Parkinson Canada

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CANADIAN GUIDELINE FOR PARKINSON DISEASE, 2ND EDITION

Note: This full version of the Canadian Guideline for Parkinson Disease has been copyedited to be consistent with the summary article published in *CMAJ*, but has not been peer reviewed.

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PARKINSON DISEASE

VISUAL SUMMARY OF RECOMMENDATIONS FROM THE **CANADIAN GUIDELINE FOR PARKINSON DISEASE, 2ND ED**

COMMUNICATION

- People with Parkinson disease should be encouraged to participate in choices about their own care.
- Communication should be in verbal and written form.
- Discussions should aim to achieve a balance between providing realistic information and promoting optimism.
- Families and caregivers should be informed about the condition and available support services.

DIAGNOSIS AND PROGRESSION

- Parkinson disease should be suspected in anyone with tremor, stiffness, slowness, balance problems or gait disorders.
- CT or MRI brain scanning should not be routinely used to diagnose Parkinson disease.
- Patients, especially young, who request genetic testing should be assessed by a movement disorders specialist.
- No therapies are effective for slowing or stopping brain degeneration in Parkinson disease.

TREATMENT

- Levodopa is the most effective medication and may be used early.
- A regular exercise regimen begun early has proven benefit.
- Patients with possible diagnosis of Parkinson disease may benefit from a trial of dopamine replacement therapy to help with diagnosis.
- Impulse control disorders can develop on dopaminergic therapy at any stage in the disease but are more common in patients on dopamine agonists.
- Deep brain stimulation and gel infusion are now routinely used to manage motor symptoms.
- Rehabilitation therapists experienced with Parkinson disease can help newly diagnosed patients, and others through all stages.

PALLIATIVE CARE

- The palliative care needs of people with Parkinson disease should be considered throughout all phases of the disease.
- If the patient asks, the option of medical assistance in dying should be discussed.

NONMOTOR FEATURES

- Botulinum toxin A helps control drooling.
- Drug therapy for low blood pressure includes midodrine, fludrocortisone and domperidone.
- Management of depression should be tailored to the individual and their current therapy.
- Dementia should not exclude a diagnosis of Parkinson disease, even if present early.
- Rapid eye movement sleep behaviour disorder can pre-date the diagnosis of Parkinson disease.

INTRODUCTION

The aim of the Canadian Guideline for Parkinson Disease is to enhance the care for all Canadians with Parkinson disease that:

- is based on the best published evidence
- involves expert consensus when there is a lack of evidence
- offers practical clinical advice
- takes into account patient choice and informed decision-making
- is relevant to the Canadian health care system

The initial Canadian Guideline for Parkinson Disease (hereafter, "Canadian guideline") were created with the support of Parkinson Society Canada and published in 2012.[1] They were based on a comprehensive search to identify previously published guidelines on Parkinson disease up to 2008 and were appraised using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. At that time the goal was not to create new recommendations but to select from high-quality guidelines whose recommendations were clinically most relevant for health care delivery in Canada. The authors of each section incorporated new information into the discussion section following each section of recommendations that included information up until 2011. Emphasis had been placed on making these guidelines usable and accessible to all health care professionals who manage patients with Parkinson disease. It is generally recommended that guidelines be reassessed for validity at least every 3 years.[2]

The updated Canadian guideline was supported by a grant from Parkinson Canada (formerly Parkinson Society Canada). The method followed was designed with the assistance of Dr. Brian Hutton and his Knowledge Synthesis Group at the Ottawa Methods Centre, Ottawa Hospital Research Institute. This update is based on the ADAPTE process, which is a systematic approach to adapt an existing guideline from one cultural, environmental, geographic and health care context and apply it to another without losing the applicability and validity of the recommendation.[3]

The target users for the final, extensively revised document are health care professionals. However, it may also be used by policy-makers, funding bodies and people with Parkinson disease and their families. These recommendations are intended to serve as a guide for health care providers, and clinical discretion should be used by all who are following the Canadian guideline recommendations. The information

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should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time that information is developed and when it is published or read); does not mandate any particular course of medical care; and is not intended to be a substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. The definitive judgment is made by the appropriate health care professional(s) based on all the data available for an individual person. It is recognized that resource problems and individual patient preference may make it difficult to put into practice every recommendation in this guideline. However, it is meant to improve the standard of care and access to care for individuals with Parkinson disease in all regions of Canada.

The Canadian guideline was updated with input from movement disorder specialists, functional neurosurgical specialists, family physicians, nurses, methodologists, psychiatrists, physiotherapists, occupational therapists, pharmacists, neuropsychologists, and Parkinson Canada, as well as individuals with Parkinson disease. No participants or authors received any personal funding for the creation of the guideline.

The Canadian guideline was completed in 2018 and will be reviewed in 2023. All correspondence and comments regarding the recommendations in this guideline should be sent to:

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METHODOLOGY FOR UPDATING THE CANADIAN GUIDELINE

(D. Grimes, B. Hutton, M. Fitzpatrick, P. Barbeau)

The overall objective was to identify recently published scientific evidence for the purpose of updating specific recommendations (as identified by a panel of clinical experts) from the 2012 Canadian Guidelines on Parkinson's disease.[1] When resources are limited, the ADAPTE process can be used to conduct a full systematic review or to avoid duplication of effort if it is known that existing systematic reviews and recommendations have already been published on their topic.[3] It was considered an appropriate strategy for the current objective of updating the Canadian guideline.

Guidelines should be updated on a timely basis to reflect the emergence of new evidence. The ADAPTE handbook references the need for an update and the implications it could have on existing recommendations, such as discontinuing the guideline, discontinuing some recommendations but not the entire guideline, or rewriting recommendations that are in need of updating.[3] However, the methods to update a guideline derived from ADAPTE processes are not clearly outlined. Therefore, we used components of the ADAPTE process to execute the literature update, which in turn helped inform the update. This included identifying guidelines or topics in need of updating, searching for existing general clinical practice guidelines (CPGs), systematic reviews and key publications, mapping the existing recommendations from our search to the recommendations that needed updating, and using a consensus process to make decisions on the appropriate recommendations to be used.

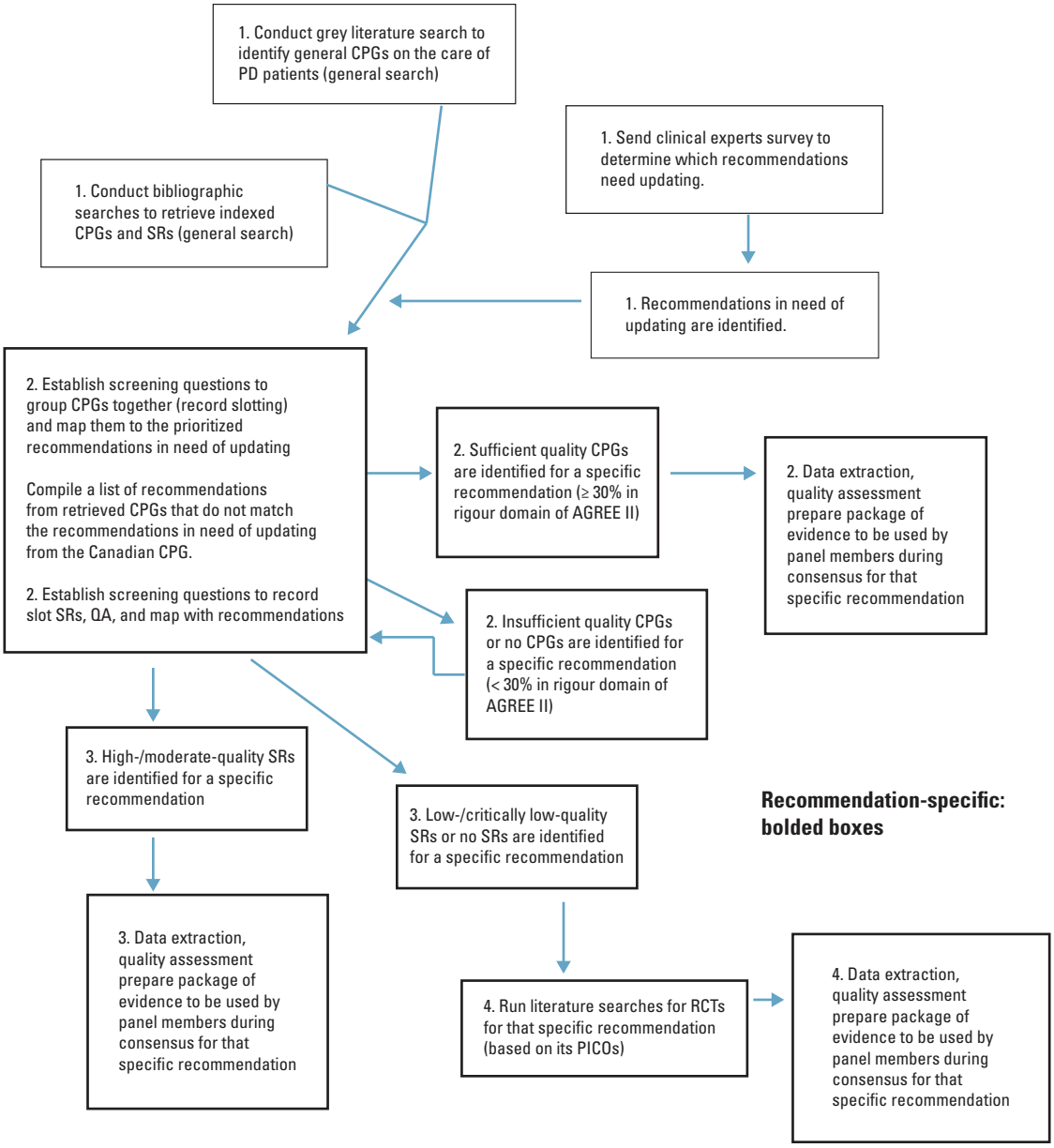
A series of surveys were sent out to a panel of clinical experts to establish insight from the clinical community as to which recommendations from the 2012 Canadian guidelines needed to be prioritized for updating. The surveys were implemented electronically using FluidSurveys software[4] (SurveyMonkey[5] as of December 2017). The panel of clinical experts were asked to assess (i) the validity of each recommendation based on the experts' knowledge and (ii) whether the experts were aware of new evidence pertaining to that recommendation when their response suggested a need for updating. For those recommendations still considered valid, the experts were asked if they were aware of any new evidence that would change the grade or strength of evidence. A total of 16 clinical experts completed the surveys (16/16; 100%).

Owing to the nature of the update, an overarching PIPOH (Population, Intervention/Topics, Professionals, Outcomes, Health care setting) question was proposed (Supplemental Table 7). This allowed us to identify general CPGs on the care of patients with Parkinson disease. Specific screening questions to group CPGs together were then established and mapped to the prioritized recommendations that were in need of updating, identified by the panel experts.

In the current review, if no sufficiently high-quality CPGs or no CPGs were identified in the grey literature search, then a staged approach to identification of evidence was implemented, where first moderate- to high-quality systematic reviews were systematically searched for and used as evidence. In the absence of such reviews, or if there were no systematic reviews, then we next performed a general search of randomized controlled trials (RCTs) in regard to Parkinson disease (Figure 1). Search strategies are available in the Search Strategies section.

We used Distiller Systematic Review (Distiller SR; Evidence Partners, Inc., Ottawa, Canada) Software[6] to screen the articles for relevancy. Methodological quality assessment

Figure 1. Staged approach for identifying evidence



Note: AGREE II = Appraisal of Guidelines for Research & Evaluation CPG = clinical practice guideline, PD = Parkinson disease, PICO = patient, intervention, comparison and outcome, QA = quality assurance, RCT = randomized controlled trial, SR = systematic review.

tools depending on the study design were used to assess risk of bias. The AGREE II tool was used to assess the rigour of CPGs,[7] the 16-point A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2)[8] was used to assess systematic reviews, and the Cochrane Risk of Bias tool was used for screening RCTs.[9] Refer to Supplemental Methods for a detailed account of risk of bias assessments. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and description outlining the processing of identifying CPGs and systematic reviews (Supplemental Figures 1 and 2) and RCTs (Supplemental Figure 3) can be found in Supplemental Methods.

In tandem with the quality assessment process, 2 reviewers mapped (grouped) relevant existing CPGs and, if necessary, systematic reviews and RCTs with the recommendation (old guideline numbering) that was in need of updating.

Packages of information (including strengths of evidence, citations, and summaries of new studies) were compiled in the form of cover-letter summaries for distribution to the differing teams with expertise in each area of Parkinson disease (communication, diagnosis, treatment, etc.) in order to facilitate the panel members' efforts in the updating process of the Canadian guideline.

Nine CPGs, some of which are updates of CPGs previously adapted from the 2012 Canadian guideline, were mapped to the recommendations in need of updating[10–18] (Supplemental Table 1), and 16 systematic reviews[19–34] were included in the update where the recommendation was not already addressed by a CPG (Supplemental Table 2). Twenty-four RCTs were mapped to recommendations not already addressed by CPGs or systematic reviews: pharmacologic therapies for motor symptoms (n = 6),[35–40] surgery (n = 7),[41–47] other treatment options (n = 9),[48–56] autonomic dysfunction (n = 2)[57,58] (Supplemental Table 3).

Before the consensus meeting, several additional topics were identified that were felt to be important and were not initially captured because of the stringent topic search conducted. These included i) depression and Parkinson disease, because the initial search had been restricted to amitriptyline as it was the only antidepressant included in the original guideline; ii) pimavanserin, and iii) rotigotine. These topics were not addressed in any of the CPGs; therefore, data were extracted from systematic reviews for these topics and cover-letter summaries were produced. The citations are summarized in Supplemental Table 4.

A full-day consensus meeting was held on April 8, 2017. Summary cover-letter documents were developed for each recommendation in need of updating, to provide a high-level summary of the evidence found in the update. Participants attending the consensus meeting (Supplemental Table 5) used these summaries along with the full text of each article to determine whether sufficient evidence existed to "… discontinue the use the guideline; discontinue/withdraw some of the recommendations but not the entire guideline; re-do the systematic review; or re-write only those recommendations needing an update as long as the validity of the guideline is not compromised."[3] A substantial number of recommendations from the 2006 National Institute for Health and Care Excellence (NICE) guideline were adapted into the 2012 Canadian guideline. An updated version of the NICE guideline was not identified in the literature search, as its publication date was scheduled for June 2017. However, a draft version of the updated NICE guideline was available from October 2016, and the authors used it to update relevant sections, including forming the basis of the new section on palliative care. Upon publication of the NICE guidelines, the rigour was assessed and data were extracted in a post-hoc analysis.

Four smaller working groups created at the meeting were charged with reviewing all relevant material and recommendations on their topic. They then presented their recommendations back to the entire group for further discussion, and this served as the basis for the initial voting matrix for each recommendation. An open voting process and summary discussion method identified 5 main areas on which to base the guidelines: communication, diagnosis and progression, treatment, nonmotor features, and a new section on palliative care.

At the meeting, additional recommendations that required updating were identified that had not been identified by the original survey. Consensus members used recommendations from the identified CPGs during the consensus meeting to update or create new recommendations that were felt to be lacking in the 2012 Canadian guideline. For example, the area of genetic screening was identified as a topic of interest, and a recommendation in this regard was identified in the Scottish Intercollegiate Guidelines Network (SIGN) guideline, where routine genetic screening for Parkinson disease is not recommended (good practice point [GPP]). If no appropriate recommendation was found in the available CPGs, the topic would be sent to the methods group for a post-hoc screen of the quality CPGs, systematic reviews, and RCTs that had been identified in the literature search. Consensus members could then generate a new recommendation from the relevant sources identified post hoc. The topics included in the post-hoc screen are summarized in Supplemental Table 6.

The guidance panel made substantial effort to try and maintain the phrasing of original recommendations, but some have been modified slightly to achieve standardized terminology or to make the recommendation more specific. The source for all the original recommendations (e.g., NICE, American Academy of Neurology [AAN]) is referenced at the end of each Canadian guideline recommendation (Table 1). When the recommendation was created by the authors from systematic review or RCT evidence, the recommendation is referenced with "CAN." The systems for determining the level of evidence that were used across the guidelines differed slightly, but the grade for the recommendation was maintained from the original source; i.e., grade A, B, GPP, and so on (Tables 2 and 3).

Table 1. Guidelines used for the Canadian guideline

Abbreviation	Full source name
AAN	American Academy of Neurology[64]
EFNS	European Federation of Neurological Societies[11,16]
MDS	Movement Disorder Society[26]
NICE	National Institute for Health and Clinical Excellence[102,103]
SIGN	Scottish Intercollegiate Guidelines Network[17]

After the meeting and post-hoc screening, we created a voting matrix, organized into the 5 main themes with subsections. We conducted online voting using SurveyMonkey[5] to ensure that the majority (> 75%) agreed on each of the recommendation points. The response to the survey was 71% (27/38). One recommendation did not reach 75% agreement but was considered to be an essential topic to include. The section lead modified the wording of this recommendation and the newly worded recommendation was sent out for voting. The response to the second survey was 53% (20/38) and 75% of respondents were in agreement with the recommendation. Ninety-seven recommendations formed the basis

Table 2. Grading scheme from SIGN, EFNS, NICE

Grade of recommendation	Evidence
A	At least 1 meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
GPP	Recommended best practice based on the clinical experience of the guideline development group.

Note: EFNS = European Federation of Neurological Societies, GPP = good practice point, NICE = National Institute for Health and Clinical Excellence, RCT = randomized controlled trial, SIGN = Scottish Intercollegiate Guidelines Network.

Table 3: Levels of evidence*

1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias. High-quality systematic reviews of case–control or cohort studies
2++	High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding or bias and a substantial risk that the relationship is not causal
3	Nonanalytic studies (e.g., case reports, case series).
4	Expert opinion

Note: RCT = randomized controlled trial.
*When no grade was assigned or when a guideline was created from SR or RCT, the SIGN 2010[17] grading table was used.

for the authors of each chapter. The authors for each section were instructed to limit references to only key information that was not part of the CPG, systematic review or RCT used to create the recommendation.

Dissemination

During the development of these guidelines, consideration has been given to various methods of dissemination and the practical issues of implementation of each recommendation in a Canadian context. Parkinson Canada will assist in disseminating the print and electronic versions of the guideline to health care providers, individuals with Parkinson disease and their families, as well as post the full guideline on its website. The previous guideline was downloaded more than 40,000 times and was available in both English and French. The updated guideline will be presented at national, provincial and regional meetings of health care professionals across disciplines. Feedback from these presentations will be encouraged, to identify local and national barriers as well as ways to enhance the implementation of the recommendations. As part of the Parkinson Canada affiliation with the Neurological Health Charities Canada, the guideline will assist in advocacy efforts to federal and provincial governments to improve the care of individuals with Parkinson disease and other brain diseases. A clear limitation to the implementation of this guideline is a lack of adequate access to health care providers with expertise in dealing with individuals with Parkinson disease. This includes not only specialty physicians but also nurses and speech and occupational and physical therapists with adequate training to deal with patients who have this very complex condition. Access to palliative care treatment is also lacking for Canadians with neurodegenerative disease and needs to be addressed at local and national levels of care delivery. Resource management, particularly in advanced stages, could be a potential ethical issue. Deep brain stimulation therapy and levodopa-carbidopa enteric gel (Duodopa) infusion therapy are expensive and complex to use, with most centres having limited budgetary or human resources with respect to the number of procedures they can perform and continue to manage. The cost of care for neurodegenerative diseases in general will increase as our population ages. The limits that our publicly funded health care system can provide need to be addressed, but are outside the scope of this guideline.

