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Review

Addressing Comorbidities in People with Parkinson's Disease: Considerations From An Expert Panel

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Abstract. In the UK, guidance exists to aid clinicians and patients deciding when treatment for Parkinson's disease (PD) should be initiated and which therapies to consider. National Institute for Health and Care Excellence (NICE) guidance recommends that before starting PD treatment clinicians should discuss the following: the patient's individual clinical circumstances; lifestyle; preferences; needs and goals; as well as the potential benefits and harms of the different drug classes. Individualization of medicines and management in PD significantly improves patients' outcomes and quality of life. This article aims to provide simple and practical guidance to help clinicians address common, but often overlooked, co-morbidities. A multi-disciplinary group of PD experts discussed areas where clinical care can be improved by addressing commonly found co-morbidities in people with Parkinson's (PwP) based on clinical experience and existing literature, in a roundtable meeting organized and funded by Bial Pharma UK Ltd. The experts identified four core areas (bone health, cardiovascular risk, anticholinergic burden, and sleep quality) that, if further standardized may improve treatment outcomes for PwP patients. Focusing on anticholinergic burden, cardiac risk, sleep, and bone health could offer a significant contribution to personalizing regimes for PwP and improving overall patient outcomes. Within this opinion-based paper, the experts offer a list of guiding factors to help practitioners in the management of PwP.

Keywords: Parkinson's disease, individualized treatment, clinical guidelines, bone density, cardiovascular risk, anticholinergics, sleep quality

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INTRODUCTION

The information in this article was gathered at a roundtable meeting organized and funded by Bial Pharma UK Ltd. A group of 10 experts was established to discuss recent developments in Parkinson's disease (PD), with the purpose of developing expert advice to enhance clinical practice in PD. More information on each party's involvement can be found at the end of this manuscript. This expert group held three meetings between 2017 and 2019, with each meeting focusing discussion on a different key area of PD aiming to create consensus documents [1]. In 2019, the group (9 experts) met to discuss the impact of the holistic personalized medicine approach on PD and key factors that influence treatment choice. Although multiple aspects were considered through discussion, the panel chose to focus on four key co-morbidities to address, which impact personalized treatment choice and clinical management: anticholinergic burden, cardiac risk, sleep, and bone health. These are further discussed within this paper. It is important to highlight that there are a number of other factors that impact treatment opinion and that the four areas discussed within this paper have been chosen by the experts based on their practical experience. The considerations and treatment suggestions in this article solely represent the view of the authors as experts in the field of PD.

INITIAL TREATMENT CONSIDERATIONS

In the United Kingdom (UK), guidance exists to aid clinicians and patients deciding when treatment for PD should be initiated and which therapies to consider. The National Institute for Health and Care Excellence (NICE) guidance recommends that before starting any PD treatment clinicians should discuss the following: the patient's individual clinical circumstances; lifestyle; preferences; needs and goals; as well as the potential benefits and harms of the different drug classes. Current UK guidelines recommend levodopa as first-line therapy for patients experiencing motor symptoms which affect their quality of life [1], while, if this is not the case, a choice of non-ergot or transdermal dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors, should be considered for people in the early stages [2, 3]. The PD Med trial aimed at investigating which of the three drug groups provided the most effective long-term symptom control in 1,620 patients followed for up to 9 years. The study suggested initial levodopa treatment as the most beneficial for patient-rated mobility [3].

For adjunctive treatment of motor symptoms, in the UK, NICE recommends clinicians offer a choice of dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors but does not distinguish between adjunctive therapies in terms of sequence or suitability [2]. This opinion, although UK focused, is broadly shared in other national guidelines or expert opinion-based recommendations.

PRACTICAL, PRAGMATIC CONSIDERATIONS TO DRIVE PRACTICE TOWARDS PERSONALIZED MEDICINE

A multi-disciplinary group of PD experts, including neurologists, physicians, geriatricians, and PD Nurse Specialist (PDNS), discussed areas where clinical care could be improved by addressing commonly found co-morbidities in people with Parkinson's (PwP) including depression, anxiety, psychosis, bladder dysfunction, and bone health. Older PwP have a higher risk of multi-morbidity, including vascular disease and diabetes. A holistic assessment of the patient's functional ability associated co-morbidities and current pharmacotherapy can offer the potential to improve the patient's overall wellbeing [4]. This approach forms the basis of the evidence-based comprehensive geriatric assessment, which has been shown to reduce mortality and improve independence in older people admitted to hospital, compared to those receiving usual medical care [5]. Here we discuss key considerations in the care of PwP in relation to comorbidities, with practical tips on how to address them.

