

A Review on Pharmacological Treatment of Idiopathic Parkinson's Disease

Bhupendra Shah*

Department of Internal Medicine, BP Koirala Institute of Health Sciences (BPKIHS), Dharan 56700, Nepal

Abstract

Parkinson's disease is the second most common chronic neurodegenerative disease of central nervous system predominant in elderly people characterised by tremor, akinesia, rigidity and gait disturbances. The annual cost of management of Parkinson's disease is double than that of control population. Evidence-based management of Parkinson's disease in developing nation is unmet needs. This article is authors' endeavour to summarise the facts in different publications on Parkinson's disease. Electronic databases like MEDLINE/Pub Med, Google Scholar, IMSEAR (Index Medicus for South-East Asia Region) and Scope med were extensively searched with MeSH (Medical Subject Headings) terms "Parkinson's disease", "treatment", and "anti-Parkinson drugs" from the earliest possible date of 1966 to March 2017. Articles in any languages especially those published in recent years were given preference. This review deals mostly with evidence based management of Parkinson's disease.

Keywords: Parkinson's disease; Anti-Parkinson drugs; Treatment

Introduction

Parkinson's disease is the second most common chronic neurodegenerative disease of central nervous system usually of elderly people characterised by tremor, akinesia, rigidity and gait disturbances [1]. The prevalence of Parkinson's disease is 100-200/100000 population and is increasing with time [2]. The annual cost for management of Parkinson's disease patient is twice as much as a control population [3]. Hence the Parkinson's disease has huge physical, social and the financial impact on the health sector, therefore evidence based management is desirable worldwide. This review is an author endeavour to highlight upon the evidence based management of idiopathic Parkinson's disease which will enhance the quality of life of patient by appropriate use of antiparkinson medication.

Methods

Electronic databases like MEDLINE/Pub Med, Google Scholar, IMSEA (Index Medicus for South-East Asia Region) and Scopemed were extensively searched with Mesh (Medical Subject Headings) terms like "Parkinson's disease", "treatment", and "anti-parkinson drugs" from earliest possible date of 1966 to March 2017. Articles in any language especially those published in recent years and randomised controlled trial were given preference. A total of 52 articles was analysed for this study. No prior inclusion and exclusion criteria for the articles were made. No statistical significance was calculated among the articles.

Evidence based treatment

Parkinson's disease is a chronic progressive neurodegenerative disorder. Making a diagnosis of Parkinson's disease and revealing it to patient has huge mental impact on patient and caregiver as there is no definite cure for the disease. Patients and their caregivers need to be counselled empathically regarding the diagnosis, the possible natural course of the disease, expected a response to treatment and adverse effects related to treatment. Therapy depends on the severity of symptoms, co-morbidity, functional disability, cognitive function and patient's desire.

Treatment of motor symptoms

Levodopa/carbidopa: Levodopa [3,4-dihydroxy-l-phenylalanine] is an amino acid which is metabolised by aromatic l-amino acid decarboxylase to form dopamine [4]. Levodopa is readily

absorbable through facilitated transport system in the small intestine. It has $t_{1/2}$ of 90 minutes which explains the rapid fluctuation in its plasma concentration [5]. To counteract this problem levodopa are combined with amino acid decarboxylase inhibitor like carbidopa or benserazide which prevents the peripheral conversion of levodopa into dopamine. Levodopa is the most effective drug for the symptom control in Parkinson's disease. In comparison to amantadine and benzhexol, Levodopa is more effective for reducing the functional disability and decreasing all motor manifestations of Parkinson's disease [6]. The Elldopa study conducted by Parkinson study group showed levodopa/carbidopa slows the progression or at least improve the clinical symptoms of Parkinson disease, however, the imaging data didn't support the above-mentioned finding [7]. The starting dose of levodopa/carbidopa is 100/25 mg thrice daily which can be increased up to 1500/375 mg based upon the symptoms [8]. Dyskinesias, dystonia, freezing of gait, wearing off effect, on and off phenomenon are dopaminergic side effects of levodopa therapy whereas nausea, headache and dizziness are common non-dopaminergic side effects [7]. Motor fluctuations and dyskinesia occurs in up to 50% of Parkinson's disease patient treated with levodopa therapy. These motor complications are more with higher dose, longer duration and in younger patients [9]. Although combination of levodopa/carbidopa with Entacapone improves the clinical symptoms of Parkinson's disease, it hastens the development of dyskinesia [10].

