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Management of Levodopa Medication for Older People with Parkinson's Disease Living in a Nursing Home Setting.

Summary

This article discusses the medication management of levodopa in older people who have Parkinson's and live in a nursing home setting. It provides a detailed description of the diagnostic criteria, motor and non-motor clinical features of Parkinson's disease. Against this clinical picture the benefits and challenges of levodopa medication management are considered. A person-centered approach is championed as it supports collaborative clinical assessment and decision making between nurses and residents. To fully appreciate why a person-centered approach is important to safe and effective medication practice the pharmacological basis of levodopa management is explained. An empowerment approach to medication management is advocated that facilitates self-medication by residents. To this end the importance of continuous professional development for nursing home staff is discussed.

Keywords

Dopamine, gait disorders, levodopa, medication concordance, motor fluctuations, nursing homes, medication management, nurse documentation, Parkinson's disease, person-centered care.

Introduction

The nursing home was privately owned and provided care for 70 older people needing long term care. Residents had a range of co-morbidities including dementias for which the home had a dedicated unit. No residents had pressure sores and only one resident had an indwelling external urinary catheter. Two registered nurses administered all medications during 12-hour day and night shifts. Each resident with Parkinson's disease was over 75 years of age and all had been prescribed levodopa for at least 4 years. They were at an advanced stage and had co-morbidities that included chronic obstructive pulmonary disease and dementia. Although only numbering 7 residents my experience of the daily nursing challenges posed by management of their levodopa medication gave rise to this article.

Parkinson's Disease

James Parkinson (1817), a London physician, first described Parkinson's disease in 'An essay on the shaking palsy'. It is caused by an imbalance between two neurotransmitters called dopamine and acetylcholine that communicate with voluntary muscle cells to produce smooth movement. Dopamine is produced in the largest basal ganglia structure, the corpus striatum, comprising the caudate and lentiform nuclei (Figure 1). The basal ganglia structures lie deep in the brain and control autonomic movements of skeletal muscle (Tortora and Grabowski, 2013). The

action of dopamine on muscle is inhibitory while that of acetylcholine is excitatory. In Parkinson's disease dopamine levels are reduced resulting in a loss of inhibitory influences on the excitatory mechanisms of acetylcholine. This produces the disordered movement of increased cholinergic activity characteristic of Parkinson's disease (Davie, 2008). Dopamine is not used to treat Parkinson's because it cannot cross the blood-brain barrier. Its amino-acid precursor levodopa, can and is used to replenish depleted dopamine in the brain (JFC, 2014). Parkinson's disease is among the most common chronic degenerative conditions of the nervous system in Western Europe.

Globally, an estimated ten million people are living with Parkinson's (Parkinson's Disease Foundation, 2016). Due to difficulties diagnosing Parkinsonism under-recognition of cases is widely acknowledged (Weerkamp et al, 2014). Recent studies in North East Scotland (Caslake et al, 2013), and North East England (Duncan et al, 2014) reported an annual incidence of 17.9 and 15.9 per 100 000 respectively. Across the UK the prevalence rate for Parkinson's is reported to be 27.4 per 10,000 of the population (Parkinson's UK, 2009) with no major geographical variations in England and Wales (Wickremaratchi et al, 2009). With increasing longevity, it is expected that prevalence rates will rise and Parkinson's UK (2009) forecast a 26.7% increase over their 2009 prevalence figures by 2020.

Of note is the marked difference in prevalence between females, 24.1 per 10,000, and males, 30.9 per 10,000 (Parkinson's UK, 2009). Risk of Parkinson's is far greater in people over 60 years (Mao et al, 2013), with the highest prevalence rate among people aged over 80 years (Horsfall et al, 2013). Onset can be early in life during the 40's and 50's (Wickremaratchi et al, 2009). Despite possible negative impact on the health and wellbeing of caregivers and withstanding the complex care requirements of Parkinson's, most people in the UK continue to live in their own homes cared for by their partner who receive varied formal support. With disease progression their support needs increase in areas such as symptom management, lifestyle adjustment, relationship change and planning for the future (Lageman et al, 2015).