- PwP are at a greater risk of fractures than non-PwP, particularly hip fractures [6, 7];
- Evidence increasingly highlights a link between PD and an increased risk of cardiovascular disease [8];
- The cumulative effect of anticholinergic therapies can cause adverse events, including falls, delirium, and cognitive impairment [9, 10]. Avoidance of medications which add to the anticholinergic burden is important and less universally practiced than avoiding medications with anti-dopaminergic effect in PwP;
- Sleep disturbances adversely affect quality of life independent of stage or severity of PD [11]

and specific subtypes of PwP are at risk of sleep attacks which may impact on driving and swimming [12].

BONE HEALTH

Studies from the UK show that the risk of osteoporotic fractures is doubled in PwP compared to individuals in the same age group who are not suffering from PD. PwP have a four-fold increase in risk of hip fractures [7, 13]. This results in increased hospitalization rates, with prolonged length of stay [13]. Contributory factors include an increased risk of falling in PwP as well as lower bone mineral density in PwP than age and gender-matched healthy controls [7, 13]. Post-menopausal female patients are at greater risk of osteopenia and osteoporosis [7, 13, 14], which is often undiagnosed [13].

A meta-analysis of 14 studies evaluating bone mineral density (BMD) in PwP showed significant lower BMD in PwP, with an overall combined mean difference of –0.06 (95% CI –0.08, –0.03), when compared to age-matched healthy controls. A subgroup gender analysis also showed that female PwP had an overall lower BMD compared to male PwP [7]. Patient management should therefore focus both on the reduction of fall risk and the optimization of bone mineral density.

Reducing risk of falls

The patient history should be carefully taken to identify patients with a history of falls or who are at risk of falls—specifically focusing on factors such as freezing, festination, shuffling, or near fall events. PwP should be assessed for other factors contributing to the fall risk, such as orthostatic hypotension and balance impairment. The former should be appropriately treated where possible, with guidance available from the Royal College of Physicians [15]. A detailed review of the management of falls and fall risk is outside the scope of this review, but the reader is directed to a comprehensive review by Pfortmueller et al. [16].

Optimizing bone mineral density

Treating low bone mineral density and maintaining bone health fall into two main recommendations: 1) A general adaptation to a healthier lifestyle, which includes exercise, paired with vitamin D and calcium supplementation to prevent deficiency, as well as general nutrition guidance (e.g., reduced consumption of alcohol); 2) Medical treatment [6].

Reduced mobility is believed to be a major contributing factor to the decrease in BMD seen in PwP, although vitamin D deficiency, nutritional and iatrogenic factors also play an important role [6, 17]. Serum level of vitamin D is significantly lower in PwP compared to healthy controls and serum 25-hydroxy-vitamin D concentration progressively decreases with increase in severity of motor symptoms [6, 17]. In their three-year study, Sleeman et al. showed a small but significant correlation between vitamin D status at baseline and disease motor severity at 36 months in patients with PD [18].

Mobility can become a regressive cycle: while reduced mobility is a likely contributing factor to osteoporosis in PD, osteoporosis itself increases fracture risk, which can lead to further reduction in mobility, potentially aggravating the patient's motor symptoms [19]. The psychological impact of reduced mobility and the fear of falling should also not be underestimated and should form part of a holistic assessment. Studies have shown that fear of falling in the elderly often leads to a higher number of falls due to lack of confidence. Additionally, fear of falling can stop patients from actively moving, which feeds into the regressive cycle of reduced mobility [20]. Appropriate exercise recommendations for all PwP are important as cross-sectional studies have shown a positive correlation between bone mineral density and exercise. Adequate exercise can help patients with osteoporosis as well as preserve bone mineral density in other patients [21].

