The Aeromedical Implications of Parkinson's Disease

Tania Jagathesan; Michael D. O'Brien

BACKGROUND: Parkinson's disease is a progressive neurodegenerative disorder which is encountered in the pilot population and has clinical features that can impact on the flying role. This retrospective study reviewed the United Kingdom Civil Aviation Authority (UK CAA) experience of Parkinson's disease. The aeromedical implications of the condition are discussed and the UK CAA policy for the certificatory assessment of pilots with Parkinson's disease is described.

METHODS: A search of the UK CAA medical records database from 1990 to 2015 identified 34 pilots with a diagnosis of Parkinson's disease. Data was extracted for the class of medical certificate, time from first symptoms to diagnosis, age at diagnosis, the time from diagnosis to loss of certification and the reasons for loss of certification.

RESULTS: Of 15 professional (Class 1) and 19 private (Class 2) pilots, the mean time from onset of symptoms to diagnosis was 36 and 19 mo, respectively. The mean ages at diagnosis were 55 and 59 yr, respectively. The mean interval from diagnosis to loss of certification was 21 (0-93) and 37 (0-84) mo, respectively. The reasons for loss of certification are considered.

CONCLUSION: In the UK, pilots diagnosed with Parkinson's disease may be granted medical certification depending on their functional ability and the side effect profile of medication. The aeromedical implications of Parkinson's disease and the UK CAA policy for the certification of pilots with Parkinson's disease are discussed.

KEYWORDS: bradykinesia, tremor, rigidity, pilots.

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Parkinson's disease, first described by James Parkinson in 1817,[25] is a progressive neurodegenerative disorder of the substantia nigra, locus cereleus, caudate nucleus, putamen, and pallidum. Pathologically, there is loss of pigmented dopaminergic neurons and the presence of Lewy bodies. The cardinal motor features are bradykinesia, rigidity, tremor, and postural instability. The nonmotor features include mental health problems, dementia, sleep disturbance, autonomic disturbance, and pain, all of which may occur early and can have implications for a pilot's fitness to fly.

The incidence of Parkinson's disease is 20 in 100,000 person years between 50 and 59 yr, rising to 90 in 100,000 person years between the ages of 70 and 79, giving a prevalence of 1% in those over 60 yr of age.[18] The onset is usually in the fifth to seventh decades, but may be much earlier. Parkinson's disease is about one and a half times more common in men than in women. Although inevitably progressive, the rate of progression is variable, with some subjects managing minimal symptoms for many years without significant disability. This study examined the United Kingdom Civil Aviation Authority (UK CAA) experience of Parkinson's disease and the aeromedical implications of the condition.

METHODS

The UK CAA database holds personal details, medical history, reports, results of investigations, and correspondence on all applicants and medical certificate holders from 1990 to 2015. A search of this database was performed using the diagnostic terms 'Parkinson's Disease' and 'Parkinsonism' and 36 subjects were identified. Two individuals were excluded for a diagnosis of benign familial tremor. Of the 34 remaining subjects, 15 were professional pilots (European Union Class 1 certificate holders) and 19 were private pilots (European Union Class 2 certificate holders). Each subject's medical record was reviewed for gender, age at symptom onset, time from first symptoms to diagnosis, time from diagnosis to loss of medical certification, and the

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reasons for loss of certification. This anonymized study did not require ethical approval.

RESULTS

The results for professional pilots are shown in **Table I** and for private pilots in **Table II**. The normal procedure is that the medical certificate of a pilot is temporarily suspended on declaration of the diagnosis until a full certificatory assessment has been undertaken by the regulator or the aviation medical examiner. If the assessment is satisfactory, the suspension is lifted and the pilot can regain certification.

All of our subjects were men. For professional pilots, the mean time from onset of symptoms to diagnosis was 36 mo (4–168, median 18). However, in two commercial airline pilots, Parkinson's disease was not diagnosed until 10 and 14 yr after the initial presentation of a resting tremor and these have skewed the mean, as illustrated by a median time of 18 mo. The mean age at diagnosis was 55 yr (37–66). Of the 15 professional pilots, 8 (53%) did not regain certification; reasons included choosing not to reapply, being denied certification due to the severity of the disease, starting unacceptable medication, and the development of unrelated cardiovascular pathology. For professional pilots, the mean interval from diagnosis to loss of certification was 21 mo (0–93, median zero).

