Chapter

The Role of the Primary Care Physician in the Management of Parkinson's Disease Dementia

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Abstract

Dementia is a frequent complication of Parkinson's disease with an annual incidence of around 10% of patients with Parkinson's disease. If dementia occurs in patients with Parkinson's disease, it is typically many years or decades after the onset of Parkinson's disease. It is devastating for both patient and family or caretaker when a patient with Parkinson's disease develops dementia. Primary care physician is at the center of the care team for the patient. This chapter discusses the pivotal role of the primary care physicians in the management of patients with Parkinson's disease dementia. A guide is provided to emphasize the art of practice for Primary care physicians which consists of knowing when and how to introduce a comprehensive ongoing care plan for individual patient with Parkinson's disease dementia. Recommendations for maintaining some patients with Parkinson's disease dementia in a status of relative independence are discussed. Indications for initiation of palliative care are also discussed.

Keywords: Primary care physicians, Parkinson's disease dementia, management, palliative care

1. Introduction

Parkinson's disease dementia (PDD) is a well-known complication of Parkinson's disease (PD), with an annual incidence of around 10% of patients with PD and a cumulative prevalence of 75–90% of those with a disease duration of 10 years or more [1–3]. Dementia is an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform independent activities of daily living (IADLs) [4]. Symptoms of dementia can be seen in most of the neurodegenerative diseases, such as Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), Creutzfeldt-Jakob disease (CJD), frontotemporal dementia, Huntington's disease, normal pressure hydrocephalus [5, 6]. The general risk factors for dementia include lower education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution [7]. It is devastating for both patient and family or caretaker when a patient with PD develops dementia because both PD and dementia have a protracted course, with progressive but insidious development of disability [8]. Primary care physicians (PCPs) stand in a unique

position for caring for patients from early to terminal stage of their life and play an important role in the management of PDD patients, including in screening, diagnosis, and treatment. It is important to provide individual, realistic, and affordable options of care to every unique patient and his/her family [9, 10].

2. Screening for the early symptoms and signs of PDD

PD impacts people in different ways. Not everyone will experience all the symptoms of PD at the same time or follow the same pattern. But PCPs should be familiar with the common symptoms or typical patterns of progression in PD that are defined in stages [11–13]. PCPs should also know the risk factors that make PD patients more likely to experience dementia because the clinical symptoms of both syndromes can overlap to a high degree. PCPs should always consider seeking reversible medical conditions that can affect mental function in PD patients. A flowsheet (**Table 1**) for screening generated here should help PCPs and their team to achieve this goal during a patient's routine annual wellness visit (AWV) or general visit.

In addition to above mentioned risk factors [7], genetic risk factors are concerning too. One gene, identified to be a risk factor, is the apolipoprotein E gene which presents in three allelic forms (ε2, ε3, and ε4), of which the ε4 allele is a risk factor for AD [23, 24]. Recognizing some other factors in PD patients is also important for early diagnosis of PDD [25, 26]. Those other factors include advanced age at time of diagnosis of PD, experiencing excessive daytime sleepiness, hallucinations before the onset of other dementia symptoms, a history of mild cognitive impairment, more severe motor impairment symptoms than most people with PD, having a specific PD symptom that causes a person to have difficulty starting to take a step or to halt mid-step while walking.

Items	Purpose
Age	recognize this is a risk factor
Stage of PD	severity of motor impairment from PD, another risk factor for PDD
cognitive functions	search cognitive function stage including attention, executive, and visuospatial functions
Dementia Screen Indicator [14]	screening possible high-risk patients. If it is negative, follow up periodically. If it is positive, further investigation is needed.
Geriatric Depression Scale [15, 16]	search for mood disorders
PHQ-9 screen for depression [17, 18]	further evaluation of depression
MoCA [19]	early detection of cognitive impairment
Qmci [20]	differentiating MCI and NC
MMSE + CDT [21, 22]	to stage mental dysfunction, better specificity and sensitivity

AWV: annual wellness visit; PHQ-9: patient health questionnaire-9; MCI: mild cognitive impairment; NC: normal cognitive. MoCA: Montreal cognitive assessment; Qmci: quick mild cognitive impairment; MMSE: mini-mental state examination. CDT: clock drawing test.
The information needed to arrive at the diagnosis requires the clear demonstration that cognitive impairment negatively impacts daily living. This issue is determined by the patient and caregiver interview, and generally focuses on the patient's autonomy, the ability to manage finances, to cope in social situations, and to utilize equipment that is part of daily living.

Table 1.
For routine AWV in PD patient in addition to routine questionnaire.

It is important to search for reversible medical conditions affecting mental dysfunction that may mimic dementia. Electrolyte imbalance, such as hyponatremia or hypernatremia, may cause neuropsychiatric manifestations [27–29]. A personality change such as increasing irritability may be a symptom of hypernatremia, hypercalcemia, hypocalcemia, hypophosphatemia, or hypomagnesemia. In most instances, correction of such underlying electrolyte imbalance will alleviate the psychiatric symptoms. PCPs should pay close attention to age-related limitations of fluid homeostasis, especially in PD patients because that can change the mental function in PD patients gradually and insidiously. Vitamin D deficiency has been associated with neuropsychiatric conditions such as PD, schizophreniform disorder, multiple sclerosis (MS), AD and autism spectrum disorder [30]. PCPs should always be alerted that the side effects of medications can also cause various symptoms and signs of mental disorders that can mimic dementia [31]. Those common drugs include anxiolytics (Benzodiazepines), antiseizure medications (e.g. carbamazepine), antidepressants (e.g. tricyclics), narcotics (e.g. hydrocodone), certain medications for PD (e.g. pramipexole, ropinirole), some hypertension medications (e.g. beta-blockers), sleeping medications (non-benzodiazepine, zolpidem.), medications for incontinence (anticholinergics, oxybutynin.), and some antihistamines (first generation, e.g. hydroxyzine and diphenhydramine).