Vitamin D supplementation may be used in isolation or, if appropriate, in conjunction with bisphosphonates to decrease bone turnover and increase bone mineral density in PD, in line with guidance from NICE [22]. Several randomized placebo-controlled trials have shown a significant decrease in fracture incidence with vitamin D and calcium supplementation (although specific PD populations are not reported) [23]. Meta-analyses show bisphosphonates are associated with a statistically significant reduced risk of vertebral fracture compared with placebo (hazard ratio (HR) 0.45; credible interval (CrI) 0.31 to 0.65) and a statistically significant reduced risk of hip fracture compared with placebo (HR 0.67; CrI 0.48 to 0.96) [22].

The use of BMD as a sole predictor of fracture risk has proven to be suboptimal, with low reliability [24, 25]. This has led to the development of different fracture risk prediction algorithms, which use multiple

patient risk factors to assess the probability of fracture [25]. Two fracture risk assessment tools that are endorsed by NICE are the Fracture Risk Assessment Tool (FRAX) and the QFracture [26]. Both tools provide probability scores of major osteoporotic fractures (MOF) allowing appropriate risk mitigation to be implemented [25].

Overall, the bone health outcomes for PwP could be significantly improved by:

- Following national guidelines for bone protection in PD in line with the recommendation from the revised algorithm BONE-PARK [13], which applies The National Osteoporosis Guideline Group (NOGG) [13] guidance specifically to PwP [27].
- Clinicians should also consider additional factors that are amenable to intervention such as:
    - Providing patient with education and lifestyle advice to maintain their bone health;
    - Reviewing medication: e.g., paying attention to management of orthostatic hypotension and the anticholinergic burden (prolonged exposure to anticholinergic drugs has been associated with an increased fall risk in older patients) [10, 28, 29];
    - Considering different types of physiotherapy [30];
    - Ensuring vitamin D replete, treating where deficiencies exist [22, 23] supplementation to prevent deficiency when appropriate;
    - Considering bisphosphonate therapy where appropriate [22, 23].

CARDIOVASCULAR RISK AND HYPERHOMOCYSTEINEMIA

There is increasing evidence of shared pathological processes between PD and cardiovascular disease [8, 31], including mitochondrial dysfunction, excessive reactive oxygen species, and elevated homocysteine levels [32–34].

Cardiovascular risk is under-recognized and undertreated in PwP [35]. An analysis of UK-based cohorts comprising 2909 PwP demonstrated that 37.2% of PwP with high vascular risk (Framingham score > 20%) were treated with statins, compared with 80% of the population in primary care [35]. The study highlighted a potential link between vascular risk factors (e.g., diabetes and hypertension) and a worsening neurological status. Diabetes was linked to worse global cognition, greater axial impairment and progression of motor scores while hypertension correlated with worse executive function and delayed memory [35]. The role of cholesterol in the manifestation of PD and the impact of statins in this context is unclear, with studies suggesting that higher cholesterol levels have a positive impact on PD risk and progression [36]. Nevertheless, there is no suggestion that patients with PD derive less benefit from cholesterol-lowering medication or hypertension management in terms of prevention of cardiovascular events or cognitive decline. Therefore, the risk-benefit needs to be carefully considered for each individual patient, highlighting the importance of an individualized medical treatment approach.

Another aspect relevant to both PD and cardiovascular disease is elevation of homocysteine levels [37]. Increased homocysteine has been implicated as a risk factor for vascular disease, brain atrophy [38], cognitive impairment [38, 39], and osteoporosis [39, 40]. Homocysteine levels have been shown to be higher in PwP than in age-matched controls and to increase further with levodopa treatment [41] but not with dopamine agonist therapy [42, 43]. Higher homocysteine levels predict worse motor and cognitive progression in PwP [38, 39] and have been shown to be associated with increased aortic stiffness and impaired diastolic function [37] in PwP on levodopa therapy.

Some evidence suggests that COMT inhibitors may prevent levodopa-associated increases in homocysteine levels, possibly by acting on peripheral levodopa metabolism [42, 44, 45] with more consistent results for tolcapone than for entacapone or opicapone, with these latter two reporting either a trend to reduced homocysteine levels or levels which were not significantly changed from pre-treatment [43, 45–47].

Overall, outcomes for PwP could be significantly improved by:

- Reviewing patients' cardiovascular risk (QRISK2);
- Recommending primary and secondary prevention medications where appropriate.

OVERALL MEDICATION REVIEW AND ANTICHOLINERGIC BURDEN

A full medication review should be undertaken with PwP as part of routine care; limiting the recording of medications to those for PD is inadequate.

