Parkinson's Disease: Medical Treatment of Moderate to Advanced Disease

Oksana Suchowersky, MD, FRCPC, FCCMG

Address
Movement Disorders Program, University of Calgary,
Area 3, Health Sciences Centre, 3350 Hospital Drive NW,
Calgary, Alberta T2N 4N1, Canada.
E-mail: osuchowe@ucalgary.ca

Current Neurology and Neuroscience Reports 2002, **2:**310–316
Current Science Inc. ISSN 1528–4042

Parkinson's disease, a common neurodegenerative disorder, results in significant morbidity 10 to 15 years after disease onset and increased mortality. Levodopa is the mainstay of therapy and provides benefit for the duration of the illness. However, within 5 years, up to 50% of individuals develop fluctuations, including dyskinesias, wearing off, and "on/off" effects. Optimal management of Parkinson's disease patients requires careful titration of medications, with use of polypharmacy, including levodopa, dopamine agonists, catechol-*O*-methyltransferase inhibitors, amantadine, and anticholinergics in order to maintain good motor function and quality of life. With advancing disease, problems such as dysphagia, dysarthria, and gait and balance abnormalities occur, which are not responsive to dopaminergic medication. Due to extradopaminergic neuronal system degeneration, autonomic dysfunction can also be prominent. Recognition and management of these problems is helpful in improving quality of life in late-stage disease. In very late stages, dementia may complicate treatment, requiring discontinuation of combination therapy and use of low-dose levodopa with atypical neuroleptics.

Introduction

Parkinson's disease (PD), characterized by the triad of bradykinesia, rigidity, and rest tremor, is a common neurodegenerative disease affecting approximately 1% of individuals over the age of 60 years [1,2]. As no neuroprotective strategy has been shown to be definitively effective, treatment is aimed at restoring the dopamine deficiency. A number of symptomatic treatments, such as dopamine agonists, amantadine, selegiline, and anticholinergics, can be used as monotherapy in the early stages, helping the patient maintain a good quality of life [3]. However, disease progression results in essentially all patients requiring the institution of levodopa therapy within a few years.

Initially, use of a levodopa preparation given three to four times a day will produce a prolonged, stable benefit. Fluctuations begin as early as 2 years after initiation of therapy, and within 5 years up to 50% of patients will develop loss of effectiveness with motor fluctuations (Table 1) [4–6].

Disease progression results in an initial overall loss of benefit, then each dose of levodopa lasts for a shorter period of time ("wearing off"). "Off" dystonia is characterized by cramping that occurs after the levodopa effect has worn off, and is seen most commonly in the early hours of the morning.

Dyskinesias occur at peak dose of levodopa effect, most commonly resulting in choreoathetosis. Initially these are mild, occurring only briefly and/or with stress [7]. In some individuals, dyskinesia can be present only when the levodopa is becoming effective ("wearing on"), or "wearing off." Younger patients may have a specific type of dyskinesia referred to as dyskinesia–improvement–dyskinesia (D-I-D).

With disease progression, duration of action of levodopa becomes increasingly shorter, lasting only 1 to 2 hours. Dyskinesia lasts longer in duration and becomes more severe, resulting in disability. "Square wave" dyskinesias are seen (*ie*, the patient is dyskinetic for the duration of levodopa effect). Myoclonus and dystonia can be superimposed on chorea [7]. Painful "off" dystonia can occur at any time when medication benefit has worn off. Patients also develop "on/off" effects: rapid and unpredictable fluctuations not related to timing of medication. At this stage, small changes in plasma or brain concentration of levodopa will result in a major shift in therapeutic benefit [8]. Disease progression results in significant disability in 10 to 20 years after onset, as well as increased mortality [1,2].

The development of fluctuations are due to a number of factors: 1) progressive loss of the pre- and postsynaptic dopaminergic system; 2) autonomic dysfunction, resulting in erratic absorption of levodopa from the gut [9]; and 3) competition of levodopa with neural amino acids for transport across the blood brain barrier.