It is unclear whether early detected cognitive impairment and interventions for dementia patients have a significant effect on their long-term outcomes [32, 33]. But early detection of cognitive impairment can allow for identification and treatment of reversible causes. It also may help patients understand and adhere to medical treatment plans and provide a basis for advance planning for patients and their families [34]. Unfortunately, underdiagnosis of Alzheimer's and other dementias in the primary care setting is not uncommon [35].

Many screening tools have been developed for medical providers to identify dementia patients earlier. These can be used for screening in PD patients. These tools are summarized in **Table 2**. A dementia screening indicator is generated to help PCPs plan the next steps of management [14]. First, it starts with three simple questions if you think your patient may have cognitive impairment based on (1) your observations, (2) concerns of the patient or (3) concerns of family or others. If the answer is yes for one of these three questions, the patient should be screened for cognitive impairment. Second, is the patient 80 or older? If yes, the patient should be screened for cognitive impairment. If not 80 or older, the dementia screening indicator should be administered. The dementia screening indicator consists of 7 items that include (1) age, (2) years of education, (3) body mass index (BMI), (4) history of type 2 diabetes, (5) history of stroke, (6) function of management of

Screening tool	Characteristic	Usage
Screen Indicator [35]	simple, easily administered in PCP settings.	identify high risk patients for MCI and dementia
MoCA [14]	early detection of cognitive impairment	High specificity and sensitivity for screening MCI
Qmci [19]	needs more administrate effort	more sensitive in differentiating MCI and NC
MMSE [20]	comprehensive evaluation	Able to stage dementia, but less sensitive to screen MCI

MCI: mild cognitive impairment; NC: normal cognitive. MoCA: Montreal cognitive assessment; Qmci: quick mild cognitive impairment; MMSE: mini-mental state examination.

Table 2.
Comparison of different screening tools for mental status.

money or medication and (7) depression. If the total point score is more than 22, the patient should be screened for cognitive impairment, with an instrument such as those described below [14].

One commonly used screening tool is the Montreal Cognitive Assessment (MoCA; range 0–30; follow-up evaluation to screening recommended if score is <26). MoCA requires about 10–15 minutes to administer and is useful in early detection of cognitive impairment, including MCI with executive dysfunction [19].

The quick mild cognitive impairment (Qmci) has six domains with total score 100; five orientation items (country, year, month, day, and date with a maximum score of 10), five registration items (score ≤ 5) and a clock drawing test (score ≤ 15), each scored within 1 min. It also has a delay recall (DR) section (timed at 20 seconds with score ≤ 20), a verbal fluency (VF) test (in 60 seconds with score ≤ 20) and a logical memory (LM) test with 30 seconds for administration and 30 seconds for response (score ≤ 30). It can be administered and scored in ~5 minutes. The Qmci is more sensitive than the Standard Mini-Mental State Examination (SMMSE) in differentiating MCI and normal cognition (NC), making it a useful test, for MCI in clinical practice, especially for older adults [20].

The Mini-Mental State Examination (MMSE) that was developed more than 4 decades ago is still a gold standard exam for comparison. It is a brief test, taking ~7 to 10 minutes to complete. The pooled estimate across 15 studies resulted in 89 percent sensitivity (95% CI, 0.85 to 0.92) and 89 percent specificity (95% CI, 0.85 to 0.93) to detect dementia at a cutoff of ≤23 or ≤ 24 [21]. It is less sensitive to the presence of MCI and less thoroughly evaluated in the domains of executive function, higher-level language skills, and complex visuospatial processing. The most sensitive combination of screening tools is the MMSE and Pfeffer Functional Activities Questionnaire (PFAQ) (94.1%). The best specificity is the combination of the MMSE and Clock Drawing test (CDT) [22, 36].

3. Diagnosis of PDD

After the clinical bedside screening test with suspicious PDD as shown in **Table 1**, orchestrating further investigations as outlined in **Table 3** should be the next step to obtain more evidence to make the diagnosis of PDD. Laboratory studies and imagining studies should be carried out before making the diagnosis. Obtaining basic laboratory data on complete blood count (CBC), comprehensive

Items needed to be done	**Purpose**
Review list of medications that patient is taking	search for side effects of medications.
Laboratory investigation: CMP, CBC, lipid, TSH, B12, CRP	search for reversible causes of mental function change.
Imaging study (MRI of head)	rule out other pathology, identify atrophy of the brain.
Referral for neurological consultation	confirm diagnosis
nonpharmacological intervention	improve symptoms
Pharmacological treatment	prevent or delay the progression of dementia
Health maintenance care	preserve the ability for daily activities
Palliative care/hospice	improve quality of life

Table 3.
Steps for management of suspected PDD patient.

