initiated is limited. Some studies suggest that bromocriptine treatment may prevent the onset of response fluctuations, but compliance is limited due to the high dosing, resulting in side effects.

## NEW THERAPIES

Three new drugs have been approved by the Health Protection Branch in the past two years. This includes two new dopamine agonists, ropinirole and pramipexole. Tolcapone, belonging to a new class of drugs, the catechol-O-methyltransferase (COMT) inhibitors was approved, but recently withdrawn in Canada due to liver toxicity. (It is still available in the USA with frequent LFT monitoring) However, another COMT inhibitor, entacapone, is currently under development and should be released soon. These new agents offer new options for the treatment of Parkinson’s disease, due to differences in mechanisms of action and side effect profiles, from the previously available drugs.

### COMT Inhibitors

COMT inhibitors reduce levodopa metabolism in the periphery to improve the pharmacokinetics of the levodopa with an increase in the area under the curve. Neither tolcapone nor entacapone change the peak concentration of levodopa in the blood (Cmax), or the time to reach peak concentration (Tmax). This results in an increase in the availability of levodopa to the brain, and studies have shown that both are beneficial in reducing the amount of “off” time in advanced patients, in the order of 30-50%. Studies have also been performed in early PD patients with a stable response to levodopa, showing an improvement in the activities of daily living.<sup>5</sup>

### Dopamine Agonists

Ropinirole and pramipexole are both non-ergot dopamine receptor agonists that act mainly on the D-2 class of receptor. Pramipexole, in particular has a high affinity for the D-3 recep-

tor. These drugs have been shown to be effective both in early Parkinson’s disease patients as monotherapy as well as in combination with levodopa in advanced disease.<sup>6</sup>

With ropinirole, most patients have a clinical benefit at 6 mg/day with the average dose used in the trials between 12-15mg/day. Titration to therapeutic benefit occurs within 4-6 weeks.

Pramipexole has a faster onset to benefit, with many patients showing significant improvement within three weeks. The typical dose range of clinical benefit is between 1.5 and 4.5 mg/day.

## NEUROSURGICAL PROCEDURES

Over the past five years, due to improvement in surgical techniques, a number of neurosurgical techniques have been added to our armamentarium in the management of PD patients with Parkinson’s disease.<sup>7</sup> These include the use of stereotactic thalamotomy, pallidotomy and deep brain stimulators (DBS) into these regions as well as the subthalamic nucleus. Understanding the specific clinical benefits with each type of procedure is crucial for allowing appropriate patient selection. Thalamotomy/thalamic DBS are helpful in tremor control. Pallidal procedures result in improvements in dyskinesias, as well as bradykinesia, rigidity and in some cases tremor in the “off” states. Subthalamic nucleus DBS insertion can result in good control for all PD symptoms and may improve gait and balance abnormalities.

Most movement disorder centers would not advise surgery unless all available medical options have failed. The best candidates are younger patients that do not have cognitive problems. Significant surgical morbidity is present with some patients experiencing stroke, hemorrhage and cognitive decline. The procedure is long and may be difficult for the patient to undergo. The main disadvantage for DBS insertion is that of cost. Long term outcome is still being studied.

Fetal cell transplants are still under development, though appear promising.

## COSTS OF TREATMENT

Table 1 shows the relative costs in Ontario of the medication available to treat Parkinson’s disease. For those who have not previously examined the costs, they are substantial. Some patients on combination treatment may take up to \$15,000/year of medications. The cost of neurosurgery is difficult to determine. There are the fixed costs of hospitalization and surgical fees, but if successful they are front-loaded and may actually reduce the costs of other treatment. The cost of DBS units is large at approximately \$8,000 per unit. After installation, there may be significant hospitalization costs to adjust the setting, and the batteries need to be replaced every two to three years depending on their usage.

As physicians, we are interested in improving the quality of life of our patients. However, in today’s health care environment, cost effectiveness needs to be considered as part of our decision making process.