"Wearing off" is thought to be the result of the gradual loss of dopamine synthesis by the striatonigral system and decreasing capacity of dopamine storage. Post-synaptic changes in the striatum and pallidal projections may play a role. Dyskinesias are less well understood, but likely are

Table 1. Effect of levodopa on motor response

Loss of effectiveness
"Wearing off
End of dose deterioration
"Off" dystonia
Other "off" symptoms (*eg*, sensory abnormalities, dysphoria)
Dyskinesia
Peak dose
Diphasic (dyskinesia–improvement–dyskinesia)
"Wearing off"/"wearing on" dyskinesia
"On/off" effects

related to postsynaptic changes and influences from other neurotransmitters within the striatum [10•,11]. Dopaminergic denervation is a requirement, as long-term treatment with levodopa of patients without PD does not result in dyskinesia. Pulsatile stimulation is another prerequisite: use of short-acting dopaminergic medications in MPTP monkeys has induced dyskinesias, whereas continuous delivery of levodopa or dopamine agonists results in their improvement [8,12].

Medical Therapy of Moderate Disease

Levodopa/carbidopa therapy

Levodopa/carbidopa remains the mainstay of PD therapy (Table 2). Administration of small doses of the rapid-acting preparation regularly throughout the day is recommended for constant receptor stimulation. Alternatively, the patient may benefit from the slow-release (SR) preparation, (Sinemet CR [Bristol-Myers Squibb, Princeton, NJ]) or levodopa/carbidopa extended release, which also offers the convenience of a less frequent dosing schedule [5]. The SR formulation can be very helpful taken at bedtime to decrease nocturnal "off" dystonia. The SR formulation, with a slower absorption, has a slower time to benefit, and some patients may benefit from addition of a regular-acting levodopa taken with the SR for a more rapid "kick start." Increasing levodopa may result in, or exacerbate, dyskinesias. In particular, the SR formulation may result in worsening dyskinesias later in the day. As the SR formulation has 80% bioavailability as compared with the rapid-release formulation, dose adjustment is required when switching from one preparation to the other.

Dopamine agonists

Dopamine agonists (DAs) have the advantage of acting directly on postsynaptic receptors and a longer half-life. Four DAs are currently available in North America: two ergot derived (bromocriptine, pergolide), and two non-ergot derived (pramipexole, ropinirole). All have been proven to be useful in advanced disease by decreasing fluctuations and allowing a decrease in levodopa dose [13–15]. Initiation of any of the DAs requires a low starting dose taken on a full stomach, with very gradual upward titration, until an appropriate therapeutic dose is reached (Table 3).

Side effects are more common with DAs than with levodopa, the most common one being nausea, which affects approximately 30% of patients. Leg edema occurs in up to 13% of individuals. Somnolence and excessive daytime sleepiness can be seen, and sudden sleep attacks are of particular concern [16•,17]. This appears to be a class effect for all DAs as well as levodopa [16•,17,18].

Few direct comparison studies of the four agonists have been done [19••,20]. Currently, it does not appear that any one DA offers significant therapeutic advantage over the others, but if a patient experiences side effects or lack of benefit from one DA, it is worthwhile trying one of the others. The ergot-derived DAs have the added risk of pleuropulmonary fibrosis, and regular monitoring is indicated. Ropinirole is metabolized by cytochrome P450 CYP1A2, and drugs such as ciprofloxacin and estrogens may reduce its clearance. Pramipexole, which is excreted in urine, should be used with caution in the setting of renal disease.

Catechol-*O*-methyltransferase inhibitors

When levodopa is administered with carbidopa, inhibition of dopa decarboxylase results in the enzyme catechol-*O*-methyltransferase (COMT) metabolizing levodopa peripherally to 3-0-methyldopa. Two currently available COMT inhibitors, tolcapone and entacapone, are effective in blocking the activity of this enzyme, which is localized in the gut, liver, and blood. Both drugs significantly prolong the duration of levodopa activity by decreasing systemic elimination and increasing the area under the curve. Time of maximum concentration (T_{max}) and maximum concentration (C_{max}) are not increased [21,22]. Daily "on time" is increased by approximately 1 hour, and 50% of patients are able to decrease total levodopa dose [23].