In private pilots, the mean time from onset of symptoms to diagnosis was 19 mo (0–39, median 17). The mean age at diagnosis was 59 yr (38–72). Of the 19 private pilots, 3 (16%) did not regain certification; 2 chose not to reapply and 1 was denied certification due to unacceptable medication. The mean interval from diagnosis to loss of certification was 37 mo (0–84, median 45).

Of the 34 subjects, only 2 pilots were recorded to have lost certification due to disease progression. One was an airline pilot, with marked rigidity and bradykinesia that progressed to involve both upper limbs, who lost certification at the age of 46, 51 mo following the diagnosis. The other was a private pilot who had severe bradykinesia in the right hand, causing difficulties with writing and dexterity, leading to the loss of certification 15 mo after the diagnosis at the age of 60. However, it is highly likely that those pilots who started unacceptable medication and those who did not reapply for medical certification following the expiry of their medical certificates also did so due to disease progression. The last pilot in this series was assessed as recently as 3 mo ago. None of the 34 pilots were flying at the time of the study.

For over 20 yr, the UK CAA has only permitted the drugs amantidine and selegiline for the treatment of Parkinson's disease in pilots on the basis of their side effect profiles. All other medication has been considered unacceptable. Of our 34 subjects, 8 were disqualified due to unacceptable medication. One private pilot had continued flying while taking levodopa and benserazide hydrochloride for 7 yr without declaring his medication to the CAA, which was eventually disclosed by his General Practitioner.

DISCUSSION

It should be noted that the database of a regulatory organization presents significant problems for the analysis of medical information, as data is not collected prospectively and often relies on information obtained from the subject or external medical reports. For this study, all relevant information was available except for three private pilots in whom it was not possible to determine when their symptoms first occurred. All pilots were required to provide a medical report from a neurologist for a certificatory assessment.

In our series, it is interesting that the time from the first symptoms to diagnosis was longer in professional than in private pilots; however, once a diagnosis has been made, the professional pilots continued to fly for a shorter period of time than the private pilots, despite there being similar age profiles in both groups. A possible explanation may be that professional pilots avoided a formal diagnosis for as long as possible

Table I. UK CAA Experience, 1990-2015, Professional Pilots.

AGE AT DIAGNOSIS (yr)	TIME FROM FIRST SYMPTOMS TO DIAGNOSIS (mo)	TIME FROM DIAGNOSIS TO LOSS OF CERTIFICATION (mo)	REASON FOR LOSS OF CERTIFICATION
37	46	22	Unacceptable medication: ropinarole
42	24	51	Disease progression
50	24	93	Did not reapply
53	18	0	Disease severity
53	12	0	Unacceptable medication: pramipexole
53	12	39	Did not reapply
54	122	75	Did not reapply
55	12	0	Disease severity
55	8	0	Unacceptable medication: ropinarole
56	10	14	Did not reapply
57	48	0	Did not reapply
59	168	26	Unacceptable medication: L-Dopa/carbidopa
61	4	0	Did not reapply
62	12	0	Did not reapply
66	19	0	Cardiovascular pathology

Table II. UK CAA Experience, 1990-2015, Private Pilots.

AGE AT DIAGNOSIS (yr)	TIME FROM FIRST SYMPTOMS TO DIAGNOSIS (mo)	TIME FROM DIAGNOSIS TO LOSS OF CERTIFICATION (mo)	REASON FOR LOSS OF CERTIFICATION
38	0	3	Did not reapply
46	36	52	Did not reapply
49	NK	40	Did not reapply
51	39	52	Did not reapply
54	0	45	Did not reapply
55	12	60	Did not reapply
58	9	15	Disease progression
59	NK	52	Did not reapply
60	NK	0	Unacceptable medication: ropinarole
60	0	46	Did not reapply
63	36	84	Did not reapply
63	15	73	Unacceptable medication: L-Dopa/benserazide
63	27	15	Unacceptable medication: L-Dopa/benserazide
64	36	46	Did not reapply
64	36	2	Did not reapply
65	36	36	Unacceptable medication: L-Dopa/carbidopa
66	18	18	Did not reapply
71	0	0	Did not reapply
72	0	0	Did not reapply

NK: Not known.

due to concerns regarding the potential implications for their careers. Following a diagnosis, a lack of confidence performing the job and the psychological and financial closure from claiming on loss of license insurance policies may have contributed to the shorter times from diagnosis to loss of certification in professional pilots than private pilots. However, such theories are speculative and should be made cautiously in view of the small number of subjects in each group.