Table 1
Drugs with anticholinergic potential (list is not exhaustive, British English spelling has been adopted) grouped based on the ARS point ranking system. The drugs were grouped on scores of 1 to 3 (moderate, strong, and very strong, respectively). A final point total greater than or equal to 3 was considered a serious risk [53]

Medications with anticholinergic effect		
Very strong	**Strong**	**Moderate**
3 points per drug	**2 points per drug**	**(1 point per drug)**
Amitriptyline	Amantadine	Carbidopa-Levodopa
Atropine	Baclofen	Entacapone
Benzatropine	Cetirizine	Haloperidol
Carisoprodol	Cimetidine	Methocarbamol
Cyproheptadine	Clozapine	Metoclopramide
Chlorpheniramine	Cyclobenzaprine	Mirtazapine
Chlorpromazine	Desipramine	Paroxetine
Dicycloverine (also known as Dicyclomine)	Loperamide	Pramipexole
Diphenhydramine	Nortriptyline	Quetiapine
Fluphenazine	Olanzapine	Ranitidine
Hyoscyamine (also known as Hyoscine)	Prochlorperazine	Risperidone
Imipramine	Pseudoephedrine	Selegiline
Meclizine	Tolterodine	Trazodone
Oxybutynin		Ziprasidone
Perphenazine		
Promethazine		
Thioridazine		
Thiothixene		
Tizanidine		
Trifluoperazine		

Very strong risk: final points total ≥ 3. Adapted for the Brazilian pharmacopoeia.

Clinicians should be aware of treatments for other related conditions such as hay fever, hypertension or vestibular disturbance that may have an impact on PD symptoms.

Medications with known anticholinergic activity are used to treat a wide range of conditions. The anticholinergic effect might be intended (for example bladder antimuscarinics) or unintended (for example as with amitriptyline [46]). Anticholinergic therapies can cause adverse events including urinary retention, orthostatic hypotension and constipation. Prolonged exposure has been associated with an increased risk of falls, dementia, delirium (worsening) and cognitive impairment, particularly in older people [10, 28, 29, 48–52]. Risacher et al. showed an association between moderate/high anticholinergic burden and reduced cerebral metabolism, as well as decreased cortical volume and thickness of the temporal cortex, increased ventricular volume and global brain atrophy [49].

Medicines with anticholinergic properties should be considered carefully in older PwP [10, 49]. However, avoiding the introduction of medicines with anticholinergic properties is not always possible as these therapies are used for co-morbidities likely to occur with PD or with the age profile of PwP, including urinary incontinence, hypertension, respiratory disorders, and depression [10, 28]. Gorzoni et al. reported a list (not exhaustive) of drugs with varying anticholinergic potential (Table 1) reflecting the medical records of older adults hospitalized in the medical ward of a teaching hospital collated as part of a study evaluating the applicability of the Anticholinergic Risk Scale (ARS) as an indicator of risk of iatrogenic delirium [28, 53, 54].

Clinicians should consider the anticholinergic burden of medications for co-morbidities when conducting a medication review and consider changing medication class where possible. Several published rating scales exist to aid healthcare professionals ranking medications from low to high anticholinergic effect (Table 2); online tools are also available to assist calculation of anti-cholinergic burden (ACB) including the ACB calculator [28, 29, 55, 56].

Overall outcomes for PwP have the potential to be improved by:

- Conducting a full medication review;
- Minimizing the overall burden of drugs with anticholinergic action by:
  - Incorporation of anticholinergic burden scales in routine clinical prescribing;
  - Changing therapies for co-morbid conditions where appropriate.