SECTION 1: COMMUNICATION

COMMUNICATION

(J. Miyasaki & J. Gordon)

Good communication is at the heart of every interaction between people with Parkinson disease, their caregivers and health professionals. Health care professionals committed to clear and empathic communication can make a meaningful difference to their patients. When people with Parkinson disease know what health care professionals recommend and why, they can participate in shared decision-making and this can result in improved adherence to a shared plan.

When a patient is newly diagnosed, health care professionals must explain the basis of the diagnosis, how this might affect the person's relationships and ability to function in their daily life, and provide hope. Providing information regarding what to expect in the future requires an assessment of how much information an individual wants or needs at that particular time. One size does not fit all. With time, Parkinson disease complicates every aspect of daily living. What were previously routine tasks now demand full attention and often result in frustration and anxiety. Parkinson disease can compromise a person's ability to earn an income and can complicate relationships with partners, family and friends. The progression of the disease can lead to increased dependency, which may lead to feelings of being a burden, eroded self-worth and increased strains on personal relationships. Stressors such as threats to employment and social isolation are not uncommon. Beyond the need for medical care, people living with Parkinson disease need understanding and support as they struggle to maintain independence and adapt to living with a chronic condition.

A person-centred approach to care and treatment requires open communication with health care professionals who can provide the appropriate amount of evidence-based and, where sufficient evidence does not exist, useful information. People with Parkinson disease should have the opportunity to make informed decisions based on full disclosure of all relevant information.

Issues to consider when communicating with people with Parkinson disease and their caregivers:

- Style, manner and frequency of communication that is compassionate and respectful
- Ease of access for those receiving information in a timely and appropriate manner throughout the progression of Parkinson disease
- Honesty and sensitivity in tailoring information to meet changing medical needs
- Encouragement of self-management by people with Parkinson disease to meet individual needs and preferences
- Inclusion of caregivers and families who are also affected by Parkinson disease and require information and support in medical visits

Communication should be supported by the provision of evidence-based information in a form that is tailored to the needs of the individual. The treatment, care and information provided should be culturally appropriate and in a form that is accessible to people who have additional needs, such as people with physical, cognitive or sensory disabilities, or who do not speak or read English. Where possible, the written material provided should include instructions for medication use. Unless specifically excluded by the patient, caregivers and family members should have the opportunity to be involved in the discussion and decisions about the person's care and treatment.

C1 Communication with people with Parkinson disease should be aimed at empowering them to participate in the judgments and choices about their own care NICE (grade: D; source: NICE[102]).

C2 Discussions should be aimed at achieving a balance between the provision of honest, realistic information about the condition and the promotion of a feeling of optimism (grade: D; source: NICE[102]).

C3 Because people with Parkinson disease may develop impaired cognitive ability, a communication deficit or depression, they should be provided with both verbal and written communication throughout the course of the disease — which should be individually tailored and reinforced as necessary — and consistent communication from the professionals involved (grade: D, GPP; source: NICE[102]).

C4 Families and caregivers should be given information about the condition, their entitlements to care assessment and the support services available (grade: D, GPP; NICE[102])

C5 People with Parkinson disease should have a comprehensive care plan agreed upon between the individual, their family and caregivers and all health care providers (grade: D, GPP; source: NICE[102]).

C6 People with Parkinson disease should be offered an accessible point of contact with specialist services (grade: D, GPP; source: NICE[102]).

The impact of Parkinson disease is borne out in the many changes and accommodations that people living with the condition and their caregivers must make. Difficulty with writing and speaking, and loss of independence, may lead to social withdrawal and isolation as well as depression, frustration and anger. Access to services such as primary care, therapies for speech, exercise programs and emo-

tional support is critical to manage the disease and live with dignity.

An interdisciplinary or multidisciplinary team approach in developing a care plan tailored to the unique needs of the individual is critical for maintaining quality of life. No one group (primary care physician or neurologist, for example) can meet all the needs of those with Parkinson disease. A multidisciplinary approach uses multiple disciplines working in tandem to address patient needs. An interdisciplinary approach uses team members who may see patients simultaneously and develop a single plan for patients. Interdisciplinary practice is more feasible in a dedicated Parkinson clinic, while multidisciplinary approaches are available throughout Canada (through community resources and home-care programs). Physicians and allied health professionals need to be knowledgeable about Parkinson disease in order to provide specific services to the individual, and these services should be coordinated from a central location.

Individuals with Parkinson disease in rural settings have more challenges accessing services and programs and must travel greater distances to access health care. Access to homecare may not be possible owing to geographic isolation. Navigating the complex health and social service systems can be daunting. Health care professionals can help by understanding and being sensitive to the many challenges facing people living with Parkinson disease and the potential barriers to accessing care and support. The disease affects both the person living with it and his or her caregiver and family. It is important that both the person and the caregiver have access to the same information and services.

 Appendix to: Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guideline for Parkinson disease. *CMAJ* 2019. doi: 10.1503/cmaj.181504.

SECTION 2: DIAGNOSIS AND PROGRESSION

DIAGNOSIS AND PROGRESSION

(M. Schlossmacher & E. Fon)

Parkinson disease is characterized by a constellation of clinical manifestations, which include slowness of movement (bradykinesia), rest tremor, rigidity and postural instability. Parkinson disease is a complex disorder that can be difficult to diagnose clinically, especially in the early stages when only some of its cardinal signs may be present. A diagnosis based on its etiology is impractical because several distinct variants exist that produce a shared clinical phenotype. For more than 75% of "typical Parkinson disease" cases, we consider the etiology to be that of a "complex disease." There, allelic variants ("nature") and environmental factors ("nurture") interact with each other in neurologically still-healthy individuals; the initiation of subsequent changes in the peripheral autonomic nervous system or in the central nervous system are further modified by the effects of sex ("gender") during the passage of time over decades ("aging") to generate what we come to recognize as Parkinson disease. Moreover, truly monogenic forms of Parkinson disease and bona fide toxin exposure–linked parkinsonism account for only a minority of cases. Hence, the diagnosis of Parkinson disease is still based predominantly on its clinical features (Figure 2).

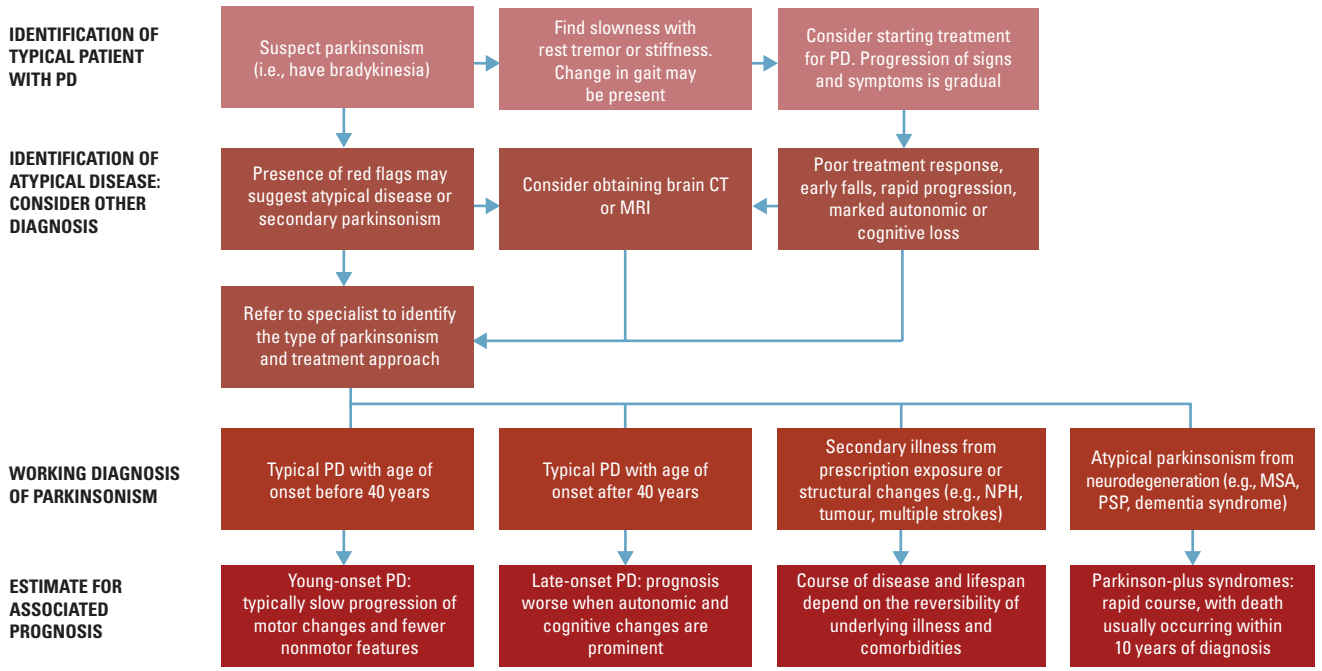
Until 2015, the most widely accepted clinical criteria for the diagnosis of typical Parkinson disease were those proposed by the UK Parkinson's Disease Society Brain Bank.[59] In 2015, Postuma et al. revisited this issue and, on behalf of the Movement Disorder Society (MDS), published their clinical diagnostic criteria for clinically established Parkinson disease (i.e., for living patients without any features that would be atypical for Parkinson disease) and for "probable Parkinson disease" (where the number of supportive signs for Parkinson disease outweigh the presence of some atypical features)[60]; for simplicity, we refer to both entities hereafter as "typical Parkinson disease" (Figure 2).

C7 Parkinson disease should be suspected in people presenting with tremor, stiffness, slowness, balance problems or gait disorders (grade: D, GPP; source: NICE[102]).

C8 Parkinson disease can be diagnosed using the MDS Clinical Diagnostic Criteria (grade: GPP; source: CAN).

There is no universally accepted, readily available marker to specifically define Parkinson disease with sufficient sensitivity to distinguish it from other parkinsonian syndromes. Nevertheless, typical Parkinson disease must be differentiated from secondary parkinsonism or tremor — for example, that resulting from neuroleptic drug exposure or structural changes in the brain (such as from normal pressure hydrocephalus, multiple small vessel

Figure 2. Diagnosis and prognosis of Parkinson disease



Note: CT = computed tomography, MRI = magnetic resonance imaging, MSA = multiple system atrophy, NPH = normal pressure hydrocephalus, PD = Parkinson disease, PSP = progressive supranuclear palsy.

Appendix to: Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guideline for Parkinson disease. *CMAJ* 2019. doi: 10.1503/cmaj.181504.

disease strokes ["vascular parkinsonism"] and tumours). It should also be separated from other neurodegenerative forms of parkinsonism, which include multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome and several dementia syndromes. Ideally, patients suspected of having Parkinson disease or a related movement disorder should be referred to a neurologist, and if possible to a specialized movement disorders clinic or centre for evaluation.

Typical Parkinson disease involves the degeneration of dopamine neurons, along with loss of other neuronal clusters, and in most late-onset cases, the presence of intracellular inclusion bodies (referred to as Lewy bodies) at the time of autopsy. However, Lewy bodies occur in many disorders of the brain, including in individuals who do not have any clinically detectable features of Parkinson disease. Intriguingly, in some variants of typical Parkinson disease, such as in those with young-onset, recessively inherited forms of it, Lewy body inclusion may be absent in surviving neurons. Moreover, expecting neuropathological assessment of brain tissue for diagnostic purposes is not realistic in living patients; in the future, peripheral organ biopsy (e.g., skin) may serve as a surrogate marker of brain pathology. Of note, up to 20% of patients diagnosed in life with typical Parkinson disease have an alternative diagnosis at autopsy. Given the potential error in making a diagnosis of Parkinson disease, patients should be followed routinely, and the diagnosis should be reconsidered, if atypical features emerge. In regions of the country where appropriate hospital services can be accessed, consideration should be given during routine patient visits to obtaining consent for postmortem autopsy examination.

The development of reliable, clinical or preclinical tests would undoubtedly aid in the early identification of patients with typical Parkinson disease or those who are at risk for it (such as those suffering from an REM-sleep associated behavioural disorder). Several drug challenges or diagnostic tests have been proposed to aid in the diagnosis of Parkinson disease or in the differentiation between Parkinson disease and other parkinsonian syndromes. If an individual has Parkinson disease then he or she should respond to dopamine replacement therapy (e.g., levodopa-carbidopa 600 mg/d) and therefore, if they do have a clear response, this can be used to help reinforce that an accurate diagnosis has been established. Many caveats exist, including ensuring that one is measuring improvement in bradykinesia and not other symptoms that may show a lesser therapeutic response (i.e., tremor, balance difficulties) or that the patient's motor difficulties are so mild that a positive response might be hard to gauge. To date, no single test has been shown to have sufficient sensitivity and specificity to reliably diagnose Parkinson disease at the time of a patient's first visit, and by inference, to distinguish Parkinson disease from other forms of parkinsonism.

C9 Clinicians should be aware of the poor specificity of a clinical diagnosis of Parkinson disease in the early stages of the disease, and consider this uncertainty when giving information to the patient and when planning management (grade: C; source: SIGN[17]).

C10 Patients should be offered long-term, regular follow-up to review the diagnosis of Parkinson disease. This should include a review of the ongoing benefits in those started on dopamine replacement therapy (grade: GPP; source SIGN[17]).

C11 Patients initially considered to have a possible diagnosis of Parkinson disease may benefit from a trial of dopamine replacement therapy to assist with an accurate diagnosis (grade: GPP; source: SIGN[17]).

C12 Patients with suspected Parkinson disease, with substantial disability or exclusion criteria or red flags as per the MDS diagnostic criteria, should be seen by a clinician with sufficient expertise in movement disorders to make the diagnosis (grade: GPP; source: SIGN[17]).

C13 Acute challenge testing with either levodopa or apomorphine should not be used in the diagnosis of Parkinson disease. Patients with suspected Parkinson disease should be considered for a trial of chronic levodopa treatment (grade: A; source: SIGN[17]).

Imaging modalities have been extensively researched over the years for a more accurate diagnosis of Parkinson disease, in the differential diagnosis of parkinsonian disorders as well as in the consideration of a possible progression marker for typical Parkinson disease. However, to date, no single test has been shown to have sufficient sensitivity and specificity to accomplish all 3 objectives.

C14 Objective olfactory testing is not recommended in the diagnosis of Parkinson disease.

C15 Routine use of functional imaging is not recommended for the differential diagnosis of Parkinson disease and Parkinson plus disorders such as progressive supranuclear palsy and multiple system atrophy (grade: C; source: SIGN[17]).

C16 Positron emission tomography (PET) scanning is not recommended as part of the diagnostic work-up of parkinsonian syndromes, except within a research framework (grade: GPP; source: SIGN[17]).

C17 ^{123}I-ioflupane single-photon emission computed tomography (^{123}I-FP-CIT SPECT) scanning should be considered as an aid to clinical diagnosis in patients where there is uncertainty between Parkinson disease and nondegenerative parkinsonism or tremor disorders (grade: B; source: SIGN[17]).

C18 Computed tomography or magnetic resonance imaging (MRI) brain scanning should not be routinely applied in the diagnosis of idiopathic Parkinson disease (grade: C; source: SIGN[17]).

Parkinson disease is a heterogeneous disorder with clinical presentations that vary substantially from patient to patient. A number of studies have examined the issue of clinical subtypes of typical Parkinson disease and the associated comorbidities, as well as the response to treatment — this to determine whether any features could be correlated with a more rapid progression of some forms (such as to dementia and to the loss of one's ability to live independently). Such information may be helpful in guiding health care workers, patients and their families in the planning for long-term care.

However, to date, our ability to subtype patients is poor, with substantial overlap, and patients may not remain in their initially subtyped category (e.g., a patient presenting with a tremor-predominant form of Parkinson disease, but then rapidly developing substantial postural instability, which may indicate the onset of progressive supranuclear palsy instead).

Parkinson disease is a progressive disorder in which neuronal degeneration and clinical symptomatology tend to gradually worsen, despite effective symptomatic treatment. The most optimal treatment approach would arrest, or at least, slow the inexorable progression, but such an effective intervention has not yet been established.

Multiple clinical trials of putative neuroprotective compounds have been explored; although some compounds have shown initial promise, the results in general have been disappointing. There are several possible reasons for this. Three of them are that: i) previously explored interventions occurred too late in the disease process; ii) our field faces the challenge of convincingly establishing bona fide neuroprotection for pharmacologic compounds (or surgical interventions) that may also have a symptomatic effect; and iii) as of early 2017, no trial had been conducted that specifically targeted a genetic risk factor or, for that matter, the elusive environmental risk association.

C19 Vitamin E should not be used as a neuroprotective therapy for people with Parkinson disease (grade: A; source: NICE[103]). Co-enzyme Q10 should not be used as a neuroprotective therapy for people with Parkinson disease (grade: A; NICE[103]).

C20 Levodopa (GPP), amantadine (GPP), dopamine agonists (pramipexole, ropinirole, rotigotine, apomorphine, bromocriptine) (grade: A), or monoamine oxidase (MAO) inhibitors (selegiline, rasagiline) (grade: A) should not be used as neuroprotective therapies for people with Parkinson disease, except in the context of clinical trials (CAN).

Early-phase trials are under way that focus on the metabolism of synuclein, and oligomeric species thereof, as a target for safety and early proof-of-principle studies. We envision that in the future, personalized medicine efforts will increasingly mandate the matching of a subset of our patients diagnosed with typical Parkinson disease with their presumed disease pathogenesis for specific, newly developed experimental therapies. To date, there is no established therapy for any one of the genetic risk factors that have been convincingly identified in the development of either early-onset, monogenic parkinsonism or for the "complex disease-type," late-onset Parkinson disease variant.

C21 Genetic testing for monogenic parkinsonism is not recommended in routine clinical practice (grade: GPP; source: SIGN[17]).

C22 Patients who request genetic testing, particularly those with young-onset parkinsonism, should be assessed in a specialist movement disorders clinic for consideration of counselling and testing (grade: GPP; source: SIGN[17]).

