Chapter 4. Answers to Revised Key Questions

1. What are the results of neuroimaging studies (CT, MRI, PET, SPECT) or other diagnostic tests in determining the diagnosis of PD?

The use of CT to diagnose PD was not addressed in any of the studies in the database. Evidence suggests that MRI may be useful to rule out conditions other than PD, but not for diagnosing PD. Evidence regarding SPECT and PET scans was inconsistent. Some studies reported these scans could distinguish advanced PD from normal controls; however, these conditions should be clinically distinguishable without the need for neuroimaging studies. Differentiating atypical parkinsonism from PD is clinically more difficult, but studies were inconsistent in their conclusions regarding ability of SPECT or PET scans to distinguish between these conditions. The role of SPECT and PET scans in diagnosing PD remains unclear. More research should be done looking at combinations of tests for diagnosing PD.

2. What are the results of L-dopa challenge in PD? What are the accuracy, sensitivity and specificity of this test for diagnosing PD?

Lack of a reference standard limits the ability to quantify accuracy, sensitivity, and specificity of the apomorphine and L-dopa challenge tests. Current published evidence does not support the use of L-dopa or apomorphine challenge tests for diagnosing PD.

3. What is the efficacy of medication used to treat early PD? What is the efficacy of initial treatment with L-dopa vs. a dopamine agonist?

- Meta-analysis suggests that treatment with DAs plus L-dopa may control PD symptoms better than treatment with L-dopa alone, but this was not a consistent finding.

- In studies in which patients were randomized to L-dopa vs. L-dopa plus DAs, the combination of L-dopa plus DAs resulted in better UPDRS scores than L-dopa alone. This was true in both short and long-term (greater than one year) studies.

- In studies where patients were randomized to L-dopa vs. DAs, where additional L-dopa was discretionary, L-dopa alone resulted in better UPDRS scores than DAs (with or without additional L-dopa).

- Treatment with DAs was associated with lower L-dopa doses.

- There is no evidence that different DAs vary in treatment effects in patients with early PD.

- This review found no consistent evidence that treatment with DAs plus selegiline controlled PD symptoms better than treatment with L-dopa alone in patients with early PD; however, treatment with selegiline was associated with a delay in requirement for L-dopa.

- These meta-analysis results should be viewed with caution, as they are based on the small number of RCTs that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

- With regard to initial treatment of L-dopa vs. DAs, only one study compares a DA to placebo without the addition of L-dopa as needed.[213] In this study, the DA clearly performed better than placebo. In another study, bromocriptine and L-dopa were compared as monotherapy and combination therapy.[204] While dystonia was less frequent in the bromocriptine monotherapy group, no other significant differences were observed. These studies do not provide enough evidence to make a conclusion regarding the efficacy of initial treatment with L-dopa vs. a DA.

4. What is the evidence for neuroprotection with selegiline, Vitamin E, or Vitamin C?

There is evidence that vitamin E is not neuroprotective in PD. There is insufficient evidence to evaluate the efficacy of other medications as potential neuroprotective agents in PD.

5. What is the efficacy of medication used to treat late PD? What is the efficacy of medication used to treat patients who have an insufficient response to L-dopa? What are the outcomes of treatment of medication-induced side effects?

- This review found no consistent evidence that treatment with DAs plus L-dopa controlled PD symptoms better than treatment with L-dopa alone in patients with advanced PD; however, treatment with DAs was associated with lower L-dopa doses.

- There is no evidence that different DAs vary in treatment effects in patients with advanced PD.

- Treatment with COMT inhibitors combined with L-dopa showed significantly greater efficacy in treating PD symptoms than than treatment with L-dopa alone in patients with advanced PD. Use of COMT inhibitors was associated with lower L-dopa doses; however, long term (greater than seven months) results are lacking, and hepatotoxicity is a potentially lethal side effect that has been rarely associated with tolcapone. Treatment of medication-induced side effects is addressed in question 6.

- These meta-analysis results should be viewed with caution, as they are based on the small number of RCTs that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

6. What are the outcomes of treatment for patients who experience motor fluctuations and/or dyskinesias while taking L-dopa?