The aeromedical concerns of Parkinson's disease are the clinical features of the disease and the response to adverse effects from medication. Parkinson's disease has a range of motor and nonmotor features. The cardinal motor features, all of which are aeromedically relevant, include tremor, rigidity, bradykinesia, and loss of balance and postural reflexes, which can affect dexterity, coordination, accuracy, and the speed of actions performed while flying. In addition, patients may develop soft, less distinct, monotonous speech and, in advanced cases, speech may become slurred and poorly articulated, potentially affecting their interaction with other pilots or with air traffic controllers. The nonmotor features are autonomic disturbance causing constipation, sweating abnormalities, sexual dysfunction, sleep disorders, depression, anhedonia, psychosis, and dementia.[17] In one study, the frequency of nonmotor features was reported as fatigue in 58%, anxiety in 56%, leg pain in 38%, insomnia in 37%, urinary urgency and nocturia in 35%, difficulty maintaining concentration in 31%, and depression in 23%.[4] Another symptom that can be distracting is musculoskeletal pain, which has a prevalence of between 40 and 85%, caused by abnormal posture, rigidity, and akinesia and is usually more marked in the early morning.[5] These nonmotor problems are most prevalent later in the illness, but may also occur early and their evaluation is an important part of the neurology assessment. Although none of our pilots had nonmotor symptoms, there may have been an element of under-reporting by pilots due to concerns for their careers, as well as deficiencies in the medical record. The commonest recorded clinical features in our pilots were bradykinesia, tremor, and rigidity.

There is considerable variation in the rate of progression of the disease. Some patients are disabled early in the course of the disease, while others are not significantly affected for many years. The longest period of time that a pilot returned to flying following a diagnosis was almost 8 yr in a professional pilot and 7 yr in a private pilot and neither was on medication, while eight professional pilots and three private pilots were considered unfit at the first assessment due to the severity of the disease, demonstrating the wide variability of the condition.

Mild cognitive impairment may develop, usually as a late feature of the disease; however, studies have shown it can also occur in 24%[21] and 36%[9] of newly diagnosed patients. Characteristic cognitive symptoms include slow mental processing, difficulty multitasking, and decreased attention or concentration, with deficits in tasks that require planning[22] or responding to new stimuli,[3] all of which are critical in flying. It has been postulated that mild cognitive impairment may be a prodromal state to Parkinson's disease dementia. The point prevalence rate of dementia in Parkinson's disease is 40%[1] and this increases during the course of the disease, reaching 78% after 8 yr[2] and 83% after 20 yr.[12] Evidence of cognitive impairment or dementia is disqualifying for medical certification. The most relevant test for cognitive impairment in pilots is a simulator check or medical flight test. None of our 34 pilots had evidence of cognitive impairment and none had reported failure of simulator checks or medical flight tests, nor had colleagues or employers reported any concerns about performance, nor were there any reported aircraft incidents.

Depression in Parkinson's disease is common, occurring in about 30–40%[16,26,29] and is normally associated with greater disability and a rapid progression of motor symptoms. If suspected, depression rating scores should be performed and recommended screening tests include the Hamilton Depression Scale and the

Beck Depression Inventory.[28] Subsequently, if indicated, an assessment should be undertaken with a psychiatrist. In our series, no pilots reported symptoms of depression; however, there may have been a degree of both under-diagnosis and under-reporting. Concurrent depression in a pilot with Parkinson's disease is not compatible with medical certification.

Psychosis is another reported complication of Parkinson's disease and is characterized by visual hallucinations and delusions. The estimated prevalence ranges from 4 to 45 per 1000 Parkinson's disease patients,[13] but this is usually seen in advanced disease following prolonged treatment and is mainly due to chronic exposure to dopaminergic medication,[27] so this is not relevant in our pilot population, where these drugs are not permitted.

Parkinson's Plus Syndromes are a heterogeneous group of neurodegenerative conditions distinct from Parkinson's disease and include multisystem atrophy, progressive supranuclear palsy, parkinsonism-dementia-amyotrophic lateral sclerosis, corticobasal degeneration, and diffuse Lewy body disease. Patients may be initially diagnosed with Parkinson's disease in the early stages of these conditions and the diagnosis subsequently changed to one of the Parkinson's Plus syndromes. One of our private pilots was originally diagnosed with Parkinson's disease, but 2 yr later developed autonomic symptoms and the diagnosis was changed to multisystem atrophy. In view of their debilitating features, these syndromes are incompatible with medical certification.