SECTION 3: TREATMENT

TREATMENT OF MOTOR SYMPTOMS

(J. Miyasaki)

Many symptomatic treatments are available for Parkinson disease. These include medications, surgical procedures, physiotherapy, occupational therapy and other support services. All of these treatments can have a substantial impact on improving an affected individual's quality of life and should be made available. Despite the increase in nonpharmacologic treatments, individuals with Parkinson disease become more reliant on their medication to maintain their ability to function as the disease progresses. A balance between the adverse effects of the medication and the benefit often becomes more difficult with time. Although impulse control disorders are classically identified as problem gambling and shopping, binge eating, craving sweets and hypersexuality, in practice, any behaviour that is excessive, out of keeping from previous behaviour and impairs occupational or relational functioning may be an impulse control disorder. Hence, painting, hobbyism or going on long "walk-abouts" have been described in this spectrum. Medication schedules become more complex and the timing of when medications are given becomes crucial. Late or missed doses can result in confusion and, at the least, often results in worse motor symptom control. Abrupt withdrawal of medications, either inadvertent because of admission to hospital, or purposeful for a drug holiday or to see "how the patient manages without medication," is not appropriate in those with a diagnosis of Parkinson disease. Patients may have neuroleptic malignant syndrome or worsening of motor symptoms that does not recover, depending on the length of dopaminergic medication cessation. Neurologic involvement during hospital stays can improve patient safety and, in particular, the patient's usual neurologist should be contacted for insight and guidance.

C23 People with Parkinson disease should have regular access to the following:

- Clinical monitoring and medication adjustment
- A continuing point of contact for support, including home visits, when appropriate
- A reliable source of information about clinical and social matters of concern to people with Parkinson disease and their caregivers, which may be provided by a Parkinson disease nurse specialist (grade: C; source: NICE[102]).

C24 Antiparkinsonian medication should not be withdrawn abruptly or allowed to fail suddenly owing to poor absorption (e.g., gastroenteritis, abdominal surgery), to avoid the potential for acute akinesia or neuroleptic malignant syndrome (grade: D, GPP; source: NICE[102]).

C25 The practice of withdrawing patients from their antiparkinsonian drugs (so-called "drug holidays") to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome (grade: D, GPP; source: NICE[102]).

C26 In view of the risks of sudden changes in antiparkinsonian medication, people with Parkinson disease who are admitted to hospital or care homes should have their medication: i) given at the appropriate times, which in some cases may mean allowing self-medication; ii) adjusted by, or adjusted only after discussion with, a specialist in the management of Parkinson disease (grade: D, GPP; source: NICE[102]).

C27 Surveillance for dopamine dysregulation syndrome should be undertaken in patients receiving levodopa or intermittent apomorphine (grade: GPP; source: SIGN[17]).

C28 When starting dopamine agonist therapy, people and their family members and caregivers (as appropriate) should be given verbal and written information about the following, and the discussion should be recorded as having taken place (grade: GPP; source: NICE[103]):

- The increased risk of developing impulse control disorders when taking dopamine agonist therapy, and that these may be concealed by the person affected.
- The different types of impulse control disorders (e.g., compulsive gambling, hypersexuality, binge eating and obsessive shopping).
- Who to contact if impulse control disorders develop.
- The possibility that if problematic impulse control disorders develop, dopamine agonist therapy will be reviewed and may be reduced or stopped.

C29 It should be recognized that impulse control disorders can develop in a person with Parkinson disease who is on any dopaminergic therapy at any stage in the disease course (grade: GPP; source: NICE[103]).

 Appendix to: Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guideline for Parkinson disease. *CMAJ* 2019. doi: 10.1503/cmaj.181504.

PHARMACOLOGIC THERAPY FOR MOTOR SYMPTOMS IN EARLY PARKINSON DISEASE

(A. Rajput & O. Suchowersky)

Once the diagnosis of Parkinson disease is made, the next decision is the type of treatment. Pharmacologic therapy in Parkinson disease patients should be tailored to the individual with the goal of reducing motor symptoms and improving quality of life without causing adverse effects. There is no one medication that is recommended for treatment initiation. Factors that influence this decision include symptom severity; whether the symptoms affect the dominant hand; embarrassment; ability to continue working or participating in activities such as hobbies; cost; and patient preference. If symptoms are very mild, the patient may choose not to begin therapy. Some patients are resistant to starting dopaminergic medications out of concern about adverse effects or fear of limited duration of benefit. There is no evidence to suggest that any of the medications, in particular levodopa, are toxic. In fact, a good argument can be made that treatment should be begun earlier rather than later for dopaminergic neuronal "sparing."

Levodopa remains the most effective medication for the treatment of motor symptoms. It is always given in combination with carbidopa (Sinemet) or benserazide (Prolopa) to prevent decarboxylation in the periphery. As it is associated with a higher risk for the development of motor complications (fluctuations and dyskinesia), keeping the dose as low as possible to provide symptomatic benefit is generally recommended. A controlled-release (CR) formulation of levodopa-carbidopa is available in Canada, but there is no evidence that it is superior to the regular formulation of levodopa-carbidopa in preventing motor fluctuations. The combination of levodopa-carbidopa with entacapone (Stalevo) also does not delay the development of motor fluctuations.

C30 Before starting treatment for people with Parkinson disease, the following should be discussed (grade: GPP; source: NICE[103]):

- The person's individual clinical circumstances; e.g., their symptoms, comorbidities and risks from polypharmacy
- The person's individual lifestyle circumstances, preferences, needs and goals
- The potential benefits and harms of the different drug classes.

C31 Levodopa may be used as a symptomatic treatment for people with early Parkinson disease (grade: A; source: NICE[102]).

C32 The dose of levodopa should be kept as low as possible to maintain good function in order to reduce the development of motor complications (grade: A; source: NICE[102]).

C33 Controlled-release formulations of levodopa or adding entacapone are not effective for delaying motor complications (grade: A; EFNS[11]).

Dopamine agonists stimulate dopamine receptors directly. Unlike levodopa, they do not need to be converted in the brain to be active. Dopamine agonists are the second most potent class of medication (after levodopa) for control of motor symptoms in Parkinson disease with good evidence that they can be used in early Parkinson disease with success. Dopamine agonists should be slowly titrated to a clinically effective dose. Adverse effects during upward titration may include nausea, lightheadedness, sleepiness and, in some cases, hallucinations. Compared with levodopa, dopamine agonists are less likely to cause fluctuations in early disease but are less effective in controlling motor symptoms. Dopamine agonists are also associated with a higher prevalence of adverse effects (hallucinations, leg edema, excessive daytime somnolence, impulse control disorders) and are more expensive than levodopa. In patients older than 70 years, dopamine agonists should be used with caution, if not avoided. Ergot-derived dopamine agonists should not be used as first-line treatment in Parkinson disease. If using an ergot-derived agonist (bromocriptine is the only one currently available in Canada), baseline erythrocyte sedimentation rate (ESR), renal function, cardiac echocardiogram and chest x-ray are recommended before starting treatment and annually as long as the patient remains on the medication because of the risk of pleuropulmonary and cardiac valve fibrosis. As nonergot-derived agonists (pramipexole, ropinirole, rotigotine) do not carry this risk, or require this monitoring, they are preferred to an ergot-derived agonist. Rotigotine transdermal patch has adverse effects similar to the other dopamine agonists and may be appropriate when an oral medication is not preferred. Application-site reactions are a unique feature of this and the patch should be changed every 24 hours but not placed in the same area of skin for 14 days. There is no good evidence that one dopamine agonist is superior to another regarding control of motor symptoms in Parkinson disease. Thus, if one results in adverse effects, another could be substituted. Overall the adverse effect profiles are similar.

C34 Dopamine agonists may be used as a symptomatic treatment for people with early Parkinson disease (grade: A; source: NICE[102]).

C35 A dopamine agonist should be titrated to a clinically efficacious dose. If adverse effects prevent this, another agonist or a drug from another class should be used in its place (grade: D, GPP; source: NICE[102]).

C36 Ergot-derived dopamine agonists (e.g., bromocriptine) should not be used as first-line treatment for Parkinson disease (grade: B; source: SIGN[17]).

C37 When an ergot-derived dopamine agonist is used, patients should undergo (grade: GPP; source: SIGN[17]):

- Baseline echocardiographic screening and regular follow-up echocardiographic testing to identify cardiac abnormalities

- Baseline laboratory (ESR, serum creatinine) and radiologic (e.g., chest x-ray) investigations with regular follow-up surveillance to identify serosal fibrosis.

Monoamine oxidase B inhibitors prevent the breakdown of dopamine in the brain. Two medications in this class are available in Canada: selegiline and rasagiline. Each has been shown to have mild but definite symptomatic benefit as monotherapy in early Parkinson disease.

C38 Monoamine oxidase B inhibitors may be used as a symptomatic treatment for people with early Parkinson disease (grade: A; source: NICE[102]).

Amantadine is a medication with probably multiple, but poorly understood mechanisms of action. It may be used as monotherapy, but adverse effects such as livedo reticularis and leg edema must be monitored. There is also a need to use this medication with caution in patients with renal dysfunction.

C39 There is insufficient evidence to support the use of amantadine in the treatment of patients with early Parkinson disease (grade: A; source: SIGN[17]).

Anticholinergics, such as trihexyphenidyl and benztropine, may be considered in young patients with early Parkinson disease and prominent tremor. However, use in Canada is currently limited owing to substantial adverse effects. They are not recommended in older people, as they tend to cause confusion and memory difficulties.

C40 Anticholinergic drugs should not be used as first-line treatment in patients with Parkinson disease (grade: B; source: SIGN[17]).

Although the classic tremor seen in Parkinson disease is a resting tremor, some patients have an associated postural tremor. Beta blockers may be considered in this situation.

C41 Beta-adrenergic antagonists may be used in the symptomatic treatment of selected people with postural tremor in Parkinson disease, but should not be drugs of first choice (grade: D, GPP; source: NICE[102]).

Table 4. Medications for treatment of *de novo* patients (rating of evidence)

Class	Examples
MAO-B inhibitors	Rasagiline (grade: A) Selegiline (grade: A)
Dopamine agonists	Pramipexole (grade: A) Ropinirole (grade: A) Rotigotine transdermal patch (grade: A) Bromocriptine
Levodopa	Levodopa-carbidopa immediate-release (grade: A) Levodopa-benserazide immediate-release (grade: A)
Amantadine	(grade: D)
Anticholinergics (should not be used as first-line treatment)	Benztropine (grade: B) Trihexyphenidyl (grade: B)

Note: MAO-B = monoamine oxidase B.

Table 5. Potential benefit and harms of initial Parkinson disease medication options

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor symptom improvement	+++	++	+
Motor complications	+++	++	+
Specific adverse events*	++	+++	+

Note: MAO-B = monoamine oxidase B.
*Impulse control disorders, excessive sleepiness, and hallucinations.

PHARMACOLOGIC THERAPY FOR MOTOR SYMPTOMS IN LATER PARKINSON DISEASE

(T. Mestre, S. Cresswell & A. Lafontaine)

Levodopa is the gold-standard pharmacologic treatment, and eventually all patients with Parkinson disease will need treatment with levodopa. In advancing Parkinson disease, the response to levodopa changes, from being substantial and sustained in earlier stages to progressively becoming shorter or erratic or both. Most commonly, patients will experience "end-of-dose deterioration" or predictable "wearing-off": in its mildest form, predictable "wearing-off" is experienced early in the morning ("morning akinesia") or when patients delay intake of levodopa during the day. Progressively, on-phases with good response to levodopa become shorter, not lasting until the next dose of levodopa is due. Other forms of motor

fluctuations include unpredictable offs, delayed-on responses, dose failure, and on- and off-period freezing. In addition, patients can start to have involuntary movements that are broadly referred as "dyskinesia." The most common form of dyskinesia occurs during on-phases at peak plasma level of levodopa, in the form of chorea and dystonia (peak-dose dyskinesia). With advancing disease, dyskinesia can become more severe and disabling, and the therapeutic window of levodopa during which patients are relieved from their parkinsonian symptoms and do not have dyskinesia becomes narrower. In this situation, small increases in levodopa dose to improve parkinsonian symptoms will likely result in dyskinesia. Less common forms of dyskinesia occur when dopamine levels are low, either in the transition between on and off times (biphasic; also called diphasic dyskinesia) or during off-time (off-period dystonia). Overall, motor complications have a substantial impact on the quality of life of patients.

C42 The choice of an adjunct to levodopa for people with Parkinson disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy should take into account (grade: GPP; source: NICE[103]):

- The person's individual clinical circumstances; e.g., their Parkinson disease symptoms, comorbidities and risks from polypharmacy
- The person's individual lifestyle circumstances, preferences, needs and goals
- The potential benefits and harms of the different drug classes

For predictable "wearing-off," an initial approach could be changing the frequency or dose or both of levodopa, which can lead to a more demanding regimen for patients and dyskinesia. Another strategy is to consider adding other antiparkinsonian treatments such as a catechol-*O*-methyltransferase (COMT) inhibitor, a MAO-B inhibitor or a dopamine agonist. As a rule of thumb, all antiparkinsonian treatments can lead to dyskinesia, but levodopa will more likely result in dyskinesia.

Both entacapone, a COMT inhibitor, and rasagiline, a MAO-B inhibitor, have shown in clinical trials to reduce off-time by a similar magnitude of 1 to 1.5 hours per day. Entacapone is taken with each dose of levodopa and is generally well tolerated, although it can lead to diarrhea. Patients should be informed about a harmless orange discoloration of their urine. Tolcapone is more effective than entacapone but has limited availability because of its associated hepatotoxicity. Opicapone is a newer COMT inhibitor that is currently available in European countries but not in Canada. It has similar efficacy to entacapone, but the advantage of a single daily dose. Rasagiline is taken once daily and is generally well tolerated. Although the older selegiline is pharmacologically similar to rasagiline, there are insufficient data from adequately controlled, randomized trials to recommend it for levodopa-related motor fluctuations.

C43 Catechol-*O*-methyl transferase inhibitors (entacapone) and MOA-B inhibitors (rasagiline) may be considered for the reduction in off-time in patients with advanced Parkinson disease who have motor fluctuations (grade: A; source: SIGN[17]).

Dopamine agonists have been shown in clinical trials to be helpful for "wearing-off." Pramipexole, ropinirole and rotigotine are available in Canada and can reduce off-time by about 1.5 to 2 hours per day. The transdermally administered rotigotine has the comfort of a single daily administration. Dopamine agonists may allow for a reduction in the dose of levodopa, which can lead to a reduction in dyskinesia. Switching from one agonist to another can occasionally be helpful if adverse effects are an issue.

It is important to note that the more common or distinct adverse effects of dopamine agonists include drowsiness, sudden onset of sleep, ankle edema and impulse control disorders. It is recommended to carefully screen patients for pre-existing drowsiness and tendencies toward compulsive disorders, such as gambling, before prescribing dopamine agonists. Discussing potential adverse effects with the patient and, ideally, a family member or care partner and monitoring for such potential problems throughout the course of treatment is crucial. Impulse control disorders are estimated to occur in about 20% patients treated with dopamine agonists. The adverse effect profile of rotigotine is similar to other dopamine agonists but has the potential of skin reactions associated with transdermal administration, requiring a rotation of the place of administration daily in cycles of 14 days.

Ergot-derived dopamine agonists such as bromocriptine have mostly fallen out of use owing to the risk of ergot toxicity, including erythromelalgia and fibrosis of serosal membranes.

C44 Dopamine agonists (oral [pramipexole, ropinirole] or transdermal [rotigotine]) may be considered for the management of motor complications in patients with advanced Parkinson disease (grade: A; source: SIGN[17]).

Studies comparing immediate- and modified-release preparations of levodopa (levodopa CR) show benefit in the management of "wearing-off," but have methodological shortcomings. In Parkinson disease with motor complications, levodopa CR may be erratically absorbed, resulting in delayed-on or no-on responses. Levodopa CR is most frequently used to address overnight wearing-off. It is important to remember that the overall amount of levodopa absorbed from levodopa CR is roughly 25% to 30% less than with immediate-release levodopa. The adverse effect profile is similar in both formulations.

A new formulation of levodopa-carbidopa with a combined immediate- and extended-release formulation of levodopa-carbidopa, IPX066, has shown to be a useful treatment for patients with Parkinson disease who have motor fluctuations, with potential benefits including decreased off-time of about 1 hour, and reduced levodopa dosing frequency.[39] The adverse effect profile is similar. IPX066 is currently not available in Canada.

C45 Levodopa CR may improve wearing-off (grade: C) and night-time akinesia (grade: GPP) (source: EFNS[11]).

For patients with Parkinson disease with motor complications that are still disabling after appropriate trials of the pharmacologic options above, a couple of device-assisted pharmacologic options exist. Apomorphine is a nonergot dopamine agonist that can be administered in the form of subcutaneous infusion or intermittent injection (penject). Health Canada has recently approved the latter for the acute, intermittent treatment of "off" episodes; namely, predictable "wearing-off" and unpredictable on-off fluctuations. Apomorphine for subcutaneous infusion is not available in Canada. Because of a high incidence of nausea and vomiting, it is recommended that anti-emetic treatment is started with or before starting an apomorphine subcutaneous injection. Local skin reaction and priapism are also adverse effects that should be considered. The adverse effect profile of apomorphine is overall similar to other dopamine agonists described above.

C46 Subcutaneous apomorphine infusions or intermittent injections may be considered for the management of severe motor complications, but should be provided only in units that have sufficient experience and resources (grade: C; source: SIGN[17]).

The intrajejunal levodopa-carbidopa gel infusion through a percutaneous enteral (PEG-J) tube is available in Canada and is accessible under limited use in tertiary movement disorders centres. The intrajejunal levodopa-carbidopa gel infusion has been shown to reduce off-time and increase on-time without troublesome dyskinesia by about 2 hours, when compared with standard oral levodopa. The adverse effect profile is related to, in most patients, complications from the device, requiring close collaboration between neurology and gastroenterology teams in specialized centres.

C47 Intrajejunal levodopa-carbidopa enteric gel administered through percutaneous gastrostomy may be considered for the reduction of off-time or to reduce dyskinesia (grade: C; source: EFNS[11]).

Regarding the treatment of dyskinesia, only amantadine has been shown in clinical studies to improve dyskinesia without worsening parkinsonism. It is important to be aware of the cognitive adverse effects (confusion, hallucinations) that may arise; these, as well as edema, may necessitate discontinuation of the drug. It can interfere with sleep and administration should thus be avoided later in the day. It is also associated with *livedo reticularis*, which is usually a nonlimiting adverse effect.

C48 Amantadine is recommended for the treatment of dyskinesia in Parkinson disease (200–400 mg/day) (grade: A; source: EFNS[11]).

