PARKINSON DISEASE

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Parkinsonism Clinical Guidance- Issued 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

AAN	American Academy of Neurology
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
COMT	Catechol-O-MethylTransferase
CR	Controlled Release
CT	Computed Tomography
DA	Dopamine Agonists
DAWS	Dopamine Agonist Withdrawal Syndrome
DBS	Deep Brain Stimulation
EDS	Excessive Daytime Sleepiness
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
ER	Extended Release
FDA	Food and Drug Administration
GPi	Pallidum Internum
HAS	Haute Autorite de Sante
HTA	Health Technology Assessment
ICD	Impulse Control Disorder
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
IR	Immediate Release
LCIG	Levodopa-Carbidopa Intestinal gel
MAO-B	Mono Amino Oxidase-B
MDS	Movement Disorder Society Evidence-Based
MENA	Middle East and North Africa
MHRA	Medicines and Healthcare products Regulatory Agency
MRgFUS	Magnetic Resonance imaging-guided Focused Ultrasound Surgery
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NPO	Nil Per Os (nothing by mouth)
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Parkinson Disease
PWP	Persons With Parkinson disease
REM	Rapid Eye Movement

RLS	Restless Legs Syndrome
SDI	Socio-Demographic Index
SFDA	Saudi Food and Drug Authority
SIGN	Scottish Intercollegiate Guidelines Network
SPECT	Single-Photon Emission Computed Tomography
SSRI	Selective Serotonin Receptor Inhibitor
STN	Subthalamic Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale

Executive Summary

Parkinson disease (PD) is a neurodegenerative disorder that causes both motor and nonmotor symptoms and increases in prevalence with age[1].

Motor symptoms in the early stages of PD include tremor, rigidity, and bradykinesia, with gait and balance impairment becoming more prominent with disease progression[1]. In addition to debilitating features of PD itself such as tremor, bradykinesia, anxiety, depression, and cognitive impairments, persons with PD (PWPs) experience significant comorbidities, including increased rates of infections, cardiac, pulmonary, and gastrointestinal disorders, and fall-related injuries[2–5].

The prevalence of PD in Saudi Arabia has been estimated to be 27 per 100,000 population[6]. It was found to be more common among males and its prevalence increased with advancing age, peaking in the 85–89 and 90–94 age groups in males and females, respectively[7]. Another study showed that in 2019, PD had an age-standardized point prevalence of 82.6 per 100,000 population in MENA and an age-standardized death rate of 5.3, which have increased from 1990 to 2019 by 15.4% and 2.3%, respectively[8]. The same paper showed that from 1990 to 2019 the burden of PD generally decreased with increasing socio-economic development, up to a socio-demographic index (SDI) of around 0.4, and then increased with higher levels of SDI.

PD is chronic and progressive in nature, decreasing the quality of life for both patients with the disease and their caregivers and placing an onerous economic burden on society[9]. Many published papers estimated the costs of PD. One study provided a comprehensive analysis of the economic burdens of PD in the United States and projections for the next two decades. It showed that projected PD prevalence will be more than 1.6 million with projected total economic burden surpassing $79 billion by 2037. It also claimed that the economic burden of PD was previously underestimated[10].

The treatment options for the alleviation of motor symptoms in the early stages of PD are based on the enhancement of dopaminergic tone with levodopa, monoamine oxidase inhibitors, dopamine agonists (DAs), Catechol-O-MethylTransferase (COMT) inhibitors or a combination thereof. The choice of initial treatment is influenced by the potential for neuropsychiatric adverse effects associated with DAs and dyskinesia and motor fluctuations associated with levodopa.

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to PD. The primary goal of the Council of Health Insurance (CHI) in issuing PD guidelines is to incorporate the most up-to-date clinical and economic evidence regarding drug therapies into the IDF (CHI Drug Formulary). This objective aims to ensure that patients with PD in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The

focus of the review was on Saudi, American, and European guidelines issued within the last three years.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of PD.

This report functions as an addendum to the prior CHI PD report and seeks to offer guidance for the effective management of PD.

Regarding the management of PD, multiple new medications were approved by FDA as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes, however, rasagiline (tablets) and apomorphine (solution for infusion) were the only ones recently registered by SFDA.

Selegiline and Trihexyphenidyl were withdrawn from the SFDA.

In addition, new therapies progress through the clinical trials testing pipeline each year with the goal of improving the quality of life for people with PD and, ultimately, finding a cure. As of June 2023, there are an estimated 139 potential therapies actively being tested, most still in phases 1 and 2. Within the phase 3 pipeline, there are 20 products with the majority (14 trials) being symptom management drugs. Three trials for disease-modifying therapies (DMTs) are expected t be completed in 2023: *memantine*, and Alzheimer's drug that aims to reduce cognitive impairment in Parkinson's; *ganoderma/lingzh*, mushrooms from traditional Chinese medicine are being studied for their potential to slow the progression of Parkinson's symptoms; and *buntanetap*, which reduces the production of alpha-synuclein with the goal of improving motor symptoms of Parkinson's[11].

Below is a table summarizing the major changes based on the different PD guidelines used to issue this report:

Table 1. General Recommendations for the Management of Parkinson Disease

Management of Parkinson Disease		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
Parkinson disease should be suspected in people presenting with tremor, stiffness, slowness, balance problems or gait disorders.	Grade: D, good practice point; source: NICE	Canadian guideline for Parkinson disease, 2019
There are no current disease-modifying pharmacologic treatments for PD; current PD	Not Graded	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease

pharmacologic therapy is symptomatic only.		Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.
Families and caregivers should be given information about the condition, their entitlements to care assessment and the support services available.	Grade: D, good practice point; source: NICE	Canadian guideline for Parkinson disease, 2019
Clinicians should counsel patients with early PD on the benefits and risks of initial therapy with levodopa, DAs, and monoamine oxidase type B (MAO-B) inhibitors based on the individual patient's disease characteristics to inform treatment decisions.	Level B	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.
In patients with early PD who seek treatment for motor symptoms, clinicians should recommend levodopa as the initial preferential dopaminergic therapy.	Level B	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.
Clinicians may prescribe DAs as the initial dopaminergic therapy to improve motor symptoms in select early PD patients <60 years who are at higher risk for the development of dyskinesia.	Level C	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.
Clinicians should not prescribe DAs to patients with early-stage PD at higher risk of medication-related adverse effects, including individuals >70 years, patients with a history of ICDs, and patients with preexisting cognitive impairment, excessive daytime sleepiness (EDS), or hallucinations.	Level B	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.

Levodopa is the most widely used and the safest drug. It is a drug of first choice in pregnant patients who present symptom exacerbation. Its use may be justified during pregnancy (risk/benefit assessment).	Not graded	Management of Parkinson's disease and other movement disorders in women of childbearing age 2021.
Personalized medicine approaches must be considered in future research, with the goal of moving away from a one-size-fits-all therapeutic approach to initiating treatment for motor symptoms in early PD.	Not Graded	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.
Deep brain stimulation of the subthalamic nucleus or the globus pallidus interna is effective against motor fluctuations and dyskinesia.	Grade: A; source: EFNS	Canadian guideline for Parkinson disease, 2019
Physiotherapy specific to Parkinson disease should be offered to people who are experiencing balance or motor function problems.	Grade: B; source: NICE	Canadian guideline for Parkinson disease, 2019
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	Canadian guideline for Parkinson disease, 2019

Section 3 lists the key recommendations synthesis for Parkinson Disease treatment.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Parkinson disease report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the 2020 CHI Parkinson disease report and the corresponding recommendations.

Five guidelines were used in the last version of Parkinson disease. Updates were only found for the treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology published in 2006 and updated by AAN Guideline Subcommittee in 2021.

In December 2020, the National Institute for Health and Care Excellence (NICE) amended recommendations on modafinil in line with the Medicines and Healthcare products Regulatory Agency (MHRA) safety advice: women who are pregnant or who are planning a pregnancy should not take modafinil because it may increase the risk of congenital defects[12].

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
NICE guidelines of Parkinson's disease in adults published [2017] updated (**2019**).	N/A*
Treatment of non-motor symptoms of Parkinson disease Report of the Quality Standards Subcommittee of the **American Academy of Neurology** (**2010**).	N/A*
Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review) Report of the Quality Standards Subcommittee of	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the **AAN** Guideline Subcommittee, **2021**.

the **American Academy of Neurology** (**2006**).	
Summary of the recommendations of the **EFNS/MDS-ES** review on therapeutic management of Parkinson's disease (**2016**).	N/A*
Canadian guideline for Parkinson disease (**2019**).	N/A*

**: No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.1.1 Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee (2021)

In 2002, the American Academy of Neurology (AAN) published the "Initiation of Treatment for Parkinson Disease" practice guideline, which contains recommendations regarding the use of dopaminergic medications for patients with PD.

Since 2002, many new medications and new formulations of older medications have become available for PD treatment.

The goal of this guideline is to review the current evidence on initial dopaminergic treatment of motor symptoms in early-stage PD and provide guidance to clinicians[1].

Practice Recommendations

The following recommendations pertain to the initiation of pharmacologic treatment for motor symptoms in early PD, presuming that patients have received a correct diagnosis.

There are no current disease-modifying pharmacologic treatments for PD; current PD pharmacologic therapy is symptomatic only.

Levodopa vs Dopamine agonists (DAs) vs Monoamine Oxidase Type B (MAO-B) Inhibitors

Clinical trials have failed to provide evidence of disease modification when the initial therapy prescribed is levodopa, DA, or a MAO-B inhibitor.

Initial treatment of early PD with levodopa provides greater benefit for motor symptoms than initial treatment with DAs, as shown in most studies that demonstrate greater improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) part III score for the first 5 years of follow-up.

Patient and disease characteristics influence the risk of adverse effects related to the use of levodopa and DAs and may affect initial treatment choices.

Clinicians should counsel patients with early PD on the benefits and risks of initial therapy with levodopa, DAs, and MAO-B inhibitors based on the individual patient's disease characteristics to inform treatment decisions (Level B).

In patients with early PD who seek treatment for motor symptoms, clinicians should recommend levodopa as the initial preferential dopaminergic therapy (Level B).

Clinicians may prescribe DAs as the initial dopaminergic therapy to improve motor symptoms in select early PD patients < 60 years who are at higher risk for the development of dyskinesia (Level C).

Clinicians should not prescribe DAs to patients with early-stage PD at higher risk of medication-related adverse effects, including individuals > 70 years, patients with a history of impulse control disorder (ICDs), and patients with preexisting cognitive impairment, excessive daytime sleepiness (EDS), or hallucinations (Level B).

Prescribing Levodopa

The evidence comparing immediate-release (IR) levodopa to controlled-release (CR) levodopa or levodopa/carbidopa/entacapone is either of very low confidence or did not detect differences between formulations for improvement in motor symptoms, dyskinesia, hallucinations, or adverse event-related discontinuation in early PD.

There are no studies comparing IR levodopa to extended-release (ER) carbidopa/levodopa in early PD.

Clinicians should initially prescribe IR levodopa rather than CR levodopa or levodopa/carbidopa/entacapone in patients with early PD (Level B).