Tolcapone, which is more potent and longer acting, is given initially at a dose of 100 mg three times a day (tid); this can be increased to 200 mg tid [24]. Entacapone, with a half-life of 3 hours, is given at a dose of 200 mg with each dose of levodopa, up to a maximum of 8 pills per day [25]. Both drugs have the advantage of an immediate onset of benefit, so both physician and patient know within the first few doses how much benefit to expect.

Side effects are typically dopaminergic, with 8% of patients developing dyskinesia [23]. If dyskinesias are present prior to drug initiation, the total levodopa dose should be decreased, preferably by increasing time between doses. Other side effects include nausea (12%), orange discoloration of urine (10%), and diarrhea (10%). Diarrhea can be quite severe, and typically does not respond to antidiarrheal medication, necessitating drug discontinuation.

Tolcapone has the added rare, though very significant, side effect of causing fulminant liver failure [26]. Informed consent needs to be obtained when starting tolcapone, with

Table 2. Strategies to treat motor symptoms

End-of-dose deterioration
Increase levodopa (eg, 100/25 mg tid to qid)
Substitute Sinemet CR
Add dopamine agonist
Add catechol-*O*-methyltransferase (COMT) inhibitor
"Off" dystonia (night)
Add Sinemet CR at bedtime
Add dopamine agonist at bedtime
Peak-dose dyskinesia
Smaller doses of levodopa taken more frequently
Add dopamine agonist, decrease levodopa
Add amantadine

qid—four times a day; tid—three times a day.

monitoring of liver function tests at baseline, every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months, and then bimonthly for the duration of therapy.

Amantadine

Although the exact mechanism of action is unclear, amantadine has been known for many years to have a mild symptomative benefit. More recently, it has been shown to decrease dyskinesia, sometimes quite dramatically [27]. The standard dose is 100 mg twice a day, although doses up to 300 mg/d have been used. Side effects include leg edema, livedo reticularis, and anticholinergic symptoms.

Anticholinergics

Although anticholinergics, such as trihexyphenidyl hydrochloride, are used infrequently today, they may occasionally help tremor resistant to other medications. Use in elderly patients is contraindicated due to side effects such as confusion.

Selegiline

This long-acting, selective monoamine oxidase B inhibitor was first popularized because of the finding that it may slow down disease progression [28]. This is now felt to be due to a mild symptomatic effect [29]. Selegiline may occasionally be useful added to levodopa because of prolongation of levodopa duration of action. However, as C_{max} is also increased, duration and amount of dyskinesia can be increased. Also, concern has been raised that the incidence of dyskinesia may be increased when combined with levodopa [6]. Dosing is usually 5 mg once or twice a day, with the last dose given with lunch to prevent the side effect of insomnia due to the methamphetamine metabolites.

Strategies for Optimizing Treatment in Advanced Disease

Treatment at this stage becomes an art, based on experience, with careful medication adjustments aimed at enhancing quality of life without causing side effects. Combination therapy is typically used: patients are managed on small, frequent doses of levodopa, combined with SR levodopa, DAs, and COMT inhibitors to provide more constant blood levels of medication and enhance continuous receptor stimulation.

If patients have been on one DA for a prolonged period of time with decreasing effectiveness, another DA may provide improved benefit [30•,31]. A rapid overnight switch can be done using equivalence dosing (Table 3). Occasionally, using very high doses of a DA (*eg*, 7 to 8 mg/d of pergolide) will smooth out the response and decrease dyskinesias [32], particularly if the levodopa dose can be decreased.

Amantadine is commonly added to decrease dyskinesias. If it is not helpful, medications such as clozapine [33], fluoxetine [34], propranolol [35], and buspirone [36)] can be tried. Painful dystonia can be due to an "on" or "off" effect. The addition of lithium, baclofen, and botulinum toxin injections has been reported as being helpful [37].