## TREATMENTS ON THE HORIZON

Even with the variety of the therapeutic modalities and strategies described here, patients with advanced disease become more disabled with disease progression. Fortunately, a number of new

Table 1

Medication	Formulation	Therapeutic Range	Common Dose Frequency	Cost/Month*
Sinemet	100/25** 100/10 250/25	300-2000mg/day	t.i.d – q2h	\$50.40 - \$333.00
Prolopa	100/25** 50/12.5 200/25	300-2000mg/day	t.i.d – q2h	\$37.80 – \$210.00
Levodopa/ Carbidopa	100/25** 100/10 250/25	300-2000mg/day	t.i.d. – q2h	\$37.80 - \$112.80
Sinemet CR	200/50** 100/25	400-2400mg/day	t.i.d. – q4h	\$63.30 - \$381.60
Eldepryl	5.0 mg	10mg/day	b.i.d.	\$120.60
Selegeline	5.0mg	10mg/day	b.i.d.	\$90.30
Parlodel	2.5 mg** 5.0 mg	10-40mg/day	t.i.d. - q.i.d.	\$92.40 - \$369.90
Bromocriptine	2.5 mg	10–40mg/day	t.i.d. – q.i.d.	\$67.50 - \$270.00
Permax	0.05 mg 0.25 mg** 1.0 mg	1 – 4mg/day	t.i.d.	\$104.40 - \$383.70
Requip	0.25 mg 1.0 mg 2.0 mg 5.0 mg	3.0 – 24.0mg/day	t.i.d.	\$90.00 - \$468.00
Mirapex	0.25 mg 1.0 mg 1.5 mg	1.5 – 4.5mg/day	t.i.d.	\$178.20

\* based on cost to pharmacy in Ontario and Alberta April 1999

\*\* most common dosage form used

therapies are under development, leading to further promise in treatment.

- 1 Glutamate antagonists – these have been postulated to be useful in PD patients, as glutamate has been suggested to play a role in cytotoxicity, genesis of Parkinsonian signs through the glutaminergic projection from the subthalamic nucleus to the medial globus pallidus, and in causing motor fluctuations.<sup>3</sup> Trials are ongoing with drugs such as remacemide to determine possible benefits in both early and late stage PD patients.<sup>8</sup>
- 2 Neuroimmunophilins – these are a group of small intracellular proteins with neurotrophic properties. One of these compounds GP1046 has been shown to have neuroprotective and neuroregenerative benefits, and is currently in early human trials in PD.<sup>9</sup>
- 3 Soluble dopamine agonists – several of these are under development, either older drugs in a new format such as an intranasal form of apomorphine,<sup>10</sup> or new soluble forms such as N-0923 which will be available transdermally.<sup>11</sup>
- 4 Nerve growth factors – glial cell line derived neurotrophic factor (GDNF) has been suggested to increase dopaminergic neuronal survival in animal models, and is presently in early clinical trials in PD patients.<sup>12</sup>
- 5 Adenosine 2Aa receptor antagonists – the A2a receptors are present in the basal ganglia predominantly on the striatal out-

put neurons of the indirect pathway, with projection to the external globus pallidus. Preliminary studies with one A2a adenosine receptor antagonist, KW-6002, has shown antiparkinsonian activity, without causing dyskinesia in animal models.<sup>13</sup>

#### CONCLUSION: THE NEW PARADIGM

Unfortunately, although general principles of treatment can be documented, the variety of treatment options are resulting in more unanswered questions than solutions.

As can be seen, a number of medications are now available for treatment of PD patients in the early stages as de novo therapy (Table 2). How do we choose the right one?

The following considerations are helpful in making this decision:

- 1 Level of patient disability, i.e.: if patient is having problems with activities of daily living, or ability to work is threatened, levodopa is probably indicated. Otherwise, the other drugs in Table 2 can be considered. All have a mild to moderate symptomatic benefit lasting months to years.
- 2 Discussion with patients with respect to side effect profile and potential benefit, i.e.: if the tremor is prominent, and the individual is young with no cognitive problems, for example, the choice may be amantadine, or anticholinergics.