In patients with early PD, clinicians should prescribe the lowest effective dose of levodopa (i.e., the lowest dose that provides adequate symptomatic benefit) to minimize the risk of dyskinesia and other adverse effects (Level B).

Clinicians should routinely monitor patients taking levodopa for their motor response to treatment and for the presence of dyskinesia, motor fluctuations, ICDs, EDS, postural hypotension, nausea, and hallucinations, to guide dosage titration over time (Level B).

Clinicians should counsel patients taking levodopa that higher dosages are more likely to cause dyskinesia (Level B).

Clinicians should counsel patients that in later disease stages, taking levodopa with meals may affect levodopa absorption and efficacy, but this is usually not problematic at the time of levodopa initiation in early PD (Level B).

Prescribing DAs

Clinicians should inform the patient and caregiver (when present) of important side effects of DAs before prescribing; this discussion should specifically include ICDs, EDS, sudden-onset sleep, nausea, postural hypotension, and hallucinations (Level B).

Clinicians should screen patients for cognitive impairment, EDS, sudden-onset sleep, hallucinations, orthostatic hypotension, and the presence of risk factors for ICDs before prescribing a DA (Level B).

Clinicians should screen patients for the presence of adverse effects related to DAs, including ICDs, EDS, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations repeatedly in follow-up of patients prescribed DAs (Level B).

Clinicians should involve caregivers in assessments for ICDs, EDS, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations in patients with PD (Level B).

Multiple DA medications and formulations (e.g., short-acting, long-acting, oral, and transdermal) are approved for the treatment of patients with early PD.

Clinicians should integrate patient preferences concerning formulation, mode of administration, and cost when prescribing a DA (Level B).

Clinicians should prescribe the lowest dose of DA required to provide therapeutic benefit (Level B).

Tapering and Discontinuing DAs

Clinicians should recommend tapering or discontinuation of DAs if patients experience disabling medication-related adverse effects, including ICDs, EDS, sudden-onset sleep, cognitive impairment, or hallucinations (Level B).

When DAs must be discontinued due to adverse effects, clinicians should monitor patients for symptoms of Dopamine Agonist Withdrawal Syndrome (DAWS) and, when possible, gradually decrease the dosage to minimize symptoms (Level B).

Prescribing MAO-B Inhibitors

Initial treatment with levodopa may be more likely to induce dyskinesia than initial treatment with MAO-B inhibitors.

Most patients on monotherapy with a MAO-B inhibitor will require additional therapy within 2 to 3 years compared to those being treated with levodopa or DAs.

There are no studies comparing the efficacy of selegiline and rasagiline in the treatment of early PD.

Prescribing information for selegiline and rasagiline caution against their use with selective serotonin reuptake inhibitors (SSRIs); however, serotonin syndrome is

rarely reported in patients with PD on concomitant therapy with an MAO-B inhibitor and an SSRI.

Clinicians should counsel patients with early PD on the greater motor benefits of initial therapy with levodopa compared with MAO-B inhibitors to inform treatment decisions (Level B).

Clinicians may prescribe MAO-B inhibitors as the initial dopaminergic therapy for mild motor symptoms in patients with early PD (Level C).

Suggestions for Future Research

Personalized medicine approaches must be considered in future research, with the goal of moving away from a one-size-fits-all therapeutic approach to initiating treatment for motor symptoms in early PD.

Further work is required to advance initial pharmacogenomic studies that have suggested patient-specific differences in response to some anti- Parkinson drugs, such as rasagiline and entacapone.

Similarly, further research is required to establish definitive genetic predispositions to important treatment complications such as the risk of developing ICDs with DAs or a greater risk of earlier severe dyskinesia with levodopa.

A high priority of future research should be to determine whether newer, more effective methods of providing stable levodopa plasma levels initiated soon after diagnosis will delay the onset of dyskinesia.

These could include the use of newer ER levodopa formulations, alternative modes of levodopa administration (e.g., transdermal), or longer-acting catechol-O-methyltransferase (COMT) inhibitors.

1.1.2 Canadian Guideline for Parkinson Disease (2019)

The first Canadian guideline on Parkinson disease was published in 2012. Since that guideline, there have been substantial advances in the literature on the disease, particularly with respect to diagnostic criteria and treatment options. While this guideline was included in the previous CHI report, it was developed further to include additional recommendations.

This guideline update reflects substantial changes in the literature on diagnosis and treatment of Parkinson disease and adds information on palliative care[13].

The table below describe le grades of recommendations and the level of evidence. The listed recommendations were adapted from the European Federation of Neurological Societies (EFNS)[14], National Institute for Health and Clinical Excellence (NICE 2017)[15], and the Scottish Intercollegiate Guidelines Network (SIGN)[16].

Table 3. Grading Scheme from SIGN, EFNS and NICE*

Grade of recommendations	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
Level 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

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.

*When no grade was assigned or when a recommendation was created from a systematic review or RCT, the SIGN grading table was used.

Recommendations for communication

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

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).

Because people with PD 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, good practice point; source: NICE).

Families and caregivers should be given information about the condition, their entitlements to care assessment and the support services available (grade: D, good practice point; source: NICE).

Diagnosis and progression

PD should be suspected in people presenting with tremor, stiffness, slowness, balance problems or gait disorders (grade: D, good practice point; source: NICE).

PD can be diagnosed using the Movement Disorder Society Clinical Diagnostic Criteria (grade: good practice point; source: CAN).

Patients initially considered to have a possible diagnosis of PD may benefit from a trial of dopamine replacement therapy to assist with an accurate diagnosis (grade: good practice point; source: SIGN).

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

Positron emission tomography scanning is not recommended as part of the diagnostic work-up of parkinsonian syndromes, except within a research framework (grade: good practice point; source: SIGN).

123I-ioflupane (123I-FP-CIT) single-photon emission computed tomography (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).

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

Genetic testing for monogenic parkinsonism is not recommended in routine clinical practice (grade: good practice point; source: SIGN).

Treatment

Many symptomatic treatments are available for PD. These include medications, surgical procedures, physiotherapy, occupational therapy, and other support services.

Levodopa may be used as a symptomatic treatment for people with early PD (grade: A; source: NICE7).

Levodopa remains the most effective medication for the treatment of motor symptoms and there is no reason to delay its use for those with bothersome motor symptoms.

Dopamine agonists (DAs) may be used as a symptomatic treatment for people with early PD (grade: A; source: NICE).

A DA 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, good practice point; source: NICE).

Subcutaneous apomorphine infusions or 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).

When starting DA 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:

- 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 (grade: good practice point; source: NICE).

It should be recognized that impulse control disorders can develop in a person with PD who is on any dopaminergic therapy at any stage in the disease course (grade: good practice point; source: NICE).

Device-aided therapies: Deep brain stimulation of the subthalamic nucleus or the globus pallidus interna is effective against motor fluctuations and dyskinesia (grade: A; source: EFNS).

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).

Rehabilitation: 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).

Physiotherapy specific to PD should be offered to people who are experiencing balance or motor function problems (grade: B; source: NICE).

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

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

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

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

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

For orthostatic hypotension, drug therapy includes the addition of:

- Midodrine (grade: A; source: EFNS)
- Fludrocortisone (grade: good practice point; source: EFNS)
- Domperidone (grade: good practice point; source: CAN)

Care should be taken to identify rapid eye movement (REM) sleep behavior disorder in people with PD. Melatonin or clonazepam may be useful if pharmacologic treatment is required (grade: good practice point; source: NICE).

The management of depression in people with PD should be tailored to the individual, in particular to their coexisting therapy (grade: D, good practice point; source: NICE).

For patients with PD and psychosis needing treatment:

- Quetiapine is possibly useful (grade: good practice point; source: EFNS)
- Clozapine is useful but requires monitoring (grade: A; source: EFNS)

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

For PD dementia, cholinesterase inhibitors could be added: 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: good practice point).

Memantine can be added or substituted if cholinesterase inhibitors are not tolerated or lack efficacy (grade: C). (Source: EFNS)

Palliative care

There is growing information with respect to palliative care in PD and the guideline panel therefore thought that the topic was an important addition to the new guideline.

People with PD 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-centered care (grade: D; source: NICE).

People with PD 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):

- Progression of PD
- Possible future adverse effects of medicines for PD
- 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.

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).

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: good practice point; source: CAN).

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Parkinson disease report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
Spanish Society of Neurology: Management of Parkinson's Disease and Other Movement Disorders in Women of Childbearing Age (**2020**)
Parkinsonian Drugs: Guidelines for **Japan** (**2022**)

1.2.1 Spanish Society of Neurology: Management of Parkinson's Disease and Other Movement Disorders in Women of Childbearing Age (2020)

The main challenge of Parkinson's disease in women of childbearing age is managing symptoms and drugs during pregnancy and breastfeeding.

The increase in the age at which women are having children makes it likely that these pregnancies will become more common in future.

This practice guideline published by the Spanish Society of Neurology aims to define the clinical characteristics of women of childbearing age with Parkinson's disease and the factors affecting their lives, and to establish a series of guidelines for managing pregnancy in these patients[17].

Factors related to reproduction in Parkinson's disease

Reproductive health is defined as the physical, mental, and social well-being related to the reproductive system.

Certain reproductive factors (e.g., number of pregnancies, duration of the reproductive period, cumulative length of pregnancy, number of children, and age at menopause) have been associated with later disease onset.

This may explain the lower incidence of PD among women and suggest a protective role of estrogens.

Effects of pregnancy on the symptoms and progression of Parkinson's disease

In general, published data suggest that women who receive treatment during pregnancy present better disease progression than those who do not.

Good motor function is extremely important, particularly in the period prior to delivery and in the postpartum period.

Potential effects of Parkinson's disease on pregnancy

In women with PD, many symptoms of pregnancy are expected to be exacerbated, particularly those that existed prior to pregnancy as a result of PD.

Non-motor symptoms such as anxiety or depression, sialorrhea, circadian rhythm alterations, or gastrointestinal problems including vomiting or constipation may be more pronounced in pregnant women, as these symptoms are characteristic of both pregnancy and PD.

Instability due to parkinsonism may be exacerbated in pregnant patients, who present greater mobility problems due to weight gain and the change in their center of gravity.

Antiparkinsonian treatment during pregnancy

Few studies have described the effects of dopaminergic drugs on pregnancy or their teratogenic potential.

Regarding exposure time, it is common when patients become pregnant for doses to be reduced or for some drugs to be suspended, resulting in motor impairment that frequently leads to reintroduction of the drug.

Levodopa is the most widely used and the safest drug. It is a drug of first choice in pregnant patients who present symptom exacerbation. Its use may be justified during pregnancy (risk/benefit assessment).

There is insufficient data to recommend breastfeeding. However, the risk is low (low concentration in breast milk).

In most cases, levodopa was combined with other dopaminergic drugs.

Little evidence is available on the safety of **dopaminergic agonists** in PD.

Pramipexole 0.75- 6 mg/day and Ropinirole 1-2 mg/day are potentially safe, but data are limited.

There is insufficient data to recommend breastfeeding. High risk identified compared to levodopa.

Anticholinergics such as Biperiden and Trihexyphenidyl are potentially safe, but data are limited. There is insufficient data to recommend breastfeeding as well.

Amantadine must be avoided in pregnancy and there is insufficient data to recommend breastfeeding.