Other treatment modalities are available as well. Patients with marked fluctuations may be stabilized by a constant duodenal infusion of levodopa, although this is impractical in most cases [38]. For patients with severe "off" periods, apomorphine, a rapid acting DA, may restore mobility. (Both subcutaneous and sublingual preparations will soon be available.) However, as it causes significant nausea, pretreatment with antinauseants is required [39,40]. A low-protein diet may help as well, which allows for improvement both in gastrointestinal absorption as well as central transport of levodopa [41]. Some patients prefer to have one specific meal with a higher protein content, knowing that they will be "off" afterwards. Keeping accurate diaries, to allow for a better understanding of motor fluctuations throughout the day by both physician and patient, is another treatment option. This should be coordinated with patient training for accurate identification of "on" versus "off" time, and distinguishing tremor from dyskinesia.

Patients need to understand the benefits of the medications, as well as the limitations of the disease. Counseling is helpful, as is participation in Parkinson support groups. Finally, if all else fails, surgical intervention should be considered [37].

Late-stage Motor Disturbances Not Responsive to Medication

A number of other problems can arise with disease progression that respond poorly or not at all to dopaminergic medications.

The voice may become softer and more difficult to understand. Speech therapy techniques may be helpful to teach the patient to project his or her voice. Collagen injection has been reported to be beneficial [42].

Table 3. Doses of dopamine agonists for Parkinson's disease*

Drug	Starting dose	Average therapeutic dose	Maximum dose
Bromocriptine	1.25 mg/d	25 mg/d	40 mg/d
Pergolide	0.05 mg/d	3 mg/d	5 mg/d
Pramipexole	0.125 mg tid	3.5 mg/d	4.5 mg/d
Ropinirole	0.25 mg tid	13.5 mg/d	24 mg/d

*As per the manufacturers' information
tid—three times a day.

Dysphagia can occur with resultant aspiration. Assessment by a speech pathologist with proper modification of diet is recommended.

Gait and balance problems are a major cause of disability, and assessment and counseling by a physiotherapist is important. In later stages, patients should be advised to use a cane, walker, or even wheelchair to prevent falls. Hip protectors may help to prevent fractures [43].

Nonmotor Problems

Parkinson's disease is characterized by progressive cell loss in a variety of neuronal systems, including hypothalamic neurons, small cortical neurons, cholinergic nucleus basalis of Meynert, sympathetic ganglia, parasympathetic neurons, and the olfactory bulb. This leads to other symptoms that can be as disabling and distressing as the motor ones.

Disrupted sleep is common in Parkinson's disease patients, due to sleep fragmentation as part of the disease process. This is contributed to by the effects of dopaminergic drugs; frequent nocturnal wakening occurs due to "wearing off," as do dystonic leg cramps and frequent urination. All these factors lead to excessive daytime somnolence, reported in 55% of patients [16•].

Sleep may be improved by use of the older tricyclic antidepressants (such as amitriptyline) and hypnotics. Regular exercise and avoidance of daytime naps may be helpful, as is treatment of nocturnal motor symptoms and urinary problems.

Peripheral neuropathy can occur in up to 10% of PD patients, resulting in dysesthesia. Treatment with medications such as gabapentin can be helpful.

A wide variety of disturbances result from degeneration of autonomic nervous system, including constipation, gastrointestinal motility abnormalities, urinary frequency, seborrhea, and sexual dysfunction. Elucidation of these problems can lead to effective treatment and significantly improve quality of life (Table 4).

Cognitive/Psychiatric Problems

Depression and anxiety

It has been estimated that approximately 50% of PD patients will develop depression at some point in the disease [46]. In some, this is related to the effects of dealing with the disease, but in others is an intrinsic component of the disorder itself, possibly due to serotonin depletion [47].