Dopamine agonist: Dopamine agonists mimic the endogenous neurotransmitter and act on dopamine receptor [11]. Dopamine agonists are classified into ergot derivatives and nonergot derivatives. Bromocriptine, pergolide, cabergoline and lisuride are ergot derivative whereas ropinirole and pramipexole are non-ergot dopamine agonists. They are used to manage the motor fluctuation and dyskinesia that commonly occur in levodopa monotherapy [12]. Ergot derivatives

*Corresponding author: Bhupendra Shah, Assistant Professor, Department of Internal Medicine, BP Koirala Institute of Health Sciences (BPKIHS), Dharan 56700, Nepal, Tel: 9779842560220; E-mail: bhupendra.shah@bпкиhs.edu

Received May 28, 2017; Accepted June 10, 2017; Published June 14, 2017

Citation: Shah B (2017) A Review on Pharmacological Treatment of Idiopathic Parkinson's Disease. J Neurol Disord 5: 347. doi:10.4172/2329-6895.1000347

Copyright: © 2017 Shah B. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

like bromocriptine, pergolide, cabergoline and lisuride are all effective as an adjunct or as monotherapy to delay the initiation of levodopa therapy [13–16]. Valve regurgitation was significantly increased in patients taking pergolide or cabergoline, so when patient is taking these two drugs a patient should be periodically monitored with echocardiography [17]. In CALM-PD study pramipexole was compared with levodopa for the initial therapy for Parkinson's disease. Dopaminergic motor complications were less in pramipexole group favouring its use whereas more somnolence in pramipexole group favoured initiation of levodopa [18]. Hence pramipexole is preferred in younger patient where chances of motor complications with levodopa are high, however, pramipexole is attributed to causing a decrease in cognition level, nausea, hallucinations and orthostatic hypotension [19,20]. The initial dose of pramipexole is 0.125 mg thrice daily which can be increased up to 4.5 mg/day. Ropinirole is selective non-ergot D₂ receptor agonist with 50% bioavailability. Ropinirole is effective as monotherapy as well as adjunct to levodopa in Parkinson's disease [21,22]. Prolonged release Ropinirole prolonged is more effective than immediate release in early Parkinson's disease [23]. The starting dose is 0.25 mg thrice daily which can be maximised up to 24 mg/day.

Monoamine oxidase-B inhibitors

Selegiline and Rasagiline are two the MAO-B inhibitors used in Parkinson's disease. The DATATOP study demonstrated the selegiline delayed the onset of disability and improved the symptoms of Parkinson's disease [9]. The starting dose of selegiline is 2.5 mg which can be increased up to 5 mg twice daily. Rasagiline is a new highly selective MAO-B inhibitor without having an amphetamine-like action that is distinct from selegiline. Rasagiline is effective as monotherapy in early Parkinson's disease [24]. The ADAGIO study showed the early use of rasagiline with 1 mg dose has a neuroprotective role in Parkinson's disease, however, the result was not replicated with 2 mg of rasagiline [25]. The starting dose of rasagiline is 1 mg once daily. Common side effects of MAO-B inhibitors are dizziness, headache, arthralgia and confusion.

Catechol-O-methyltransferase inhibitors

Levodopa is metabolised not only by dopa decarboxylase but also by catechol-O-methyltransferase, so the addition of COMT inhibitors like entacapone or tolcapone increases the plasma t_{1/2} of levodopa. Entacapone was found to increase the ON time response in fluctuating type Parkinson's disease and enhances the quality of life in mild-moderate Parkinson's disease [26,27]. The Stride PD study demonstrated that combination of Entacapone with Levodopa/carbidopa hasten the onset of dyskinesia with no significant improvement difference in clinical improvement with Levodopa/carbidopa [28]. The starting dose of entacapone is 200 mg with each dose of levodopa. Common problems with COMT inhibitors treatment are dark coloured urine, hepatotoxicity and increase in side effects of levodopa.

Anticholinergic agent: The rationale of using anticholinergic agents like trihexyphenidyl and benzhexol in Parkinson's disease is to reduce the excess acetylcholine in basal ganglia. Anticholinergic use reduces the tremor, however, its use in the elderly Parkinson patient increases the risk of delirium, fracture and hospitalisation and should be cautious to use in such patients [29].

Beta-blocker therapy: Beta blocker are used to control the tremor in Parkinson's disease but Cochrane review concluded that there was inadequate evidence to confirm the efficacy and

safety of beta blockers as it can exacerbate the postural hypotension in Parkinson's disease [30].