There is insufficient data to establish a recommendation for the use of MOA-B inhibitors or COMT inhibitors in pregnancy or breastfeeding. Similarly, recommendations cannot be established for the use of levodopa-carbidopa intestinal gel or subcutaneous apomorphine infusion.

Other drugs for managing Parkinson's disease during pregnancy

Serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors do not seem to increase the risk of miscarriage or birth defects but are associated with low birth weight and poor neonatal adaptation.

Tricyclic antidepressants also seem not to be associated with an increase in congenital malformations or pregnancy complications, although they do appear to affect neonatal adaptation.

Benzodiazepines should be avoided during pregnancy, as they are associated with cleft lip and palate defects when used in the first trimester, and muscle flaccidity, hypo- or hypertonia, hypothermia, respiratory problems, and neonatal abstinence syndrome when used in the third trimester.

Instead of these drugs, nonpharmacological approaches such as cognitive behavioral therapy are recommended.

Like in the general population, treatment of constipation includes abundant fluid intake and such osmotic laxatives as polyethylene glycol and lactulose.

Polyethylene glycol (FDA pregnancy risk category C) presents minimal systemic absorption; it is therefore unlikely to cause fetal abnormalities. Lactulose (FDA pregnancy risk category B) can also be used during pregnancy, if needed.

Second-line treatments for Parkinson's disease during pregnancy

Second-line treatments are mainly indicated for patients with advanced PD.

Women receiving second-line treatments for advanced PD who express a desire to have children should be given individualized information on the risks involved; it is essential to assess whether they have adequate social/family or caregiver support.

Whichever the second-line treatment used, treatment should be optimized in pregnant women with PD to reduce motor complications at each stage; pregnancy should be considered high-risk, and these women should be closely followed up by the neurology and gynecology departments.

Deep brain stimulation and ablative lesions

Deep brain stimulation (DBS) is an effective therapy in patients with advanced PD.

The potential benefits for pregnant patients are a reduction in doses of antiparkinsonian medication and improvements in wellbeing and quality of life.

Neuroablative lesions: Gamma-knife and high-intensity focused ultrasound. The potential benefits of these techniques for pregnant women are the same as those of DBS: the reduction or elimination of drugs during pregnancy.

However, they do not present the other major advantage of DBS, the ability to adjust stimulation parameters.

Continuous infusion of intestinal levodopa and subcutaneous apomorphine

Levodopa is the most widely used drug in pregnant women with PD, although the evidence on its safety is weak, and the drug can cross the placenta.

It is important to consider that endoscopic procedures are associated with potential risks to the fetus.

No published cases of pregnancy coinciding with continuous subcutaneous apomorphine infusion to treat advanced PD were identified.

Motor complications must always be prioritized and managed on an individual basis; nonetheless, even less evidence is available on the use of dopaminergic agonists during pregnancy than for levodopa.

Measures to adopt and neurological follow-up during a planned pregnancy

Motor symptoms of PD will worsen during pregnancy in approximately half of cases.

Worsening of motor symptoms is less pronounced in women who continue and adjust dopaminergic treatment during pregnancy; therefore, this treatment should be continued throughout pregnancy.

Close follow-up is needed during pregnancy to enable precise adjustment of dopaminergic medication.

Current data support the use of levodopa as the first treatment option in pregnant patients with PD presenting exacerbation of motor symptoms.

If a patient becomes pregnant, such drugs as amantadine should be avoided due to teratogenicity and increased risk of miscarriage.

In patients planning to become pregnant, amantadine should be suspended in advance, or when pregnancy is confirmed.

MAO-B inhibitors and COMT inhibitors should also be avoided due to a lack of evidence on their use in this population.

Current data are insufficient to support the routine recommendation of dopaminergic agonists or anticholinergics during pregnancy, despite the absence of known teratogenic effects.

Puerperium and breastfeeding

Puerperium is the period in which the reproductive system fully recovers following childbirth. Some general symptoms of PD can be exacerbated during this period.

Constipation can worsen, and there is an increased risk of urinary problems or hemorrhoids. A diet rich in fiber and abundant fluid intake seem advisable.

Depression may also appear or worsen in this period.

Insufficient evidence exists on the effect of PD on breastfeeding and the safety of breastfeeding when the mother is receiving antiparkinsonian medication.

Levodopa, amantadine, entacapone, and tolcapone are excreted in breast milk, and the potential effects on the infant are unknown.

Breastfeeding should be avoided in patients receiving these drugs.

No data are available on the excretion of opicapone in breast milk, or the potential.

Levodopa and dopaminergic agonists may inhibit the release of prolactin, and therefore of breast milk.

The degree to which these drugs are excreted in milk is unknown; therefore, breastfeeding is not recommended in patients receiving them.

Data are also lacking on the excretion of MAO-B inhibitors in breast milk and their effect on the infant, so patients taking these drugs should also be advised against breastfeeding.

1.2.2 Parkinsonian Drugs: Guidelines for Japan (2022)

The first guideline for PD was published in 2002 (the Guideline Committee for the Treatment of Parkinson's Disease).

Newer drugs such as rotigotine, apomorphine, and istradefylline have been added to the guidelines in Japan.

This third version published in 2022 adopted a more sophisticated handling of the evidence-based medicine, but the principles of the guideline have not changed much[18].

Clinical Efficacy and Safety of Anti-PD Drugs

The Committee made conclusion as efficacious for:

- L-dop
- Dopamine agonists {bromocriptine (probably efficacious in early-stage PD)
- Pergolide, cabergoline, pramipexole, ropinirole, rotigotine, selegiline, rasagiline
- Entacapone (advanced stage alone)
- Amantadine (early stage alone)
- Anticholinergics (probably efficacious in early stage alone)
- Droxidopa (probably efficacious in freezing and akinesia and not enough data in orthostatic hypotension)
- Zonisamide (advanced PD alone) in symptomatic treatment of motor disturbances in both early and advanced stage PD.

Regarding the safety, the Committee made conclusion as safe in selegiline, entacapone, amantadine, droxidopa, and zonisamide and probably safe in L-dopa, dopamine agonists (bromocriptine, pergolide, cabergoline, pramipexole, ropinirole), rasagiline, and anticholinergics.

The Committee mentioned about ergot dopamine agonists that cardiac valvulopathy, pleural effusion, pulmonary fibrosis, and retroperitoneal fibrosis might occur, although the incidences of these side effects were low.

The Committee recommended cardiac monitoring by echocardiography and chest X-ray when ergot dopamine agonists were used.

Ergot dopamine agonists should not be used as the first-line treatment of dopamine agonists. In addition, bromocriptine should not be considered as the first-line treatment of the early-stage PD.

Apomorphine, approved in Japan as of March 2012, is efficacious in PD and probably safe. Apomorphine is an injection, which is used as a rescue from the off period.

Istradefylline, approved in Japan as of May 2013, is efficacious in PD on L-dopa with motor complications and probably safe.

Combined tablets of L-dopa/DCI/COMT inhibitor, entacapone (Stalevo), approved in Japan as of November 2014, are efficacious and probably safe.

Intra-jejunal infusion of L-dopa/carbidopa hydrate, approved in Japan as of September 2016, is efficacious and probably safe.

Regarding orthostatic hypotension in PD, the guideline committee changed clinical effect of droxidopa to efficacious and safe.

General Discussion on the Treatment of PD

Anti-PD drugs are started, taking into consideration the severity of the symptoms, the difficulties of daily life, and occupations of the patients, (Grade B).

There is no clear benefit by delaying the anti-PD drug use (Grade B).

There is no evidence for the current treatments improving the loss of dopaminergic neurons (Grade B).

There is no evidence to enhance the degeneration of dopaminergic neurons (Grade B).

What influences the occurrence of the motor complications in PD include the maintenance doses of anti-PD drugs, selection of the anti-PD drugs at the beginning of the treatment, and the age of the patients.

Incidence of dyskinesia depends on the total doses of L-dopa, dopamine agonists, and others used (Grade C1). Starting the treatment by a dopamine agonist decreases the motor complications than L-dopa (Grade A).

The age of onset and the incidence of motor complications have an inverse relationship (Grade B).

Factors which comprise QOL include severity of the disease, dementia, depression, fall, motor complications, and insomnia (Grade B). Treatment of these factors improves QOL (Grade A).

Those patients without tremor, (rigid-akinetic form), high onset of age, elderly patients, and dementia within 1 year of onset tend to have a poor prognosis in motor symptoms and general motor disability (Grade B).

Those who have apolipoproten ε2 or ε4 tend to have dementia in future (Grade B).

Psychotomimetic drugs, gastrointestinal drugs, and anti-hypertensive drugs may cause or worsen parkinsonism (Grade C1).

When parkinsonism progresses rather acutely, consider the possibility of drug induced parkinsonism or complication of it (Grade C1).

Dopamine agonists or L-dopa should be used first. The question which drug is used depends on the patient's age, the severity of motor disturbances, and the complications of the patient."

Non-elderly people without psychiatric symptoms or dementia should be treated by a dopamine agonist and if the improvement is unsatisfactory, L-dopa should be added (Grade A).

Use L-dopa when the patient is elderly, has a safety issue particularly complicated with psychiatric symptoms or cognitive impairment, or needs immediate improvement of motor disturbances (Grade B).

No evidence of high quality exists on which dopamine agonists should be used first.

The risk of motor complications is lower when a dopamine agonist is used first (Grade A).

To start treatment with a dopamine agonist is recommended when the patient is young (generally speaking 50 years or less) (Grade B).

When a dopamine agonist is used, you should consider the severity of motor disturbances, excessive daytime sleepiness, hallucination, cardiac valvulopathy, and edema (Grade A).

Ergot dopamine agonists may cause cardiac valvulopathy (Grade B).

Do not use a non-ergot dopamine agonist to those who work as drivers of cars, operators of machines, and workers who work at high places, because of excessive daytime sleepiness and sudden onset of sleep (Grade C1).

Ergot dopamine agonists should not be the first choice of treatment (Grade C1).

Reports of excessive sleepiness by non-ergot dopamine agonist are accumulating (Grade C1).

Consider the risk of hallucination/delusion when a non-ergot dopamine agonist is used for elderly persons or to those who have cognitive impairment (Grade C1).

Improving the problematic symptoms (bradykinesia, postural instability, freezing of gait, gait disturbance, and others) is the first purpose.

The maintenance doses should be gradually increased or decreased (Grade C1).

Adjust the dosages according to the changes in the subjective feeling, the objective findings, and the side effects of the patients (Grade C1).

Unless an emergency occurs, do not change the maintenance doses of multiple drugs at one time (Grade C1).

Notify the patient that excessive daytime sleepiness and sudden onset of sleep may occur during the course of treatment of PD (Grade A).

For the sudden onset of sleep, change the dosage of anti-PD drugs, particularly, the dosage of a dopamine agonist (Grade B).

When a dopamine agonist is used, avoid working as drivers of cars, operators of machines, and in a high place (Grade C1).

As the ergot dopamine agonists (cabergoline > pergolide > bromocriptine) may cause cardiac valvulopathy, they should not be the first line dopamine agonists (Grade B).