The annual economic impact of Parkinson's for the UK is estimated at £3.3 billion. This includes the direct costs of hospital admission and nursing home care associated with progressive disability and co-morbidity (Findley, 2007). Indeed, 55% of people with Parkinson's die in hospital and 36% die in institutional care (Porter et al, 2010). It is not known how many people affected by Parkinson's live in nursing homes in the UK but Porter et al (2010) report 1.6%. The strongest predictors of admission to nursing homes include old age, hallucinations, dementia, physical dependence and a high falls rate (Buchanana et al, 2008). Other risk factors include living alone, impairment to engage in activities of daily living and depression (Makoutonina et al 2010). This information is important to inform the clinical management of Parkinson's and to anticipate the support needs of caregivers so that people affected can stay at home as long as possible.

Diagnostic Criteria

The starting point for optimal management of Parkinson's disease is an accurate diagnosis (Weerkamp et al, 2014). Therefore people with suspected Parkinson's disease should be referred quickly without treatment for specialist diagnosis (NICE, 2015a). This is because Parkinson's is difficult to diagnose as there are no specific markers to identify its onset. Cardinal diagnostic criteria are motor features. They include bradykinesia plus at least one clinical feature from rigidity, tremor and postural instability (Table 1) (Parkinson's UK, 2015). Non-motor symptoms encompass multiple body systems and can impact on the quality of daily life experienced by residents (Table 1) (NICE, 2015b). Combined with the motor symptoms they can increase a resident's need for assistance with a range of activities of daily living (NICE, 2015c).

Note on NICE Parkinson's disease guidelines. Clinical Guideline 35 (NICE, 2006) are under revision and will be available in 2017.

Levodopa Treatment

Levodopa is a dopaminergic drug used to stimulate dopamine production and control cholinergic excitation due to unopposed acetylcholine (Greenstein and Gould, 2009). To maintain good function and minimise motor complications the dose of levodopa should be as low as possible (NICE, 2015c). It is generally combined with a dopa decarboxylase inhibitor, carbidopa in co-careldopa (Sinemet) or benserazide in co-beneldopa (Madopar) (JFC, 2014). Dopa decarboxylase is an enzyme that inhibits the metabolism of levodopa to dopamine allowing a greater percentage of levodopa to cross the blood-brain barrier. This achieves effective therapeutic brain-dopamine concentrations. When used in combination with a dopa decarboxylase inhibitor levodopa is well tolerated in older or frail people, residents with severe symptoms and those who have co-morbidity (Reichmann, 2016). However, it should be used cautiously in residents who have a history of convulsions, severe pulmonary or cardiovascular disease, peptic ulcer, psychiatric illness, renal or hepatic impairment and endocrine disorders such as diabetes mellitus and osteomalacia (JFC, 2014).

Knowledge of medication side effects is essential. Levodopa has complex side effects that require careful monitoring allowing timely adjustment of medication to minimize impact on quality of life (Box 1)(Chan et al, 2008). Impulsive Control Disorder is reported in approximately 15-20% of people affected by Parkinson's (Weintraub et al, 2010). It is commonly expressed in behaviours such as uncontrollable shopping, gambling, eating, sex, and hobbies (Wiess and Marsh, 2012). Management of hallucinations and illusions is challenging particularly when the resident has dementia. Although these symptoms may result from levodopa treatment it is necessary to rule out causes such as delirium, pulmonary or urinary infections (Rabey, 2009). In the nursing home setting a nurse should discuss these issues with the resident's GP or consultant as soon as possible.

Side effects of levodopa also include abnormal involuntary movements (dyskinesias) that manifest as 'chorea' or 'dystonic' symptoms. Chorea symptoms range from

fidgiting movements to uncontrolled movement of the arms and legs. Dystonic symptoms include sustained painful muscle contractions affecting the neck, trunk and limbs (Vernon, 2009). Dyskinesias can occur when levodopa and dopamine reach maximum dose concentrations in the brain, termed peak-dose dyskinesias. When the dose of levodopa is very low in the brain dystonia can occur (Calabresi, 2010). Although there is no recognised first choice medication for Parkinson's (NICE, 2015c) no other pharmacological interventions currently available demonstrate superior clinical benefits to levodopa (Mao et al, 2013). It remains the preferred drug to control motor symptoms particularly in advanced stages of Parkinson's disease (Poewe et al, 2010) and is the drug that physicians have most clinical experience in prescribing (Schapira et al, 2009). Carefully managed it can contribute to an improved quality of life but does not slow or prevent disease progression. For these reasons it is likely that levodopa medication will be one of the main drugs administered by in nursing home settings.