SURGERY

(S. Kalia & K. Schoffer)

The surgical treatment for Parkinson disease is currently considered in patients when the optimized medical treatment has failed in treating motor symptoms (such as motor fluctuations and/or dyskinesia). Surgical lesions of the basal ganglia such as thalamotomy for treating tremor and pallidotomy for levodopa-induced dyskinesias were initially employed. However, lesions have been associated with a risk of permanent adverse effects and may not be durable in terms of benefit as the disease progresses. Although pallidotomy and thalamotomy might still be performed in select patients, deep brain stimulation is currently the surgical treatment of choice in appropriately selected Parkinson disease patients. Compared with ablative surgery, deep brain stimulation can be adjusted over time to address disease progression, has potentially reversible adverse effects, and may be used bilaterally to improve symptoms in Parkinson disease.

The most-used current targets for Parkinson disease are the subthalamic nucleus and the globus pallidus interna. Targeting the thalamus (ventral intermediate [VIM] nucleus) may be considered in patients with tremor dominant Parkinson disease where tremor has the greatest impact on the patient's quality of life, and is difficult to control with medication. Pedunculopontine nucleus stimulation could be considered as an investigational therapy for gait freezing and falls. Many studies have reported the effectiveness of subthalamic nucleus stimulation in improving levodopa-responsive signs and symptoms in the short term and also in the long term.[11] The overall improvement of activities of daily living and motor Unified Parkinson's Disease Rating Scale scores in the off medication/on stimulation condition has been reported to be 50%, on average, when compared with the off medications condition before surgery.[61] Levodopa-induced dyskinesia has also been reduced by almost 70%, on average, after surgery. Deep brain stimulation has shown superiority to medical management for quality of life in well-selected patients with early motor complications, who are operated upon.[62]

Adverse events arising from the surgical procedure include infections (6%), migration or misplacement of the leads (5%), lead fractures (5%), intracranial hemorrhage (3%) and skin erosion (1%).[61] The most reported complications possibly related to the stimulation (especially subthalamic nucleus deep brain stimulation) and persistent in long-term follow-up include eyelid opening apraxia (2% to 30%), dysarthria or hypophonia

(4% to 17%), gait disturbances (14%), postural instability (13%), weight gain (8%) and decline in verbal fluency.[63] Several factors contribute to the outcome of deep brain stimulation, such as indications and patient selection, accuracy in surgical targeting, stimulation programming and medication management. Involvement of an experienced interdisciplinary deep brain stimulation team is typically the best way to achieve this.

In 2006, the AAN Subcommittee found insufficient or weak evidence to support or refute the efficacy of globus pallidus interna or subthalamic nucleus deep brain stimulation in improving off periods, dyskinesia or motor function.[64] However, large, randomized multicentre studies comparing bilateral subthalamic nucleus surgery to the best medical treatment have now been published. These studies have shown that there was a significant improvement of motor function, dyskinesia and quality of life in the deep brain stimulation groups rather than in the medical groups, although the total number of adverse events was higher in the nonsurgical groups. These results add more evidence that not only subthalamic nucleus stimulation is superior to medical treatment in improving motor signs, but that deep brain stimulation is also more effective in improving quality of life measures.

The issue as to whether subthalamic nucleus stimulation is a better target than globus pallidus interna stimulation in certain patients with Parkinson disease is still a matter of discussion. In studies with short-term follow-up, patients who undergo globus pallidus interna deep brain stimulation have been reported to have fewer complications and similar or slightly less motor benefit. Results in the long term have been more variable, and with a possible progressive loss of clinical benefit between the 3- and the 5-year follow-up. More long-term studies are needed to clarify whether globus pallidus interna can be an equal or a better target in selected patients with Parkinson disease. Therefore, it is important to have an experienced team assess the target on a case-by-case basis.

C49 Deep brain stimulation of the subthalamic nucleus or the globus pallidus interna is effective against motor fluctuations and dyskinesia (grade: A; source: EFNS[11]).

C50 With the current evidence, it is not possible to decide if the subthalamic nucleus or globus pallidus interna is the preferred target for deep brain stimulation for people with Parkinson disease, or whether 1 form of surgery is more effective or safer than the other (grade: D; source: NICE[102]).

Ventral intermediate deep brain stimulation has been shown to be effective in the short as well as long term in patients with Parkinson disease with tremor. As expected, in these patients, axial signs worsened over the years and there was progressive loss of benefit in activities of daily living, but this is likely more related to the progression of Parkinson disease. However, the procedure may be better tolerated and a suitable choice for select patients.

C51 Thalamic deep brain stimulation may be considered as an option in people with Parkinson disease who predominantly have severe disabling tremor (grade: D; source: NICE[102]).

If deep brain stimulation is not appropriate for a patient, a multidisciplinary team may consider the option of unilateral lesions with the specific goal of reducing contralateral dyskinesias in the case of pallidotomy, and contralateral tremor in the case of thalamotomy. Bilateral lesions are considered high risk for increased complications.

C52 Unilateral pallidotomy is efficacious at reducing contralateral dyskinesia (grade: A; source: EFNS[11]).

C53 Unilateral thalamotomy improves contralateral tremor and rigidity but has no consistent effect on akinesia (grade: D; source: EFNS[11]).

There are still no clear predictive factors of surgical benefit, except for preoperative levodopa response. A significant decline of the postoperative levodopa response over the years has been reported, but this has been related to the progression of Parkinson disease.

C54 Preoperative response to levodopa should be considered as a factor predictive of outcome after deep brain stimulation of the subthalamic nucleus (grade: B; source: AAN[64]).

Other unresolved issues concern the patient's age and the duration of Parkinson disease at time of surgery. There is some evidence that patients with Parkinson disease who are older than 70 years may be at higher risk of postoperative cognitive decline, and less motor improvement compared with younger patients. Nevertheless, other studies do not report postoperative differences between younger and older patients who undergo subthalamic nucleus deep brain stimulation, and thus age alone should not serve as a selection criterion, but rather each patient assessed for potential of risk and benefit by a multidisciplinary team.

C55 Age and duration of Parkinson disease may be considered as factors predictive of outcome after deep brain stimulation of the subthalamic nucleus. Younger patients with shorter disease durations may possibly have improvement greater than that of older patients with longer disease durations (grade: C; source: AAN[64]).

REHABILITATION

(J. Miyasaki)

Previously, motor function received the primary attention of patients and physicians alike. This naturally led to concentration on pharmacologic therapies for Parkinson disease. More recently, nonmotor symptoms have become recognized as a major source of disability in Parkinson disease, and treatment focus has shifted to quality of life and maintaining it in advanced disease.

Thus, the focus on nonpharmacologic methods of treatment is emerging. Provision of education and valid information is essential to empower both patients and families in actively participating in disease management. Information sources include their physicians and nurse specialists with expertise in Parkinson disease.

Although previously relegated to later stages of illness, rehabilitative therapies have much to offer patients who have recently received a diagnosis of Parkinson disease. Evidence exists to support early institution of exercise at the time of diagnosis. Participation in rehabilitative therapies can empower patients and provide hopefulness in addition to the benefits of professional directions for physical therapy efforts. Rehabilitative specialists who can provide specific therapies to people with Parkinson disease include physiotherapists, occupational therapists, speech language pathologists or therapists, and nutritionists.

Physical and exercise therapies may include multidisciplinary rehabilitation, active music therapy, treadmill training, balance training and "cued" exercise training. These all result in benefits, but continued therapy is required to sustain them. This is particularly important in Parkinson disease, as lack of motivation is a barrier to patient adherence in the absence of scheduled lessons or training. When enrolled in formal programs, patients showed improvement in activities of daily living and motor scores, reduced bradykinesia, improved ambulation speed and decreased falls. Given the large health care burden represented by falls, and that those with Parkinson disease have an increased risk of falls, use of exercise therapy in its various forms improves patients' safety, functional ability and, therefore, would presumably reduce overall health care expenditure.

Physical and exercise therapies should focus on gait re-education, improvement of balance and flexibility, enhancement of aerobic capacity, improvement of movement initiation, improvement of functional independence — including mobility and activities of daily living — and provision of advice regarding safety in the home environment.

C56 Consideration should be given to referring people who are in the early stages of Parkinson disease to a physiotherapist with experience of the disease for assessment, education and advice, including information about physical activity (grade: B; source: NICE[103]).

C57 Physiotherapy specific to Parkinson disease should be offered to people who are experiencing balance or motor function problems (grade: A; source: NICE[103]).

Occupational therapy provides assessment of functional capacity and determines the best aids or strategies to improve functional capacity and, therefore, independence. Home safety is not easily assessed at an office visit. Occupational therapists can focus on maintenance of work and family roles, home care and leisure activities, improvement and maintenance of transfers and mobility, improvement of personal self-care activities (such as eating, drinking, washing and dressing), environmental issues to improve safety and motor function, and cognitive assessment and appropriate intervention, including approaches to apathy. Government agencies can provide assessments, and aids are partially reimbursed through government assistive aid programs.

C58 Consideration should be given to referring people who are in the early stages of Parkinson disease to an occupational therapist with experience of Parkinson disease for assessment, education and advice on motor and nonmotor symptoms (grade: B; source: NICE[103]).

C59 Occupational therapy specific to Parkinson should be offered to people who are having difficulties with activities of daily living (grade: A; source: NICE[103]).

Speech and language therapy is essential to the quality of life of patients with Parkinson disease. Hypophonia is a common problem, resulting in social withdrawal and the misperception of cognitive decline for patients. Speech language therapy can improve vocal pitch and range, leading to improved communication for patients. In advanced stages, assessment of swallowing safety is crucial. Speech language therapists, in conjunction with clinical nutritionists, make important contributions to the patient care team. Their involvement can result in identifying causes for weight loss, reduce the risk of aspiration and maintain weight.

C60 Speech and language therapy should be offered to people with Parkinson disease who are experiencing problems with communication, swallowing or saliva. Therapy should include (grade: A; source: NICE[103]):

- Strategies to improve the safety and efficiency of swallowing to minimize the risk of aspiration, such as expiratory muscle strength training
- Strategies to improve speech and communication, such as attention to effort therapies.

C61 Consideration should be given to referring people for alternative and augmentative communication equip-

ment that meets their communication needs as Parkinson disease progresses and their needs change (grade: GPP; source: NICE[103]).

C62 Discussion should take place about a diet in which most of the protein is eaten in the final main meal of the day (a protein redistribution diet) for people with Parkinson disease on levodopa who experience motor fluctuations (grade: GPP; source: NICE[103]).

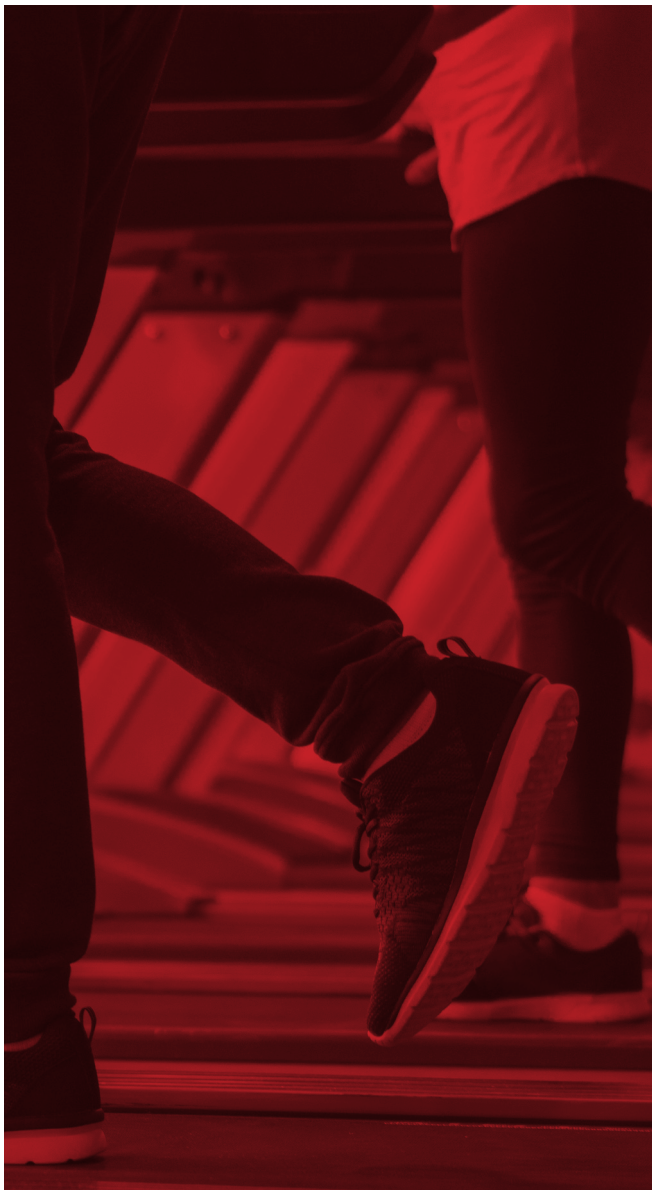
Although many patients seek alternative therapies such as acupuncture, there is insufficient evidence to recommend these modalities. As patients' receptiveness and curiosity about alternative methods of treatment increase, the medical profession will need to respond with valid scientific data to provide guidance to patients. The placebo effect is well recognized, particularly in Parkinson disease, and may in fact be mediated by dopamine. Therefore, any treatment involving Parkinson disease must be subjected to rigorous scientific methods to establish efficacy and ensure that patients are receiving the best value for their time, effort and health care expenditure.

C63 People with Parkinson disease should be advised to avoid a reduction in their total daily consumption of protein (grade: GPP; source: NICE[103]).

C64 Consideration should be given to referring people with Parkinson disease to a dietitian for specialist advice (grade: GPP; source: NICE[103]).

C65 People with Parkinson disease should be advised to take a vitamin D supplement (grade: B, GPP; source: NICE[103]).

C66 People with Parkinson disease should be advised not to take over-the-counter dietary supplements without first consulting their pharmacist or other health care professional (grade: GPP; source: NICE[103]).



SECTION 4: NONMOTOR FEATURES OF PARKINSON DISEASE

AUTONOMIC DYSFUNCTION

(S. Udow & S. Fox)

Autonomic dysfunction is a common complication of Parkinson disease and can include cardiovascular, gastrointestinal, urogenital and thermoregulatory problems. Although these symptoms are common, the quality of evidence to guide management is poor. Moreover, symptoms such as orthostatic hypotension, urinary urgency and constipation have a significant negative impact on the quality of life of patients with Parkinson disease. Thermodysregulation can result in feeling hot or cold, another common symptom in Parkinson disease. Hyperhidrosis (excessive sweating) may accompany these symptoms, and drenching sweats may occur at night. Medical conditions such as systemic illness (e.g., hyperthyroidism) need to be excluded. If hyperhidrosis is associated with motor off-time or with peak-dose dyskinesias, it can be managed with adjustment of Parkinson disease medications. Oral medications such as low doses of clonidine, tricyclic acids with anticholinergic side effects and beta blockers have been tried, but lack good evidence for their effectiveness and warrant caution with respect to adverse effects.

Sialorrhea can be cosmetically disturbing and can contribute to functional disability. A complete dysphagia assessment via video fluoroscopy and referral to speech language pathology should be considered in patients with prominent drooling because there is a clinicopathological association between drooling and oropharyngeal dysphagia. Adequate oral hygiene practices are also encouraged.

Atropine drops, ipratropium bromide spray and gum chewing are commonly suggested as a means of improving sialorrhea but adequate studies on their longer-term benefits are lacking. Glycopyrrolate has been suggested as being efficacious for the short-term treatment of sialorrhea in Parkinson disease, but there is insufficient evidence to make conclusions regarding the safety of this medication.

Botulinum toxin A injections into the salivary glands are efficacious to treat sialorrhea. This would be considered an off-label use, however, because botulinum toxin A is not covered by most provincial formularies for the treatment of sialorrhea.

C67 Botulinum toxin A is efficacious for the symptomatic control of sialorrhea in Parkinson disease (grade: A; source: MDS[26]).

Urinary urgency, frequency and nocturia are common symptoms of urinary dysfunction in Parkinson disease, but can also be caused by other conditions like urinary tract infection or prostatic hypertrophy in men. Urological assessment is indicated if an underlying cause beyond Parkinson disease is suspected. Simple nonpharmacologic measures can be applied to manage some of these symptoms. Regular visits to the bathroom at intervals can help prevent urgency. Restriction of the consumption of water or caffeinated drinks after dinner can help prevent nocturia.

Strategies to avoid incontinence include easing access to the bathroom. This can be achieved through the use of assistive devices, clearing the path of obstacles and optimizing motor symptoms overnight. A bedside urinal may be required. Use of a condom catheter may be needed in some cases, and community care services can educate patients and caregivers on the use of these devices.

Anticholinergic and antispasmodic drugs are recommended if these above-mentioned measures do not suffice to reduce urinary frequency and urgency. Both peripheral and central anticholinergic adverse effects should be considered, as these medications may cause urinary retention, dry mouth, confusion or hallucinations. Newer anticholinergic and antispasmodic medications with fewer central nervous system adverse effects may be preferred.

C68 General measures for treating urinary urgency and incontinence include before bedtime, avoiding coffee and limiting water ingestion. When symptoms appear suddenly, exclude urinary tract infection (grade: GPP; source: EFNS[11]):

- Nocturia: reduce intake of fluid after 6 pm. Sleep with head-up tilt of bed to reduce urine production
- Night-time dopaminergic therapy should be optimized
- For urinary urgency (overactive bladder), anticholinergic or antispasmodic drugs may be useful, but care must be taken with central adverse effects
- Botulinum toxin type A injected in the detrusor muscle

Symptoms of orthostatic hypotension are likely under-reported, unrecognized or absent in patients with Parkinson disease. Physicians are therefore encouraged to ask about symptoms and measure orthostatic vitals. Patients can also monitor their orthostatic vitals with a home blood-pressure cuff and should be instructed to measure supine blood pressure after lying down for 5 minutes and upright blood pressures after standing for 3 minutes.

Both inherent Parkinson disease dysautonomia and the use of dopaminergic treatments can contribute to orthostatic hypotension, but other causes should be considered. These include poor intake of fluids and adverse effects of medications such as antihypertensives, diuretics, antidepressants and alpha-blockers used to treat urinary hesitancy. In addition, comorbid conditions such as cardiac dysfunction and diabetic neuropathy can be contributory.

The consequences of orthostatic hypotension can contribute to morbidity in Parkinson disease. Syncope, for example, can be troubling in itself but can also cause injury related to falling, such as traumatic bony fractures or head injuries. Orthostatic hypotension may also contribute to cognitive impairment and nonmotor fluctuations by transiently and chronically reducing cerebral blood flow.[65] Alternatively, the

development of orthostatic hypotension may indicate a more severe disease state.