When cabergoline or pergolide is used, explain the patient that cardiac valvulopathy, or cardiac, pulmonary, or retroperitoneal fibrosis may occur (Grade B).

When pergolide or cabergoline is used, check general physical examination, EKG, and chest X-ray (Grade B).

When pergolide or cabergoline is started, check physical examination, EKG, and chest X-ray at 3–6 months from the onset of the use of the agonist and at 6– 12 months interval thereafter (Grade B).

If symptoms of cardiac valvulopathy or serous fibrosis appear, discontinue the agonist as soon, and get consultation of a cardiologist if necessary (Grade C1).

If cabergoline or pergolide has been used, explain to the patient that cardiac valvulopathy may occur (Grade B).

When the patient develops edema in the lower extremities, get examination of the cardiac and renal specialists, and rule out the serious membrane fibrosis (Grade C1).

Edema in the lower extremities may improve by the change of anti-PD drugs or the use of diuretics (Grade C1).

The cause of malignant syndrome is most frequently the sudden discontinuation of anti-PD drugs, but dehydration, infections, and severe wearing off may also cause malignant syndrome.

Early detection of the possible malignant syndrome is effective in the treatment. When the patient develops fever, you should consider malignant syndrome (Grade C1).

For mild malignant syndrome, infusion and cooling are effective, and for moderate and severe malignant syndrome, the use of dantrolene and bromocriptine is necessary (Grade C1).

What should be done if the patient must be NPO (nothing by mouth) when the patient undergoes a surgical procedure or other emergencies?

On the day of the surgical procedure, give the intravenous infusion of L-dopa without a peripheral dopa decarboxylase inhibitor for approximately one hour.

The dosage of L-dopa should be 50–100 mg per oral L-dopa 100 mg with a peripheral dopa decarboxylase inhibitor. On day 2, a similar procedure should be continued, but if the dose of day 1 is insufficient, one may increase the dosage of L-dopa (Grade C1).

If oral treatment is impossible for a long period, an intestinal stomy should be placed.

Treatment of Motor Disturbances

Use L-dopa or a dopamine agonist when accompanied by rigidity and bradykinesia until the maximum dose of each drug according to the algorism of drug-naive PD (Grade A).

When the treatment of tremor did not meet the criteria, use anticholinergic (trihexyphenidyl) when the patient is young (Grade C1). The maintenance dose should not exceed 6 mg/day.

When the tremor is almost the sole manifestation, use trihexyphenidyl by increasing the dose until its maximum dose (6 mg/day), when the patient is young (Grade C1).

When the treatment is ineffective by (1) and (2), addition of selegiline, entacapone, or zonisamide should be tried (Grade C1).

When the drug treatment interferes with the patient's life because of the tremor, recommend surgical therapy (Grade B).

How to treat diurnal fluctuation of motor disturbances such as wearing off, on-off, no-on, and delayed on?

For wearing off, entacapone (Grade A), dopamine agonists (Grade B), and zonisamide (Grade B) shorten the off period; selegiline and zonisamide improve motor disturbances during off period (Grade B).

Frequent dosing of L-dopa and changing the dopamine agonist is also effective (Grade C1). When the above treatments do not suffice, surgical treatment is effective (Grade B).

For no-on and delayed on, L-dopa into empty stomach, dissolving L-dopa into liquid, and increasing individual dose of L-dopa are effective. (Grade C1).

For on-off, try managements of wearing off, no-on, and delayed on together.

How to treat off period dystonia?

Increase the dopamine agonist (Grade B) or L-dopa. For decreasing the off-period length, reducing the dose interval is good. Adding the entacapone (Grade C1), selegiline (Grade C1), or zonisamide (Grade C1) is as good.

For the early morning dystonia, either a dopamine agonist before sleeping or L-dopa on the awakening in the morning is helpful (Grade C1).

When the medical treatment is not satisfactory, deep brain stimulation in the subthalamus is effective; disruption or deep brain stimulation of the internal segment of the globus pallidus is also effective. If the patient needs bilateral surgery, the Committee recommends deep brain stimulation.

How to treat freezing of the gait?

Adjust the anti-PD treatment when the main symptoms of the motor disturbances are remaining (Grade A).

Reduce the off period of wearing off (Grade A).

Give the patient droxidopa in freezing resistant to dopaminergic treatment (Grade B).

Use rhythmical sensory cues (Grade B) and auxiliary instruments (Grade C1).

For Peak dose dyskinesia

Reduce or discontinue selegiline and entacapone (Grade B).

Reduce individual dose of L-dopa and increase the total number of dosing (Grade C1).

Reduce daily dose of L-dopa and add or increase a dopamine agonist (Grade B).

Use or increase amantadine (the upper limit of amantadine is 300 mg per day in Japan) (Grade B).

Deep brain stimulation of the subthalamus is effective. Disruption or deep brain stimulation of the internal segment of the globus pallidus, or disruption of the subthalamus is as effective. When the patient needs bilateral surgery, the Committee recommends deep brain stimulation.

Biphasic dyskinesia

The Committee recommended the following treatments without ordering.

Discontinue entacapone (Grade C1).

Increase the number of L-dopa dosing, while the individual dose is the same or increased (Grade C1).

Increase the individual dose of L-dopa and reduce the total number of dosing so that the occurrence of dyskinesia will be easier to anticipate (Grade C1).

Use or increase amantadine (Grade C1).

Biphasic dyskinesia may improve by deep brain stimulation of the subthalamus, disruption, or deep brain stimulation of the internal segment of the globus pallidus, or disruption of the subthalamus. When the patient needs bilateral surgery, the Committee recommends deep brain stimulation (Grade C1).

To treat abnormal posture

Give the patient the standard therapy of PD for stooped posture, and physical therapy to increase the mobility of the spine (Grade C1).

No established evidence is available for camptocormia, Pisa syndrome, and dropped head, but try the drug adjustment because improved syndromes were reported (Grade C1).

To treat dysphagia, drooling, and dysarthria

Estimate the degree of dysphasia and evaluate the treatment. Exercise in dysphagia is beneficial (Grade C1).

Drooling can be reduced by using anti-cholinergic gents (Grade B).

Short-term improvement can be obtained by speech therapy for dysarthria (Grade B).

Non-drug Treatment of Motor Disturbance

When the treatment with anti-PD drugs of major motor disturbance, and motor fluctuation and dyskinesia are not satisfactory, the Committee recommends DBS of the subthalamus or of the internal segment of the globus pallidus.

DBS of the subthalamus tends to be superior to DBS of the internal segment of the globus pallidus (Grade B).

The Committee recommends DBS of the subthalamus to reduce the maintenance doses of anti-PD drugs (Grade B).

The Committee recommends DBS of the subthalamus or the internal segment of the globus pallidus, or the disruption of the internal segment of the globus pallidus on the side contralateral to the prominent motor symptoms (Grade B).

When the parkinsonian tremor is not satisfactorily treated by anti-PD drugs, the Committee recommends disruption or DBS of the thalamus, disruption, or DBS of the internal segment of the globus pallidus, or the DBS of the subthalamus (Grade B).

Motor rehabilitation is efficacious in the physical function, the QOL, muscle strength, balance, and speed of gait (Grade A).

With external stimuli, particularly the auditory stimulation improves gait (Grade A). Try music therapy (Grade C1).

Physical exercise reduces fall (Grade B).

Education and health promoting programs are efficacious in improving motor disturbances (Grade C1).

Explanation of the disease so that the patients will get a hope in future has better maintenance effect in QOL (Grade C1).

Treatment of Non-motor Symptoms

Use a hypnotic/sedative drug for the nocturnal sleep disorders that accompany PD (Grade C1).

For the sleep disorders that related to PD such as tremor, or difficulty with turnover in a bed, increase the anti-PD drugs before sleeping.

For the sleep disorders that related to PD such as nocturnal polyuria, depression, hallucination, and/or delusion should be treated as such (Grade C1).

Use clonazepam for the REM-sleep behavior disorder (RBD) (Grade C1).

Use a dopamine agonist and clonazepam for the restless legs syndrome (RLS) (Grade B).

For the difficulty of awakening, try to improve the nocturnal insomnia and reduce a dopamine agonist (Grade C1).

For depression: When the depression did not get well despite the suffice treatment of PD, give a tricyclic anti-depressant (nortriptyline, amitriptyline), a selective serotonin reuptake inhibitor (SSRI) (sertraline, fluvoxamine), or a dopamine agonist (pramipexole, pergolide) (Grade B for nortriptyline, Grade C1 for other drugs).

Apathy associated with depression should be treated as indicated. There is no treatment that can be recommended for apathy not related to depression.

For psychiatric **fatigue**, no established treatment is available (Grade C2).

For somatic fatigue related to motor disturbances, dopaminergic treatment is effective (Grade C1).

When the patient is unable to see the **hallucination** and/or delusion as an objective view, treatment should be started (Grade C1).

Discontinue the drug when hallucination or delusion occurred or progressed after the addition of the drug (Grade C1).

Adjusting facilitating factors from general physical illnesses (Grade C1). Then reduce or discontinue drugs other than L-dopa."

If there is no improvement, add an atypical anti-psychotic (GradeC1). Quetiapine is expected to reduce hallucinations and delusions without much impairment of motor symptoms (Grade C1).

Donepezil can reduce hallucinations/delusions (Grade C1).

For impulse control disorders and dopamine dysregulation syndrome: reduce dopamine replacement therapy; particularly reduce or discontinue the dopamine agonist or change to another treatment (Grade C1).

Use donepezil for **dementia** associated with PD. (Grade B).

Anti-cholinergics may worsen the cognitive and executive functions. The reduction and discontinuation of the drug can improve the function. (Improvement after discontinuation) (Grade B).

It is recommended for not using anti-cholinergics in elderly or in patients with cognitive dysfunctions (Grade D).

For orthostatic hypotension: Encourage salt intake and raise the head while laying down flat (Grade C1).

Use midodrine HCL, fludrocortisone, or DOPS (Grade C1).

For **hyperactive detrusor muscles**, use of solifenacin, tolterodine, or imidafenacin is recommended. Other anti-cholinergics, oxybutynin, propiverine, propantheline, or flavoxate can be used (Grade C1).

When anti-cholinergics are not effective or unable to use because of side effects, paroxetine or milnacipran can be used (Grade C1)."

Difficulty in voiding can be treated by urapidil, an adrenergic blocking agent. Other drugs to be considered include tamsulosin and naftopidil (Grade C1).

Encourage intake of fibrous vegetables and water for constipation (Grade C1).

As drugs, magnesium oxide, senna, sennoside, and mosapride are as effective for constipation (Grade C1).

Use domperidone for nausea (Grade C1).

Sildenafil citrate (50–100 mg at one time) is effective for male **gonadal dysfunction** (Grade B).

When the **sweating** is profuse during off period, reduce the off period as possible, and when the sweating is profuse with dyskinesia, reduce dyskinesia as possible (Grade C1).

Exclude **sensory disturbances** and pain of other diseases.

Reduce off period, as L-dopa is effective for pain during off period (Grade B).

Future Treatment and Others

High frequency magnetic stimulation to the lateral frontal anterior region may result in improvement in depression (Grade C1). Safety in the long-term stimulation has not been established (Grade C2).