Pharmacokinetic Aspects of Levodopa

Pharmacokinetics studies the body's influence on a drug over time during the processes of absorption, distribution, metabolism and excretion (Young, 2008). This knowledge enables nurses to understand factors that influence the maintenance of effective therapeutic brain-dopamine concentrations using levodopa. It has been known for some time that there is high variability between people in how the body deals with levodopa (Nutt and Fellman, 1984). Parkinson's disease can also fluctuate from day to day even when the same dose of levodopa is administered at the right time (Parkinson's UK, 2013). Factors known to influence the pharmacokinetics of levodopa include sex and advanced age, low body weight, slowed gastric emptying and food such as fat or protein. Discerning medication management can positively or adversely influence some of these factors.

The rate of gastric emptying is described as 'key' to levodopa absorption (Crevoisier et al, 2003). Meals provided prior to or concurrent with the administration of levodopa can delay its delivery to the intestinal absorption sites. This will delay and reduce its availability to the body, termed bioavailability. Suboptimal ingestion of levodopa due to slowed gastric emptying, missed doses or irregular administration of drugs can contribute to disabling motor fluctuations and increases in non-motor symptoms particularly as Parkinson's progresses (European Parkinson's Disease Association, 2015). Levodopa should be administered at least 30 minutes before residents eat protein to prevent interference with its absorption (Parkinson's UK, 2013). A full stomach also delays absorption of the drug (Crevoisier et al, 2013). Because protein and levodopa compete for transport across the intestinal wall and the blood-brain barrier possible motor fluctuations after meals can be minimised by redistribution of a resident's protein intake over the course of the day (Barichella, 2006).

Absorption of levodopa is erratic achieving variable bioavailability even when controlled-release levodopa is used (Brooks, 2008). With immediate-release levodopa motor improvement occurs 30 to 90 minutes after administration. Controlled-release

formulations maintain levodopa levels for longer periods but their slower absorption increases motor improvement latency. 'Improvement latency' is the period of time after taking a drug to its pharmacological effect (Olanow et al, 2009). On this basis controlled-release and immediate-release formulations can be administered as a morning dose. These medications can help to maintain optimal control of motor response fluctuations (Poewe et al, 2010). This pharmacokinetic knowledge enables nurses working in long term settings to produce person-centered care plans that support safe and effective medication management. For example, by documenting a resident's specific drug administration requirements in relation to their meals.

Pharmacodynamic Aspects of Levodopa

Pharmacodynamics is the study of how drugs act on the body (Greenstein and Gould, 2009). With disease progression and long-term use the capacity of levodopa to treat the motor symptoms of Parkinson's disease decreases. This is because it takes less time for levodopa medication in the body to be reduced by 50% referred to as the drug's half-life. Because the half-life of levodopa is shortened the period of time it produces an effect is correspondingly reduced (Chan et al, 2005a, 2005b). When this happens residents experience fluctuations from 'ON' periods when they experience motor benefit to 'OFF' periods when they no longer benefit from the drug (Figure 2)(Mao et al, 2013; Contin and Martinelli, 2010).

Adding Catechol-O methyltransferase (COMT) inhibitors (entacapone or tolcapone) to levodopa can improve fluctuating motor responses by increasing 'ON' periods and decreasing 'OFF' periods (Stocchi and De Pandis, 2006; Leegwater-Kim and Waters, 2007). COMT inhibitors increase the half-life of levodopa by blocking the break-down of levodopa into dopamine *before* it crosses the blood-brain barrier. This is important because dopamine cannot cross the blood-brain barrier. By allowing more levodopa to reach the brain COMT inhibitors can reduce 'OFF' periods (Vernon, 2009). They have wide ranging side effects that require careful monitoring by nurses (Box 2) (JFC, 2014). Tolcapone should only be prescribed under specialist supervision due to the risk of hepatotoxicity (JFC, 2014). Monitoring liver function is therefore important and this should be clearly communicated by nurses in the resident's person-centered care plan (Grandas and Hernández, 2007; Mizuno et al, 2007).