There is no proven neuro-protective or disease-modifying therapy for Parkinson's disease to date, so the goal of pharmacological management is to provide symptom control for as long as possible while aiming to minimize the adverse effects of the medication. Although there are many available drugs on the market which may be beneficial, these all have side effects which should be considered in pilots operating in a safety critical role. **Fig. 1** shows the mechanism of action of the different drugs we will consider.

Dopamine receptor agonists are either ergot-derived (bromocriptine, cabergoline, pergolide) or nonergot derived (pramipexole, ropinirole, rotigotine). The ergot-derived medications are no longer in common clinical use due to the risk of retroperitoneal, pleural, and pericardial fibrosis. The side effects of dopamine receptor agonists include nausea, somnolence, dizziness, constipation, hallucinations, anorexia, and vomiting.[7] Dopamine agonists can cause excessive daytime sleepiness with an 8-yr prevalence of 54%.[11] Another particular concern is the risk of microsleeps or sleep attacks, which were first described in patients treated with pramipexole or ropinirole.[10] These are sudden transitions from wakefulness to sleep without a warning prodrome. The prevalence of sleep attacks in patients treated with dopaminergic medications has been reported to be as high as 43%,[20] so these drugs are not acceptable in pilots. Furthermore, up to 17% of patients treated with dopamine receptor agonists may develop impulse control disorders, such as gambling, excessive eating, shopping, and hypersexuality,[32] which are more commonly seen in male patients with early onset disease. Any medication which may increase risk-taking behavior is incompatible with flying. Apomorphine is a dopamine receptor agonist administered subcutaneously by infusion pump in patients with advanced Parkinson's disease, so this drug is, therefore, not relevant in pilots.

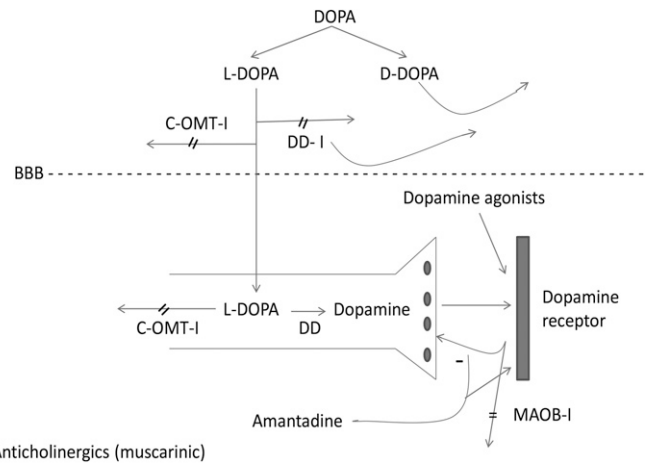

Fig. 1. Mechanism of action of medication for Parkinson's Disease. C-OMT-I: catechol-o-methyl transferase inhibitor; MAOB-I: mono amine oxidase B inhibitor; DD: dopamine decarboxylase; DDI: dopamine decarboxylase inhibitor; L-Dopa: L-dihydroxyphenylalanine; D-Dopa: D-dihydroxyphenylalanine; BBB: blood brain barrier.

Levodopa (L-Dopa) preparations combined with an extracerebral dopa-decarboxylase inhibitor, for example L-Dopa with benserazide and L-Dopa with carbidopa, are the most effective symptomatic treatments for the motor symptoms of Parkinson's disease. Although the dopa-decarboxylase inhibitor reduces the peripheral side effects of the L-Dopa, adverse effects can still occur and include dizziness, nausea, vomiting, and hypotension. Central side effects may also occur, including dyskinesia, dystonia, headache, hallucinations, and confusion. There is also a risk of unpredictable motor fluctuations due to a variable response, dose failures, and wearing-off effects, resulting in changes in motor performance, mood, and cognitive effects, which makes these preparations unsuitable for certification.[30] Somnolence is another possible side effect of particular concern. These drugs are not usually chosen as first line treatment in younger patients due to the inevitable development of motor fluctuations and dyskinesia after a short time period of time, 40% at 5 yr and 100% at 10 yr.[18]

Catechol-o-methyl transferase inhibitors (C-OMT-I), such as entacapone and tolcapone, are only prescribed in conjunction with L-Dopa to smooth out motor fluctuations and, therefore, these drugs are not relevant in the management of pilots.