Nonpharmacologic management of orthostatic hypotension includes addressing and avoiding aggravating factors. These aggravating factors include large meals (as hypotension may occur postprandially in many patients), alcohol consumption, exposure to a warm environment, dehydration and general medications that can cause hypotension. Awareness that dopaminergic treatments can worsen orthostatic hypotension is important, and medication doses may need to be adjusted. Patients should be advised to elevate the legs while sitting, and to rise slowly — particularly early in the morning, after sitting or lying for a prolonged period, or after a meal. In the absence of any cardiovascular contraindication, salt intake can be increased by adding salt to meals or consuming salt tablets or soup bouillon several times a day. Tilting the bed so that the head is higher than the feet may activate the renin–angiotensin–aldosterone system and thus raise blood pressure. Pressurized elastic stockings are often suggested, with pressures of 30–40 mm of mercury, but these can be difficult to pull on and off.

Domperidone given either before a meal or 30 minutes before each dose of dopaminergic medication may prevent peripheral vasodilation, but good evidence of efficacy is lacking. Domperidone does not cause supine hypertension and does not cross the blood–brain barrier. Mineralocorticoids such as fludrocortisone can be prescribed,[66] with a morning dose that may avoid supine hypertension at night. This may cause pedal edema, and may be problematic in patients who are immobile. Alpha-receptor agonists such as midodrine can be a good choice but may cause supine hypertension.

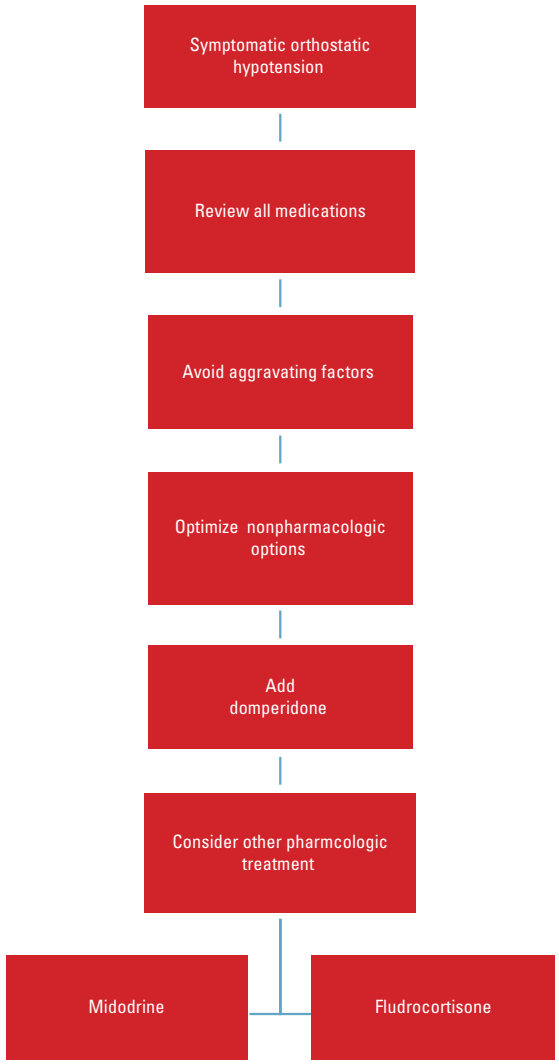
C69 For orthostatic hypotension general measures would include the following (grade: GPP; source: EFNS[11]):

- Avoid aggravating factors such as large meals, alcohol, exposure to a warm environment and drugs known to cause orthostatic hypotension, such as diuretics or antihypertensive drugs. Levodopa and dopamine agonists may also worsen orthostatic hypotension.
- Increase salt intake in symptomatic orthostatic hypotension.
- Ensure head-up tilt of the bed at night.
- Wear elastic stockings.
- Highlight postprandial effects. In some patients, hypotension occurs only postprandially. Warning the patient about this effect and taking frequent small meals may be helpful.

C70 For orthostatic hypotension, drug therapy includes the addition of:

- Midodrine (grade: A; source: EFNS[11])
- Fludrocortisone (grade: GPP; source: EFNS[11])
- Domperidone (grade: GPP; source: CAN)

Figure 3. Treatment of orthostatic hypotension



Constipation can pre-date the onset of Parkinson disease symptoms by decades. Both lower gastrointestinal (GI) dysfunction and slowing of transit time through the GI tract contribute to constipation in Parkinson disease, and evacuating hard stool can compound this issue. Constipation can also contribute to morbidity in Parkinson disease, as it may interfere with intestinal absorption of levodopa-carbidopa and other antiparkinsonian treatments. Weight loss related to malabsorption and early satiety can also be partially a result of constipation.

Nonpharmacologic measures can improve stool quality and frequency of bowel movements. These include consumption of fruits and vegetables with high-fibre content, in addition to increased consumption of water. Care must be taken not to aggravate urinary symptoms with increased water drinking. In addition, anticholinergic medications may slow GI motility, so discontinuation of these agents should be considered. Physical activity can also promote GI motility.

Many laxatives are available, and act differently to improve constipation. Bulk-forming laxatives such as Metamucil and

psyllium draw water into the stool to create large, soft stools, and larger stools help trigger evacuation of bowels. Lubricant laxatives coat the stool surface, allowing the stools to hold water and pass more easily. Suppositories lubricate the anus for easy passage of stools. Stool softeners such as docusate help mix fluid into stools to soften them. Osmotic laxatives such as lactulose or polyethylene glycol soften the stool by drawing fluid into the bowel from nearby tissue. Stimulant or irritant laxatives such as bisacodyl should not be used for a more than a few days, as they may cause the bowel to lose tone. Finally, domperidone can improve GI motility.

C71 For gastrointestinal motility problems in Parkinson disease, general measures for treating constipation should be applied (source: EFNS[11]):

- Increased intake of fluid and fibre is recommended (grade: GPP)
- Increased physical activity can be beneficial (grade: GPP)
- Polyethylene glycol solution (macrogol) is recommended (grade: A)
- Fibre supplements such as psyllium (grade: B) or methylcellulose and osmotic laxatives (e.g., lactulose) are recommended (grade: GPP)
- Short-term irritant laxatives are recommended for selected patients (grade: GPP)
- The use of drugs with anticholinergics activity should be reduced or discontinued (grade: GPP)
- Domperidone should be added (grade: B)

Erectile dysfunction is common in men with Parkinson disease with dysautonomia, mood dysfunction, motor disability and medication adverse effects possible contributing factors.

C72 For individuals with Parkinson disease with erectile dysfunction (source: EFNS[16]):

- Drugs associated with erectile dysfunction (e.g., alpha blockers) or anorgasmia (e.g., selective serotonin reuptake inhibitors [SSRIs]) should be discontinued. Dopaminergic therapy can have both negative and positive effects on this symptom (grade: GPP)
- Sildenafil 50–100 mg, 1 h before sex, can be tried in patients with Parkinson disease with these problems (grade: B)
- Other drugs of this class, such as tadalafil (10 mg, 30 min–12 h before sex) or vardenafil (10 mg, 1 h before sex) can be alternative choices (grade: GPP)
- In some patients, apomorphine injections (5–10 min before sex) can also be an alternative treatment (grade: GPP)
- Intracavernous injections of papaverine or alprostadil can be considered in selected patients (grade: GPP)

COGNITIVE IMPAIRMENT

(M. Zurowski)

Dementia in Parkinson disease is common, especially in those with an older age of onset, and its frequency increases with disease duration. As patients with Parkinson disease live longer, this problem will become increasingly difficult to manage.

As with psychosis, after ruling out other potential medical disorders that contribute to dementia (thyroid dysfunction, B12 deficiency, etc.), it is generally recommended that medications be simplified to minimize potential untoward central nervous system effects that accentuate the cognitive dysfunction. There is evidence in favour of discontinuing anticholinergics, amantadine, tricyclics, tolterodine, oxybutynin and benzodiazepines.

There are several treatment options for symptoms of Parkinson disease dementia with modest potential benefit. There has been enough research on the use of cholinesterase inhibitors donepezil and rivastigmine to suggest they should be considered for use. There is less evidence to support the use of memantine or galantamine in Parkinson disease dementia.

C73 The diagnoses of dementia associated with Parkinson disease and of mild cognitive impairment in Parkinson disease can be made using the MDS Clinical Diagnostic Criteria. These require reports of subjective cognitive decline and difficulties on psychometric testing (grade: GPP; source: CAN).

C74 For Parkinson disease dementia, cholinesterase inhibitors could be added (source: EFNS[11]): rivastigmine (grade: A), donepezil (grade: A), or galantamine (grade: C). There may be idiosyncrasy in clinical response and adverse effects, so it is worth trying an alternative agent (grade: GPP). Memantine can be added or substituted if cholinesterase inhibitors are not tolerated or lack efficacy (grade: C).

C75 No interventions have been proven to reduce the risk of progression of Parkinson disease from mild cognitive impairment to dementia but lifestyle modifications, such as engaging in cognitive and social activities and physical exercise, are encouraged (grade: GPP; source: CAN).

SLEEP DISORDERS

(R. Postuma)

A variety of sleep disorders affect patients with Parkinson disease. The major sleep disorders in Parkinson disease include insomnia, excessive daytime somnolence, REM sleep behaviour disorder, and restless legs syndrome.

Experienced by up to 60% of patients with Parkinson disease, insomnia is usually characterized by difficulty staying asleep (i.e., sleep maintenance insomnia), although sleep-onset insomnia may also occur. The etiology of insomnia is multifactorial and can include motor symptoms of Parkinson disease (e.g., pain, tremor), medication adverse effects, restless legs syndrome, depression and nocturia. This necessitates a thorough history, to detect reversible causes. Insomnia may also be a primary feature of the disorder, as sleep regulating centres degenerate in Parkinson disease.

C76 A full sleep history should be taken from people with Parkinson disease who report sleep disturbance (grade: D, GPP; NICE[102]).

Randomized controlled trial evidence for insomnia treatment in Parkinson disease is relatively limited. In general, nonpharmacologic treatment for insomnia consists of sleep hygiene measures and cognitive behavioural therapy. These have consistently been demonstrated as effective in primary (psychophysical insomnia), and also some forms of secondary insomnia (although they may be less effective than for primary insomnia).

C77 Good sleep hygiene should be advised in people with Parkinson disease with any sleep disturbance and includes (grade: D, GPP; source: NICE[102]):

- Avoidance of stimulants (e.g., coffee, tea, caffeine) in the evening
- Establishment of a regular pattern of sleep
- Comfortable bedding and temperature
- Provision of assistive devices, such as a bed lever or rails to aid with moving and turning, allowing the person to get more comfortable
- Restriction of napping in the late afternoon and early evening
- Advice about taking regular and appropriate exercise to induce better sleep
- Advice to avoid remaining in bed for long periods of time if unable to sleep
- A review of all medication and avoidance of any drugs that may affect sleep or alertness, or may interact with other medication (e.g., selegiline, antihistamines, H2 antagonists, antipsychotics and sedatives).

In terms of pharmacologic therapy, melatonin for insomnia in Parkinson disease has shown modest benefit (e.g., improvement of sleep time by 10 minutes in 1 study[11]) and there may be benefit to improving control of dopaminergic symptoms at night. One randomized trial of night-time levodopa therapy demonstrated benefit on self-reported sleep quality, whereas a second found mild improvement in self-reported sleep duration and nocturnal akinesia but no effect on overall sleep quality. Trials using dopamine agonists have also found possible benefit on subjective symptoms of night-time sleep, although results on objective measures show no benefit. Sedating antidepressants at low dose may be beneficial; there has been a large positive trial for doxepin 1–6 mg in sleep maintenance insomnia in older adults without Parkinson disease, and a positive trial for 50 mg trazodone in Alzheimer disease. In Parkinson disease itself, there has been only a small pilot RCT of doxepin 10 mg at bedtime, which showed improvement on subjective sleep measures (Scales for Outcomes in PD-Sleep Scale [SCOPA-Sleep] and Insomnia Severity Index) with no evidence of worsening of cognition (Montreal Cognitive Assessment scores improved relative to placebo).

C78 Optimization of night-time dopaminergic treatment (grade: B), melatonin (grade: B) and low doses of sedating antidepressants such as doxepin or trazodone (grade: GPP) may be beneficial for subjective symptoms of insomnia in Parkinson disease (source: EFNS[11]).

REM sleep behaviour disorder is characterized by the loss of normal muscle tone during REM sleep and is commonly experienced by patients with Parkinson disease. Patients act out their dream content and may punch, kick, talk, shout and fall out of bed. Injury is quite common. REM sleep behaviour disorder can pre-date the diagnosis of Parkinson disease and most patients with idiopathic REM sleep behaviour disorder in middle age will develop a neurodegenerative synucleinopathy.[67] The exact pathological mechanism is unclear but animal models implicate deficits in medullary and pontine nuclei controlling REM sleep. In systematic observational studies, both clonazepam (0.25–1 mg hs) and melatonin (3–12 mg hs) could suppress REM sleep behaviour disorder; clonazepam was more effective than melatonin, but had a higher adverse effect profile, particularly with sedation, balance impairment and cognitive changes. A single, small randomized crossover trial[103] demonstrated possible benefit of melatonin on REM sleep behaviour disorder symptoms and REM atonia, as measured by polysomnography. Other therapies have been assessed, with conflicting results from observational studies. In general, many cases of REM sleep behaviour disorder are mild and do not require pharmacologic treatment. However, in all cases, consideration should be given to safety; injury to patients or bed partners is the main adverse effect of the disorder.

C79 Care should be taken to identify REM sleep behaviour disorder in people with Parkinson disease. Melatonin or clonazepam may be useful, if pharmacologic treatment is required (grade: B, GPP; NICE[103]).

Restless legs syndrome is characterized by a sensation of urge to move the legs, which is worse at night, exacerbated by rest and relieved by activity. Restless legs syndrome in the general population is commonly treated with dopaminergic agents, opioids or γ-aminobutyric acid (GABA)-ergic agents, although no RCTs specific to Parkinson disease have been performed. It is unclear to what degree frequency of restless legs syndrome is increased in Parkinson disease, especially early in disease, as symptoms of the syndrome can overlap with other symptoms of parkinsonism. In patients with Parkinson disease who by definition require treatment for prolonged periods with dopaminergic agents, augmentation (increased severity of restless legs syndrome caused by dopaminergic treatment) can occur, and be difficult to manage. Symptoms similar to restless legs syndrome can also occur in off periods, and these symptoms may then respond to optimization of dopaminergic therapy. Restless legs syndrome can be exacerbated by iron deficiency, so clinicians should generally check ferritin levels in patients with the syndrome.

C80 Care should be taken to identify and manage restless legs syndrome in people with Parkinson disease and sleep disturbance (grade: GPP; source: NICE[103]). Patients with bothersome restless legs syndrome should be screened for iron deficiency. Potential treatments include optimization of dopaminergic therapy or GABA-ergic agents such as pregabalin (grade: GPP; source: CAN).

Excessive daytime sleepiness is also common in Parkinson disease. In mild cases, patients fall asleep when inactive, but when severe, patients fall asleep even in stimulating conditions such as eating, walking or working. Sudden sleep attacks while driving have been reported. The etiology of excessive daytime sleepiness is multifactorial. Insomnia and fragmented sleep due to restless legs syndrome can cause somnolence during the day, although on average, patients with excessive daytime sleepiness sleep more deeply than those without. Medications, particularly dopaminergic medications, commonly exacerbate somnolence. Sleep apnea can present with somnolence, although it is not clear that mild apnea is an important cause of somnolence in Parkinson disease. The primary reason for excessive daytime sleepiness, however, is probably degeneration of central sleep regulation centres in the brainstem — that is, excessive daytime sleepiness is a primary feature of Parkinson disease, which increases in prevalence as the disease progresses.

There have been 3 trials of modafinil, a psycho-stimulant with an unknown mechanism. Two clinical trials found an improvement in excessive daytime sleepiness in Parkinson disease; however, a third showed no effect. The amplitude of effect of modafinil is modest and is not covered by many provincial drug plans, which may limit its use. There are no clear data that caffeine has a lasting benefit for improving somnolence in Parkinson disease. Physicians are advised to be aware of their provincial legislation regarding driving in persons who are experiencing sleep attacks — in many provinces, inability to safely drive is legally reportable to licensing agencies.

C81 People with Parkinson disease who have daytime sleepiness or sudden onset of sleep should be advised not to drive, and to consider any occupational hazards. Their medicines should be adjusted to reduce its occurrence (grade: GPP; source: NICE[103]).

C82 Modafinil should be considered for the treatment of excessive daytime sleepiness in people with Parkinson disease, only if a detailed sleep history has excluded reversible pharmacologic and physical causes (grade: B, GPP; source: NICE[103]).

DEPRESSION

(M. Zurowsky)

Neuropsychiatric symptoms frequently manifest even before the onset of motor symptoms of Parkinson disease and become more prominent and increasingly challenging to treat with disease progression. They contribute to increasing disability and have a negative impact on quality of life. Given the myriad of neurotransmitter changes present in Parkinson disease, it should not be assumed that standard pharmacologic treatment for these symptoms in patients without Parkinson disease will be as effective or necessarily tolerated (e.g., dopamine antagonists for psychosis). Despite this, there is indeed a paucity of high-level research trials to support the choice of symptomatic therapies for neuropsychiatric symptoms in Parkinson disease. It should also be noted that there are many other neuropsychiatric manifestations in Parkinson disease not addressed, including but not limited to anxiety, apathy, impulse control disorders and fatigue. The lack of sufficient research in the management of these additional problems prevents us from providing recommendations.

Depression is common throughout the course of Parkinson disease, including in early untreated cases. It has a major impact on both patient and caregiver quality of life. Owing to the many overlapping features common to depression and Parkinson disease, both before and while on treatment (loss of facial expression, hypophonic speech, slowed movement, reduced appetite

and sleep disorders), depression in Parkinson disease often goes on unrecognized. A high index of suspicion must be maintained for this nonmotor symptom. Self-report scales are useful in screening for depression in Parkinson disease, with the Geriatric Depression Scale (GDS-30) and Patient Health Questionnaire-9 (PHQ-9) being preferred options.

C83 Clinicians should have a low threshold for diagnosing depression in Parkinson disease (grade: D, GPP; source: NICE[102]).

C84 Clinicians should be aware that there are difficulties in diagnosing mild depression in people with Parkinson disease because the clinical features of depression overlap with the motor features of PD (grade: D, GPP; source: NICE[102]).

C85 Self-rating or clinician-rated scales may be used to screen for depression in patients with Parkinson disease (grade: C; source: SIGN[17]):

- Diagnosis of depression should not be made on the basis of rating scale score alone (grade: GPP; source: SIGN[17]).
- Assessment or formulation of depression should be carried out via clinical interview, with a focus on low mood, and with due caution in relation to interpretation of cognitive or somatic symptoms that may be symptoms of Parkinson disease rather than depression (grade: GPP; source: SIGN[17]).
- Relatives or caregivers who know the patient well should be invited to provide supplementary information to assist the diagnosis, particularly in the context of cognitive impairment (grade: GPP; source: SIGN[17]).