Monoamine oxidase type-B (MAO-B) inhibitors (selegiline and rasagaline) are licensed to use alone or in combination with levodopa to treat 'OFF' periods in Parkinson's disease (JFC, 2014). They block the action of monoamine oxidase type-B, an enzyme that breaks down levodopa in the brain. In this way it prolongs the action of levodopa thereby supporting prescription of smaller levodopa doses (Greenstein and Gould, 2009). Nurses need to monitor for their wide ranging side effects (Box 3) (JFC, 2014). Selegiline combined with levodopa should be avoided or used cautiously for residents who have postural hypotension. Its abrupt withdrawal must be avoided (JFC, 2014). Application of pharmacodynamic knowledge to person-centered monitoring and assessment enables nurses to identify specific observations they should be make in relation to each resident. For example, documentation of the need to monitor

resident response and end-of-dose 'OFF' periods.

Safe Management of Levodopa

Registered nurses have a responsibility to ensure safe and reliable administration of medication and to monitor for side-effects (NMC, 2010; An Bord Altranais, 2007). Combining levodopa with decarboxylase inhibitors has the important benefit of enabling use of lower levodopa doses helping to limit side-effects. The therapeutic success of this combination is reflected in the rare reporting of side effects as being dose-limiting (JFC, 2014). However, when combined with the exact titration requirements of levodopa medications the possibility of adverse interactions is increased (Williams et al, 2008).

From the beginning to the end of a resident's stay nurse documentation should reflect person-centered care (Jefferies et al, 2010). It is a fundamental practice approach expected of nurses working with older people (An Bord Altranais, 2009) and views the nurse/resident as a collaborative partnership in clinical decision-making. Before admission to the nursing home a comprehensive pre-admission assessment should be conducted incorporating a detailed medication history. McCormack and McCance (2006) suggest a biographical approach as this captures the values, beliefs and preferences of the person and 'fosters a connectedness between the patient and the caregiver' (Broderick and Coffey, 2013, p310). Thus, medication management should aim to 'empower people with Parkinson's disease to participate in judgments and choices about their own care' (NICE, 2015d, p3).

Evidence shows that incomplete or incorrect documentation like omission of allergy status places residents at risk (National Patient Safety Agency, 2007). Pharmacological control through administration of levodopa medication at the 'right time' (Parkinson's UK, 2016a; 2016b) is central to maintaining the independence and wellbeing of residents with Parkinson's. Routine removal of a resident's medication control on admission to a nursing home will result in anxiety that nurses might not administer their Parkinson's medication on time. 'Getting their medication on time is one of the most basic, important things for people with this condition' (Parkinson's UK, 2013, p41, wife caregiver). Asking previously self-medicating residents to hand over control of their medication can feel like an attack on their precious but declining independence. The importance of residents taking their Parkinson's medication on time cannot be understated. It is critical to the maintenance of the uniform stimulation of the brains dopamine receptors so that their parkinsonian motor symptoms are controlled. This helps to maximize each resident's independence and quality of life. Whether administration is by nurses or residents each resident's care plan should communicate medication times especially if they lie outside the usual drug round times.

Medication administration requirements at meal times should be documented (Parkinson's UK, 2013) so that residents are protected from increased motor and non-motor symptoms due to suboptimal ingestion of levodopa (European Parkinson's

Disease Association, 2015). As stated care planning should identify any specific medication related observations the nurse should monitor. For levodopa the response and end-of-dose wearing off should be noted. Revision of medication to improve a resident's motor function can produce changes in their daily energy expenditure resulting in weight loss or gain. Routine assessment of resident's nutritional status can check their diet provides sufficient energy intake and ensure early identification of weight loss (Cereda et al, 2010).

Medication regimes may include treatment for non-motor manifestations as well as for co-morbidities. Deterioration in pulmonary and cardiovascular disease, psychiatric illness or endocrine disorders may increase levodopa medication risk (JFC, 2014). There should be regular multi-disciplinary review with the prescribing doctor of changing needs to ensure maintenance of the resident's quality of life and wellbeing (NICE, 2015d). Nurses need to be aware of the potential risk of acute akinesia or neuroleptic malignant syndrome if antiparkinsonian medication is abruptly withdrawn or fails suddenly due to poor absorption such as if a resident has gastroenteritis (NICE, 2016c).