Amantadine: Amantadine is approved by the USFDA for use in Parkinson disease. Its acts by increasing the release of dopamine, NMDA antagonism and anticholinergic effect [31]. Amantadine improves motor symptoms of Parkinson disease and decreases the functional disability by 15%. The response with this drug is seen earlier than levodopa [6]. Amantadine use is an independent predictor for better survival in Parkinson's disease [32]. Dyskinesia due to levodopa therapy is significantly decreased by the use of amantadine [33]. The starting dose of amantadine is 100 mg once daily which can be increased up to 400 mg daily. Adverse effects of amantadine are dry mouth, headache, confusion, leg edema and constipation [6].

Deep brain stimulation (DBS) surgery

Deep brain stimulation was approved by the US FDA in 2002 as a therapy for Parkinson's disease. Patient with adequate response to dopaminergic therapy, on-off fluctuations, dyskinesias impairing quality of life, medication-resistant tremor and reasonable cognitive function are good candidates for DBS [34]. Levodopa can be discontinued in 50% of patients of Parkinson's disease who underwent subthalamic deep brain stimulation [35]. Deep brain stimulation of subthalamic nucleus is better than medication to improve the mobility, emotional well-being, activities of daily living, and bodily discomfort in severe Parkinson's disease [36]. There is no difference in motor improvement between globus pallidum stimulation and subthalamic stimulation, however, depression deteriorate more in subthalamic stimulation than pallidal stimulation [37]. There is no significant difference in cognition level between subthalamic stimulation and pallidal stimulation [38]. Adverse events of DBS are intraparenchymal haemorrhage, intracerebral infection and decline in verbal fluency [39-41].

Treatment of non-motor features

Sleep disorders in Parkinson's disease: Sleep disorders are common in Parkinson's disease. Common causes of sleep disorders in Parkinson's disease are Parkinson's disease associated motor complication (nocturnal cramps, rigidity, akinesia), side effects of antiparkinsonian medication, psychiatric complications of Parkinson disease and other associated sleep disorders like insomnia, restless leg syndrome and excessive daytime sleepiness [42]. The management of sleep disorders in Parkinson's disease begins with the identification of the problem, adjustment of levodopa or dopamine agonist, counselling for maintaining good sleep hygiene.

Antidepressant in Parkinson disease: Parkinson's disease is not only a disease with motor manifestation but also has non-motor features which are usually unrecognised and untreated. In a study done by Worku DK et al. the prevalence of depression in Parkinson's disease was 57.4% [43]. Patient of Parkinson's disease with depression are more functionally impaired. [44]. Managing depression in Parkinson's disease decreases the disability and improves the quality of life [45]. Tricyclic antidepressants are not favoured due to anticholinergic and cardiac side effects. Paroxetine and Venlafaxine are both effective to decrease the depression in patients with Parkinson's disease. [46]

Antipsychotics in Parkinson's disease: Psychosis, hallucination and confusion are common problems in patients with Parkinson's disease treated with long-term dopaminergic treatment. Clozapine, an atypical antipsychotic is effective to control drug-induced psychosis

and tremor in Parkinson's disease [47]. Agranulocytosis is the major problem and need to be monitored weekly in patients taking clozapine.

Dementia in Parkinson's disease: The 8 year prevalence of dementia in Parkinson's disease is 78.2% [48]. Dementia is Parkinson's disease is a major determinant for decreasing the quality of life and stress burden to the primary caregiver [49]. Rivastigmine, a cholinesterase inhibitor, is effective in decreasing the dementia in Parkinson's disease [50].

Physical exercise in Parkinson disease: Postural instability is one of the cardinal symptoms of Parkinson's disease which results in frequent falls. Physical exercise is a part of treatment for Parkinson's disease to enhance the functional independence [51]. Tai chi training is more effective than stretching and resistance exercise in improving postural stability and incidence of falls in mild to moderate Parkinson's disease [52].

Conclusion

Parkinson's disease is a disease of public health concern. The cost of management of it is increasing. Recognition of motor and non-motor manifestation like depression, psychosis, sleep disorders and dementia is must to plan the care of the patient. Non-ergot dopamine agonists for young and Levodopa/Carbidopa for an elderly patient of Parkinson's disease is initial drug of choice. Adverse effects of antiparkinsonian drugs are inevitable and should be discussed with the patient and caregiver before starting the treatment to increase the adherence to medication. Patients should be screened for non-motor features as well and managed properly to enhance the quality of life and increase the satisfaction of patients. Deep brain stimulation surgery is showing promising role and becoming a new hope for patients with advanced Parkinson's disease, however, the cost of surgery and need of expertise limit this therapeutic modality to the developed nation. Disease-modifying antiparkinson agent is desirable and may be a field of interest for research in Parkinson's disease in future.