Table 2
Comparison of various anticholinergic scales

Expert opinion-based rating scales	Description	Number of anticholinergic medicines listed (N)
Carnahan 2006 [56], USA	Anticholinergic Drug Scale (ADS) is a four-point (0–3) scale that ranks anticholinergic drugs based on receptor binding studies and expert opinion	117
Ancelin 2006 [52], France	Activities-specific Balance Confidence Scale (ABC) is a four-point scale (0–3) based on serum anticholinergic activity (SAA), drug administration, possible drug interaction effects, potential blood-brain barrier permeability and expert opinion	27
Han 2008 [9], USA	Clinician-rated anticholinergic score (CrAS) is a four-point scale (0–3) based on pre-existing published anticholinergic scales and expert opinion	60
Rudolph 2008 [54], USA	Anticholinergic Risk Scale (ARS) is a four-point scale (0–3) based on anticholinergic potential, extensive literature review and expert opinion	49
Boustani 2008 [73], USA	Anticholinergic Cognitive Burden (ACB) is a four-point (0–3) scale developed based on published data, anticholinergic activities in relation to cognitive function, and expert opinion	88
Ehrt 2010 [51], Norway	Anticholinergic Activity Score (AAS) is a five-point scale (0–4) based on existing evidence (Chew 2008 [75]) and expert opinion	99
Sittironnarit 2011 [74], Australia	Anticholinergic Load (ACL) is a four-point (0–3) scale based on pre-existing published anticholinergic scales (SAA) and expert opinion	49

SLEEP

PD is commonly accompanied by sleep disturbance. Sleep problems in PwP are multifactorial and fall within the broad categories of insomnia, motor, urinary and neuropsychiatric problems. Sleep disorders include sleep initiation failure, sleep fragmentation, parasomnias, vivid dreams and rapid eye movement sleep behavior disorder [57, 58]. Additionally, dopamine replacement therapies may wear off during the night, causing discomfort, stiffness, difficulty moving in bed, or other symptoms to disrupt sleep [57]. Sleep can also be impacted by PD complications of autonomic disturbance resulting in bladder dysfunction, and psychiatric features such as depression and anxiety, as well as non-motor symptoms of pain and restless legs symptoms. In addition, respiratory manifestations of sleep-disordered breathing and sleep apnea are common in PD [57–60]. Collectively these problems can lead to insomnia (generally related to difficulties with sleep maintenance rather than initiation) and daytime hypersomnolence [59, 60]. Like other non-motor symptoms, sleep problems can pre- date motor symptom onset (Table 3) [60]. There is a plethora of evidence highlighting that sleep disturbances adversely affect quality of life independent of stage or severity of PD. Approximately three quarters of PwP suffer some form of sleep problem [60, 61] with some estimates as high as 98% [59] compared with 40% in the general older population [60, 62, 63].

Clinicians also need to consider the impact of sleep disturbance on carers of PwP, with motor symptom severity and poor sleep in PwP being associated with poor sleep in spouses/partners [62]. Diagnosis and treatment of sleep problems in PwP has the potential to significantly improve patient wellbeing and reduce carer sleep disturbance [64–66].

Adequate treatment of sleep disorders in PwP requires an accurate diagnosis. This can be challenging due to the diverse and overlapping nature of sleep disorders and contributing factors, as well as under-recognition and reporting by patients. Therefore, proactive discussions about sleep should be included in consultations, informed by NICE guidance [66] and considering co-morbidities such as chronic pain, medical disorders (such as chronic obstructive pulmonary disease, heart failure or gastro-esophageal reflux disease) and psychological disorders (such as stress, anxiety, or depression), as well as medications and substance use, including caffeine, alcohol, nicotine, and illicit drugs [67, 68].

Utilizing a verified tool to assess sleep disorders can be helpful in supporting individualized care, such as the Parkinson's Disease Sleep Scale 2, which differentiates motor and non-motor contributors to poor sleep helping to guide treatment and management (Table 4) [69, 70].

Excessive daytime sleepiness (EDS) is a common non-motor symptom in PD, affecting up to 50% of patients [70]. Clinicians need to consider the potential effects of EDS on both quality of life and as a

Table 3
Classification of Parkinson's disease features that impact sleep or are associated with sleep problems [59]

Parkinson's disease features impacting sleep	
Insomnia	Fragmentation of sleep (sleep-maintenance insomnia)
	Sleep-onset insomnia
Motor and non-motor function related	Akinesia (difficulty turning)
	Restless legs
	Periodic limb movements of sleep
	Nocturnal off-period-related tremor
	Dystonia
	Dyskinesias
	Off-period-related pain/paraesthesia/muscle cramps
Urinary difficulties	Nocturia
	Nocturia with secondary postural hypotension
	Off-period-related incontinence of urine
Neuropsychiatric/parasomnias	Depression
	Vivid dreams
	Altered dream content
	Nightmares
	Night terrors
	Sleep talking
	Nocturnal vocalizations
	Somnambulism
	Hallucinations
	Panic attacks
	Off-period-related panic attacks
	Rapid eye movement (REM) behavior disorder
	Non-REM-related sleep disorders
	Akathisia