Medication concordance

The term 'concordance' embraces a consensual person-centered approach to medication management that places emphasis on a consultative non-judgmental partnership between resident and nurse. In contrast the term 'compliance' shouts judgmental professionals and reinforces the notion of passive residents (Haynes et al, 2005). NICE (2015c) advises the choice of treatment should consider a resident's presenting clinical features and their lifestyle. It also states that the resident's medication preference should only be determined after the short and long-term benefits and drawbacks of their medication choices have been explained. Medication concordance is important. It can slow a resident's disease progression, prevent complications, help achieve optimal wellbeing and improve quality of life (Williams et al, 2008).

'Sub-optimal compliance' is significant if less than 80% of medication is taken within prescribed doses and intervals. Increasing complexity of medication regimen is strongly correlated with sub-optimal compliance (Malek and Grosset, 2015). Levodopa has a short plasma half-life and therefore requires multiple daily doses that can produce marked swings of therapeutic effect. Resulting motor fluctuations can lead to concordance issues due to the frustration felt by residents of their debilitating effect. Development of individualised simple person-centered treatment plans can improve concordance by residents and nurses. Complex regimes may be viewed as a burden (Fargel et al, 2007).

Didactic sensitive discussion of the medication regimes with residents can help to encourage their concordance. Nurses need to spend time with residents who have depression and dementia to facilitate medication concordance (Daley et al, 2012). Respect of dignity and rights can be shown by nurses adopting a medication

administration ethos that views their role as acting 'on behalf of the resident rather than to the resident' (Centre for Policy on Aging, 2011).

Education and Support

The 3rd World Parkinson Congress (World Parkinson Coalition, 2016) championed the empowerment of people living with Parkinson's to be involved their care. Parkinson's is challenging because it is often characterised by changes in symptoms from one moment to the next as in ON/OFF syndrome. This can result in loss of confidence and independence (Mao et al, 2013). Self-help education programmes develop self-regulation skills through activities that include stress management, dealing with depression or anxiety and maintaining social competence (Macht et al, 2007; A'Campo et al, 2010).

Healthcare professionals that lack neurological expertise are likely to contribute to poor clinical outcomes for people who have Parkinson's (Royal College of Physicians, 2011). Universal access of nursing home staff, residents and their families to the expertise of *Parkinson's Disease Nurse Specialists* would help to address this issue. NICE (2015d) recommend this arrangement for purposes of advice, clinical monitoring and medication adjustment. Nurse Specialists have been shown to relieve the negative impact of Parkinson's on the daily lives of individuals and families affected (Hellqvist and Berterö, 2015; RCN, 2010), '... She changed my life from being a scared, shaking mess to a much happier person. She gives me hope' (Parkinson's UK, 2013, p14).

A survey of people with Parkinson's admitted to hospital, and who were not self-medicating, found nearly 33% did not get their medication on time *every* time and that 25% felt this prolonged their hospital stay (Parkinson's Disease Society, 2008). It is so important for nurses working in long term care to engage in training on medication management specific to Parkinson's. Free resources and on-line courses are available for nursing home staff (Parkinson's UK, 2016c; 2016d) including a 'Get It On Time' training DVD (Parkinson's UK, 2016a; 2016b). This testimony captures the positive impact training of nurses can have for people with Parkinson's, 'Thanks to the Get It On Time campaign, staff at my local hospital now understand that I need my medication on time ...' (Parkinson's UK, 2011, p12).

Conclusion

This case study has explored the pharmacokinetic and pharmacodynamic aspects of levodopa medication because this knowledge underpins safe and effective person-centered medication management in nursing home settings. Discussions on safe medication management and concordance reveal the substantial daily challenges faced by nurses caring for residents who have Parkinson's disease. In particular it explains why administration of Parkinson's medication at the 'right time' is crucial to the health and wellbeing of these residents. Future practice should continue to develop a person-centered approach to medication management that is embedded in excellent care planning. Wherever possible it should support residents to self-medicate. Management of medication treatment for long term conditions is a key nursing role in nursing home

settings. Ongoing professional development and updating in pharmacology and medication management relevant to the conditions of residents can equip nurses to maintain the independence of residents and enhance their quality of life.