The monoamine-oxidase-B inhibitors (MAOB-I) rasagiline and selegiline can provide some symptomatic benefit as monotherapy in the early stages of the disease by inhibiting the breakdown of the patient's own residual dopamine and without involving extraneous L-Dopa or dopamine agonism.[14,19] These drugs are usually well-tolerated with side effects that are mild and transient, so that once a pilot has been stabilized on a low dose, these are acceptable for flying. Rasagiline is preferred to selegiline because it is buccally absorbed and does not have a first pass hepatic metabolism and the potential for amphetamine-like side effects.

Amantadine, originally developed as an antiviral agent for influenza A, is thought to act by promoting dopamine release from presynaptic fibers and blocking the reuptake of dopamine. It may provide some short-term relief of the symptoms of mild, early-stage Parkinson's disease. Possible side effects include nausea, dizziness, and livedo reticularis; however, these are usually mild, transient, and dose-dependent, so that once stabilized on a low dose this drug is acceptable in pilots.[31]

Anticholinergic (muscarinic) drugs, such as orphenadrine, trihexyphenidyl and procyclidine, may improve Parkinsonian symptoms, particularly tremor, since dopamine depletion causes a state of relative cholinergic overactivity. However, the modest benefits of this class of drugs are offset by their adverse effects, including impaired memory, confusion, hallucinations, and dry mouth; therefore, these drugs are not permitted in pilots.[15]

Deep brain stimulation is effective for drug-induced dyskinesias and is only used for the treatment of advanced Parkinson's disease in the UK and so is not relevant in our pilot population. Stem cell therapy is associated with major uncertainties regarding outcomes, including the efficient generation of dopamine-producing neurones, the success of the graft, and the risk of tumor formation. The high cost, potentially unpredictable end result, and prolonged period of time after treatment to achieve stability makes this treatment option unlikely to be either chosen by pilots or advised by their physicians. Certification would be wholly dependent on the achievement of a successful outcome without the development of complications for a prolonged period of time. Gene therapy and other experimental treatments are not compatible with certification.

There is no international consensus on the certification of pilots with Parkinson's disease. The Federal Aviation Administration allows the certification of pilots following a complete neurological evaluation and excludes the use of dopamine agonists.[8] Transport Canada allows pilots to fly with only minimal disease and excludes the use of L-Dopa or dopamine agonists.[23] Australia's Civil Aviation Safety Authority permits certification for minimal disease and allows the use of L-Dopa with carbidopa, C-OMT-I, MAOB-I, and amantidine, but not dopamine agonists or anticholinergic drugs.[24] The UK CAA follows the European Union regulations issued by the European Aviation Safety Agency and these do not stipulate specific requirements for Parkinson's disease.[6] However, the UK CAA takes a cautious view of the potential side effects of medication which is not shared by some other regulators, particularly with regard to the use of L-Dopa preparations. The UK CAA has developed a policy for pilots flying with Parkinson's disease that requires a clinical assessment with a neurologist on a 6-mo basis at a minimum. At this assessment, a full review of both nonmotor and motor features of the disease is undertaken. Additional screening tests to detect depression and cognitive impairment may be performed if deemed appropriate. The degree of motor disability and the possibility of cognitive impairment are assessed by a simulator check or a medical flight test on a 6-mo basis. These are rigorous tests of both motor and cognitive function domains and are directly relevant to the pilot's working environment. A long-term multicrew restriction is required for professional pilots in view of the potential fluctuations in performance and deterioration in functional status due to the progressive nature of the disease. Private pilots may be permitted unrestricted certification. The only medications acceptable for certification are amantadine, rasagiline, or selegiline, once stabilized on a maintenance dose for at least 3 mo. The doses are limited to 200 $mg \cdot d^{-1}$ for amantadine, 1 $mg \cdot d^{-1}$ for rasagiline, or 10 $mg \cdot d^{-1}$ of selegiline to minimize adverse effects.

In conclusion, UK CAA pilots with Parkinson's disease may be granted medical certification depending on their functional ability and the nature of their treatment. Our experience has shown positive outcomes with UK pilots being able to successfully continue flying for many years.