Few studies have examined the benefits of various antidepressants in the treatment of depression in PD patients, but it appears that most of the drugs currently available can be used effectively. Tricyclic antidepressants, particularly amitriptyline, have been the most widely prescribed over the years, and may be helpful not only for depression, but also for insomnia, drooling, and urinary frequency. Selective serotonin reuptake inhibitors are the most commonly used antidepressants currently [48]. Although they have the theoretical possibility of worsening the parkinsonism, this does not appear to be a practical consideration [49]. Use with selegiline is contraindicated, due to the potential of causing serotonin syndrome [50].

Anxiety occurs in approximately 40% of PD patients [51], and may respond to benzodiazepines or antidepressants.

Some patients experience depression and anxiety as part of a "wearing off" effect. This is best treated with medication adjustment to decrease the "wearing off" phenomenon.

Hallucinations

Hallucinations typically appear 10 to 15 years after disease onset. Initially, these are visual, well formed, consist of people or animals, and tend to appear toward evening or during the night. These are in part related to anti-PD medications, and are thought to be due to excessive stimulation of dopamine receptors in the mesolimbic/mesocortical pathways. Other factors may be postsynaptic receptor alteration and serotonin abnormalities [52]. Initially, cognitive impairment is absent and insight is maintained. Later, psychotic features may emerge, including delusions and paranoid ideation.

The first step in treating hallucinations is to decrease medication intake, particularly in the evening. Medications such as selegiline, dopamine agonists, and anticholinergics should be discontinued. If hallucinations continue, use of quetiapine [53] or clozapine [54] is recommended. Ondansetrone has also been reported as being helpful [55]. Other more traditional antipsychotic medications should be avoided, as they will result in worsening of the parkinsonism. The atypical neuroleptics, risperidone and olanzapine, can be tried at low doses, but they worsen

Table 4. Treatment of autonomic symptoms

Symptom	Treatment
Postural hypotension	Increase fluid/salt intake
	Decrease antihypertensives
	Fludrocortisone
	Midodrine
Urinary urgency/frequency	Amitriptyline
	Oxybutin
	DDAVP [44]
Constipation	Increase fluid
	Increase exercise
	Stool softeners
Nausea, bloating, cramping	Domperidone
	Ondasnsetron
Sialorrhea	Amitriptyline
	Oral anticholinergics
	1% atropine solution (applied sublingually)
	Botulinum toxin injections
Seborrhea	Steroid cream
	Ketoconazole cream
Sexual dysfunction	Sildenafil [45]
	Yohimbine

DDAVP—1-deamino (8-D-arginine) vasopressin.

PD symptoms at higher doses [56]. If all else fails, electroconvulsive therapy has been reported to be helpful, and has the additional benefit of transiently improving PD symptoms [57], although it is contraindicated with any evidence of underlying cognitive dysfunction.

Dementia

Many patients are aware of slowness of thinking and word-finding difficulties, particularly when the medications are wearing off. However, 20% to 30% of patients will eventually develop dementia in the later stages of the disease [58]. This is heralded by progressively worsening hallucinations, followed by short-term memory problems, executive function deficits, and visuospatial abnormalities.

Treatment includes simplification of the drug regimen and use of antipsychotic medications (Table 5). As treatment of hallucinations may result in decreased mobility, counseling for the family is important to allow for realistic expectations. At this time, there is no evidence that use of acetylcholinesterase inhibitors is helpful.

Conclusions

Although Parkinson's disease is a progressive neurodegenerative disorder that eventually will result in significant disability, a large number of medications are now available for symptomatic treatment. Good motor function and quality of life can be maintained for several decades after disease onset. Neurologists must be aware not only of the medications, but effective strategies in their use for the optimization of therapeutic benefit.