Electro-convulsive treatment should be considered only when drug refractory depression requires rapid improvement (Grade 1C).

No scientific base is present for electro-convulsive treatment anticipating improvement in motor dysfunctions (Grade 2C). Long-term safety has not been established (Grade C2).

It is not recommended to transplant fetal midbrain, although there is a report showing that transplantation of fetal midbrain is effective, if the patient is young and only has a mild disturbance of motor function (Grade D).

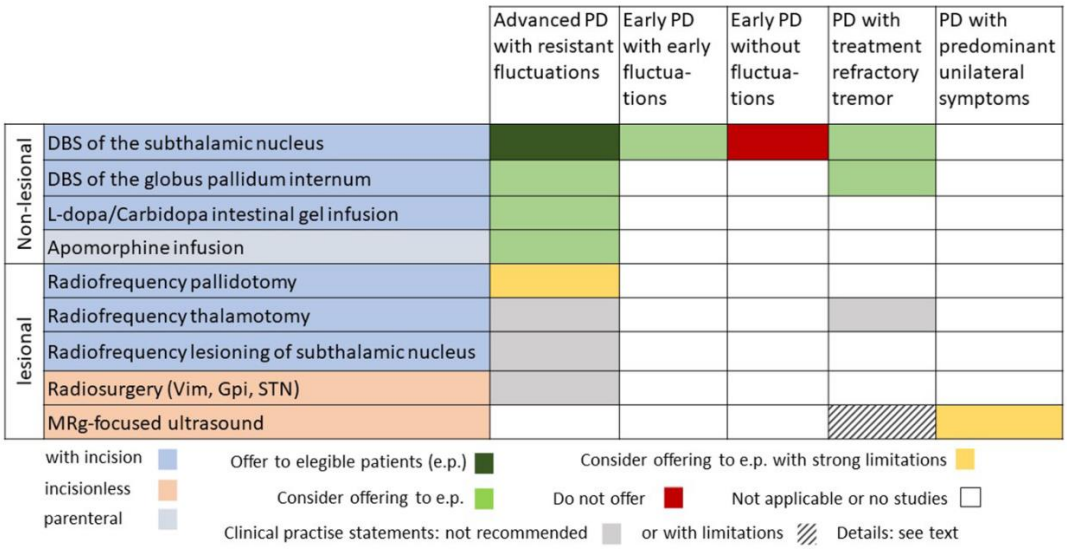
There is not enough data to discuss effects of transplantation (Grade C2).

There is not enough data to discuss the effects of gene therapy (Grade C2).

1.2.3 European Academy of Neurology/Movement Disorder Society Guideline on the Treatment of Parkinson's Disease: Invasive Therapies (2022)

These treatment guidelines were commissioned by the European Academy of Neurology and the European section of the Movement Disorder Society and are an update on the 2013 version previously published. They are developed according to the GRADE methodology.

Evidence for invasive therapies in PD is heterogeneous. Only some of these therapies have a strong scientific basis. They differ in their profile of effects and have been tested only for specific patient groups[19]. Figure 1 and table 5 summarize the main recommendations.



DBS, deep brain stimulation; Gpi, pallidum internum; l- dopa, levodopa; MRg, magnetic resonance imaging guided; PD, Parkinson's disease; STN, subthalamic nucleus; Vim, ventralis intermedius

Figure 1. *Recommendations for invasive therapies tested in different patient groups with randomized controlled studies. Retrieved from the 2022 European Academy of Neurology/Movement Disorder Society Guideline.*

Table 5. Summary of Recommendations for Invasive Therapies in Advanced Parkinson Disease

Recommendation	Evidence
Nonlesional therapies	
Offer subthalamic nucleus-deep brain stimulation (STN-DBS) to people with advanced PD if fluctuations are not satisfactorily controlled with medication or if tremor cannot be controlled with medication	15 voters, 100%
Consider offering STN-DBS to people with early PD and early fluctuations	15 voters, 100%
Do not offer DBS to people with early PD without fluctuations	16 voters, 100%
Both STN- DBS and pallidum internum (GPi)- DBS are effective to treat symptoms of advanced PD with fluctuations, but dopaminergic medication can be more reduced with STN-DBS	16 voters, 100%
Intrajejunal levodopa/carbidopa pump for advanced PD	
Consider offering levodopa-carbidopa intestinal gel (LCIG) for people with advanced PD if fluctuations are not satisfactorily controlled with medication	15 voters, 100%
Apomorphine infusion for advanced PD	
Consider offering apomorphine pump infusion for people with advanced PD if fluctuations are not satisfactorily controlled with medication	15 voters, 100%
Radiofrequency thermocoagulation	
Consider offering unilateral pallidotomy with radiofrequency thermocoagulation to people with advanced PD who experience troublesome fluctuations and for which DBS or pump therapies is not a treatment option	16 voters, 100%
RCTs for unilateral radiofrequency thermocoagulation of the thalamus for parkinsonian tremor or advanced PD are not available, and formal recommendations are not possible. As DBS has a better safety profile, this GL task force does not recommend this treatment if safer treatments are available	16 voters, 100%
RCTs for unilateral radiofrequency thermocoagulation of the STN for people with PD are not available. Due to potential high risks for AEs, it is not recommended by the GL task force	16 voters, 100%
Radiosurgery with gamma radiation	
RCTs for unilateral gamma radiation radiosurgery of any of the three target nuclei are not available for people with PD. Due to	16 voters, 100%

potential high risks for AEs, this GL task force does not recommend this treatment	
Magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS)	
No sufficient RCTs available for uni- or bilateral MRgFUS of the thalamus for medically resistant tremor in PD. Despite promising preliminary data, this treatment should only be applied within clinical studies or registries	16 voters, 100%
Do not use MRgFUS of the pallidum for advanced PD with fluctuations outside clinical studies	16 voters, 100%
Consider using unilateral MRgFUS of the STN in people with distinctly unilateral PD only within clinical studies or registries due to the limited data on this new treatment	16 voters, 100%

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs to delist due to withdrawal from the market among others, and the fourth details drug that have been recently approved by the FDA and/or EMA but are currently SFDA-registered.

2.1 Additions

Since the last CHI report published in 2020, rasagiline (oral tablets) and apomorphine (solution for infusion) were registered by the SFDA.

2.1.1 Rasagiline

Table 6. Rasagiline Drug Information

SCIENTIFIC NAME RASAGILINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	G20
Drug Class	Anti-Parkinson Agent
Drug Sub-class	MAO Type B Inhibitor
ATC Code	N04BD02

Pharmacological Class (ASHP)	28:16.04.12 Monoamine Oxidase Inhibitors
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Parkinson disease: Oral:** Monotherapy or adjunctive therapy (not including levodopa): 1 mg once daily (maximum: 1 mg/day). Adjunctive therapy with levodopa: Initial: 0.5 mg once daily; may increase to 1 mg once daily based on response and tolerability (maximum: 1 mg/day).
Maximum Daily Dose Adults*	10 mg/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Kidney Impairment:** Mild to moderate impairment: No dosage adjustment necessary. Severe impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, rasagiline is primarily renally eliminated. **Hepatic Impairment:** Mild impairment (Child-Pugh score 5 to 6): Maximum dose: 0.5 mg once daily Moderate to severe impairment (Child-Pugh score 7 to 15): Use is not recommended.
Prescribing edits*	AGE, CU, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): Can be used as monotherapy or as adjunctive therapy.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a neurologist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	

EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Headache, dyspepsia, depression, flu-like symptoms, depression Most serious: Post marketing: malignant melanoma, delirium, psychotic symptoms
Drug Interactions*	Risk X: Alcohol Alpha-/beta- agonists Amphetamines Apraclonidine Atomoxetine Atropine, ophthalmic Bezafibrate Bromperidol Buprenorphine Buproprion Butorphanol Carbamazepine Carbinoxamine Codeine Cyclobenzaprine Cyproheptadine Deutetrabenazine Dexmethylphenidate Dextromethorphan Diamorphine Diethylpropion Diphenoxylate EPINEPHrine Fenfluramine FentaNYL FluvoxaMINE Gepirone Guanethidine HYDROmorphone Indoramin Iobenguane Radiopharmaceutical Products

	Isometheptene Levomethadone Levonordefrin Linezolid Meptazinol Mequitazine Methadone Methotrimeprazine Methyldopa Methylene blue Methylphenidate Metoclopramide Mianserin MAO inhibitors (type B) Morphine Nefazodone Normethadone Opium Oxymorphone Ozanimod Pheniramine Pholcodine Pizotifen Reboxetine SSRIs Serotonergic agents Serotonergic non-opioid CNS depressants Serotonergic opioids (high-risk) SNRIs Solriamfetol St John's Wort Sufentanil Tapentadol Tetrabenazine TCAs Tyrosine Valbenazine Viloxazine
Special Population	**Surgical patients:** according to many of the MAO inhibitor manufacturers, use within 10 days prior to elective

	surgery is contraindicated. The decision to continue or withhold MAO inhibitors must be done in collaboration with the patient's psychiatrist. Currently, an MAO-safe anesthetic technique which excludes the use of meperidine and indirect-acting adrenergic agonists is recommended for patients requiring continued MAO inhibitor therapy
Pregnancy	Adverse effects have been observed in animal reproduction studies. Information related to rasagiline use in pregnancy is limited
Lactation	It is not known if rasagiline is present in breast milk. The decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	- Concomitant use of an monoamine oxidase inhibitor (including selective MAO-B inhibitors), meperidine, methadone, propoxyphene, or tramadol within 14 days of rasagiline; concomitant use with cyclobenzaprine, dextromethorphan, or St John's wort. - Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. - Canadian labeling: Additional contraindications (not in the US labeling): Hypersensitivity to rasagiline or any component of the formulation; concomitant use with serotonin and norepinephrine reuptake inhibitors; selective serotonin reuptake inhibitors;

	tapentadol; tricyclic, tetracyclic, or triazolopyridine antidepressants.
Monitoring Requirements	Blood pressure (baseline, at periodic intervals, and as clinically indicated); liver and renal function (baseline and as clinically indicated); skin examination for presence of melanoma (at periodic intervals).
Precautions	- CNS effects - Dyskinesia - Impulse control disorders - Hypertension - Melanoma - Orthostatic hypotension - Serotonin syndrome - Somnolence - Hepatic impairment - Psychotic disorders - Antiparkinsonian discontinuation syndrome - Tyramine-containing products
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Parkinson disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for rasagiline.

Table 7. Rasagiline HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATIONS
Rasagiline	NICE	Not available
	CADTH	Not available
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT – RASAGILINE

Rasagiline can be used as monotherapy or in combination with levodopa for the treatment of Parkinson's disease. There are no recommendations by HTA bodies regarding its use.