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REFERENCES

1. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003; 60(3):387–392.
2. Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord. 2005; 20(10):1255–1263 [Review].
3. Alevriadou A, Katsarou Z, Bostantjopoulou S, Kiosseoglou G, Mentenopoulos G. Wisconsin Card Sorting Test variables in relation to motor symptoms in Parkinson's disease. Percept Mot Skills. 1999; 89(3, Pt 1):824–830.
4. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, et al. PRIAMO study group The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009; 24(11):1641–1649.
5. Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. Mov Disord. 2012; 27(4):480–484 [Review].
6. EASA Aircrew Regulation. Regulation (EU) No. 1178/2011. [Accessed 23 August 2015.] Available from http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:311:FULL:EN:PDF.
7. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004; 351: 2498–2508.
8. Federal Aviation Administration Guide for Aviation Medical Examiners. Washington (DC): Federal Aviation Administration; July 29 2015:134 & 282.
9. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004; 127(Pt. 3):550–560.
10. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology. 1999; 52(9):1908–1910.
11. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology. 2006; 67(5):853–858.
12. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008; 23(6):837–844.

13. Holt RJ, Sklar AR, Darkow T, Goldberg GA, Johnson JC, Harley CR. Prevalence of Parkinson's disease-induced psychosis in a large U.S. managed care population. J Neuropsychiatry Clin Neurosci. 2010; 22(1):105–110 .
14. Ives NJ, Stowe RL, Marro J, Counsell C, Macleod A, et al. Monoamine oxidase type B inhibitors in early Parkinsons's disease: meta-analysis of 17 randomised trials involving 3525 patients. BMJ. 2004; 329(7466):593–596.
15. Katzenschlager R, Sampaio C, Costa J, Lees A. Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database Syst Rev. 2002; (2):CD003735.
16. Ketharanathan T, Hanwella R, Weerasundera R, de Silva VA. Major depressive disorder in Parkinson's disease: a cross-sectional study from Sri Lanka. BMC Psychiatry. 2014; 14:278.
17. Khoo TK, Yarnall AJ, Duncan GW, Coleman S, O'Brien JT, et al. The spectrum of non-motor symptoms in early Parkinson disease. Neurology. 2013; 80(3):276–281.
18. Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet. 2009; 373(9680):2055–2066.
19. Macleod AD, Counsell CE, Ives N, Stowe R. Monoamine oxidase B inhibitors for early Parkinson's disease. Cochrane Database Syst Rev. 2005; (3):CD004898.
20. Manni R, Terzaghi M, Sartori I, Mancini F, Pacchetti C. Dopamine agonists and sleepiness in PD: review of the literature and personal findings. Sleep Med. 2004; 5(2):189–193.
21. Muslimović D, Post B, Speelman JD, De Haan RJ, Schmand B. Cognitive decline in Parkinson's disease: a prospective longitudinal study. J Int Neuropsychol Soc. 2009; 15(3):426–437.
22. Owen AM, James M, Leigh PN, Summers BA, Marsden CD, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain. 1992; 115(Pt. 6):1727–1751.
23. Parkinson's Disease. Degenerative disease of the brain. Handbook for Civil Aviation Medical Examiners. Ottawa, Ontario (Canada): Transport Canada; 2004:N-16. Report No.: TP 13312.3/2004.
24. Parkinson's disease. Designated AME Clinical Practice Guidelines. Canberra (Australia): Civil Aviation Safety Authority. [Accessed 23 August 2015]. Available from http://services.casa.gov.au/avmed/guidelines/parkinsons.asp.
25. Parkinson J. Essay on the shaking palsy. London: Sherwood, Neely, and Jones; 1817.
26. Prado RC, Barbosa ER. Depression in Parkinson's disease: study of 60 cases. Arq Neuropsiquiatr. 2005; 63(3B):766–771.
27. Rabey JM. Hallucinations and psychosis in Parkinson's disease. Parkinsonism Relat Disord. 2009; 15(Suppl. 4):S105–S110 [Review].
28. Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord. 2007; 22(8):1077–1092.
29. Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2001; 13(2):187–196 [Review].
30. Van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. CNS Drugs. 2003; 17(7):475–489 [Review].
31. Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology. 1998; 50(5): 1323–1326.
32. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010; 67(5):589–595.