**Table 2****Medical Therapies Shown to be Effective in De Novo PD Patients (used as monotherapy)**

Anticholinergics	Prolopa
Amantadine	Pramipexole
Selegiline	Ropinirole
Sinemet	Pergolide
Sinemet CR	Bromocriptine

- 3 “Neuroprotective” strategy – if the physician or patient feel that levodopa use should be delayed, but some disability is present, then a number of choices have been suggested including amantadine, selegiline, or the dopamine agonists.
- 4 Cost – for patients without health care coverage, generic levodopa/carbidopa and bromocriptine may be the most affordable.

In advanced patients, with response fluctuations, combination therapy is used (Table 3). Many patients will end up on at least levodopa, along with a dopamine agonist. Other added drugs could include a COMT inhibitor, selegiline, and amantadine. It is not uncommon to have patients on three or four different PD medications. The importance of understanding the potential advantages, interactions, and side effects cannot be underestimated, as well as the clinical experience of knowing what combination is most useful in different response patterns.

Are the new agonists better than the previous drugs? Studies as yet are limited, but preliminary data with ropinirole and pramipexole show similar efficacy compared to bromocriptine (but were not powered to assess the differences). Pramipexole was superior to bromocriptine when considering the speed of onset of benefit, and showed improvement in “wearing off” in advanced disease.<sup>14</sup> Without head to head comparisons of ropinirole vs. pramipexole, and the new agonists vs. pergolide, we are unable as yet to make educated choices. Furthermore, no studies have been published assessing if a patient is on one of the older agonists, whether there are advantages to switching to one of the newer agents.

Should we start with levodopa or dopamine agonists in *de novo* patients? As the new agonists have been shown to be effective as monotherapy in early Parkinson’s disease, and comparison trials with levodopa are underway, we will know in the next few years if starting with agonists delays the onset of wearing off, and/or dyskinesias. These studies are also being conducted with the use of either PET or SPECT measurements of the presynaptic nerve terminals to assess the progression of the disease, and hopefully answer the question of neuroprotection. Until these studies are completed, the early use of these drugs is speculative and it must be emphasized that there is no current evidence to support one class of drug over the other in humans.

In a patient with wearing off, are there advantages to using a COMT inhibitor compared to an agonist? The COMT inhibitors have a rapid onset of benefit (often seen even with the first dose) and often do not require titration to achieve therapeutic benefit. On the other hand, careful levodopa titration is required and the process may induce dyskinesias and other levodopa related side effects. If a patient has had previous problems with severe dyskinesias, we would be cautious in using a COMT inhibitor. If a

**Table 3****Medical Treatment Useful in Treatment of Advanced PD Patients (to be added to levodopa preparations) to alleviate response fluctuations and dyskinesias**

amantadine	pramipexole
selegiline	ropinirole
bromocriptine	(tolcapone)*
pergolide	(entacapone) #

\* now available only in the USA

# not yet released

patient has hallucinations, one should avoid agonists and consider adding the COMT inhibitor. Overall, our clinical judgement is to use the least amount of medication that allows the patient to do the things important to him or her. We think this minimalist approach reduces the risks of treatment and always allows us to keep the ultimate goal of therapy: to improve the quality of life in our patients without producing side effects.

Where do the new neurosurgical procedures fit in? This also is an ongoing debate. Clearly when all medical options fail and the patient does not have cognitive problems and is willing to undergo the risks of surgery, the choice should be offered. Which procedure will be the most effective depends on the clinical scenario.

**CONCLUSION**

Treatment of patients with PD remains controversial, and depends to a large extent on the treating clinician’s experience, and familiarity with various therapeutic options. Ongoing studies will hopefully answer the questions posed in this review, allowing for an improvement in the therapies, using the principle of evidence based medicine.

One thing is clear, the variety of drugs available at the present time allows for more choice for our patients, easier adjustment to decrease side effects and choosing the combination that best suits their individual symptom profile.

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