2.1.2 Apomorphine

Table 8. Apomorphine Drug Information

SCIENTIFIC NAME APOMORPHINE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	G20
Drug Class	Anti-Parkinson agent
Drug Sub-class	Dopamine Agonist
ATC Code	N04BC07
Pharmacological Class (ASHP)	Dopamine agonist
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	Subcutaneous
Dose (Adult) [DDD]*	Initial test dose 0.2 mL (2 mg), medical supervision required. Subsequent dosing is based on both tolerance and response to initial test dose. - If patient tolerates test dose and responds: Starting dose: 0.2 mL (2 mg) as needed; may increase dose in 0.1 mL (1 mg) increments every few days; maximum dose: 0.6 mL (6 mg) - If patient tolerates but does not respond to 0.2 mL (2 mg) test dose: Second test dose: 0.4 mL (4 mg) - If patient tolerates and responds to 0.4 mL (4 mg) test dose: Starting dose: 0.3 mL (3 mg), as needed for "off" episodes; may

	increase dose in 0.1 mL (1 mg) increments every few days; maximum dose: 0.6 mL (6 mg) - If patient does not tolerate 0.4 mL (4 mg) test dose: Third test dose: 0.3 mL (3 mg) - If patient tolerates 0.3 mL (3 mg) test dose: Starting dose: 0.2 mL (2 mg) as needed for "off" episodes; after a few days, may increase dose up to 0.3 mL (3 mg). Medically supervise for any subsequent dose increases >0.3 mL (3 mg). - If therapy is interrupted for >1 week, restart at 0.2 mL (2 mg) and gradually titrate dose.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered kidney function:** Mild to moderate impairment: Initial test dose: 0.1 mL (1 mg); Starting dose: 0.1 mL (1 mg) as needed. Severe impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Hepatic impairment:** Mild to moderate impairment: No dosage adjustment necessary; use caution. Severe impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a neurologist.	

PA (Prior Authorization): Should be provided only in units that have sufficient experience and resources.	
QL (Quantity Limit): N/A	
ST (Step Therapy): For use in advanced Parkinson disease.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Angina pectoris, chest pain, chest pressure, hypotension, orthostatic hypotension, syncope, nausea, oral paresthesia, vomiting, injection-site reaction, bruising at injection site, dizziness, drowsiness, yawning Most serious: Falling, hallucination, dyskinesia
Drug Interactions*	Alcohol (ethyl) Alizapride Amisulpride (injection) Amisulpride (oral) Antiemetics (5HT3 antagonists) Bromperidol Methotrimeprazine Metoclopramide Sulpiride
Special Population	Older adult: Adverse effects (confusion and hallucinations), some serious, are reported more frequently in patients ≥ 65 years; use with caution. Patients at risk for torsades de pointes: Use with caution in patients with risk factors for torsades de pointes (hypokalemia, hypomagnesemia, bradycardia, concurrent use of drugs that prolong QTc, or genetic predisposition).
Pregnancy	Adverse events have been observed in animal reproduction studies.
Lactation	It is not known if apomorphine is excreted in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding

	during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to apomorphine, any component of the formulation, or to a sulfite; concomitant use with 5-HT3 antagonists. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. Canadian labeling: Additional contraindications (not in US labeling): Concomitant use with antihypertensives or vasodilators; severe hepatic or renal impairment.
Monitoring Requirements	Supine and standing BP and pulse (for SUBQ, monitor Predose and 20-, 40-, and 60 minutes post dose with each test dose); signs and symptoms of hemolytic anemia; orthostatic hypotension; drowsiness or sleepiness; mental status and behavioral changes.
Precautions	- GI effects: Severe nausea and vomiting may occur. Pretreatment with antiemetic (eg, trimethobenzamide) is necessary and should be started 3 days prior to initiation of therapy and continued only as long as necessary to control nausea/vomiting, and generally no longer than 2 months. - Hallucinations/psychosis: May cause hallucinations or psychotic-like behavior or thoughts which may be severe; avoid in patients with major psychotic disorders. - Hemolytic anemia: if it occurs, consider discontinuing treatment. - Hypersensitivity reaction: if it occurs, discontinue and do not restart.

	- Impulse control disorders: Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases. - Orthostatic hypotension/syncope: Carefully monitor for signs and symptoms of postural hypotension (especially during dose escalation). Avoid ethanol during therapy. - Pleural/retroperitoneal fibrosis: monitor closely for signs and symptoms of fibrosis; effects may or may not be reversible. - Priapism: severe priapism may require medical attention. - Somnolence: Use with caution in patients receiving other CNS depressants or psychoactive agents. Effects with other sedative drugs or ethanol may be potentiated.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Parkinson disease treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for apomorphine.

Table 9. Apomorphine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATIONS
Apomorphine	NICE	Not available
	CADTH[20]	**February 2021:** Recommendation available for sublingual formulation
	HAS	Not available
	IQWIG	Not available
	PBAC	Not available

CONCLUSION STATEMENT – APOMORPHINE

Subcutaneous apomorphine infusions or 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). There are no recommendations issued by HTA bodies regarding its use.

2.2 Modifications

There are no new modifications regarding the prescribing edits mentioned in the previous CHI report.

2.3 Delisting

Selegiline and Trihexyphenidyl were withdrawn from the SFDA.

2.4 Other Drugs

The following drugs detailed below are approved by the FDA and/or EMA for the management of Parkinson disease but are not currently registered by the SFDA.

2.4.1 Levodopa Inhalation

In December 2018, the FDA approved levodopa inhalation powder for intermittent treatment of "off" episodes in people with PD. The recommended dose is 84 mg up to 5 times daily as needed when symptoms of an "off" period return; maximum: 84 mg/dose and 420 mg/day. The concurrent use or within 14 days of nonselective MAOIs (eg, phenelzine, tranylcypromine) use is a contraindication to the use of inhaled levodopa. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information[21].

Approval was based on the SPAN-PD trial, a randomized, double-blind, placebo-controlled, phase 3 trial published in *Lancet Neurology* in 2019. 351 patients were enrolled and randomly assigned to receive CVT-301 (levodopa inhalation) 60 mg (115 patients), CVT-301 84 mg (120 patients), or placebo (116 patients). The least-squares mean difference in UPDRS motor score change from predose to 30 min postdose was -5·91 (SE 1·50, 95% CI -8·86 to -2·96) for the placebo group, and -9·83 (1·51; -12·79 to -6·87) for the CVT-301 84 mg group (between-group difference -3·92 [-6·84 to -1·00]; p=0·0088)[22].

2.4.2 Opicapone

ONGENTYS® (opicapone), is a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor, approved by the FDA in 2020 and indicated for adjunctive treatment of Parkinson's disease in patients treated with levodopa

and carbidopa. Opicapone has no therapeutic effect on its own. Instead, it enhances the therapeutic effect of levodopa by inhibiting peripheral conversion of levodopa to 3-O-methyldopa, which also allows for increase CNS exposure to levodopa and Dopamine. Main characteristics are listed in the table below:

Table 10. Opicapone Drug Information

ONGENTYS® (Opicapone)	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2020
EMA	Yes, 2016
MHRA	No
PMDA	No
Indication (ICD-10)	G20
Drug Class	Dopaminergic anti-Parkinson drug
Drug Sub-class	Reversible catechol-O-methyltransferase (COMT) inhibitor
ATC Code	N04BX04
Pharmacological Class (ASHP)	Reversible catechol-O-methyltransferase (COMT) inhibitor
DRUG INFORMATION	
Dosage Form	**Capsule: 25 mg and 50 mg.**
Route of Administration	Oral use
Dose (Adult) [DDD]*	The recommended dosage is 50 mg administered orally once daily at bedtime. Patients should not eat food for 1 hour before and for at least 1 hour after intake of ONGENTYS.
Maximum Daily Dose Adults*	100 mg per day
Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	The recommended dosage in patients with moderate hepatic impairment is 25 mg orally once daily at bedtime; avoid use in patients with severe hepatic impairment. No dosage adjustment is required for patients with mild, moderate, or severe renal impairment.

Prescribing edits*	AGE, CU, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): Approved as adjunctive treatment to levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a neurologist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common adverse reactions (≥4% and > placebo): dyskinesia, constipation, blood creatine kinase increased, hypotension/syncope, and weight decreased.
Drug Interactions*	Concomitant use of ONGENTYS with non-selective MAO inhibitors is contraindicated [see Contraindications. Selective MAO-B inhibitors can be used concomitantly with ONGENTYS.
Special Population	Pregnancy: Based on animal data, may cause fetal harm. Avoid use in patients with end-stage renal disease.
Pregnancy	The background risk for major birth defects and miscarriage in patients with Parkinson's disease is unknown.
Lactation	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ONGENTYS and any potential adverse effects on the breastfed infant from ONGENTYS or from the underlying maternal condition.
Contraindications	Concomitant use of non-selective monoamine oxidase (MAO) inhibitors. History of pheochromocytoma,

	paraganglioma, or other catecholamine secreting neoplasms.
Monitoring Requirements	- Monitor patients with severe renal impairment for adverse reactions and discontinue ONGENTYS if tolerability issues arise. - Monitor patients for hypotension (orthostatic and non-orthostatic) and advise patients about the risk for syncope and presyncope. If these adverse reactions occur, consider discontinuing ONGENTYS or adjusting the dosage of other medications that can lower blood pressure. - Monitor for changes in heart rate, rhythm, and blood pressure in patients concomitantly treated with ONGENTYS and drugs metabolized by COMT.
Precautions	- Cardiovascular Effects with Concomitant Use of Drugs Metabolized by Catechol-O-Methyltransferase (COMT): May cause arrhythmias, increased heart rate, and excessive changes in blood pressure. Monitor patients when treated concomitantly with products metabolized by COMT. - Falling Asleep During Activities of Daily Living: Advise patients prior to treatment. - Hypotension/Syncope: If occurs, consider discontinuing ONGENTYS or adjusting dosage of other medications that can lower blood pressure. - Dyskinesia: May cause or exacerbate dyskinesia; consider levodopa or dopaminergic medication dose reduction. - Hallucinations and Psychosis: Consider stopping ONGENTYS if occurs.

	- Impulse Control/Compulsive Disorders: Consider stopping ONGENTYS if occurs. - Withdrawal-Emergent Hyperpyrexia and Confusion: When discontinuing ONGENTYS, monitor patients and consider adjustment of other dopaminergic therapies as needed.
Black Box Warning	None
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The below table lists the health technology Assessment recommendations of ONGENTYS® (Opicapone) by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH). Key conclusions are listed verbatim from their original source.