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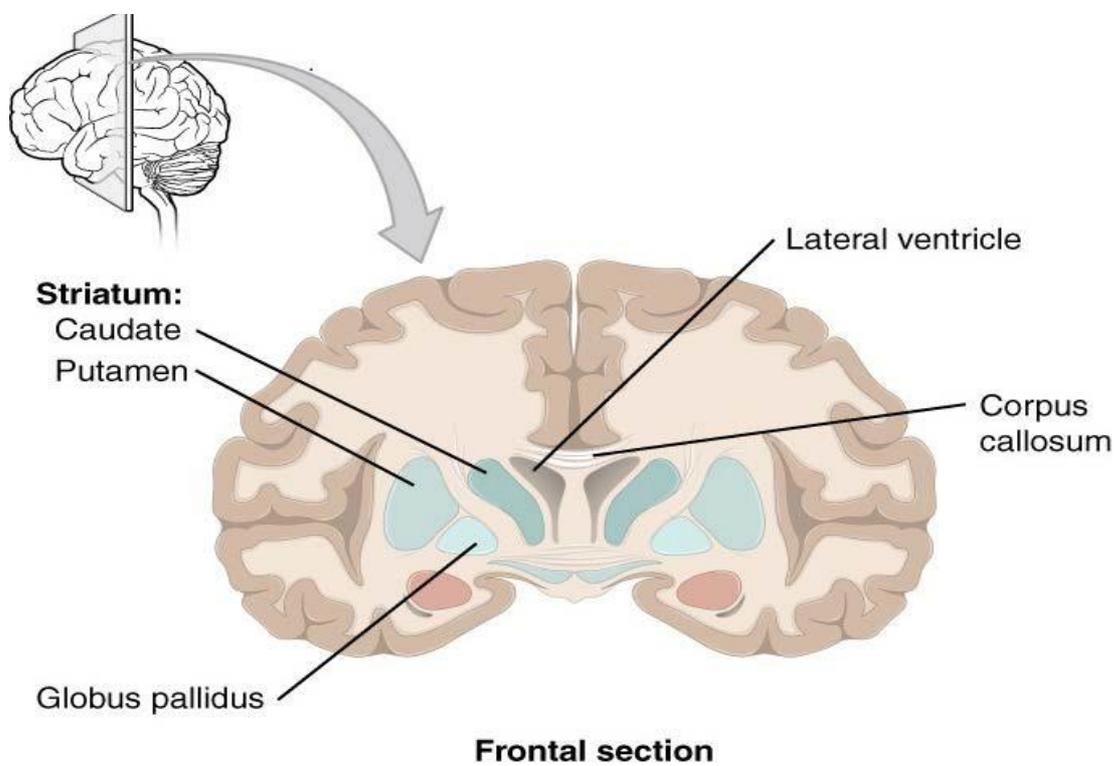
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August 6th 2016 new word count is 5214 including reference list

Figure 1 Frontal Section of the Basal Ganglia Nuclei.



(Lecturio, 2016)

Table 1 Clinical Features of People with Parkinson’s Disease

Motor Symptoms	Non-Motor Symptoms
Tremor (involuntary shaking and trembling) Bradykinesia (slowness in movement) Rigidity Postural instability (loss of postural reflexes)	Cognitive impairment Bradyphrenia (slowness of thought) Tip-of-the-tongue phenomenon (word finding)
Hypomimia (loss of facial expression, mask-like face) Dysarthria Dysphagia Sialorrhoea (drooling)	Depression Apathy, fatigue Anhedonia (symptom of major depressive disorders. Loss of interest in previously rewarding enjoyable activities) Other behavioural /psychiatric issues
Decreased arm swing Shuffling gait Festination (gait of quickening and shortening steps) Difficulty arising from chair or turning in bed	Sensory symptoms Anosmia (loss of sense of smell) Ageusia (loss of taste functions of the tongue) Pain (shoulder, back) Paresthesias
Micrographia (small cramped hand writing) Cutting food Feeding Hygiene Slow activities of daily living	Dysautonomia (umbrella term for several medical conditions that cause malfunction of the autonomic nervous system) (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhoea) Weight loss
Glabellar reflex (primitive reflex where the eyes shut if the individual is tapped between the eyebrows) Blepharospasm (sustained enforced closing of the eye lids. Can be painful. May be called eye dystonia) Dystonia (abnormal muscle tone resulting in muscle spasm and abnormal posture) Striatal deformity (deformities of the hand and the foot) Scoliosis (a sideways curvature of the spine) Camptocormia (abnormal severe involuntary forward flexion of the thoracolumbar spine)	Sleep disorders (Rapid Eye Movement behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