Conflict of Interest

The author declares conflict of interest to none

Acknowledgement

I acknowledge Prof. Sanjib Sharma and Dr Iekjhung Thapa for constant motivation.

References

- Nutt JG, Wooten GF (2005) Clinical practice: Diagnosis and initial management of Parkinson's disease. *N Engl J Med* 353: 1021-1027.
- Marras CTC (2004) Epidemiology of Parkinson's disease. In: Watts RL KW, editor. *Movement disorders, neurologic principles, and practice* (2nd edn). McGraw-Hill, New York, USA, PP. 177-196.
- World Health Organization (2006) *Neurological disorders: a public health approach*. *Neurol Disord public Health challenges* 41-176.
- Lewitt AP (2008) Levodopa for the Treatment of Parkinson's Disease. *N Engl J Med* 359: 2468-2475.
- Contin M, Martinelli P (2010) Pharmacokinetics of levodopa. *J Neurol* 257: S253-261.
- Parkes JD, Baxter RC, Marsden CD, Rees JE (1974) Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 37: 422-426.
- Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, et al. (2004) Levodopa and the progression of Parkinson's disease. *N Engl J Med* 351: 2498-2508.
- Connolly BS, Lang AE (2014) Pharmacological Treatment of Parkinson Disease. *J Neurol* 311: 442-449.
- Controlled M, Trial C, Disease P (1989) DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Parkinson Study Group. Arch Neurol* 46: 1052-1060.
- Stocchi F, Rascol O, Kieburtz K, Poewe W, Jankovic J, et al. (2010) Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol* 68: 18-27.
- Quinn N1 (1995) Drug treatment of Parkinson's disease. *BMJ* 310: 575-579.
- Uitti RJ, Ahlskog JE (1996) Comparative Review of Dopamine Receptor Agonists in Parkinson's Disease. *CNS Drugs* 5: 369-388.
- Agid Y, Destée A, Durif F, Montastruc JL, Pollak P, et al. (1998) Tolcapone, bromocriptine, and Parkinson's disease. *Lancet* 350: 2-5.
- Kulisevsky J, López-Villegas D, García-Sánchez C, Barbanjo M, Gironell A, et al. (1998) A six-month study of pergolide and levodopa in de novo Parkinson's disease patients. *Clin Neuropharmacol* 21: 358-362.
- Laihinén A, Rinne UK, Suchy I (1992) Comparison of lisuride and bromocriptine in the treatment of advanced Parkinson's disease. *Acta Neurol Scand* 86: 593-595.
- Del Dotto P, Colzi A, Musatti E, Strolin Benedetti M, Persiani S, et al. (1997) Clinical and pharmacokinetic evaluation of L-dopa and cabergoline cotreatment in Parkinson's disease. *Clin Neuropharmacol* 20: 455-465.
- Zanettini R, Antonini A, Gatto G, Gentile R, Tesi S, et al. (2007) Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 356: 39-46.
- Parkinson Study Group (2000) A randomized controlled trial comparing pramipexole with levodopa in early Parkinson's disease: design and methods of the CALM-PD Study. *Clin Neuropharmacol* 23: 34-44.
- Brusa L, Bassi A, Stefani A, Pierantozzi M, Peppe A, et al. (2003) Pramipexole in comparison to L-dopa: a neuropsychological study. *J Neural Transm* 110: 373-380.
- Schapira AH V, McDermott MP, Barone P, Comella CL, Albrecht S, et al. (2013) Pramipexole in patients with early Parkinson's disease (PROUD): A randomised delayed-start trial. *Lancet Neurol* 12: 747-755.
- Brooks DJ, Torjanski N, Burn DJ (1995) Ropinirole in the symptomatic treatment of Parkinson's disease. *J Neural Transm Suppl* 45: 231-238.
- Brooks DJ, Abbott RJ, Lees AJ, Martignoni E, Philcox DV, et al. (1998) A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. *Clin Neuropharmacol* 21: 101-107.
- Stocchi F, Hersh BP, Scott BL, Nausieda PA, Giorgi L (2008) Ropinirole 24-hour prolonged release and ropinirole immediate release in early Parkinson's disease: a randomized, double-blind, non-inferiority crossover study. *Curr Med Res Opin* 24: 2883-2895.
- Parkinson Study Group (2002) A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 59: 1937-1943.
- Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, et al. (2009) A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 361: 1268-1278.
- Brooks DJ, Sagar H, Group U-IES (2003) Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six-month study. *J Neurol Neurosurg Psychiatry* 74: 1071-1079.
- Fung VS, Herawati L, Wan Y, Movement Disorder Society of Australia Clinical Research and Trials Group, QUEST-AP Study Group (2009) Quality of life in early Parkinson's disease treated with levodopa/carbidopa/entacapone. *Mov Disord* 24: 25-31.
- Liashchenko EA, Skripkina NA, Levin OS (2013) [Influence of levodopa, stalevo on dyskinesia in Parkinson's disease: STRIDE-PD study]. Vol. 11, *Zhurnal neurologii i psikiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossijskoj Federatsii, Vserossijskoe obshchestvo neurologov* [i] *Vserossijskoe obshchestvo psikiatrov* 62-68.
- Crispo JAG, Willis AW, Thibault DP, Fortin Y, Hays HD, et al. (2016) Associations between anticholinergic burden and adverse health outcomes in Parkinson disease. *PLoS One* 11.
- Crosby NJ, Deane KH, Clarke CE (2003) Beta-blocker therapy for tremor in Parkinson's disease. *Cochrane Database Syst Rev* CD003361.
- Lees A (2005) Alternatives to levodopa in the initial treatment of early Parkinson's disease. *Drugs Aging* 22: 731-740.