Table 5. Treatment of dementia in advanced Parkinson's disease

Discontinue
- Anticholinergics
- Amantadine
- Selegiline
- Dopamine agonists
- Sinemet CR

Use regular-acting levodopa in smallest doses needed

Use antipsychotics
- Quetiapine (25–100 mg/d)
- Clozapine (6.25–150 mg/d)
- Ondansetron (12–24 mg/d)
- Risperidone* (0.5–3 mg/d)
- Olanzapine* (2.5–5 mg/d)

*May worsen parkinsonism.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bennett DA, Beckett LA, Murray AM, *et al.*: **Prevalence of parkinsonian signs and associated mortality in a community population of older people.** *N Engl J Med* 1996, **334:**71–76.
2. Morens DA, Davis JW, Grandinetti A, *et al.*: **Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men.** *Neurology* 1996, **46:**1044–1050.
3. Miyasaki JM, Martin W, Suchowersky O, Lang AE, Weiner JW: **Practice parameter: initiation of treatment for Parkinson's disease – an evidence based review.** *Neurology* 2002, **58:**11–17.
4. Miyawaki E, Lyons K, Pahwa R, *et al.*: **Motor complications of chronic levodopa therapy in Parkinson's disease.** *Clin Neuropharmacol* 1997, **20:**523–530.
5. Koller WC, Hutton JT, Tolosa E, Capilldeo R, and the Carbidopa / Levodopa Study Group: **Immediate-release and controlled release carbidopa / levodopa in PD.** *Neurology* 1999, **53:**1012–1019.
6. Parkinson Study Group: **Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa.** *Ann Neurol* 1996, **39:**37–45.
7. Luquin MR, Scipioni O, Vaamonde J, Gershanik O, Obeso JA: **Levodopa induced dyskinesias in Parkinson's disease: clinical and pharmacological classification.** *Mov Disord* 1992, **7:**117–124.
8. Nutt JC, Holford NH: **The response to levodopa in Parkinson's disease: imposing pharmocological law and order.** *Ann Neurol* 1996, **39:**561–573.
9. Djaldetti R, Baron J, Ziv I, Melamed E: **Gastric emptying in Parkinson's disease: patients with and without response fluctuations.** *Neurology* 1996, **46:**1051–1054.
10. • Bedard PJ, Blanchet PJ, Levesque D, *et al.*: **Pathophysiology of L-Dopa-induced dyskinesias.** *Mov Disord* 1999, **14(suppl 1):**4–8.

Good review of the proposed mechanisms resulting in dyskinesias.

11. Chase TN, Engber TM, Mouradian MM: **Contribution of dopaminergic and glutaminergic mechanisms to the pathogenesis of motor response complications in Parkinson's disease.** *Adv Neurol* 1996, **69:**497–501.
12. Chase TN, Engber TM, Mouradian MM: **Palliative and prophylactic benefits of continuously administered dopaminomimetics in Parkinson's disease.** *Neurology* 1994, **44(suppl 6):**S15–S18.