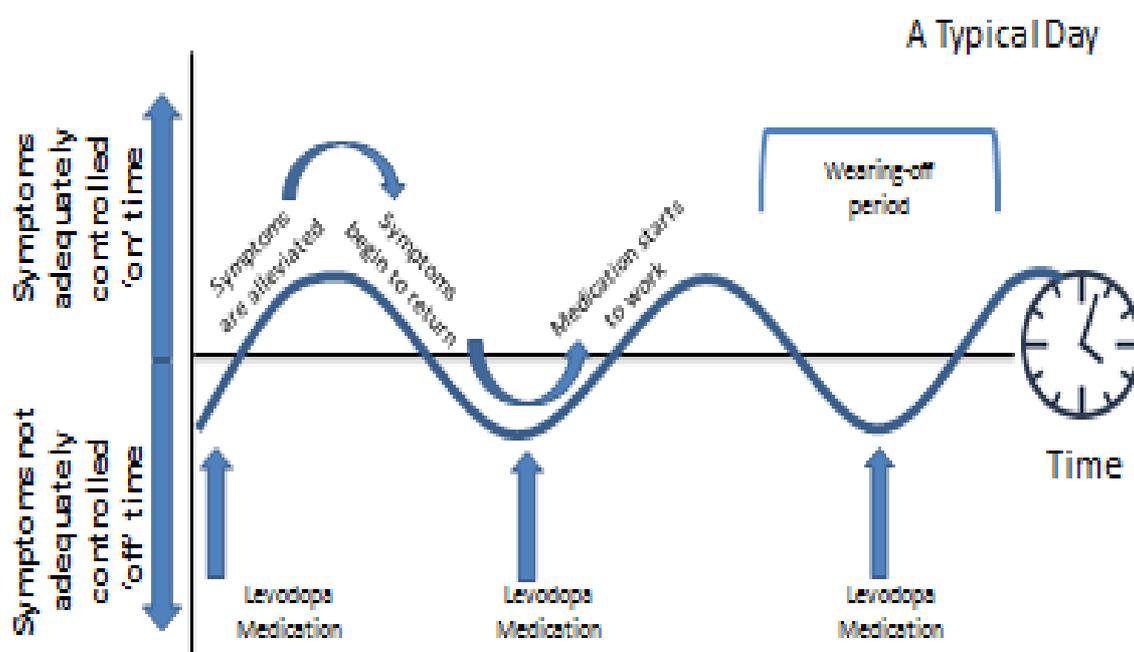
(Adapted from Jankovic, 2008)

Box 1	Side effects of Levodopa
<ul style="list-style-type: none">▪ Nausea, vomiting▪ Taste disturbances, anorexia▪ Dry mouth▪ Postural-hypotension▪ Hallucinations, illusions▪ Drowsiness▪ Mood change, depression▪ Alteration of libido▪ Impulsive Control Disorder <p>(Chan et al, 2008)</p>	

Box 2	Side effects of COMT inhibitors
<ul style="list-style-type: none">▪ Nausea, vomiting▪ Dry mouth▪ Abdominal pain, constipation, diarrhoea▪ Reddish brown discolouration of the urine▪ Sweating▪ Confusion, hallucinations▪ Dizziness▪ Fatigue, insomnia▪ Dyskinesias▪ Hepatotoxicity (Tolcapane) <p>(JFC, 2014)</p>	

Box 3	Side effects of MAO-B inhibitors
<ul style="list-style-type: none">▪ Nausea▪ Dry mouth, stomatitis, mouth ulcers▪ Nasal congestion▪ Constipation, diarrhoea▪ Sweating▪ Hair loss▪ Bradycardia▪ Hypertension, hypotension,▪ Depression▪ Headache hair loss and sweating▪ Confusion▪ Dizziness, impaired balance▪ Fatigue▪ Movement disorders, myalgia <p>(JFC, 2014)</p>	

Figure 2 End of dose 'wearing-off' in levodopa treated residents



(European Parkinson's Disease Association, 2015)

Location of Changes to Revised Article 6th August 2016

(In the order they occur in the article)

Reviewer 1. Point 3 **Abstract**. Simplified sentence construction and ensured no words are missing.