32. Uitti RJ, Rajput a H, Ahlskog JE, Offord KP, Schroeder DR, et al. (1996) Amantadine treatment is an independent predictor of improved survival in Parkinson's disease. *Neurology* 46: 1551-1556.
33. Metman LV, Del Dotto P, LePoole K, Konitsiotis S, Fang J, et al. (1999) Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol* 56: 1383-1386.
34. Okun MS (2012) Deep-brain stimulation for Parkinson's disease. *N Engl J Med* 367: 1529-1538.
35. Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, et al. (2002) Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. *Neurology* 58: 396-401.
36. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, et al. (2006) A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. *N Engl J Med* 355: 896-908.
37. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, et al. (2010) Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 362: 2077-2091.
38. Odekerken VJ, Boel JA, Geurtsen GJ, Schmand BA, Dekker IP, et al. (2015) Neuropsychological outcome after deep brain stimulation for Parkinson disease. *Neurology* 84: 1355-1361.
39. Terao T, Takahashi H, Yokochi F, Taniguchi M, Okiyama R, et al. (2003) Hemorrhagic complication of stereotactic surgery in patients with movement disorders. *J Neurosurg* 98: 1241-1246.
40. Blomstedt P, Bjartmarz H (2012) Intracerebral infections as a complication of deep brain stimulation. *Stereotact Funct Neurosurg* 90: 92-96.
41. Zahodne LB, Okun MS, Foote KD, Fernandez HH, Rodriguez RL, et al. (2009) Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change. *Clin Neuropsychol* 23: 385-405.
42. Barone P, Amboni M, Vitale C, Bonavita V (2004) Treatment of nocturnal disturbances and excessive daytime sleepiness in Parkinson's disease. *Neurology* 63: S35-38.
43. Worku DK, Yifru YMPD (2014) Prevalence of depression in Parkinson's disease patients in Ethiopia. *J Clin Gastroenterol* 1: 1-12.
44. Liu CY, Wang SJ, Fuh JL, Lin CH, Yang YY, et al. (1997) The correlation of depression with functional activity in Parkinson's disease. *J Neurol* 244: 493-498.
45. Menza M, Dobkin RD, Marin H, Mark MH, Gara M, et al. (2009) The impact of treatment of depression on quality of life, disability and relapse in patients with Parkinson's disease. *Mov Disord* 24: 1325-1332.
46. Richard IH, McDermott MP, Kurlan R, Lyness JM, Al PGC et al. (2012) A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology* 78: 1229-1236.
47. Scale GI (1999) Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. *N Engl J Med* 340: 757-763.
48. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P (2003) Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 60: 387-392.
49. Corallo F, De Cola MC, Lo Buono V, Di Lorenzo G, Bramanti PMS (2017) Observational study of quality of life of Parkinson's patients and their caregivers. *Psychogeriatrics* 17: 245-245.
50. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, et al. (2004) Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 351: 2509-2518.
51. Dibble LE, Addison O, Papa E (2009) The effects of exercise on balance in persons with Parkinson's disease: a systematic review across the disability spectrum. *J Neurol Phys Ther* 33: 14-26.
52. Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, et al. (2012) Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med* 366: 511-519.