13. Lieberman A, Olanow CW, Sethi K, *et al.*: **A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease.** *Neurology* 1998, **51:**1057–1062.
14. Lieberman A, Ranhosky A, Korts D: **Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study.** *Neurology* 1997, **49:**162–168.
15. Guttman M, for the International Pramipexole-Bromocriptime Study Group: **Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease.** *Neurology* 1997, **49:**1060–1065.
16.• Hobson D, Lang AE, Martin WR, *et al.*: **Excessive daytime sleepiness and sudden onset sleep in Parkinson's disease: a survey by the Canadian Movement Disorders Group.** *JAMA* 2002, in press.
Most recent and extensive study reporting the prevalence of excessive daytime somnolence and sleep attacks in Parkinson's disease patients using a variety of dopaminergic medications. The authors conclude that use of the Epworth Sleepiness Scale in combination with Inappropriate Sleep Composite Score may be a sensitive method for predicting which patients are at risk for falling asleep when driving.
17. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S: **Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole.** *Neurology* 1999, **52:**1908–1910.
18. Pal S, Bhattacharya KF, Agipito C, *et al.*: **A study of excessive daytime sleepiness and its clinical significance in three group of Parkinson's disease patients taking pramipexole, cabergoline and levodopa mono and combination therapy.** *J Neurol Transm* 2001, **108:**71–77.
19.•• Tan EK, Jankovic J: **Choosing dopamine agonists in Parkinson's disease.** *Clin Neuropharm* 2001, **24:**247–253.
Excellent review of the available dopamine agonists, discussing the literature that addresses comparison studies.
20. Hanna PA, Ratcos L, Ondo WG, *et al.*: **A comparison of the therapeutic efficacy of pergolide and pramipexole in Parkinson's disease.** *J Neurol Tansm* 2001, **108:**63–70.
21. Parkinson Study Group: **Entacapone improves motor fluctuations in levodopa treated Parkinson's disease patients.** *Ann Neurol* 1997, **42:**747–755.
22. Tolcapone Study Group: **Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa treated parkinson's patients.** *Mov Disord* 1999, **14:**38–44.
23. Rinne UK, Larsen JP, Siden A, *et al.*: **Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations.** *Neurology* 1998, **51:**1309–1314.
24. Suchowersky O, Bailey P, Pourcher E, Bulger L, Facciponte G: **Comparison of two doses of tolcapone added to levodopa in nonfluctuating patients with PD.** *Clin Neuropharm* 2001, **24:**214–220.
25. Holm KJ, Spencer CM: **Entacapone. A review of its use in Parkinson's disease.** *Drugs* 1999, **58:**159–177.
26. Assal F, Spahr L, Hadengue A, *et al.*: **Tolcapone and fulminant hepatitis.** *Lancet* 1998, **352:**958.
27. Verhagen-Metman L, Dotto PD, LePoole K, *et al.*: **Amantadine for levodopa-induced dyskinesias. A 1 year follow-up study.** *Arch Neurol* 1999, **56:**1383–1386.
28. Parkinson Study Group: **Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease.** *N Engl J Med* 1993, **328:**176–183.
29. Parkinson Study Group: **Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa.** *Ann Neurol* 1996, **39:**29–36.
30.• Goetz CG, Blasucci L, Stebbins GT: **Switching dopamine agonists in advanced Parkinson's disease. Is rapid titration preferable to slow?** *Neurology* 1999, **52:**1227–1229.
This study looks at the pros and cons of doing a rapid versus slow changeover from one dopamine agonist to another, and concludes that a rapid switch is safe and effective.
31. Gimenez-Roldan S, Esteban EM, Mateo D: **Switching from bromocriptine to ropinirole in patients with advanced Parkinson's disease: open label pilot responses to three different dose-ratios.** *Clin Neuropharm* 2001, **24:**346–351.
32. Schwartz J, Arnold G, Gasser T, Hundemer HP: **High-dose therapy with pergolide – results of a perspective, randomized study.** *Parkinsonism Rel Disord* 2001, **7(suppl):**S129.
33. Bennett JP, Landow ER, Dietrick S, Schuh LA: **Supression of dyskinesias in advanced Parkinson's disease: Moderate daily clozapine does provide long-term dyskinesia reduction.** *Mov Disord* 1994, **9:**409–414.