Table 4
Suggested treatment strategies for some sleep disorders in PD, as reviewed in Klingelhoefer et al. (2014) [69]. The list is not intended as a guideline for first- or second-line use. Wherever possible the generic names of treatments were listed in alphabetical order. Some suggested treatments in the table may fall outside the licensed indication of these medicines and were considered by the authors as useful for addressing patients' needs where no other alternatives were available. Bial Pharma UK Ltd does not recommend or endorse the use of medicines outside their respective licensed indications

Insomnia-related symptoms: fragmented sleep with problems in sleep onset and maintenance	Pharmacological strategies for sleep initiation failure	Short-acting benzodiazepines Non-benzodiazepine hypnotics: zopiclone
	Pharmacological strategies for sleep fragmentation	Melatonin, pregabalin *(not licensed for this indication)*
	Nonpharmacological measures	Avoid alcohol at night, caffeine and tobacco Daytime exercise and exposure to sunshine Relaxation and cognitive therapies
RBD	Pharmacological strategies	Clonazepam *(not licensed for this indication)* Melatonin (immediate and slow release
Urinary symptoms: nocturia	Pharmacological strategies	Consider night-time transdermal rotigotine patch If detrusor instability: mirabegron, trospium
		If morning hypotension: desmopressin nasal spray; aim to avoid diuretics, antihypertensives or vasodilators
	Nonpharmacological measures	Decrease evening fluid intake empty bladder prior to bed catheters/bedside commode If associated with postural hypotension, head-up tilt of bed
Sleep apnea	Nonpharmacological measures	NIV, CPAP, MRS, soft plate implants
EDS	Pharmacological strategies	Caffeine tablets, Modafinil
RLS/PLM	Pharmacological strategies	Dopamine agonists (transdermal rotigotine may be preferable), gabapentin *(not licensed for this indication)*

COMT, catechol O-methyltransferase; RBD, REM sleep behavior disorder; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; MRS, mandibular responding splint; EDS, excessive daytime sleepiness. RLS, restless legs syndrome; PLM, periodic limb movement.

contributor to poor sleep. EDS is a known adverse effect of dopaminergic therapy, which can result in some PwP experiencing sudden-onset sleep attacks, about which patients should be counselled. In this regard, particular attentions should be paid for PwP with specific PD subtypes, such as the serotonergic one, manifesting non-motor symptoms as somnolence and fatigue [12]. This subgroup would need a more specific personalized strategy, which, additionally to counselling on lifestyle advice and adaptations for any daily activity for which sleepiness could be a problem, also includes avoidance of dopamine D3 receptor active agents (such as pramipexole and ropinirole) and proactive recognition and treatment of fatigue [12]. Many validated tools have been developed for EDS assessment, such as the Epworth Sleepiness Scale, but only the SCales for Outcomes in PArkinson's Disease-Sleep (SCOPA- S) has been specifically validated for PD [61, 70, 71].

Overall, sleep outcomes for PwP could be significantly improved by:

- Asking simple sleep screening questions regularly;
- Considering the use of formal sleep scales in clinical evaluation of PwP;
- Considering specific management of sleep disorders depending on etiology.

SUMMARY

In this review, we have discussed the importance of recognizing, assessing, and managing bone health, cardiovascular risk, anticholinergic burden, and sleep disturbance in the care of PwP. Future studies could be designed to test the extent to which recognizing and addressing these might offer a significant contribution to personalizing medication regimes for PwP and improving overall outcomes for both the PwP and their care partner. An example of how personalization of treatment approaches might be implemented is the recently proposed "*Parkinson's vital dashboard*" [72]. Consideration and adaptation of prescribing are critical and where resource and clinic burden allow, screening and scoring will promote individual optimization of care.

1) Consider – impact of polypharmacy and PD treatment to overall health;
2) Screen – undertake risk assessments for common co-morbidities including bone health, cardiovascular risk, sleep disorders and anticholinergic burden;
3) Quantify – if possible, using specialized questionnaires and scoring tools to allow informed shared decision-making regarding medications for both PD and co-morbidities;
4) Individualize treatment – bespoke medication changes subsequent to holistic assessment.

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