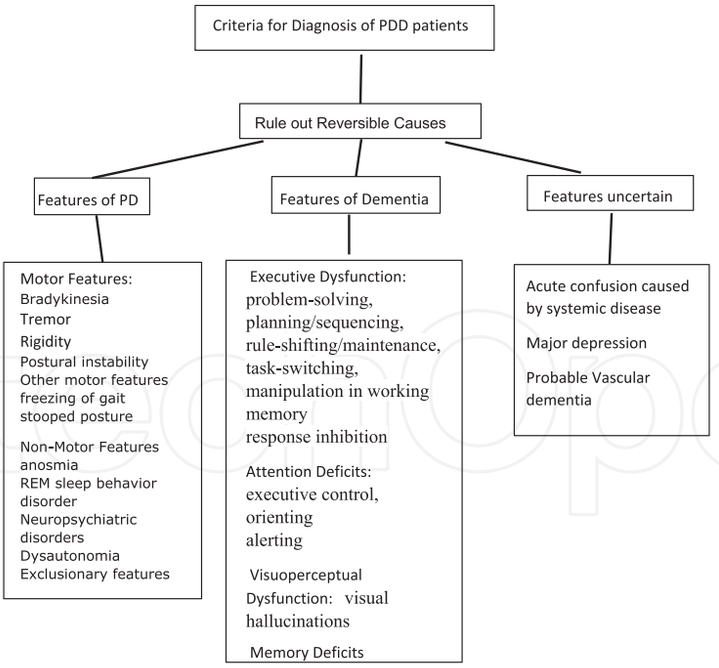

Figure 1.
Criteria for diagnosis of PDD patient.

metabolic panel (CMP), thyroid stimulating hormone (TSH) should be done to understand the basic homeostatic condition of the patients. Checking the levels of vitamin B12, B1, and B6 is proper to search for a reversible pathological cause of mental function change. Brain imaging studies, MRI or CT, will help to distinguish common pathological conditions, including hydrocephalus, atrophy of the brain, vascular disease, or tumor [37, 38].

Criteria to establish the diagnosis of PDD are depicted in **Figure 1**. There are feature domains in these criteria, including features of PD and dementia as well as uncertain features. In the end, a collaborative neurological consultation should be considered to make the diagnosis of PDD [39–43].

4. Treatment guidelines for PDD

The fundamental goals of treatment for PPD patients are to reduce suffering caused by the cognitive and accompanying symptoms, while delaying progressive cognitive and physical decline. How to reach these goals is a challenge to medical providers, patients, and families because the severity of PD, mood disorders, hearing defects, and mental function declining can overlap and affect each other. That needs comprehensive evaluation, planning, and cooperation/coordination with neurologists. An algorithm shown in **Figure 2** will help PCPs to orchestrate the treatment plan with patients and their families.

4.1 Non-pharmacological intervention for PDD

The non-pharmacological interventions that combine diet, exercise, cognitive training, and vascular risk monitoring improve cognition in people at risk for cognitive decline [44–46]. Physical exercise, both aerobic (walking, swimming) and anaerobic/conditioning (resistance training, Tai chi), improves cardiovascular health through benefits on blood pressure and stroke risk [47]. Some trials suggest these interventions may positively affect cognitive and physical function and promote patients' functional independence, improve their well-being and that of their

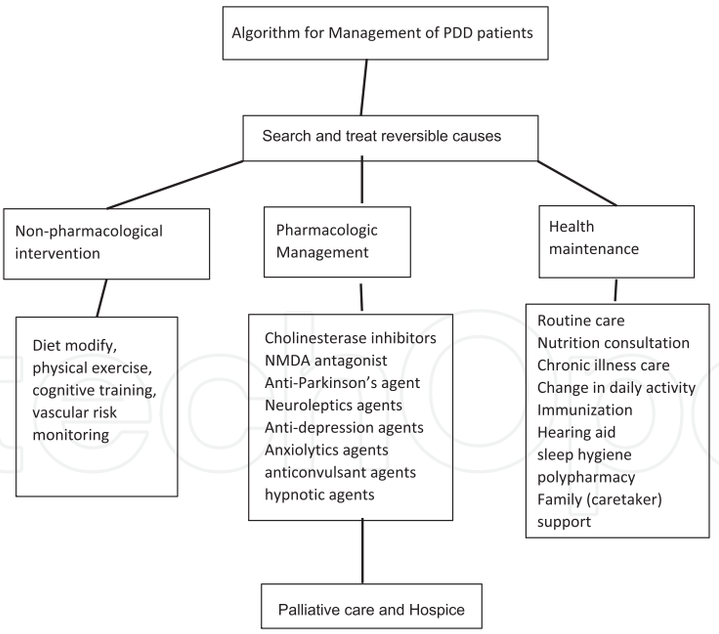

Figure 2.
Algorithm workflow for management of PDD patient.

caregivers. Cognitive training and activities such as reading and playing cognitively engaging games (e.g., chess, bridge) may help maintain cognition and function, improve processing speed, and reduce daytime sleepiness [48].

Music therapy may help maintain cognition or improve quality of life, as some studies revealed that recovery of verbal memory and focused attention improved significantly in patients who listened to their favorite music daily. Besides the improvement in cognitive functions, there was also a substantial mood improvement in this group of patients [49]. Falls have several psychosocial impacts, including fear of falling and reduced self-efficacy, leading to decreased independence, reduced social participation and diminished health-related quality of life [50]. Prescribing cane, walker, or physical and occupational therapies for prevention of falling is one of the responsibilities of PCPs. Moderate intensity outdoor group activities like Nordic Walking and Walking seem to improve motor and non-motor symptoms in patients with Parkinson's disease [51]. Physical activity may assuage the degeneration of motor skills, lessen depression, and increase the quality of life of PDD patients.