34. Durif F, Vidailhet M, Bonnett AM, Blin J, AAgid Y: **Levodopa-induced dyskinesias are improved by fluoxetine.** *Neurology* 1995, **45:**1855–1858.
35. Carpentier AF, Bonnett AM, Vildailhet M, Agid Y: **Improvement of levodopa-induced dyskinesia by propranolol in Parkinson's disease.** *Neurology* 1996, **46:**1548–1551.
36. Bonifati V, Fabrizio E, Cipriani R, Vanacore N, Meco G: **Buspirone in levodopa-induced dyskinesias.** *Clin Neuropharmacol* 1994, **17:**73–82.
37. Lang AE, Lozano AM: **Parkinson's disease, Second of Two Parts.** *N Engl J Med* 1998, **339:**1130–1143b.
38. Sage JI, Sonsalla PK, McHale DM, Heikkila RE, Duvoisin RC: **Clinical experience with duodenal infusions of levodopa for the treatment of motor fluctuations in Parkinson's disease.** *Adv Neurol* 1990, **53:**383–386.
39. Colosimo C, Merello M, Hughes AJ, Sieradzan K, Lees AJ: **Motor response to acute dopaminergic challenge with apomorphine and levodopa in Parkinson's disease: implications for the pathogenesis of the on-off phenomenon.** *J Neurol Neurosurg Psychiatry* 1996, **60:**634–637.
40. Ondo W, Hunter C, Almaguer M, *et al.*: **Sublingual apomorphine in patients with fluctuating Parkinson's disease.** *Mov Disord* 1999, **14:**664–668.
41. Bozek C, Suchowersky O, Purves SJ, Calne S, Calne DB: **Effect of protein intake on Sinemet efficacy.** *Clin Neuropharm* 1986, **9:**196–199.
42. Berke GS, Gerrast B, Kreiman J, Jackson K: **Treatment of parkinson hypothonia with percutaneous collagen augmentation.** *Laryngoscope* 1999, **109:**1295–1299.
43. Kannus P, Parkkari J, Niemi S, *et al.*: **Prevention of hip fractures in elderly people with the use of a hip protector.** *N Engl J Med* 2000, **343:**15406–15413.
44. Suchowersky O, Furtado S, Rohs G: **Beneficial effect of intranasal desmopressin for nocturnal polyuria in Parkinson's disease.** *Mov Disord* 1995, **10:**337–340.
45. Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ: **Treatment of erectile dysfunction with sildenafil (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypertension.** *J Neurol Neurosurg Psychiatry* 2001, **71:**371–374.
46. Dooneief G, Mirabello E, Bell K, *et al.*: **An estimate of the incidence of depression in idiopathic Parkinson's disease.** *Arch Neurol* 1992, **49:**305–307.
47. Sanno M, Stern Y, Williams J, *et al.*: **Coexisting dementia and depression in Parkinson's disease.** *Arch Neurol* 1989, **46:**1284–1286.
48. Richard IH, Kurlan R: **A survey of antidepressant use in PD.** *Neurology* 1997, **49:**1168–1170.
49. Dell'Angnello G, Ceravalo R, Nuti A, *et al.*: **SSRIs do not worsen Parkinson's disease: evidence from an open-label prospective study.** *Clin Neuropharm* 2001, **24:**221–227.
50. Richard IH, Kurlan R, Tanner C, *et al.*, for the Parkinson Study Group: **Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease.** *Neurology* 1997, **48:**1070–1077.
51. Saint-Cyr JA, Taylor AE, Lang AE: **Neuropsychological and psychiatric side effects in the treatment of Parkinson's disease.** *Neurology* 1993, **43(suppl 6):**S47–S52.
52. Klawans HL: **Psychiatric side effects during the treatment of Parkinson's disease.** *J Neurol Transm* 1998, **27(suppl):**117–122.
53. Pars MA, Bastani B: **Quetiapine (Seroquel) in the treatment of psychosis in patients with PD.** *J Neuropsychiatry Clin Neurosci* 1998, **10:**216–219.

54. Factor SA, Friedman JH: **The emerging role of clozapine in the treatment of movement disorders.** *Mov Disord* 1997, **12:**483–496.
55. Zoldan J, Friedberg G, Weizman A, Melamed E: **Ondansetron, a 5-HT3 antagonist for visual hallucinations and paranoid delusional disorder associated with chronic L-DOPA therapy in advanced Parkinson's disease.** *Adv Neurol* 1996, **69:**541–544.
56. Ford B, Lynch T, Greene P: **Risperidone in Parkinson's disease.** *Lancet* 1994, **344:**681.
57. Hurwitz TA, Calne DB, Waterman K: **Treatment of dopaminomimetic psychosis in Parkinson's disease with electroconvulsive therapy.** *Can J Neurol Sci* 1988, **15:**32–34.
58. Mohr E, Mendis T, Grimes JD: **Late cognitive changes in Parkinson's disease with an emphasis on dementia.** In *Behavioral Neurology of Movement Disorders. Advances in Neurology,* vol 65. Edited by Werner WJ and Lang AE. New York: Raven Press; 1995:97–113.