Symptomatic treatment of depression in Parkinson disease has been poorly studied. There is insufficient evidence in the literature to suggest that treatment with levodopa will improve depression, and only weak support for the efficacy using the dopamine agonist pramipexole. There have been anecdotal reports of the MAO-B medication selegiline helping depression, but this has yet to be confirmed in adequate studies. In general, when symptoms of depression are confined to off-time, they may respond well to any treatment that will reduce fluctuations and improve on-time.

Amitriptyline had been the only recommended treatment of depression in Parkinson disease without dementia, based on the AAN guideline published in 2006. However, there have now been many, mostly small studies, using a wide variety of medications including tricyclic antidepressants (e.g., nortriptyline, desipramine), SSRIs (e.g., paroxetine, sertraline, citalopram), serotonin and norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine) and dopamine agonists (e.g., pramipexole), but no best therapy recommendation can be made from these data. The principles guiding the use of antidepressants in Parkinson disease are similar to those guiding their use in other medically ill populations in general: start low and go slow, with the effective dose often being less than that recommended for the general population. Electroconvulsive therapy remains a potentially lifesaving treatment in major depression and has been used successfully in Parkinson disease, but sufficient trials in Parkinson disease depression do not exist. Cognitive behavioural therapy is another option for treating depression, but evidence is also lacking specifically in Parkinson disease.

C86 The management of depression in people with PD should be tailored to the individual — in particular, to their co-existing therapy (grade: D, GPP; source: NICE[102]).

PSYCHOSIS

(M. Zurowski)

Psychotic features occur in up to 50% of cases with Parkinson disease and once evident, typically persist as a problem through the subsequent course of illness. Symptoms range from illusions of presence, through minor hallucinations (preservation of insight into the false nature of the phenomenon) to true hallucinations. Visual hallucinations are the most common; auditory hallucinations are rare, and paranoid delusions may also occur. It is important to distinguish hallucinations from vivid dreams. Hallucinations may respond to treatment differently than delusions.

Not all hallucinations require treatment if insight is preserved. If they are sufficiently problematic to the patient or caregiver, then alteration in treatment is required. It is important to ensure the patient is in a safe, quiet, well-lit, calming environment, and that any precipitating medical problems are ruled out. Eliminating all nonessential central nervous system active medications is important and often overlooked. If these steps do not control hallucinations, then reducing or stopping antiparkinsonian medications that have a greater potential for worsening psychosis relative to the parkinsonian benefit may be needed. The risk of rapid discontinuation of dopaminergic medications worsening psychosis or causing potential neuroleptic malignant syndrome needs to be kept in mind and monitored.

C87 All people with Parkinson disease and psychosis should receive a general medical evaluation and treatment for any precipitating condition (grade: D, GPP; source: NICE[102]).

C88 For Parkinson disease patients with psychosis, polypharmacy should be reduced (grade: GPP; source: EFNS[11]):

- Anticholinergic antidepressants should be reduced or stopped; anxiolytics or sedatives should be reduced or stopped.

- Antiparkinsonian drugs should be reduced. Anticholinergics should be stopped; amantadine should be stopped; dopamine agonists should be reduced or stopped; MAO-B and COMT inhibitors should be reduced or stopped; and lastly, levodopa should be reduced.

C89 Hallucinations and delusions should not be treated if they are well tolerated by the person with Parkinson disease and their family members and caregivers (as appropriate). Even minor hallucinations or delusions should be considered a marker of disease progression, and should warrant a general medical evaluation and treatment for any precipitating factors (grade: GPP; source: NICE[103]).

If following the above suggestions is inadequate, then the addition of an antipsychotic medication may be necessary. In making this choice, typical antipsychotic medications (phenothiazines, butyrophenones) should be avoided owing to their potential for exacerbating Parkinson disease motor symptoms. There is less agreement in the literature with regard to the use of atypical antipsychotics, although olanzapine shouldn't be considered. Risperidone and aripiprazole also worsen motor symptoms. Quetiapine may have a lower potential for causing worsening of parkinsonism and is considered to be a safe treatment option, but its efficacy is questionable. It may be more effective in treatment of delusions rather than hallucinations.

Clozapine use is the best-supported pharmacologic option in the treatment of psychosis in Parkinson disease. However, its use is complicated by the possibility of agranulocytosis, and government-mandated hematologic monitoring is required. Other adverse effects include dose-dependent excessive sedation and orthostatic hypotension. Once psychotic symptoms improve, clozapine should be continued, as shown by two studies that demonstrated the reoccurrence of symptoms when clozapine was stopped.[68,69] A small comparative trial of clozapine and quetiapine in Parkinson disease psychosis demonstrated equal efficacy of quetiapine, which would suggest it may still be considered first to avoid the more intensive monitoring required with clozapine. The quetiapine dose used was up to 150 mg/day in this study.

When the choice is made to use antipsychotic agents, it must be recognized that they confer an increased risk of mortality in a dose-dependent manner and their use should be balanced with the benefits of mitigating the significant mortality risk of untreated psychosis.[70]

An additional potential pharmacologic intervention that has been suggested for psychosis is the cholinesterase inhibitors rivastigmine and donepezil, but their use to date is not supported by any high-level studies. There is concern that motor worsening, particularly tremor, can occur with this class of medication. As a result, any recommendations still await large, placebo-controlled investigation. Electroconvulsive therapy remains a potentially lifesaving treatment in psychosis and has been used successfully in Parkinson disease, but sufficient trials in Parkinson disease psychosis do not exist. A recent addition to the treatment armamentarium of PD psychosis is pimavanserin, a selective serotonin 5-hydroxytryptamine 2A (5-HT2a) inverse agonist.

C90 For patients with Parkinson disease and psychosis needing treatment:

- Quetiapine is possibly useful (grade: GPP; source: EFNS[11]).

- Clozapine is useful but requires monitoring (grade: A; source: EFNS[11]).

C91 With the exception of quetiapine and clozapine as described in C90, all other antipsychotics should be avoided in Parkinson disease psychosis (grade: GPP; source: EFNS[11]). Olanzapine (grade: A), risperidone (grade: C) and aripiprazole (grade: GPP) can worsen parkinsonism (harmful) (source: EFNS[11]).

C92 Pimavanserin could be considered as a treatment for Parkinson disease psychosis (grade: B; source: CAN).

SECTION 5: PALLIATIVE CARE

PALLIATIVE CARE

(J. Miyasaki & J. Gordon)

There is growing information with respect to palliative care in Parkinson disease. Palliative care employs a multidisciplinary approach to address the symptoms and existential suffering, which is important to the patient and family. Thus, it is theoretically appropriate at any stage of illness. A holistic approach involving family member and caregivers (as appropriate) to discuss prognosis, shared decision-making and advanced care planning, as well as available resources for end of life care, is appropriate. Palliative care specialists are gaining expertise in the care of those with Parkinson disease, offering more involvement of palliative services where appropriate. Long-term care facilities in particular provide palliative care services in the community. In advanced stages, physiotherapy, occupational therapy, speech therapy and dietician services are limited, but can still have an impact on quality of life. In the advanced stage of Parkinson disease, the emphasis of care should shift from an aggressive medical approach to optimize motor function, to a palliative care approach in which the focus is balancing motor, cognitive and behavioural symptoms and providing comfort and support.

Traditionally, management of Parkinson disease has been focused on drug treatment and multidisciplinary care for a long-term, slowly progressive disorder. Palliative care specialists have not routinely been involved. Owing to the long duration of the disease and the difficulty in predicting the time of death, people with Parkinson disease are frequently refused access to hospice and palliative care centres.

End of life choices, including advance care planning with an open and frank discussion with the patient and the person designated as decision-maker, should be initiated early in the disease process. Conversations occurring in the ambulatory setting are likely to be more productive and less crisis-driven than leaving such conversations until an acute stay in hospital. The preparation of an advanced care directive should be discussed with the person with Parkinson disease, and guidance and support should be provided to substitute decision-makers who may have to make difficult decisions regarding life-sustaining treatment. If family and health care professionals have participated in a process of communication throughout the disease progression, the problems associated with interpretation and application of advanced directives are much less likely to occur. Relevant tools in a health care provider's province or territory should be used to guide advance care plans or goals of care discussions.

C93 People with Parkinson disease and their family members and caregivers (as appropriate) should be offered opportunities to discuss the prognosis of their condition. These discussions should promote people's priorities, shared decision-making and patient-centred care (grade: D; NICE[103]).

C94 People with Parkinson disease and their family members and caregivers should be given appropriate verbal and written information about the following, and it should be recorded that the discussion has taken place (grade: D; source: NICE[103]):

- Progression of Parkinson disease
- Possible future adverse effects of medicines for Parkinson disease
- Advance care planning, including orders for advanced decisions to refuse treatment and do not attempt resuscitation, and lasting power of attorney for finance and health and social care
- Options for future management
- What could happen at the end of life
- Available support services; for example, personal care, equipment and practical support, financial support and advice, care at home and respite care

C95 When discussing palliative care, it should be recognized that family members and caregivers may have different information needs from the person with Parkinson disease (grade: D; source: NICE[103]).

C96 Consideration should be given to referring people at any stage of Parkinson disease to the palliative care team to give them and their family members or caregivers (as appropriate) the opportunity to discuss palliative care and care at the end of life (grade: D; source: NICE[103]).

C97 Palliative care requirements of people with Parkinson disease should be considered throughout all phases of the disease; this includes an option of medical assistance in dying (grade: GPP; source: CAN).

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL MATERIAL

(D. Grimes, B. Hutton, M. Fitzpatrick, P. Barbeau)

Supplemental Table 1. Mapping of newly identified CPGs to recommendations in need of updating

CPG identified in update	Recommendation from 2012 Canadian Guideline
Ferreira et al., 2013[11]* (EFNS[11])	C39, C44, C45, C63, C65, C68, C69, C70, C71, C72, C73, C80
Oertel et al., 2011(a)[15]†	C35, C36, C39
Oertel et al., 2011(b)[16]†(EFNS[16])	C44, C45, C46, C48, C63, C65, C68, C69, C70, C71, C72, C73, C80, C84
Herrmann et al., 2013[10]	C72, C73
Zesiewicz et al., 2010[12]	C80, C84
Waldemar et al., 2007[13]	C72, C73
Keus et al., 2014[14]	C54
SIGN 2010[17]	C11, C13, C14, C15, C22, C28, C35, C36, C38, C39, C69, C70,
Fox & Timmons, 2016[18]	C1, C2, C3, C4, C5, C6, C7, C8
Postuma et al., 2015[60]‡	C9, C13

Note: CPG = clinical practice guideline, EFNS = European Federation of Neurological Societies, SIGN = Scottish Intercollegiate Guidelines Network.
*The 2013 update to Oertel et al., 2011 (a)[15] and Oertel et al., 2011 (b)[16] above, which is an update of both Horstink et al., 2006 EFNS CPGs[71,72] included in the 2012 Canadian guideline.
†The 2011 update to both Horstink et al., 2006 EFNS CPGs.[71,72]
‡Publication did not satisfy the criteria for either a CPG or systematic review, but was included as it was identified as pertinent by the expert panel.

Supplemental Table 2. Mapping of newly identified systematic reviews to recommendations in need of updating

Systematic reviews identified in update	Recommendation from 2012 Canadian Guideline (not already addressed by CPGs from update)*
Negida et al., 2016[19]	C22
Hart et al., 2009[20]	C22
Baker et al., 2010[2]	C22
Talati et al., 2009(a)[22]	C22
Talati et al., 2009(b)[23]	C22
Caslake et al., 2009[24]	C22
Zhou et al., 2013[25]	C22
Fox et al., 2011[26]	C42, C46, C48, C49, C55, C56, C57
Liu et al., 2014[27]	C46, C48
Tan et al., 2016[28]	C46, C48
Xie et al., 2016[29]	C46, C48
Herd et al., 2012[30]	C56
Lee et al., 2009[31]	C57
Lee et al., 2008[32]	C57
Lee et al., 2013[33]	C57
Seppi et al., 2011[34]	C61

Note: CPG = clinical practice guideline.
*Some recommendations in need of updating had multiple components to the statement, and thus may have not have been covered entirely by a CPG identified from the update.

Supplemental Table 3. Mapping of newly identified RCTs to recommendations in need of updating

RCTs identified in update	Recommendation from 2012 Canadian Guideline (not already addressed by CPGs or systematic reviews from update)*
Olanow et al., 2014[38]	C42
Slevin et al., 2015[35]	C42
Stocchi et al., 2014[36]	C42
Pahwa et al., 2014[37]	C42
Hauser et al., 2011[40]	C42
Hauser et al., 2013[39]	C42
Odekerken et al., 2015[41]	C51
Zahodne et al., 2009[42]	C51
Locke et al., 2011[43]	C51
Daniels et al., 2011[44]	C51
Witt et al., 2011[45]	C51
Daniels et al., 2010[46]	C51
Nakamura et al., 2007[47]	C51
Clarke et al., 2016[49]	C55
Clarke et al., 2009[55]	C55
Sturkenboom et al., 2012[73]	C55
DiFrancisco-Donoghue et al., 2017[48]	C57
El-Tamawy et al., 2012[50]	C57
Ginis et al., 2016[51]	C57
Byl et al., 2015[52]	C57
Azarpaikan e al., 2014[54]	C57
van den Heuvel et al., 2014[53]	C57
Antonini et al., 2006[74]	C61
Perissinotto et al., 2015[57]	C80
Zesiewicz et al. 2015[58]	C80

Note: CPG = clinical practice guideline, RCT = randomized controlled trial.
*Some recommendations in need of updating had multiple components to the statement, and thus may have not have been covered entirely by a CPG or systematic review identified from the update.

Supplemental Table 4. Mapping of newly identified systematic reviews to new topics that may need to be included as a recommendation

Systematic reviews identified in update	New topic not appearing in the 2012 Canadian Guideline
Skapinakis et al., 2010[75]	Depression
Seppi et al,. 2011[34]	Depression
Yasue et al., 2016[76]	Pimavanserin
Zhou et al., 2013[25]	Rotigotine

Supplemental Table 5. Consensus conference attendees

Julius Anang (MD)	Greta Mah (PH)
Elaine Book (SW)	Soania Mathur (PWP)
Melanie Cohn (NP)	Tiago Mestre (MD)
Silke Cresswell (MD)	Janis Miyasaki (MD)
Grace Ferrari (PC)	Andrea Moser (GP)
Susan Fox (MD)	Tejal Patel (PH)
Jan Goldstein (PT)	Ron Postuma (MD)
Joyce Gordon (PC)	Michelle Ploughman (PT)
David Grimes (MD)	Alex Rajput (MD)
Karen Hall (OT)	Michael Schlossmacher (MD)
Gigi van den Hoef (RN)	Kerry Schoffer (MD)
Chris Honey (FN)	Kyna Squarey (MD)
Suneil Kalia (FN)	Sean Udow (MD)
Lucie Lachance (RN)	Mateusz Zurowski (P)
Ivar Mendez (FN)	

Note: FN = functional neurosurgeon, GP = general practitioner (family physician), MD = movement disorders neurologist, NP = neuropsychologist, OT = occupational therapist, P = psychiatrist, PC = Parkinson Canada member, PH = pharmacist, PT = physiotherapist, PWP = person with Parkinson, RN = registered nurse, SW = social worker.

Supplemental Table 6. Mapping of CPGs and RCTs to new topics identified by expert opinion that should be included as a recommendation

CPGs and RCTs identified in update	New topic needing a recommendation
Oertel et al., 2011(a)[15]* Oertel et al., 2011(b)[16]*(EFNS[16]) SIGN 2010[17]	Apomorphine infusion and oral
Oertel et al., 2011(b)[16]*(EFNS[16]) Schoffer et al., 2007[77]	Domperidone
Isaacson et al., 2016[78] Biaggioni et al., 2015[79] Kaufmann et al., 2014[80] Hauser et al., 2014[81] Zhao et al., 2015[82]	Droxidopa for orthostatic hypotension
No CPGs, systematic reviews, or RCTs identified	Marijuana
Litvan et al., 2011[83]†	Diagnosing mild cognitive impairment
Oertel et al., 2011(b)[16]* (EFNS[16])	Ondansetron for nausea
Ferreira et al., 2013[11]‡ Oertel et al., 2011(b)[16]*(EFNS[16])	Pallidotomy and thalamotomy

Note: CPG = clinical practice guideline, EFNS = European Federation of Neurological Societies, RCT = randomized controlled trial.

* The 2011 update to both Horstink et al., 2006 EFNS CPGs.[71,72]

† Labelled as a guideline but does not satisfy our definition of a CPG (SR methods required); therefore included based on expert opinion and consensus.

‡The 2013 update to Oertel et al., 2011 (a)[15] and Oertel et al., 2011 (b)[16] above, which is an update of both Horstink et al., 2006 EFNS CPGs[71,72] included in the 2012 Canadian guideline.

Identifying recommendations in need of update

A total of 16 clinical experts completed the surveys. The numbers of experts assigned to each subsection of the 2012 Canadian guideline to identify which recommendations needed updating were as follows: communication, *n* = 2; diagnosis and progression, *n* = 2; pharmacologic therapy in early Parkinson disease, *n* = 2; pharmacologic therapy in late Parkinson disease, *n* = 2; surgery, *n* = 3; other treatment options, *n* = 1; mental health, *n* = 2; sleep disorders, *n* = 1; and autonomic dysfunction, *n* = 1.

The surveys were implemented electronically using FluidSurveys software.[4] The first survey was sent out via email on August 24, 2016. Reminder follow-up emails were sent out 2, 3, and 4 weeks after the initial mail-out with the intended goal of maximizing receipt of experts' input. The second survey was sent out in a similar manner on September 21, 2016.

Microsoft Excel software was used to tabulate the survey responses, which in turn formed the basis to determine which recommendations would be subjected to the process of an update. Once survey data were analyzed, David Grimes reviewed the results to determine whether any recommendations not considered for an update should be reconsidered.

Literature search

For existing CPGs, as was done with the previous Canadian guideline, we searched various grey literature sources on August 29, 2016, including the National Guideline Clearinghouse (www.guideline.gov), the Guidelines International Network (www.g-i-n.net/), National Library of Guidelines, CPG Infobase, TRIP Medical Database and Google Scholar.

To identify indexed CPGs and systematic reviews, an experienced medical information specialist (B.S.) developed the search strategy through an iterative process in consultation with the review team. The strategy was peer reviewed before execution by another senior information specialist using the Peer Review of Electronic Search Strategies (PRESS) framework.[84] Using the Ovid platform, we searched Embase and Ovid MEDLINE, including E-pubs Ahead of Print and In-Process & Other Non-Indexed Citations on September 2, 2016. We also searched the Cochrane Library on Wiley (limited to Cochrane Database of Systematic Reviews, DATE, and HTA databases) on the same date.

Strategies used a combination of controlled vocabulary (e.g., "Parkinson Disease," "Guidelines as Topic," "Technology assessment, biomedical") and keywords (e.g., Parkinson*, guideline*, systematic review*). Vocabulary and syntax were adjusted across databases. Searches were restricted to the publication years 2006 to the present. Research undertaken only in animals and opinion pieces were removed from the results.