4.2 Pharmacologic management for PDD

As described above, PCPs should oversee all medications that PDD patients take before considering pharmacologic treatment for dementia symptoms in PDD patients, because PDD patients usually take medications for PD and other comorbidities. PCP should be familiar with the most common pharmacologic therapies for PD patients, although these are usually initiated by neurologists. These medications include carbidopa-levodopa, monoamine oxidase-B inhibitors, and dopamine agonists. Knowing the effects and side effects of these medications will help PCP to recognize when mental status changes in PD patients are attributable to medication side effects or interactions of medications. It will also help PCPs avoid the interaction of medications when prescribing therapeutic medications either for symptoms of dementia or for other medical conditions. Before any medication is prescribed, potential side effects should be counseled, fully disclosed, and well explained (to the best of your knowledge) to patients and

their families or caregivers. This would be critical for those with limited mental capacity to increase compliance and to decrease avoidable incidents. In addition, based on our clinical experience, for lower body mass patients, low-dose initiation of medication and slow titration should be considered. Effective treatment monitoring requires periodic reevaluation of cognition, function, neuropsychiatric and behavioral symptoms, and medication reconciliation. Five drugs, 4 of which are currently available for prescription in the United States, yield modest symptomatic benefit for cognitive symptoms of AD dementia [38]. These drugs may be also beneficial for PDD patients. Their usages are discussed below and summarized in **Table 4**.

4.2.1 Acetylcholinesterase inhibitors

This class of medications can exhibit significant clinical impact in mild to moderate dementia patients and can also benefit severe dementia patients. Acetylcholinesterase inhibitors, including Donepezil, Rivastigmine and Galantamine, inhibit the brain enzyme acetylcholinesterase, thereby promoting relative increases in acetylcholine abundance at the synaptic cleft for cholinergic neurotransmission. Donepezil 5 to 10 mg can be taken once a day orally. This is the one most widely used. Side effects of nausea, gastrointestinal (GI) cramps, and dizziness could be minimized by being taken after dinner. Rivastigmine 1.5 to 6 mg twice daily orally, or 4.6 to 9.5 mg transdermal patch once a day is another option. Clinical trials in DLB and PDD have established this agent's clinical efficacy better than other drugs in this class. Another cholinergic drug is Galantamine 4 to 12 mg twice a day orally or extended release 8 to 24 mg once a day orally. This agent has shown less consistent benefit on function and behavior. Tacrine is no longer being used clinically because of liver toxicity, and the above newer agents have better tolerance profiles.

4.2.2 Memantine (Namenda)

Memantine is one of the N-methyl-D-aspartate (NMDA) non-competitive antagonists which might slow down the neurodegenerative process by blocking Glutamate's overstimulation of the NMDA receptors, and thus reduce excitotoxicity. Memantine alone or combined with Donepezil is another option commonly used for moderate to severe Alzheimer's disease. A meta-analysis reported that use of memantine to treat behavioral and psychological symptoms of dementia (BPSD) yielded modest decreases in scores on the Neuropsychiatric Inventory Questionnaire and improvement of symptoms, although sedation was reported to be a major side effect [38]. Memantine can be taken 5 to 10 mg twice a day orally or extended-release form 7 to 28 mg once a day orally. This agent should be considered to initiate at the moderate to severe stages of PDD, because severe dementia in PD most commonly has concomitant AD pathology. In addition to the above 2 categories of drugs, the following other medications that are commonly used in PDD patients are also addressed in below and in **Table 4**.

4.2.3 Anti-Parkinsonian agents

Selegiline 5 mg twice a day orally is also commonly used. Despite lack of confirmatory outcome data, some believe that this anti-Parkinsonian disease medication may have a neuroprotective effect against PDD, based largely on animal models.

Medications commonly used in PCP setting for the pharmacologic management of PDD		
A. Cholinesterase inhibitors.		
1	Donepezil (Aricept)	first line to choose, it should be taken after dinner to lessen the impact of GI side effects.
2	Rivastigmine (Exelon)	Topical patch, Rivastigmine will decrease GI side effects and oral medication burden
B. NMDA antagonist.		
1	Memantine (Namenda)	for moderate to severe dementia, combined with Cholinesterase inhibitor showing better efficacy and less GI side effects
C. Neuroleptics agents		
1	Quetiapine (Seroquel)	commonly first to choose for relative safety profile for sedation and wider dosing range to titrate
2	Olanzapine (Zyprexa)	effective against psychiatric symptoms but less favorable metabolic impacts
3	Risperidone (Risperdal)	usually considered when Quetiapine and Olanzapine failed
D. Anti-depression medications		
a. SSRI		
1	Escitalopram (Lexapro)	low dose initiation, better option towards anxious clinical manifestation
2	Citalopram (Celexa)	good alternative for Escitalopram
3	Sertraline (Zoloft)	long clinical usage and experience for positive psychiatric symptoms
4	Fluoxetine (Prozac)	long clinical usage and experience for negative psychiatric symptoms
b. the Others		
1	Mirtazapine (Remeron)	well adopted in geriatric population for hypnotic and appetite enhancement profiles
2	Trazodone	classical and safe sleep aid in low dose
3	Bupropion (Wellbutrin)	less sexual function disturbance and stamina boosting characters considered
4	Venlafaxine (Effexor)	good feature for general anxiety symptoms
5	Nortriptyline (Pamelor)	well adopted for muscle relaxing, hypnotic and appetite boost but alert on anticholinergic side effect in geriatric population
E. Anxiolytics, anticonvulsant, and hypnotic medications		
1	Buspirone	less clinical effectiveness but very safety profile favored on anxiety background management
2	Valproic acid (Depakote)	mood stabilizer or clinical symptoms complicated with epilepsy
3	Carbamazepine (Tegretol)	mood stabilizer or clinical symptoms complicated with epilepsy
4	Gabapentin (Neurontin)	mood stabilizer or clinical symptoms complicated with neuropathic pain
5	Zolpidem (Ambien)	most widely used hypnotic agent but alert in sleeping walk reported often
6	Zaleplon (Sonata)	short acting for helping waking up in the middle of night