Table 11. Opicapone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Opicapone	**CADTH**	**2022:** Submission was temporarily suspended. It was voluntarily withdrawn by the sponsor on 9 Jun 2022.
	NICE	**2017:** Evidence summary reviewed 1 randomized placebo- and active-controlled trial in people with Parkinson's disease of at least 3-year duration, who were taking a stable dose of levodopa and experiencing end-of-dose motor fluctuations: Overall, opicapone was well tolerated with a relatively low incidence of adverse events compared with placebo and entacapone. Dyskinesia was the most commonly reported adverse event. **Specialists who commented on this evidence summary suggested that Opicapone may be an option to consider when entacapone is not tolerated or is inadequate at controlling symptoms.**

		The NICE guideline on Parkinson's disease makes recommendations on the place in therapy of adjuvant treatments. The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment.
	HAS	N/A
	IQWIG	**2017:** The data presented by the company were unsuitable to draw conclusions on the added benefit of Opicapone in comparison with the appropriate comparator therapy (ACT). No relevant data were available for the benefit assessment of Opicapone in comparison with the ACT in adults with Parkinson disease and end-of-dose motor fluctuations. No relevant data were available for the assessment of opicapone as adjunctive therapy to levodopa/ DOPA decarboxylase inhibitors (DDCI) preparations in adult patients with Parkinson disease and end-of-dose motor fluctuations who cannot be stabilized on those combinations. Hence there was no hint of an added benefit of Opicapone in comparison with the ACT. An added benefit is therefore not proven.
	PBAC	N/A

CONCLUSION STATEMENT – OPICAPONE

ONGENTYS® (Opicapone) is a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor, indicated for adjunctive treatment of Parkinson's disease in patients treated with levodopa and carbidopa. opicapone has no therapeutic effect on its own. It was approved by both FDA and EMA but not registered by SFDA yet. Although it was mentioned in the NICE guidelines and the comments of specialist suggested that it may be an option to consider when entacapone is not tolerated or is inadequate at controlling symptoms, the IQWIG HTA assessment stated that there was no hint of an added benefit of Opicapone in comparison with appropriate comparatory therapies. An added benefit is therefore not proven. Based on the above and knowing that Opicapone is not SFDA registered yet, **we do not recommend adding Ongensys® adjunctive treatment of Parkinson's disease.**

2.4.3 Istradefylline

NOURIANZ® is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes approved by FDA in 2019. Main characteristics are listed in the table below:

Table 12. Istradefylline Drug Information

NOURIANZ™ (Istradefylline)	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2019
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	G20
Drug Class	Miscellaneous anti-parkinson agent
Drug Sub-class	Adenosine receptor antagonist
ATC Code	N04CX01
Pharmacological Class (ASHP)	Selective adenoside A2A receptor antagonist
DRUG INFORMATION	
Dosage Form	**Tablets: 20 mg and 40 mg**
Route of Administration	Oral use
Dose (Adult) [DDD]*	The recommended dosage is 20 mg orally once daily. The dosage may be increased to a maximum of 40 mg once daily. May be taken with or without food. Patients with hepatic impairment: Maximum recommended dosage with moderate hepatic impairment is 20 mg once daily; use of NOURIANZ in patients with severe hepatic impairment should be avoided. Patients who smoke 20 or more cigarettes per day (or the equivalent of another tobacco product): Recommended dosage is 40 mg once daily.
Maximum Daily Dose Adults*	40 mg

Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	None
Prescribing edits*	AGE, CU, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): Approved for the treatment of Parkinson disease, in combination with levodopa/carbidopa, in adult patients experiencing "off" episodes.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a neurologist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	The most common adverse reactions (at least 5% and more frequent than placebo) were dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia.
Drug Interactions*	Strong CYP 3A4 inhibitors: Recommended maximum dosage with concomitant use is 20 mg once daily. Strong CYP 3A4 inducers: Avoid use
Special Population	Pregnancy: Based on animal data, may cause fetal harm.
Pregnancy	The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.
Lactation	The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NOURIANZ, and any potential adverse effects on the breastfed infant from NOURIANZ or from the underlying maternal condition.
Contraindications	None

Monitoring Requirements	- Closely monitor patients with moderate hepatic impairment for adverse reactions when on NOURIANZ treatment. Avoid use of NOURIANZ in patients with severe hepatic impairment (Child-Pugh C). - Monitor patients for dyskinesia or exacerbation of existing dyskinesia.
Precautions	- Dyskinesia: Monitor patients for dyskinesia or exacerbation of existing dyskinesia Hallucinations / Psychotic Behavior: Consider dosage reduction or stopping NOURIANZ if occurs. - Impulse Control / Compulsive Behaviors: Consider dosage reduction or stopping NOURIANZ if occur.
Black Box Warning	None
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

None of the health technology Assessment agencies/institutes/authorities including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), provided a recommendation for NOURIANZ™ (Istradefylline).

CONCLUSION STATEMENT – ISTRADEFYLLINE

NOURIANZ™ (Istradefylline) is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes approved by FDA in 2019. It is not registered by SFDA yet. None of the HTA authorities provided an assessment for the use of Istradefylline for PD. At the same time, it was only recommended by the Japanese guidelines as adjunctive therapy for PD. **As a result, we do not recommend adding NOURIANZ™ (Istradefylline) for PD patients especially as it is not SFDA registered.**

2.4.4 Safinamide

XADAGO® (safinamide) is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes approved by FDA in 2017.

XADAGO has not been shown to be effective as monotherapy for the treatment of PD. Main characteristics are listed in the table below:

Table 13. Safinamide Drug Information

XADAGO® (safinamide)	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2017
EMA	Yes, 2015
MHRA	Yes, 2016
PMDA	No
Indication (ICD-10)	G20
Drug Class	Anti-Parkinson agent
Drug Sub-class	Monoamine oxidase inhibitor type B (MAO-B)
ATC Code	N04BD03
Pharmacological Class (ASHP)	Monoamine oxidase inhibitor type B (MAO-B)
DRUG INFORMATION	
Dosage Form	**Tablets: 50 mg and 100 mg**
Route of Administration	Oral use
Dose (Adult) [DDD]*	Start with 50 mg administered orally once daily at the same time of day; after two weeks, the dose may be increased to 100 mg once daily, based on individual need and tolerability. Hepatic Impairment: Do not exceed 50 mg once daily in patients with moderate hepatic impairment; contraindicated in patients with severe hepatic impairment.
Maximum Daily Dose Adults*	100 mg
Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	Hepatic Impairment: Do not exceed 50 mg once daily in patients with moderate hepatic impairment; contraindicated in patients with severe hepatic impairment.

Prescribing edits*	AGE, CU, MD
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): Approved as adjunctive treatment to carbidopa/levodopa in patients with Parkinson disease experiencing "off" episodes.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a neurologist.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common adverse reactions (incidence on XADAGO 100 mg/day at least 2% greater than placebo) were dyskinesia, fall, nausea, and insomnia.
Drug Interactions*	Selective Serotonin Reuptake Inhibitors: Monitor patients for serotonin syndrome. Sympathomimetic Medications: Monitor patients for hypertension. Tyramine: Risk of severe hypertension. Substrates of Breast Cancer Resistance Protein (BCRP): Potential increase in plasma concentration of BCRP substrate.
Special Population	Pregnancy: Based on animal data, may cause fetal harm.
Pregnancy	Pregnancy Category C
Lactation	T Skin discoloration, presumed to be caused by hyperbilirubinemia resulting from hepatobiliary toxicity, was observed in rat pups indirectly exposed to safinamide through the milk during the lactation period. It is not known whether this drug is present in human milk. Decision should be made whether to discontinue nursing or to discontinue

	the drug, taking into account the importance of the drug to the mother
Contraindications	Concomitant use of the following drugs: - Other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (e.g., linezolid). - Opioid drugs (e.g., tramadol, meperidine and related derivatives); selective norepinephrine reuptake inhibitors; tri-or tetra-cyclic or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John's wort. - Dextromethorphan A history of a hypersensitivity to safinamide Severe hepatic impairment (Child-Pugh C)
Monitoring Requirements	- Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting XADAGO. Medication adjustment may be necessary if elevation of blood pressure is sustained. - Periodically monitor patients for visual changes in patients with a history of retinal/macular degeneration, uveitis, inherited retinal conditions, family history of hereditary retinal disease, albinism, retinitis pigmentosa, or any active retinopathy (e.g., diabetic retinopathy). - Monitor patients for symptoms of serotonin syndrome if selective serotonin re-uptake inhibitors are used by patients treated with XADAGO. - Monitor patients for increased pharmacologic or adverse effect of

	the BCRP substrates if XADAGO is used concomitantly.
Precautions	- May cause or exacerbate hypertension - May cause serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs - May cause falling asleep during activities of daily living - May cause or exacerbate dyskinesia; consider levodopa dose reduction - May cause hallucinations and psychotic behavior - May cause problems with impulse control/compulsive behaviors - May cause withdrawal-emergent hyperpyrexia and confusion.
Black Box Warning	None
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The below table lists the health technology Assessment recommendations of XADAGO® (safinamide) by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH) and Institute for Quality and Efficiency in Healthcare (IQWIG). Key conclusions are listed verbatim from their original source.

Table 14. Safinamide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Safinamide	**CADTH**	**2020:** The CADTH Canadian Drug Expert Committee (CDEC) recommends that safinamide **should not be reimbursed** for the treatment of for add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing "OFF" episodes while on a stable dose of levodopa. Onstryv (safinamide tablets) is indicated as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD) in patients experiencing off episodes while on a stable dose of levodopa. Onstryv has not been shown to be effective as monotherapy for the treatment of PD.

		The relative efficacy of safinamide compared with other add-on treatments used for PD is unclear due to major limitations associated with the manufacturer-submitted indirect treatment comparison (ITC) and one published ITC. The main limitations of both studies were inadequate reporting of study and patient characteristics. The lack of comparative data to other MAO-B inhibitors, in particular, makes the reversible inhibition mechanism of safinamide uncertain in terms of clinical impact on the patient. There is no evidence that safinamide addresses an unmet need that is not already addressed by other add-on treatments currently reimbursed for the treatment of PD, including better management of OFF episodes, improved quality of life, or improved non-motor outcomes relevant to patients such as sleep, pain, mood and constipation.
	NICE	**2017:** Safinamide is the third MAO-B inhibitor licensed in the UK as add-on treatment to levodopa in people with Parkinson's disease who are experiencing motor fluctuations. It is more expensive than other MAO-B inhibitors. There are no head-to-head studies comparing the efficacy and safety of safinamide with other active treatments, including other MAO-B inhibitors. The NICE guideline on Parkinson's disease makes recommendations on the place in therapy of adjuvant treatments. The choice of treatment will depend on the person's clinical and lifestyle characteristics, and their preferences, after an informed discussion about the benefits and risks of treatment[23].
	HAS	N/A
	IQWIG	**2017:** No suitable data were available for assessing the added benefit of safinamide, neither for a direct comparison nor for an indirect comparison. Hence the added benefit of safinamide versus the ACT is not proven.
	PBAC	N/A

CONCLUSION STATEMENT – SAFINAMIDE

XADAGO® (safinamide) is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes approved by FDA in 2017, it was approved by FDA, EMA and MHRA, but not registered by SFDA yet. None of the three HTA authorities provided a positive recommendation for reimbursement of Sadinamide for PD patients. At the same time, none of the above guidelines recommended its use. As a result, **we do not recommend adding XADAGO® (safinamide) for PD patients especially as it is not registered by SFDA.**

Section 3.0 Key Recommendations Synthesis

Parkinson disease (PD) is a neurodegenerative disorder that causes both motor and nonmotor symptoms and increases in prevalence with age.

Parkinson disease is chronic and progressive in nature, decreasing the quality of life for both patients with the disease and their caregivers and placing an onerous economic burden on society.

The treatment options for the alleviation of motor symptoms in the early stages of PD are based on the enhancement of dopaminergic tone with levodopa, monoamine oxidase inhibitors, dopamine agonists (DAs), or a combination thereof.

The choice of initial treatment is influenced by the potential for neuropsychiatric adverse effects associated with DAs and dyskinesia and motor fluctuations associated with levodopa.

Three new medications were approved by FDA as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes, however, none of them was registered by SFDA.