Reviewer 1. **Introduction** Paragraph 1: increased description of the nursing home added

Reviewer 1. Point 2 and 5. **Parkinson's Disease** Paragraphs 1 description of neurotransmitters and paragraph 3 non-motor symptoms removed. Link to the nursing home context inserted.

Reviewer 1. Point 1. **Levodopa Treatment**, punctuation, last sentence of paragraph 1

Reviewer 1. Point 2 and 5. **Levodopa Treatment**, paragraph 2, side effects in box 1 and sentence refined re ICD. Link to the nursing home context inserted.

Reviewer 1. Point 1. **Levodopa Treatment**, paragraph 3, punctuation

Reviewer 1. Point 2. **Levodopa Treatment**, paragraph 4, Link to the nursing home context inserted.

Reviewer 1. Point 1. **Pharmacokinetic Aspects of Levodopa**. Paragraph 1 punctuation.

Reviewer 1. Point 1. **Pharmacokinetic Aspects of Levodopa**. Paragraph 3 punctuation.

Reviewer 1. Point 1. **Pharmacokinetic Aspects of Levodopa**. Paragraph 4 Link to the nursing home context inserted.

Reviewer 1. Point 1. **Pharmacodynamic Aspects of Levodopa**. Paragraph 1 punctuation.

Reviewer 1. Point 2 and 5. **Pharmacodynamic Aspects of Levodopa**. Paragraph 2. Side effects of COMT inhibitors into box 2. Link to the nursing home context inserted.

Reviewer 1. Point 1, 2 and 5. **Pharmacodynamic Aspects of Levodopa**. Paragraph 3. Side effects of MAO-B inhibitors into box 3. Link to the nursing home context. Brackets inserted as suggested by reviewer.

Reviewer 1. Point 2. **Safe Management of Levodopa. Paragraph 2**. Link to the nursing home context.

Reviewer 1. Point 2. **Safe Management of Levodopa. Paragraph 2**. Link to the nursing home context. Also explained need for medication to be on time with in context of the paragraph.

Reviewer 1. Point 1 and 2. **Medication concordance.** Paragraph 1. Punctuation and link to the nursing home context.

Reviewer 1. Point 2. **Medication concordance.** Paragraph 2 link to the nursing home context.

Reviewer 1. Point 1. **Education and Support.** Paragraph 1 punctuation

Reviewer 1. Point 1. **Education and Support.** Paragraph 1. Suggested wording inserted.

Reviewer 1. Point 1. **Education and Support.** Final paragraph refined.

Reviewer 1. Point 4. **Conclusion** revised.

Reference revisions

Diagram references added to reference list

Reviewer 1. Ensure refs have issue number and are correct.

Please note that:

Davie C (2008) A Review of Parkinson's Disease. *British Medical Bulletin*. 86, 107-129 does not have an issue number.

Findley L (2007) The economic impact of Parkinson's disease. *Parkinsonism and Related Disorders*. 13, S8–S12 does not have an issue number.

Haynes R, McDonald H, Garg A et al (2002) Interventions for helping patients to follow prescriptions for medications. *Cochrane Database of Systematic Reviews*. Issue 2. Does not have a volume number

Poewe W, Antonini A, Zijlmans C et al (2010) Levodopa in the treatment of Parkinson's disease: an old drug still going strong. *Clinical Interventions in Aging*. 5, 229-238 does not have an issue number.

Reviewer 2

Reviewer 2: PD NICE Guidance 2015 citations provided with electronic addresses

Reviewer 2: PD Clinical Guidelines 2006 stated as information in the margin of the article. Also inserted into list of full references.