Medications commonly used in PCP setting for the pharmacologic management of PDD		
7	Eszopiclone (Lunesta)	effective hypnotic but dizziness and fainting caution in geriatric population
8	Ramelteon (Rozerem)	quite safe agent but efficacy limited to certain population
9	Suvorexant (Belsomra)	relatively new in market and quite safe agent but efficacy limited in higher dose

Table 4.
Common medications for PDD patients.

4.2.4 Neuroleptics agents

Agitation, aggressive behavior, psychosis, and especially visual hallucinations are often encountered in the early stages, particularly in PDD compared to other types of dementia like AD or VD. For this reason, this class of medicines may be more often required in the early stage PDD compared to other types of dementia, but needs to be dosed and monitored closely. The second-generation antipsychotic agents or atypical antipsychotic agents are currently preferred due to their relatively tolerable side effect profiles with less risk of 'neuroleptic sensitivity', (i.e., motor, and cognitive deterioration) [52]. Also, metabolic abnormalities, especially serum glucose increases, need to be closely monitored during treatment. Over sedation caused by high dose or frequent dosing should be discussed with family members or caregivers for adjusting neuroleptic doses promptly and safely. Institutional abuse of this class of medicine has been reported. These are common second-generation neuroleptics agents: (1) Quetiapine (Seroquel) 12.5 to 100 mg per day orally; (2) Olanzapine (Zyprexa) 2.5 to 10 mg per day orally; (3) Risperidone (Risperdal) 0.25 to 1 mg per day orally; (4) Aripiprazole (Abilify) 10 to 30 mg per day orally; (5) Ziprasidone (Geodon) 20 to 160 mg per orally.

4.2.5 Antidepressant medications

Geriatric depression is a common and treatable comorbidity in patients with dementia. Several tools are validated to screen for depression in older patients. The five-item Geriatric Depression Scale is brief and sensitive. It is as effective as the 15-item Geriatric Depression Scale and does not require clinician administration [52]. In patients with depression and dementia, treatment for depression should usually be initiated first. Pseudodementia, or depression causing cognitive impairment, is diagnosed if the impairment resolves with treatment of the depression. These antidepressant medications have been widely used for mild to moderate uncomplicated depression disorders in the primary care setting [53, 54]. Selective serotonin reuptake inhibitors (SSRIs) are the first line treatment of choice. Patients who do not respond to two or more SSRI agents may choose agents from the other group of antidepressants. These are commonly prescribed SSRI antidepressant medications: (1) Escitalopram 5 to 10 mg per day orally; (2) Citalopram 10 to 20 mg per day orally; (3) Sertraline 25 to 100 mg per day orally; (4) Fluoxetine 10 to 40 mg per day orally. Other antidepressants include: (1) Mirtazapine 7.5 to 30 mg before bedtime orally; (2) Trazodone 50 to 150 mg before bedtime orally; (3) Bupropion 75 to 300 mg per day orally; (4) Venlafaxine 25 to 300 mg per day orally; (5) Nortriptyline 10 to 100 mg before bedtime orally. Three new antidepressants are currently available. One is Vilazodone (Viibryd) that can be started at an initial dose of 10 mg orally once a day for 7 days, followed by 20 mg orally once a day for an additional 7 days, then a maintenance dose of 40 mg orally once a day.

Second one is Levomilnacipran (Fetzima) with initial dose of 20 mg orally once a day for 2 days, then increased to 40 mg orally once a day; Maintenance dose: 40 to 120 mg orally once a day. The third novel antidepressant is Vortioxetine (Trintellix) with dosage of 5 to 10 mg per day orally.

4.2.6 Anxiolytics, anticonvulsants, and hypnotic medications

In advanced disease stages, a significant portion of these patients develop behavioral disorders which are sometimes severe enough to incur a big burden, although not sensed well by patients themselves but mainly by caregivers and family members. Symptoms include anger with exploding tantrums, wandering, suspiciousness or paranoia, wakefulness at nighttime and incontinence, and inappropriate sexual behavior [55, 56].

Benzodiazepines can be carefully prescribed to the patients with agitation and anxiety, using a short acting agent, and on an as needed basis. While prescribing this class of medication, caution must be considered in high priority to balance potential side effects and clinical benefit. Best practices include starting with low dose treatment, while continually monitoring for fall incidence, declines in renal and hepatic function, lethargy, and any other undesirable side effects, especially in elderly patients.

5. Maintaining PDD patients' general health

The most important aspect of the management of PDD is to maintain PDD patients' general health in terms of preventive medicine, and to keep them as independent as possible in activities of daily living (ADL).