After the implementation of the staged approach, we noted there were several recommendations that needed updating but were not addressed by sufficient-quality CPGs or high- or moderate-quality systematic reviews. After consultation with our information specialist, it was determined that because we had > 6 research questions (recommendations) that needed updates from RCT evidence, a general search of RCTs in regard to Parkinson disease would be the most suitable searching option. Using the same databases and year limitations outlined above, a search was conducted on December 8, 2016. A selective mapping process followed (outlined in subsequent chapters).

Specific details regarding the search strategies used and the list of grey literature results are provided in Supplemental Figure 1. Duplicates from the grey literature search and the bibliographic search were identified and removed.

Screening and rigour/risk of bias assessment

The articles were uploaded into an online systematic review software package, DistillerSR Software (Evidence Partners, Inc., Ottawa, Canada)[6] for level 1 (title and abstract) and 2 (full-text) screening. Level 1 consisted of 1 reviewer screening for relevancy based on title and abstracts. A second reviewer verified those records deemed not relevant by the first reviewer. At level 2, the full text was retrieved and both reviewers independently assessed the article for relevancy. Conflicts were resolved by consensus or a third team member. A pilot testing phase between both reviewers was implemented on a sample of articles before full screening commenced.

For practical considerations, articles not available electronically were ordered via interlibrary loan. If the article was not

Supplemental Table 7: Overview of PIPOH question and additional details

Question component	Inclusion	Exclusion
Population	Patients with PD	
Intervention/Topics	Communication, diagnosis and progression, general treatment, nonmotor features of PD (mental health) as described in the 2012 Canadian PD Guideline	
Professionals to whom guideline will be targeted	Health care professionals, stakeholders (policy-makers, funding bodies), PD patients and their families	
Outcomes (expected, patient, system, public health)	Dependent on recommendations being updated; however, may have included new treatment options, more specific recommendations, updated diagnostic criteria, etc.	
Health care setting or context where guideline is implemented	Primary practice, communities	
Databases	Grey literature: National Guideline Clearinghouse (www.guideline.gov), the Guidelines International Network (www.g-i-n.net/), National Library of Guidelines, CPG Infobase, TRIP Medical Database, Google Scholar Bibliographic databases: MEDLINE, Embase, Cochrane Library	
Years searched	CPGs and SRs: 2006* to September 2, 2016 RCTs: 2006* to December 8, 2016	
Languages	English or French	
Study design	Staged approach†: -CPGs: had to have more than 1 author and must have cited scientific evidence for the recommendations made (by SR methods) -SRs: must have satisfied definition of a SR: (i) more than 1 database searched; (ii) reported selection criteria; (iii) quality assessment of included studies was reported; (iv) provided a list and synthesis of included studies. -RCTs	-CPGs that did not rely on evidence from SRs. -SRs that did not satisfy our inclusion criteria. -Literature reviews, non-randomized controlled clinical trials, quasi-experimental studies, observational studies, case reports or case series, commentaries and editorials.

Note: CPG = clinical practice guideline, PD = Parkinson disease, PIPOH = Population, Intervention/Topics, Professionals, Outcomes, Health care setting, RCT = randomized controlled trial, SR = systematic review.

*The original years searched in the current Canadian guideline were from 2000 to September 2008. We have implemented a conservative 2-year overlap to ensure that all relevant data are captured.

†Evidence from sufficient-quality CPGs was to be used. However, if we were not able to locate them or if they did not exist, then high- or moderate-quality SRs were alternatively used. We incorporated RCTs if there were no high- or moderate-quality SRs or if they did not exist.

received within 30 days, it was excluded and noted in the listed reasons for study exclusions. Reports in abstract form were listed as potentially relevant studies, if applicable.

After the screening process, different tools available for methodological quality assessment of included literature were matched to each piece of evidence dependent upon the study design used. The risk of bias of included studies was assessed by 1 reviewer and verified at a minimum of 10% by a second reviewer, with the exception of CPGs, which were scored by 2 reviewers. Disagreements were resolved by consensus or a third-party adjudication.

The AGREE II tool was used to assess the rigour of CPGs.[7] A total score out of 100 (strong score) was given for each domain of the guideline being assessed.[1] Only those CPGs that had acceptable scores in the "Rigour of Development" domain (higher than 30%) were presented as potential CPGs to be used in the update, and were further quality assessed in the remaining domains.[3] The 16-point A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) was used.[8] AMSTAR 2 appraises the rigour of systematic reviews based upon criteria related to transparency and completeness of methods on various domains, including the search strategy, the process of study selection and adequacy of data analyses. AMSTAR 2 is intended only for use to evaluate systematic reviews of interventions. In its original form, the AMSTAR 2 tool proposes various domains that, if not satisfied, would be considered critical flaws and would not be considered high or moderate quality. For the purposes of an update, and to be cognizant of limited resources, we relaxed the criteria such that certain domains were not considered critical flaws if they were not fulfilled. Systematic reviews that did not satisfy the following domains were considered to have a critical flaw (weakness), and would not be considered high or moderate quality: (i) a comprehensive literature search; (ii) assessed risk of bias of individual studies; (iii) appropriate methods used for meta-analysis; and (iv) considered risk of bias of individual studies when interpreting the results.

Systematic reviews were considered to be of high quality if there were no critical flaws with no or 1 noncritical weakness. Moderate-quality systematic reviews had no critical flaws with 1 or more noncritical weakness. Low-quality systematic reviews had 1 critical flaw with or without noncritical weaknesses. Critically low-quality systematic reviews had 1 or more critical flaw with or without noncritical weakness.[8] For systematic reviews that addressed topics other than the randomized comparison of interventions (such as diagnostic accuracy studies, prevalence, studies or prognostic studies), the ROBIS tool was used.[85] Briefly, this tool consists of 3 phases. The last 2 phases were used where phase 2 assessed the methodological quality and phase 3 assessed the overall risk of bias. The systematic reviews were classified as being either high or low risk of bias.[85]

The Cochrane Risk of Bias tool was used for screening RCTs.[9] The tool assesses the methodological quality within certain domains of the study including selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases.[9]

Data extraction

Data extraction forms were developed in Microsoft Word and pilot-tested on a sample of studies. One reviewer extracted data and a second reviewer verified information for a minimum 10% random sample.[86] In addition to core publication characteristics, data collected were as follows:

CPGs: Methods of the guideline (including search strategy and research question); results of the guideline (number and types of studies included for the recommendation); a brief text summary of the evidence used to formulate the recommendation; the recommendation provided by the guideline and any limitations in need of consideration, as well as its AGREE II "rigour" score and whether we suggest the use of the guideline for updating the recommendation.

Systematic review: Methods of the systematic review (including search strategy and research question); results of the systematic review (number and types of studies); a brief text summary of the evidence, the final conclusion provided by the systematic review and any limitations in need of consideration, as well as the overall AMSTAR 2 quality assessment.

RCTs: Methods of the RCT (including research question); a brief text summary of the results; the final conclusion of the RCT; as well as any limitations in need of consideration and the quality assessment from the Cochrane Risk of Bias tool.

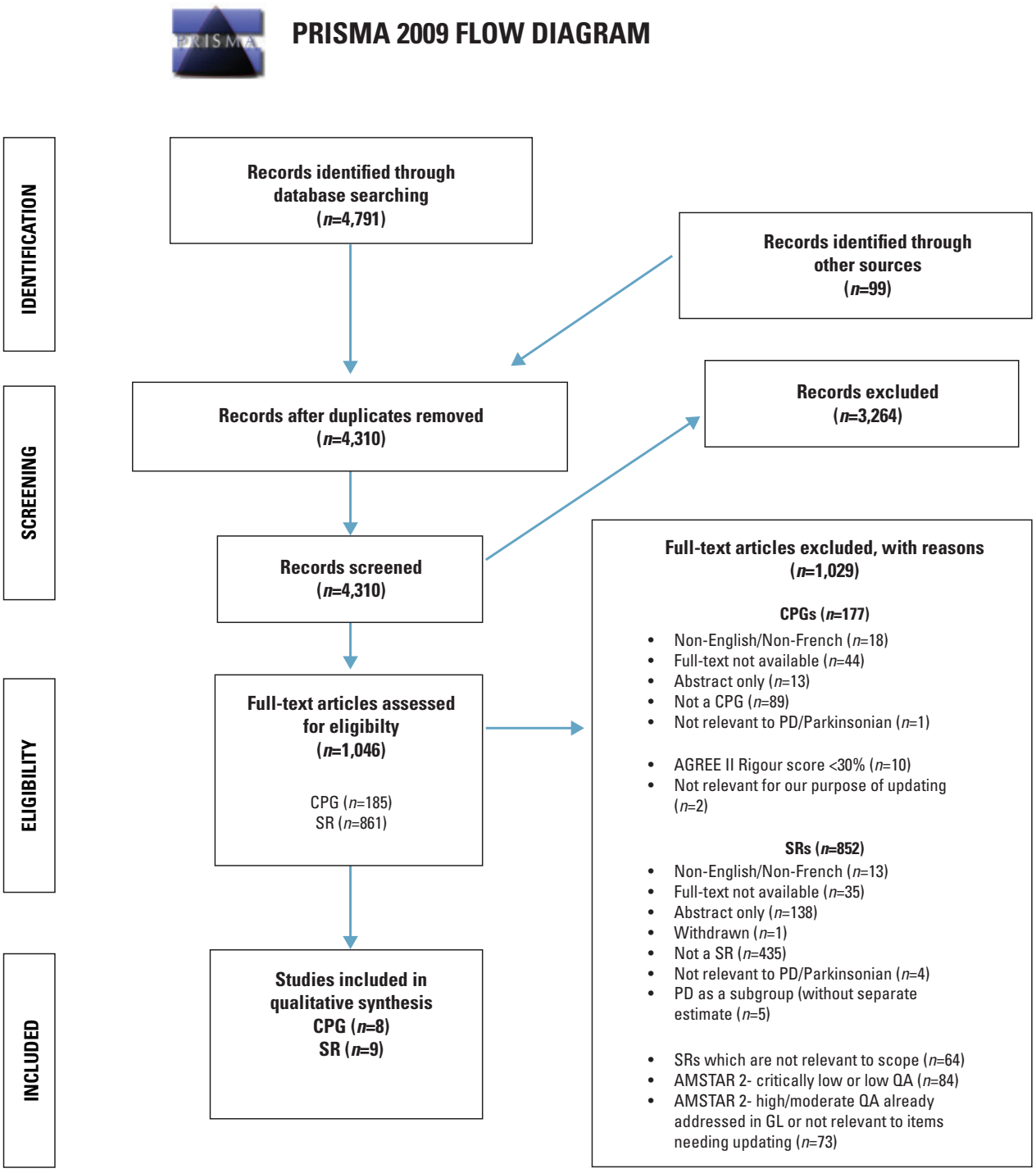
Included CPGs, systematic reviews and RCTs

From the bibliographic database search, a total of 4,791 records were identified. An additional 99 records were identified through the grey literature search for CPGs (**Supplemental Figure 1**). After the removal of duplicates, a total of 4,310 records were uploaded into DistillerSR and subjected to level 1 (title and abstract screening). A total of 3,264 were excluded, resulting in 1,046 records being assessed at level 2 (full-text screening), classified as either a CPG (n = 185) or a systematic review (n = 861).

We excluded 165 CPGs at level 2 full-text screening with reasons (**Supplemental Figure 1**). Subsequently, 20 potentially relevant CPGs remained, of which 10 were excluded because of poor AGREE II "Rigour of Development" scores,[87–96] and 2 were later excluded as they were not considered relevant for our purpose of updating (one focused on interventions for fall prevention, and the other focused heavily on health care professional guidance for occupational therapy).[73,97]

With respect to systematic reviews, 631 were excluded at level 2 with reason. We immediately excluded 64 potentially relevant systematic reviews as they were not within our scope (i.e., focused on incidence or prevalence, risk factors, etc.), mapped and excluded 84 because they were of low methodological quality, and mapped and excluded 73 of high or

Supplemental Figure 1. Process of identification of included clinical practice guidelines and systematic reviews



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097 . doi:10.1371/journal.pmed1000097

For more information, visit **www.prisma-statement.org**

Note: AGREE II = Appraisal of Guidelines for Research & Evaluation, AMSTAR 2 = A MeaSurement Tool to Assess Systematic Reviews, CPG = clinical practice guideline, GL = guideline, PD = Parkinson disease, QA = quality assessment, SR = systematic review.

moderate quality because the recommendation had already been addressed by a CPG, or it was not relevant to the item in need of updating. This resulted in the inclusion of 9 systematic reviews[19–34] in the update where the recommendation was not already addressed by a CPG.

Before quality-assessing the potentially relevant CPGs identified for the update, 2 independent reviewers used the AGREE II's Rigour of Development domain to assess the quality of the adapted CPGs from the 2012 Canadian Guideline, as this information was not readily available. All 8 previously included CPGs scored above the 30% threshold for inclusion.

For the update, 20 potentially relevant CPGs were subjected to assessment by AGREE II's Rigour of Development domain, from which those that scored ≤ 30% were excluded (n = 10) (Supplemental Figure 2). After removal of 2 CPGs that were not relevant (1 focused on interventions for fall prevention; the other focused heavily on health care professional guidance for occupational therapy), 8 CPGs remained for inclusion (some of which are updates of CPGs previously adapted from the 2012 Canadian Guideline) and were subjected to the remaining 5 domains of the AGREE II tool (Scope and Purpose, Stakeholder Involvement, Clarity of Presentation, Applicability, and Editorial Independence). Figures for each AGREE II domain for each included CPG were prepared in the packages to be used by the clinical experts during the consensus meeting to help guide their decision regarding adapting a certain CPG. All 9 CPGs were mapped to at least 1 recommendation in need of updating.

As an overall trend analysis, based on the reporting of the CPGs, the following domains tended to score highest: Rigour of Development, Scope and Purpose, Clarity of Presentation, and Editorial Independence. The following domains tended to score lower: Stakeholder Involvement and Applicability.

When CPGs were assessed individually, the European Physiotherapy guideline for Parkinson disease[14] and SIGN's guideline on diagnosis and pharmacological management of Parkinson disease[17] generally scored better on all domains, suggesting that these CPGs (or their reporting) are of better overall quality (Supplemental Table 9). The European Federation of Neurological Societies/Movement Disorder Society—European Section (EFNS/MDS-ES) updates[11,15,16] generally scored lower on all domains, suggesting that these CPGs (or their reporting) are on the lower spectrum of quality compared with the other included CPGs.

Supplemental Table 8. Methodological quality score of CPGs adapted in 2012 Canadian Guideline

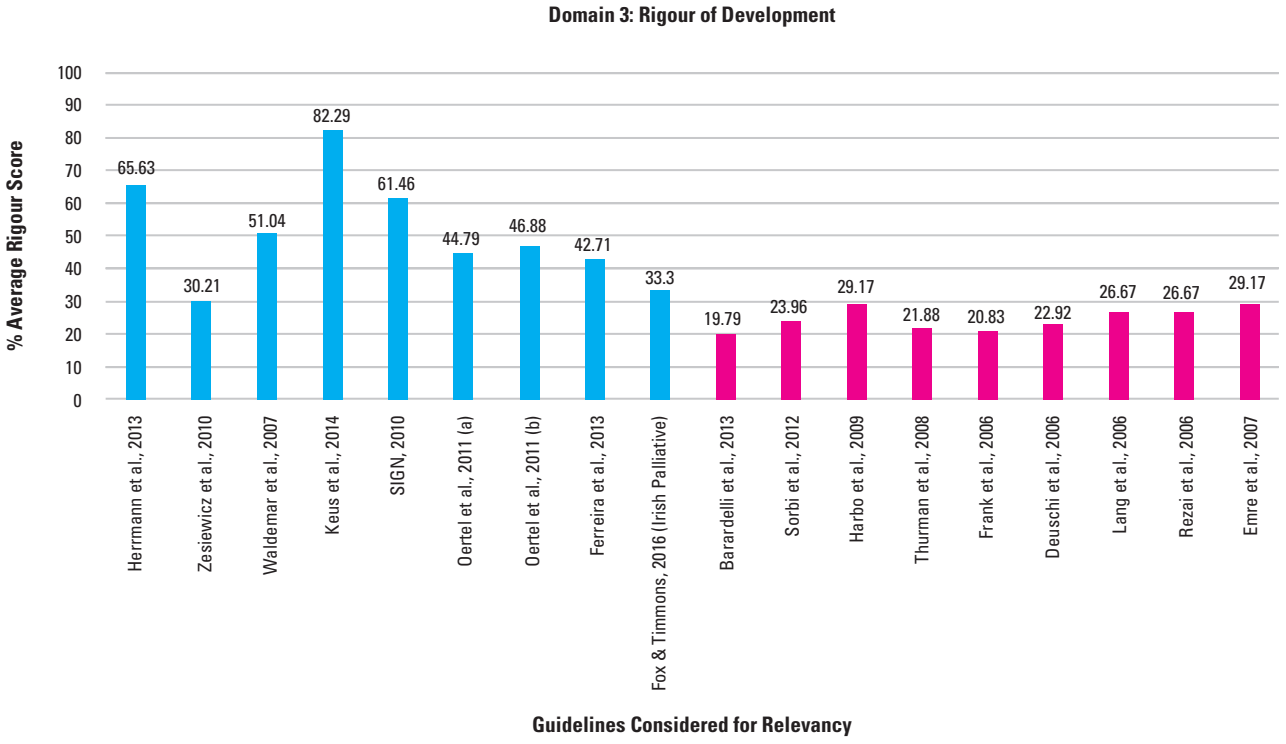
Author/Group	Title	Rigour of Development score	Anticipated updates and notes
Horstink et al., 2006[71] (EFNS/MDS-ES)	Review of the therapeutic management of Parkinson's disease: Part I: early (uncomplicated) Parkinson's disease	51.04%	Updated in 2011 (captured in update search) Updated in 2013 (captured in update search)
Horstink et al., 2006[72] (EFNS/MDS-ES)	Review of the therapeutic management of Parkinson's disease: Part II: late (complicated) Parkinson's disease	51.04%	Updated in 2011 (captured in update search) Updated in 2013 (captured in update search)
Suchowersky et al., 2006[98] (AAN)	Diagnosis and prognosis of new onset Parkinson disease (an evidence-based review)	35.42%	-
Miyasaki et al., 2006[99] (AAN)	Evaluation and treatment of depression, psychosis, and dementia in Parkinson's disease (an evidence-based review)	47.92%	-
Pahwa et al., 2006[64] (AAN)	Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review)	32.29%	Currently updating as of June 2006. Expected release was not reported.
Suchowersky et al., 2006[100] (AAN)	Neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review)	37.50%	-
Miyasaki et al., 2002[101] (AAN)	Initiation of treatment for Parkinson's disease: an evidence-based review	47.92%	-
NICE 2006[102]	Parkinson's disease: diagnosis and management in primary and secondary care	60.42%	Update in progress. Published in 2017.