Dyskinesias and motor fluctuations were rarely reported in a quantifiable manner. Lower L-dopa doses are associated with improvement in dyskinesias. Based on information from a limited

number of studies, use of DAs, selegiline, and COMT inhibitors was associated with lower doses of L-dopa.

Thirteen surgical studies reported dyskinesia scores; almost all reported improvement in mean dyskinesia scores, particularly contralateral scores, after surgery. Studies of DBS of the STN that reported L-dopa dosages showed a significant decrease in L-dopa dose after surgery. Hence, there is evidence that pharmacologic and surgical approaches to managing L-dopa side effects may be effective in reducing dyskinesias.

7. What serious adverse events are associated with medications used to treat PD?

No treatment-related deaths, hospitalizations, cancers, or life-threatening events were reported in any pharmacologic studies.

8. What are the outcomes of treatment of PD patients with psychotic symptoms or non-psychotic behavioral and psychological dysfunction?

Limited data suggests efficacy and safety of clozapine in the treatment of PD patients with dopamine-induced psychosis. Long-term RCTs (i.e., > 6 months) are needed to confirm these findings. While depression is reported to be a common finding in PD patients, this issue cannot be adequately addressed in this report, as insufficient studies met the inclusion criteria for acceptance into the database.

9. When is surgery performed on PD patients? What types of surgeries are performed and what are their outcomes?

- The overall quality of the surgery literature was lower than the quality of the pharmacologic literature, as very few RCTs were done to evaluate the efficacy and safety of surgical procedures. It must be recognized, however, that it is very difficult to perform RCTs of surgical procedures, and other study designs may have to suffice.

- Surgery studies have generally been performed on young patients with advanced PD who are suffering from intolerable drug-induced dyskinesias or motor fluctuations.

- On average, for pallidotomy and DBS, endpoint PD scale "off" scores were significantly better than baseline scores. Mean L-dopa doses did not change significantly after pallidotomy.

- DBS of the STN and GPi resulted in significant improvement in PD scale "off" scores, but only STN DBS was associated with a decrease in L-dopa doses.

- There were insufficient studies of thalamotomy to draw any conclusions regarding efficacy.

- Across all fetal brain cell transplant studies, endpoint PD scale scores were significantly better than baseline scores; however, the small sample size limits interpretation, and a

recent RCT comparing tissue transplantation to sham surgery raised important questions regarding the efficacy and long-term safety of the procedure.

- These meta-analysis results should be viewed with caution, as they are based on results of the small number of studies that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

10. What are the outcomes of rehabilitation in PD?

Short-term (≤ one month) studies of physical therapy, music therapy, speech therapy, and multidisciplinary rehabilitation programs demonstrated improvements in strength, flexibility, speech, and quality of life, but their short duration precludes any conclusions regarding their long-term efficacy. Intensive speech therapy has been shown to improve vocal intensity up to twelve months after treatment; however, these long–term results are from only one study of 22 patients.

11. What are the results of recent review articles regarding genetic testing in PD?

Recent studies have identified specific genetic mutations that are associated with familial PD, but the evidence suggests that genetics do not play a major role in most PD patients with age of disease onset > 50 years. Although current evidence is sparse, this is an area of active research, and updates of this review may be able to address genetic issues more fully.

12. What is the evidence that PD patients are treated differently or have different outcomes based on the following: age, presentation of symptoms, cognitive status, duration of illness, co-morbidities, gender, race, ethnicity, or income level?

Most of the studies in the database excluded patients with significant comorbidities; therefore, no conclusions may be drawn regarding treatment of patients with multiple disease processes. Very few studies addressed race, ethnicity, and income level. In the few studies that identified the race of their subjects, the vast majority of patients were Caucasians. No distinctions were made between outcomes in males and females. Studies in the database did not address patients at age extremes. When age of disease onset was reported, there was minimal variation, and patients with young age of onset were not well represented in the database. Very few studies reported presentation of symptoms. Therefore, evidence-based conclusions regarding differences in treatment or outcome based on differences in age, presentation of symptoms, cognitive status, duration of illness, comorbidities, gender, race, ethnicity, and income level are not possible.