Since PDD, like PD itself, is not curable nor reversible, long-term or chronic ongoing care is the highlight of primary care practice. More than 30% of Parkinson's disease patients will eventually develop dementia symptoms [57]. Therefore, early counseling and a scientific based clinical prediction to detect the subtle clinic symptoms of incipient dementia in this group of patients is an advantage that PCPs have over subspecialty physicians during their daily care and more frequent routine encounters. In the last decade, the guidelines for the Annual Wellness Visit (AWV) from Center for Medicare and Medicaid Service (CMS) has provided a good essential structure for PCPs to screen, predict, detect, and manage dementia among PD patients in daily proactive care [58, 59]. During an AWV visit, the companion of family members or caregivers is highly informative and sensitive to obtain information about patients' daily routine life patterns and memory status, and to detect subtle changes in their logical thinking and judgment. Current well-equipped telemedicine setups can provide an even better way of looking into patients' living environment and other real-life situations around them. Periodic proactive monitoring, educational discussions, and prognosis counseling are the cornerstones for taking care of those patients and their family or caregivers. Disease burden, no doubt, is detrimental to the patient. However, family and caregivers' stress and frustration cannot be ignored or underestimated during long-term, chronic stage, ongoing patient management. Especially, advanced PDD patients show hallucinations, wandering, suspiciousness and incontinence, and other behavioral symptoms. The management of these symptoms require tremendous efforts and resources from the caregiver [4, 8]. Early counseling and anticipating this potential development will prepare them psychologically in advance and help alleviate their stresses later. Also, making early arrangements to prepare for catastrophic happenings can lead to better solutions using wider resources and options, and can help

avoid caregiver burnout. All these tasks are within the scope of the PCP's practice. The following are the major tasks that PCPs should take care of for PDD patients from the beginning of disease to the end of their lives.

5.1 Annual wellness health maintenance

The mission for PCPs is to promote human beings' wellbeing in aspects of general health and quality of life [60]. According to CMS requirement, recommendations from the United States Preventive Task Force and every professional specialty association practice guideline, all patients including those with PDD must be routinely and properly screened yearly according to their age group. This includes mammograph for breast cancer; fecal occult blood test, Cologuard or colonoscopy accordingly for colon cancer, low dose chest CT for patients at high risk of lung cancer, PSA for high risk of prostate cancer, CBC for leukemia, AFP and liver sonography for liver cancer and so on, even though some clinical benefits are debatable. In most situations, all these cancer screenings are recommended to be held off at age 75 and above [58–60]. However, like anything in life, exceptions should be kept in mind for any individual whose lifespan could be more than 10 years from the day when the PCP performs these screening visits.

5.2 Schedule updating immunization

This group of PDD patients is predominantly within the category of senior citizens. They should follow the recommendation for immunizations per CMS guidelines (summarized in **Table 5**), based on the CDC's Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2021 [61].

5.3 Continuous care of concurrent medical conditions

Maintenance care for chronic illnesses, like hypertension, dyslipidemia, COPD, diabetes mellitus, depression, and chronic pain syndrome, should be routinely monitored. Relevant examination and adjustment of medications should be done as needed on an individual basis. The following should be considered accordingly: RetinaVue and urine microalbumin assay for diabetic retinopathy and nephropathy screening, spirometry for COPD evaluation, office-based tonometry for glaucoma screening, bone density measurement for females aged 65 and above and for males 70 years and above, or for those who have a history of a fracture before the ages specified in the guidelines above [60].

5.4 Counseling patients and their families about PDD

The biggest efforts should be made to communicate thoroughly with patients and their families regarding disease pathophysiology, prognosis, updated treatment guidelines and current options, potential consequences, or complications, and to patiently answer all questions sincerely and honestly in a professional manner [8, 19, 60]. A lengthy and respectful discussion with patients and their family members should be provided. For better results and efficiency, instruction should be given to patients or their families before the appointment, so that they can prepare their questions and do further research if they so choose. During the conference, attention should be paid politely. Use appropriate verbal and body languages and a comfortable office setting. Physicians should try to answer every single question, however, if time is limited or some difficulty arises, it is better to set up another appointment or location for further conversations, and to collect

Vaccine	Starting time	Interval
Influenza vaccine	Starting in autumn, until next spring at any age	1 dose annually
Pneumovax	Starting at age 65 or younger with other comorbidities.	Prevnar 13 and Pneumovax 23; one dose each within one year apart. Boost dose every 5 years
Zoster vaccine, recombinant Shingrix vaccine	Starting at age of 50	2-dose series RZV (Shingrix) 2–6 months apart
Tetanus, diphtheria, and pertussis vaccination (Tdap, Td)	Tdap followed by 1 dose Td or Tdap at least 4 weeks after Tdap and another dose Td	Td or Tdap every 10 years
COVID-19 vaccine	Starting at any age	Pfizer and Moderna mRNA are given two doses with a 3- or 4-week interval. Johnson & Johnson's is given one dose.*

**Boost dose may be needed according to the update information.*

Table 5.
Schedule updating immunization [61].

different perspectives. In this situation, listening is far more important than lecturing. Through this, PCPs might be able to understand a patients' or families' deep concern and real need, to recognize their under-the-table concerns, their inner voice, and agenda. At the end of the meeting, PCPs should make a summary and give a clear detailed picture of the treatment plan. Avoid using academic medical terminology whenever possible. Try to make sure that all medical information is delivered precisely and correctly, using lay language. Patients and their families should be well informed, allowing them to be part of the care team, and given many opportunities to be involved in the treatment, management, and planning. They should be convinced that everyone, including the patient, family, primary care provider, office supporting staff, and specialists are working together towards one goal of providing the best possible care to this individual patient and family.