ONGENTYS® (Opicapone) is a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor, indicated for adjunctive treatment of Parkinson's disease in patients treated with levodopa and carbidopa. Opicapone has no therapeutic effect on its own. It was approved by both FDA and EMA but not registered by SFDA yet. Although it was mentioned in the NICE guidelines and the comments of specialist suggested that it may be an option to consider when entacapone is not tolerated or is inadequate at controlling symptoms, the IQWIG HTA assessment stated that there was no hint of an added benefit of Opicapone in comparison with appropriate comparatory therapies. An added benefit is therefore not proven. Based on the above and knowing that Opicapone is not SFDA registered yet, **we do not recommend adding Ongensys® adjunctive treatment of Parkinson's disease.**

NOURIANZ™ (Istradefylline) is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes approved by FDA in 2019. It is not registered by SFDA yet. None of the HTA authorities provided an assessment for

the use of Istradefylline for PD. At the same time, it was only recommended by the Japanese guidelines as adjunctive therapy for PD. **As a result, we do not recommend adding NOURIANZ™ (Istradefylline) for PD patients especially as it is not SFDA registered.**

XADAGO® (safinamide) is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes approved by FDA in 2017, it was approved by FDA, EMA and MHRA, but not registered by SFDA yet. None of the three HTA authorities provided a positive recommendation for reimbursement of Sadinamide for PD patients. At the same time, none of the above guidelines recommended its use. As a result, **we do not recommend adding XADAGO® (safinamide) for PD patients especially as it is not registered by SFDA.**

No changes or modifications were made to existing drugs but some drugs were withdrawn from Saudi FDA.

Section 4.0 Conclusion

This report serves as **an annex to the previous Parkinson disease (PD) report** and aims to provide recommendations to aid in the management of PD. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with PD. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:
Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.
Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin

Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

I. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

II. What information are available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

III. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

IV. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations
https://www.whocc.no/ddd/definition_and_general_considera/

V. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Adopted

Grade of research[24]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search

The following is the result of the PubMed search conducted for PD search:

Query	Filters	Search Details	Results
parkinsonism	Guideline, in the last 5 years	("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields]) AND ((y_5[Filter]) AND (guideline[Filter]))	26
parkinson	Guideline, in the last 5 years	("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields]) AND ((y_5[Filter]) AND (guideline[Filter]))	26
((parkinson disease) AND (prakinson)) AND (parkinsonism) - Spellcheck off	Guideline, in the last 5 years	(("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields]) AND "prakinson"[All Fields] AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR	0

		"parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	
((parkinson disease) AND (parkinson)) AND (parkinsonism)	Guideline, in the last 5 years	(("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All Fields] OR "parkinsons s"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields] OR "parkinson"[All Fields] OR "parkinson s"[All Fields] OR "parkinsonian disorders"[MeSH Terms] OR ("parkinsonian"[All Fields] AND "disorders"[All Fields]) OR "parkinsonian disorders"[All Fields] OR "parkinsonism"[All Fields] OR "parkinsonisms"[All	18

		Fields] OR "parkinsons s"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	
parkinson's disease	Guideline, in the last 5 years	("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinson s disease"[All Fields]) AND ((y_5[Filter]) AND (guideline[Filter]))	18
parkinson's disease	in the last 5 years	("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinson s disease"[All Fields]) AND (y_5[Filter])	43,092

Appendix D. Treatment Algorithm

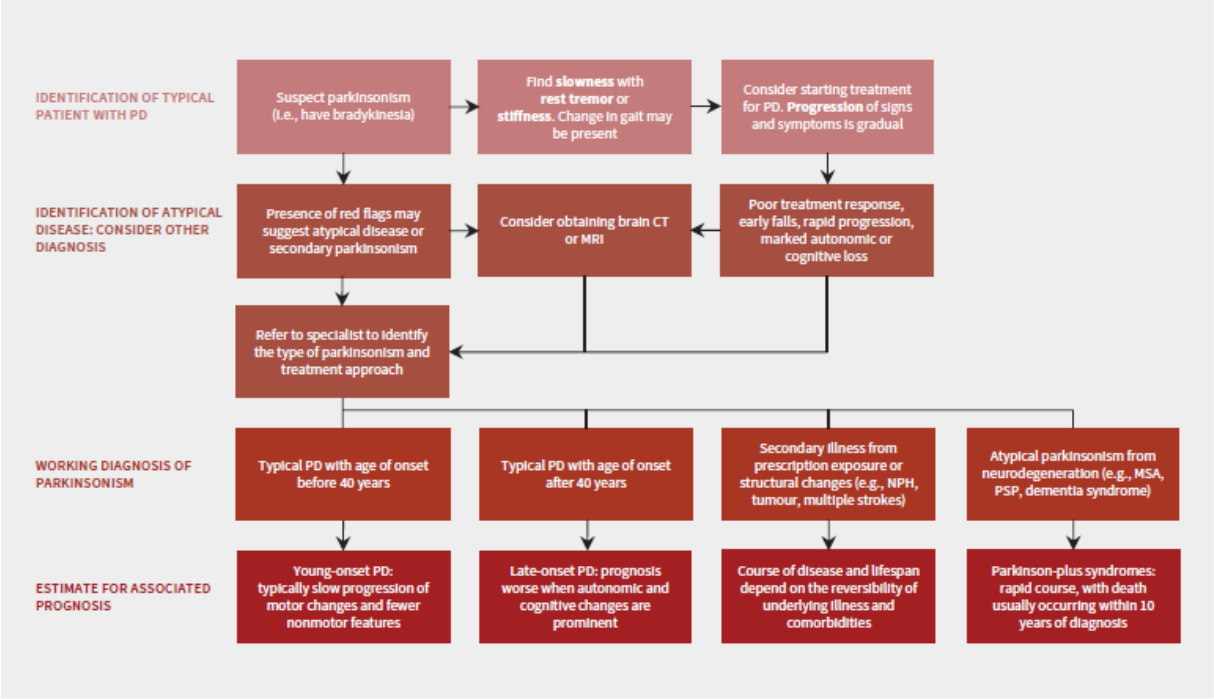

Figure 2. *Diagnosis and Prognosis of Parkinson Disease (PD)*

Adapted from Canadian guideline for Parkinson disease[13].
Note: CT = computed tomography, MRI = magnetic resonance imaging, MSA = multiple system atrophy, NPH = normal pressure hydrocephalus, PSP = progressive supranuclear palsy.

Appendix E. Scope

2020 Version	Changes Performed	2023 (Current version)	Rationale/Description
Not available	New section	Scope	Summarize the main changes and updates between the 2020 and 2023 versions
Executive Summary	New section	Background	A general overview covering pathophysiological and epidemiological aspects was added.
Section 1. Parkinson disease CLINICAL GUIDELINES			
Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology 2006.	**Updated**	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice, Guideline Summary A Report of the AAN Guideline Subcommittee, 2021.	Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary. A Report of the AAN Guideline Subcommittee Tamara Pringsheim, Gregory S. Day, Don B. Smith, Alex Rae-Grant, Nicole Licking, Melissa J. Armstrong, Rob M.A. de Bie, Emmanuel Roze, Janis M. Miyasaki, Robert A. Hauser, Alberto J. Espay, Justin P. Martello, Julie A. Gurwell, Lori Billinghurst, Kelly Sullivan, Michael S. Fitts, Nicholas Cothros, Deborah A. Hall, Miriam Rafferty, Lynn Hagerbrant, Tara Hastings, Mary Dolan O'Brien, Heather Silsbee, Gary Gronseth, Anthony E. Lang, on behalf of the Guideline Subcommittee of the AAN

			Neurology Nov 2021, 97 (20) 942-957; DOI: 10.1212/WNL.0000000000012868
Not available	New section	Canadian guideline for Parkinson disease, 2019	Grimes D, Fitzpatrick M, Gordon J, Miyasaki J, Fon EA, Schlossmacher M, Suchowersky O, Rajput A, Lafontaine AL, Mestre T, Appel-Cresswell S, Kalia SK, Schoffer K, Zurowski M, Postuma RB, Udow S, Fox S, Barbeau P, Hutton B. Canadian guideline for Parkinson disease. CMAJ. 2019 Sep 9;191(36):E989-E1004. doi: 10.1503/cmaj.181504. PMID: 31501181; PMCID: PMC6733687.
Not available	New section	Management of Parkinson's disease and other movement disorders in women of childbearing age: Part 1, 2020	García-Ramos R, Santos-García D, Alonso-Cánovas A, Álvarez-Sauco M, Ares B, Ávila A, Caballol N, Carrillo F, Escamilla Sevilla F, Freire E, Gómez Esteban JC, Legarda I, López Manzanares L, López Valdés E, Martínez-Torres I, Mata M, Pareés I, Pascual-Sedano B, Mir P, Martínez Castrillo JC. Management of Parkinson's disease and other movement disorders in woman of childbearing age: Part 1. Neurologia (Engl Ed). 2021 Mar;36(2):149-158. English, Spanish. doi: 10.1016/j.nrl.2020.05.010. Epub 2020 Jul 24. PMID: 32718872.
Not available	New section	Management of Parkinson's disease and other movement disorders in women of childbearing age: Part 2, 2021	García-Ramos R, Santos-García D, Alonso-Cánovas A, Álvarez-Sauco M, Ares B, Ávila A, Caballol N, Carrillo F, Escamilla Sevilla F, Freire E, Gómez Esteban JC, Legarda I, López Manzanares L, López Valdés E, Martínez-Torres I, Mata M, Pareés I, Pascual-Sedano B, Martínez Castrillo JC, Mir P. Management of Parkinson's disease and other movement disorders in women of

			childbearing age: Part 2. Neurologia (Engl Ed). 2021 Mar;36(2):159-168. English, Spanish. doi: 10.1016/j.nrl.2020.05.012. Epub 2020 Sep 24. PMID: 32980194.
Not available	New section	Parkinsonian Drugs: Guidelines for Japan, 2022	Mizuno, Y. (2020). Parkinsonian Drugs: Guidelines for Japan. In: Riederer, P., Laux, G., Mulsant, B., Le, W., Nagatsu, T. (eds) NeuroPsychopharmacotherapy. Springer, Cham. https://doi-org.ezproxy.aub.edu.lb/10.1007/978-3-319-56015-1_354-1
Section 2. DRUG THERAPY FOR Parkinson Disease			
monoamine oxidase type B (MAO-B) inhibitor	Addition of a medication	XADAGO® (safinamide)	indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes. Approved by FDA in 2017 Not registered by SFDA
adenosine A2A receptor antagonist	Addition of a medication	NOURIANZ™ (istradefylline)	adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease (PD) experiencing "off" episodes Approved by FDA in 2019 Not registered by SFDA
selective and reversible catechol-O-	Addition of a medication	ONGENTYS® (opicapone)	adjunctive treatment of Parkinson's disease in patients treated with levodopa and carbidopa (a peripheral DOPA decarboxylase inhibitor)

methyltransferase (COMT) inhibitor			Approved by FDA in 2020 Not registered by SFDA
Not existing	**New section**	**Section 4. Key Recommendations Synthesis**	
Not existing	**New section**	**Section 5. Conclusion**	
References	Updated	**Section 6. References**	
Appendices	Updated	**Section 7. Appendices**	