Note: AAN = American Academy of Neurology, EFNS = European Federation of Neurological Societies, MDS-ES = Movement Disorder Society—European Section, NICE = National Institute for Health and Clinical Excellence

After the exclusion of records based on our primary selection criteria, 231 systematic reviews remained. Sixty-four records had satisfied our definition of a systematic review and were related to Parkinson disease; however, the scope of their investigations was not relevant to the objectives of the update (i.e., topics addressed included studies on incidence or prevalence, onset risk factors for Parkinson disease or association studies; driving; and so forth).

An additional 83 potentially relevant systematic reviews were quality assessed and excluded because they were

Supplemental Figure 2. Potentially relevant clinical practice guidelines and corresponding AGREE II (Rigour of Development) domain score



Note: Blue bars = Included for mapping (AGREE II score ≥ 30%); red bars = excluded for further inclusion (AGREE II score < 30%). AGREE II = Appraisal of Guidelines for Research & Evaluation.

Supplemental Table 9. AGREE II scores of included clinical practice guidelines for update

CPG	D1. Scope	D2. Stakeholder	D3. Rigour	D4. Clarity	D5. Applicability	D6. Editorial Independence
Ferreira et al., 2013[11]* (EFNS[11])	47.22%	0%	42.71%	75.00%	0%	25.00%
Oertel et al., 2011(a)[15]†	36.11%	8.33%	44.79%	66.67%	0%	50.00%
Oertel et al., 2011(b)[16]† (EFNS[16])	30.56%	8.33%	46.88%	66.67%	0%	50.00%
Herrmann et al., 2013[10]	33.33%	0%	65.63%	61.11%	4.17%	58.33%
Zesiewicz et al., 2010[12]	61.11%	0%	30.21%	75.00%	0%	54.17%
Waldemar et al., 2007[13]	55.56%	38.89%	51.04%	58.33%	0%	50.00%
Keus et al., 2014[14]	83.33%	52.78%	82.29%	75.00%	29.17%	25.00%
SIGN 2010[17]	91.67%	66.66%	61.46%	86.11%	37.50%	0%
Fox & Timmons, 2016[18]	61.11%	83.30%	33.30%	16.66%	0%	25.00%

Note: AGREE II = Appraisal of Guidelines for Research & Evaluation, CPG = clinical practice guideline, EFNS = European Federation of Neurological Societies, SIGN = Scottish Intercollegiate Guidelines Network.
*The 2013 update to Oertel et al., 2011 (a)[15] and Oertel et al., 2011 (b)[16] above, which is an update of both Horstink et al., 2006 EFNS CPGs[71,72] included in the 2012 Canadian guideline.
†The 2011 update to both Horstink et al., 2006 EFNS CPGs.[71,72]

found to be of critically low or low quality (using AMSTAR 2) or exhibiting high risk of bias (using ROBIS), and thus did not meet the quality criteria necessary to be included for this update. To visualize whether they would be included had they been more methodologically sound, these reviews have been categorized into 3 categories per subsection of the 2012 Canadian Guideline (Supplemental Table 10):

- Topic addressed by a CPG (would not have been included based on staged approach)
- Topic potentially relevant to a recommendation in need of updating (not addressed by a CPG and would have likely been included in cover-letter summaries)
- Topic not relevant to the recommendation in need of updating (would not have been included).

Furthermore, an additional 68 systematic reviews were considered of moderate or high methodological quality, but they were already addressed by a CPG (staged approach) or they were not considered relevant (did not address recommendations that needed updating) (Supplemental Table 11).

After the implementation of the staged approach, it was noted that there were several recommendations in need of updating that were not addressed by sufficient-quality CPGs or high- or moderate-quality systematic reviews. After consultation with our information specialist, it was determined that because we had > 6 research questions (recommendations) that needed updates from RCT evidence, a general search of RCTs with regard to Parkinson disease would be the most suitable searching option. Using the same databases and year limitations, a search was conducted, followed by a selective mapping process. Specific details regarding the search strategies used and the list of grey literature results are provided in the Search Strategies section. Duplicates from the grey literature search and the bibliographic search were identified and removed.

Through bibliographic database searching, a total of 11,073 records were identified (Supplemental Figure 3).

Supplemental Table 10. Number of systematic reviews excluded for being of low methodological quality.

Topic	Already addressed by a CPG (would not have been included)	Potentially relevant to a recommendation in need of updating (not addressed by a CPG)	Not relevant to the recommendation in need of updating
Communication and palliative care	-	1	1
Diagnosis and progression	2	2	1
Pharmacologic therapy for motor symptoms of PD	4	2	6
Surgery	-	4	1
Mental health	3	3	10
Other treatment options	12	5	20
Sleep disorders	-	-	2
Autonomic dysfunction	-	-	3

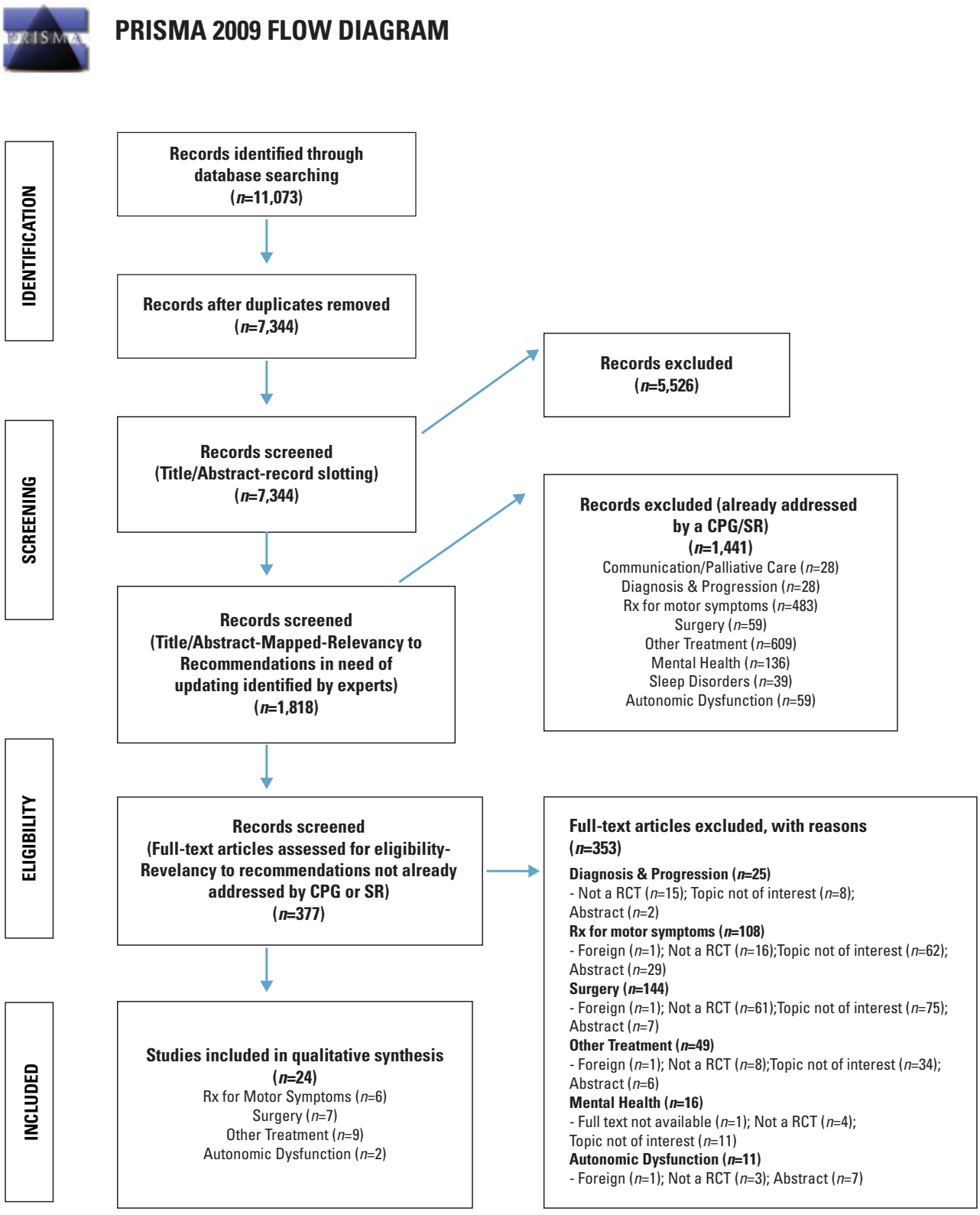
CPG = clinical practice guideline; PD = Parkinson disease.

Supplemental Table 11. Number of high or moderate methodological quality systematic reviews excluded for other reasons

Topic	Already addressed by a CPG (would not have been included)	Not relevant to the recommendation in need of updating
Communication and palliative care	-	-
Diagnosis and progression	2	2
Pharmacologic therapy for motor symptoms of PD	2	4
Surgery	-	2
Mental health	4	4
Other treatment options	22	20
Sleep disorders	-	4
Autonomic dysfunction	-	2

CPG = clinical practice guideline, PD = Parkinson disease.

Supplemental Figure 3. Process of identification of included randomized controlled trials



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097 . doi:10.1371/journal.pmed1000097

Note: CPG = clinical practice guideline, RCT = randomized controlled trial, SR = systematic review.

After removal of duplicates, a total of 7,344 records were uploaded into DistillerSR and subjected to level 1 review (title and abstract screening and record slotting into each of the subsections from the 2012 Canadian guideline), of which 5,526 were excluded. Because of the large number of records identified, records with title and abstracts containing key words such as "RCT," "random," "randomly assigned," "randomized," and so forth were sought for inclusion. Next, 1818 records were subjected to title and abstract mapping to recommendations that needed updating but were not addressed by a CPG or systematic review, of which 1,441 were excluded.

Studies that would be relevant for the subsection Communication and Palliative Care would likely come from qualitative studies presented in case-report or survey forms (for example). It is unlikely that relevant RCTs pertaining to the recommendations in need of updating in this subsection would be identified. As the search strategy had an RCT filter in place, the search yield would have been unlikely to capture these qualitative studies. Nevertheless, some RCT records that focused on some aspect of communication or palliative care were located; however, their relevancies to the update objectives are unlikely.

We assessed 377 records at full text and for relevancy to recommendations that were not already addressed previously by a CPG or systematic review. We excluded 353 records with reasons (Supplemental Figure 3). This resulted in 24 RCTs being included in the cover summaries that, based on the staged approach, were mapped to recommendations not already addressed by CPGs or systematic review: therapies for motor symptoms (n = 6);[35–40] surgery (n = 7);[41–47] other treatment options (n = 9);[48–56] autonomic dysfunction (n = 2).[57,58]

Using the Cochrane Risk of Bias tool to evaluate each RCT, we grouped the outcomes into either objective or subjective categories. Objective outcomes were usually measured through laboratory blood values or objective machinery testing. Subjective outcomes included subject-reported diaries or logs, or investigator-rated Unified Parkinson's Disease Rating Scale, quality of life scales or other rating scales or tools. The questions on "blinding" and "incomplete outcome data assessment" were completed separately for each category of outcome (if applicable).

We were unable to compare the risk of bias scores across the RCTs (collectively), as there was usually only 1 RCT that addressed a recommendation, or the PICOTs (Population, Intervention, Comparison, Outcome and Time) were not homogeneous enough across RCTs (i.e., different comparator, outcomes, etc.). The individual Cochrane Risk of Bias assessments for each RCT were provided at the consensus meeting in a summary format for all included studies.

Search strategies

CPGs and Systematic Reviews

2016 Sep 2
OVID Multifile
Database: Embase <1980 to 2016 Week 35>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

---

1 Parkinson Disease/ (169313)
2 Parkinson*.tw,kw. (215153)
3 (paralys#s adj1 agitans).tw,kw. (457)
4 or/1-3 (247957)
5 exp Animals/ not (exp Animals/ and Humans/) (13647279)
6 4 not 5 (171109)
7 (comment or editorial or interview or news or newspaper article).pt. (1696657)
8 (letter not (letter and randomized controlled trial)).pt. (1881989)
9 6 not (7 or 8) (160690)
10 limit 9 to yr="2006-current" (80995)
11 exp Guidelines as Topic/ (507144)
12 exp Clinical Protocols/ (219847)
13 Guideline.pt. (15949)
14 Practice Guideline.pt. (21793)
15 standards.fs. (610725)
16 Consensus Development Conference.pt. (10140)
17 Consensus Development Conference, NIH.pt. (757)
18 (guidance* or guideline* or standards or recommendation*).ti. (268843)
19 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (93940)
20 or/11-19 (1432890)
21 10 and 20 (1416)
22 limit 10 to systematic reviews [Limit not valid in Embase; records were retained] (39015)
23 meta analysis.pt. (72900)
24 exp meta-analysis as topic/ (43915)
25 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (234048)
26 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (273701)
27 exp Technology assessment, biomedical/ (21625)
28 (cochrane or health technology assessment or evidence report).jw. (34255)
29 or/23-28 (501137)
30 10 and 29 (2186)
31 22 or 30 (39453)
32 31 not 21 (38800)
33 21 or 32 (40216)

34 33 use ppez (2525)
35 Parkinson disease/ (169313)
36 Parkinson*.tw,kw. (215153)
37 (paralys#s adj1 agitans).tw,kw. (457)
38 or/35-37 (247957)
39 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (42691050)
40 exp human/ or exp human experimentation/ or exp human experiment/ (33723744)
41 39 not 40 (8968900)
42 38 not 41 (213842)
43 editorial.pt. (932878)
44 letter.pt. not (letter.pt. and randomized controlled trial/) (1877438)
45 42 not (43 or 44) (202231)
46 limit 45 to yr="2006-current" (122947)
47 exp practice guideline/ (396705)
48 (guidance* or guideline* or standards or recommendation*).ti. (268843)
49 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (93940)
50 or/47-49 (665563)
51 46 and 50 (1458)
52 meta-analysis/ (186948)
53 "systematic review"/ (112691)
54 "meta analysis (topic)"/ (28579)
55 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (234048)
56 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (273701)
57 biomedical technology assessment/ (20516)
58 (cochrane or health technology assessment or evidence report).jw. (34255)
59 or/52-58 (540678)
60 46 and 59 (3739)
61 60 not 51 (3595)
62 51 or 61 (5053)
63 62 use emez (3483)
64 34 or 63 (6008)
65 21 use ppez (864)
66 51 use emez (1212)
67 65 or 66 (2076)
68 remove duplicates from 67 (1753) [UNIQUE CPGS]
69 68 use ppez (829) [MEDLINE UNIQUE CPGS]
70 68 use emez (924) [EMBASE UNIQUE CPGS
71 32 use ppez (1661)
72 61 use emez (2271)
73 71 or 72 (3932)
74 remove duplicates from 73 (2809) [UNIQUE REVIEWS]
75 74 use ppez (1553) [MEDLINE UNIQUE REVIEWS]
76 from 75 keep 1-1000 (1000)
77 from 75 keep 1001-1553 (553)
78 74 use emez (1256) [EMBASE UNIQUE REVIEWS]
79 from 78 keep 1-1000 (1000)
80 from 78 keep 1001-1256 (256)

Cochrane Library
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#3 (paralys* near/1 agitans):ti,ab,kw 4
#4 {or #1-#3} Publication Year from 2006 to 2016 2871
DSR – 64 [REVIEWS]
DARE – 126 [REVIEWS]
CENTRAL – 2612 (*do not download*)
Methods – 7 (*do not download*)
HTA – 41 [REVIEWS]
NHS EED – 21 (*do not download*)
RCTs
2016 Dec 8
Overlap with 2016 Sep 2 Review & CPG search, removed
OVID Multifile
Database: Embase <1980 to 2016 Week 49>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 Parkinson Disease/ (185870)
2 Parkinson*.tw,kw. (230954)
3 (paralys#s adj1 agitans).tw,kw. (424)
4 or/1-3 (264518)
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6 4 not 5 (170029)
7 (comment or editorial or interview or news or newspaper article).pt. (1781543)
8 (letter not (letter and randomized controlled trial)).pt. (1943726)
9 6 not (7 or 8) (159595)
10 limit 9 to yr="2006-current" (78448)
11 exp Guidelines as Topic/ (550514)
12 exp Clinical Protocols/ (234976)
13 Guideline.pt. (16983)
14 Practice Guideline.pt. (23568)
15 standards.fs. (655728)
16 Consensus Development Conference.pt. (11148)
17 Consensus Development Conference, NIH.pt. (901)
18 (guidance* or guideline* or standards or recommendation*).ti. (282877)
19 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (101838)
20 or/11-19 (1540964)

21 10 and 20 (1410)
22 limit 10 to systematic reviews [Limit not valid in Embase; records were retained] (29425)
23 meta analysis.pt. (81221)
24 exp meta-analysis as topic/ (53413)
25 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (255908)
26 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (300260)
27 exp Technology assessment, biomedical/ (22345)
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33 21 or 32 (30842)
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35 clinical trials as topic.sh. (189505)
36 Randomized Controlled Trials as Topic/ (179656)
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40 or/34-39 (2407240)
41 10 and 40 (5355)
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43 33 not 42 (30571)
44 41 not 43 [OVERLAP WITH 2 SEP 2016 REVIEW & CPG SEARCH, REMOVED] (3224)
45 44 use ppez (3222)
46 Parkinson disease/ (185870)
47 Parkinson*.tw,kw. (230954)
48 (paralys#s adj1 agitans).tw,kw. (424)
49 or/46-48 (264518)
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51 exp human/ or exp human experimentation/ or exp human experiment/ (35654239)
52 50 not 51 (9404759)
53 49 not 52 (229620)
54 editorial.pt. (970131)
55 letter.pt. not (letter.pt. and randomized controlled trial/) (1938474)
56 53 not (54 or 55) (217599)
57 limit 56 to yr="2006-current" (136448)
58 exp practice guideline/ (431162)
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62 57 and 61 (1703)
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65 "meta analysis (topic)"/ (36451)
66 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (255908)
67 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (300260)
68 biomedical technology assessment/ (21193)
69 (cochrane or health technology assessment or evidence report).jw. (35566)
70 or/63-69 (591406)
71 57 and 70 (4260)
72 71 not 62 (4082)
73 62 or 72 (5785)
74 randomized controlled trial/ or controlled clinical trial/ (1189101)
75 exp "clinical trial (topic)"/ (267567)
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78 trial.ti. (394566)
79 or/74-78 (2591898)
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81 (201609* or 201610* or 201611*).dc,dd. (774865)
82 73 not 81 (5440)
83 80 not 82 [OVERLAP WITH 2 SEP 2016 SEARCH, REMOVED] (10219)
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92 90 use emez [EMBASE UNIQUE RCTS] (5331)

Cochrane Library
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