5.5 General supportive measures

General support is important, not just for PDD patients, but also for their families. Nutritional status should be evaluated, addressed, and emphasized [62]. Nutrition cannot be overemphasized and should be discussed with the caregiver and family. A well-balanced high protein diet, with adequate daily calories, and liquid intake is essential. A handbook with detailed instructions for care planning should be provided for the caregivers. The Mediterranean diet, both alone and in combination with the Dietary Approach to Systolic Hypertension (DASH) diet, may be beneficial for the prevention of cognitive decline. Further research is needed to rule out potential confounds and to better characterize the mechanisms underlying the role of nutrition in cognitive outcomes. Cessation of alcohol and cigarette smoking should be instructed. Supplement of vitamins, especially vitamin D and minerals (calcium, magnesium, zinc) should be discussed and encouraged.

Hearing loss and dementia often occur together, and hearing loss may be an independent but modifiable risk factor for subsequent dementia [63, 64]. PCPs should screen for hearing impairment and manage hearing aids for those who require them to help prevent faster deterioration of cognitive function. Patients should be encouraged to actively take part in socializing activities to maintain cognitive stimulation, such as cooperating with caregivers, family members, support

networks, community resources and adult day care facilities. Patients should be arranged to participate in cognitively stimulating activities, e.g., reading, games, etc., and personally meaningful social activities, such as playing music, conversational interactions with others, family events, etc.

Over the past decade, insomnia has variably been associated with deficits in objective cognitive functioning, increased risk of dementia, and reductions in gray matter volume and white matter integrity in networks essential for cognitive functioning [65]. Sleep pattern and sleep hygiene guidance should be discussed in detail. Proper personal hygiene improves quality of life for patients, and also avoids irritation of the oral mucosa, the perineum area, and underneath the breasts, which can also improve the quality of sleep.

Prescribing hypnotic medications may be considered as needed. Benzodiazepines (BZDs) could be an option but should be used with caution. One study showed continuous exposure to BZDs and non-benzodiazepines (non-BZDs) may contribute to the development of cognitive impairment. One should be careful when prescribing BZD or non-BZD hypnotics to patients with long-term insomnia, especially for those that are aged between 50 and 65 years. Additionally, it is best to use short acting sedatives at the lowest dosage for the therapeutic benefit, because greater exposure to these medications leads to a higher risk of developing dementia [65, 66].

The above approaches require cooperation with patients, families, caretakers, or the assisting living facilities. Although there is no concrete data to prove that the above approaches will delay the deterioration of cognitive function, these approaches will assuredly improve the quality of life for PDD patients.

5.6 Polypharmacy

Polypharmacy is another significant and epidemic issue. PCPs are at a critical and unique central position for this matter. In this age group, patients with PD are most likely struggling with multiple medical conditions, such as hypertension, high cholesterol, osteoarthritis, diabetes, malnutrition, depression, etc. Patients often visit different subspecialists such as cardiologists, nephrologists, neurologists, psychiatrists, ophthalmologists, endocrinologists, and dentists. It is a challenge to be vigilant with patients who have impaired cognitive function and are under the care of multiple physicians. It is particularly important to manage their medications to avoid drug interactions, unnecessary pills, conflict among prescriptions from different subspecialties, drug overdose, compliance issues, financial difficulty, monitoring medication refills and reconciliation of medications. Some studies reveal that polypharmacy was associated with cognitive decline in patients with newly diagnosed PD. Those findings suggest that medication reduction might serve as a promising intervention to prevent the development of dementia in patients with early PD [67, 68]. For fixed income senior citizens, financial challenge for medications is an important, but pragmatic issue to discuss. A PCP can help disadvantaged patients get into assistance programs from public or private sources and the pharmaceutical industry.

5.7 Neurology consultation

Neurologists are dependable and reliable allies and consultants in the care of PDD patients, but high-level care should be individualized. Once physician and patient relationships are established long-term, PCPs should be at the center of care planning. PCPs have the advantage of knowing and understanding patients better in terms of their medical and personal history, personality, habits, family members,

language, and cultural background. From that point of view, a PCP should be able to coordinate the best fitting specialists to take care of this individual within the guidelines of national and international standards [2, 8, 69].

6. Management of PDD patients in advanced stage

PD and dementia are incurable neurological conditions. PD patients who develop dementia usually progress to the advanced stages of disease. PDD patients often experience specific, complex, and varying needs along their disease trajectory. A palliative approach to PDD should be discussed with patients, their caretakers, and families in advance regarding management of the advanced stages of PDD, especially at the terminal periods. PDD patients may have several needs in the four domains of palliative care (physical, psychological, social, and spiritual) in addition to specific needs for a peaceful, familiar environment, and practical support [70–72]. "Person-centered care, communication and shared decision making" is among the most important domains of palliative care in dementia [73]. An algorithm for the evaluation and management of PDD patients across the disease stages is depicted in **Figure 2**, summarizing much of the above recommendations.

6.1 Counseling and guidance for advance medical directive

Counseling for advance medical directive (AMD) or advance care planning (ACP) should be routine care tasks for PCPs. Medical and advance care directives (e.g., designation of power of attorney) should be discussed as early as possible while the mental functions of patients are still competent, allowing patients and their families to have enough time to discuss and plan. ACP is a special form of ongoing communication about preferred future health care [70]. Long-term health care planning (e.g., living arrangements in the late stage of dementia) and financial planning are other important issues for patients and families to discuss and plan well in advance. In California, the Physician Orders for Life-Sustaining Treatment form or POLST (pink form) is routinely used in the PCP's office for the purpose of making the patients' advanced directives clear and easily obtainable. Physicians should explain the meaning and the consequences of the decision making with patients and family in detail. This process should be highly informative and provide guidance so that patients may come to their informed decision comfortably.

6.2 Management of advanced disease

To optimally promote quality of life and death of a person affected by a complex, incurable, and life-threatening health problem, such as dementia, care teams must address the person's physical, emotional, psychosocial and spiritual needs, as summarized in the WHO definition of palliative care. Dementia usually occurs during the later stages in PD, when clinical symptoms could be progressing quite rapidly, complicated by aging and other comorbidities. Once PD reaches such an advanced stage, the approach towards care should shift towards palliative care, or its consideration. Palliative care can start in the form of ACP if the patient and family caregiver are willing to talk about the future soon after the diagnosis of PDD. The focus of care should be well planned, but simple with straightforward symptom management. Care of the person, not disease per se, is important. This approach includes attention to physical, mental, social, and spiritual aspects, especially since there are no cures available with current interventions. **Figure 3** outlines a model

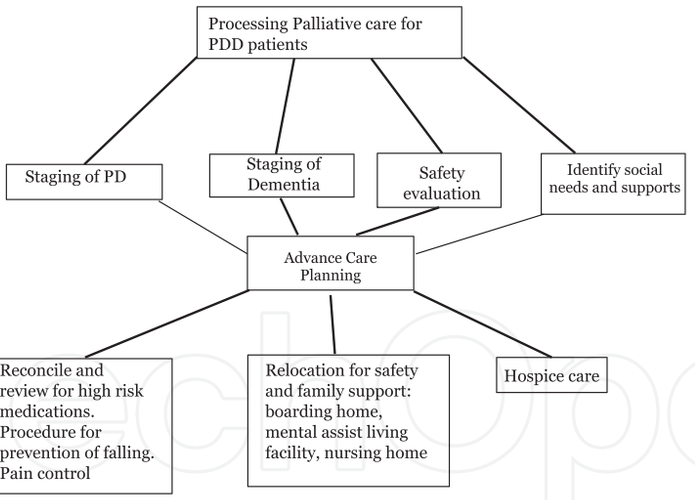

Figure 3.
Model for palliative care of PDD patients.

for palliative care of PDD patients. The palliative care should be carried out by a comprehensive team which includes physicians as leaders, registered nurses, office supportive staff, social workers, religious leaders, family members and/or supporting network, a disease focus group and so forth. An in-home model of palliative care for homebound advanced PD and PDD patients was recently introduced in 2020, which highlights the importance of medication reconciliation, home safety assessments, and appropriate monitoring and treatment of orthostatic hypotension, a leading cause of falls [71]. At this stage not only patients' needs, but also families' needs should be addressed. Options like assisted living homes, boarding care, and skilled nurse facilities should be discussed when those needs arise. The goal at an advanced stage, which may eventually progress to the level of hospice care, is to minimize the suffering and improve the quality of life for both patients and their families or caregivers.

6.3 Pain control

Pain is often difficult to assess in people with advanced dementia due to loss of communicative ability [74]. This can result in patient concerns about pain not being heard or being misinterpreted. Communication difficulties are a challenge to practitioners because there may be several possible causes of distress and possibly no particular localizing behaviors or signs associated with pain in an individual with dementia [72]. Agitation is a frequent symptom in dementia patients and may be associated with untreated pain. Studies show that agitation and aggressive symptoms decrease when pain is effectively treated [75]. Proper and effective pain control and the judicious utilization of opioid and benzodiazepine medications during palliative care is a critical step in successful care. Pain is distressful for both patients and their families and can trigger a cascade of other symptoms. For best results, a specialized pain management team, trained nurse practitioner or physician assistant may be consulted or invited into the care team. Fortunately, in the current healthcare system of the United States of America, well designed palliative care/hospice enterprises are established, and widely available for primary care physicians to adopt and refer their patients and families. This facilitates a well-designed, professional, and individually tailored optimal palliative care plan for the many stresses and discomforts associated with end of life.

6.4 Social needs management

The burden of caring for a dementia patient may be physical/medical (e.g., neglect of caregiver's own health, with potential medical complications), emotional and psychological (stress, burnout, depression), and/or financial. Prevention, early recognition, and treatment of these issues (e.g., referrals to social work for additional support), are integral to an effective management plan [76]. PCPs should engage the office staff, benefit and personnel specialists, and social workers in dealing with disease stage transitioning, personal financial issues, and interfamilial relationships. They, in many cases, need to activate available funding sources at the state and federal levels. Questions regarding the patient's driving safety and privileges should be raised at the appropriate time and stage of the disease. PCPs are the advocates of patients in protecting their loved ones from becoming burned out due to the long term duties of caregiving. In the end, PCPs function as liaisons on behalf of patients and their caregivers in not only coping with but also fighting against this devastating disease.

7. Conclusions

PCPs play an important role in the management of PDD patients. The art of practice for PCPs includes knowing when and how to introduce a comprehensive ongoing care plan for individual PDD patients. A comprehensive ongoing care plan includes (1) screening for changes in mental function regularly, (2) properly diagnosing PDD, (3) applying nonpharmacologic and pharmacologic interventions accordingly, (4) orchestrating multidisciplinary care, special therapies, and auxiliary support accordingly, (5) consulting advance medical directive and palliative care early. The optimal goal is to maintain relative independence for PDD patients, if this is safe. It is reasonable and proper to initiate palliative care and hospice for PDD patients in the advanced stage to provide better qualities of their later life experience.

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Conflict of interest

The authors declare no conflict of interest.

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