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An Independent Clinical Audit of an Alternative Treatment Paradigm for the Management of Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a chronic, degenerative disease associated with motor complication that progressively affects quality of life and causes significant disability, either related to disease progression or treatment consequences. A number of guidelines provide treatment algorithms for selection of anti-Parkinsonian medications which suggest delaying the introduction of L-dopa due to the development of motor complications following prolonged exposure. This study examines the efficacy of the treatment model, adopted within a single Australian outpatient clinic, for polypharmacy (based on initiating L-dopa and complemented with later introduction of selegiline and subsequently a dopamine agonist and thence entacapone) for the treatment of Parkinson's disease and to evaluate this approach to patient management. Of 152 patients with PD identified, 40 had been treated between 5 and 20 years and were analysed further to provide sufficient period to determine disease progression and treatment evaluation. Among the 40 long-term patients, 2.5% (1) of patients required a wheelchair and 15% (6) demonstrated motor complications. The majority of patients were coping well with their Parkinson's disease and reported good quality of life. This study demonstrates that despite accepted guidelines, adopting a treatment algorithm based on early commencement of treatment with L-dopa and maintenance of low dose therapy with polypharmacy, appears beneficial both in the short term and the long-term management of patients with Parkinson's disease.

Keywords: Parkinson's Disease; Audit; Treatment; Paradigm

Abbreviations: PD: Parkinson's Disease; AE: Adverse Effects; ER: Extended Release; PBS: Pharmaceuticals Benefits Scheme; MRN: Medical Record Number; UPDRS: Unified Parkinson's Disease Rating Scale.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder resulting from the gradual loss of pigmented dopaminergic neurons in the substantia

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negra. PD is manifested clinically by bradykinesia, tremor, rigidity, freezing of gait, postural instability and flexed posture. These motor complications can impair quality of life and cause significant disability [1]. It affects 6.3 million people around the world [2] with an incidence of 2 in 1,000 of the general population, increasing to 2% of those older than 65 years and between 6 and 8 per 1,000 in those aged between 65 and 69 years [2].

The management of PD has generated a number of guidelines, which provide treatment algorithms for selection of appropriate anti-Parkinsonian medications [3-6]. There has emerged a body of opinion advocating delayed introduction of levodopa (L-dopa), be it in combination with carbidopa (Sinemet ®) or benserazide (Madopar ®), due to the perception of potential toxicity following prolonged exposure [7,8].

In routine clinical practice, not everyone follows these guidelines, with some adopting a treatment algorithm based on personal preference, within the context of their practice, rather than adopting the guidelines based paradigm [9]. Clinical impression may be inaccurate, or misleading, and thus treatment outcomes, for such idiosyncratic treatment regimen, should be subjected to independent scrutiny and analysis to determine efficacy [10].

To do this properly requires a comparison, of the outcome of the local intervention, to that reported in the literature and perhaps a comparison between the individual treatment algorithm and the natural history of the disease [11]. 'Coalface clinical practice' does not always employ specific research method and may not adopt research evaluative tools, such as the Unified Parkinson's Disease Rating Scale (UPDRS) as is widely used within clinical trials of PD management, to assess treatment efficacy [12-14]. It follows that practice audits need to acknowledge such limitations but this should not provide an excuse to bypass proper critical appraisal of a treatment model which is based on clinical impression. It could be argued that this provides more cogent rationale to undertake such evaluative audit.

This paper reports the findings of an independent clinical audit of the treatment model adopted within a single neurologist's Australian outpatient clinic, regarding the treatment of PD.

Methods

The neurologist (RGB) developed a treatment algorithm for PD, which initiates therapy as soon as the diagnosis of PD has been made, on the basis of finding two of the three diagnostic criteria, including rigidity, bradykinesia and tremor [15] together with the patient reporting interference with quality of life.

Treatment was commenced with low dose L-dopa (initially commencing with combination therapy of L-dopa/carbidopa in a 100/25 ratio using Sinemet ® in a dosage of ½ tablet b.d). This dosage was maintained until either disease progression, the dosage was considered ineffective or the patient reported unacceptable adverse effects (AE). Depending on the nature of the AE, Sinemet ® was withdrawn or the dosage reduced. If the dosage was either inadequate or disease progression noted, the dosage was increased to I b.d. until there was recognised further disease progression or inadequate response. At this stage, assuming patient tolerance of L-dopa, the Sinemet ® was maintained at I b.d. with selegiline (Eldepryl ®) 5 mg added at a dosage of ½ b.d. This was again maintained, assuming no intolerable AE, until disease progression or lack of efficacy was observed. Following such parameter, the selegiline was increased to I b.d. until either disease progression or AE. If tolerated, then both the L-dopa and selegiline were maintained (usually at a dosage of I b.d. though occasionally the L-dopa might be increased to I t.d.s.) and a dopamine agonist added to the regimen. Initially such addition was with bromocriptine (Parlodel ®), later cabergoline (Cabaser ®) and more recently pramipexole(Sifrol ®), which is the first non-ergot derivative dopamine agonist included in the Pharmaceuticals Benefits Scheme (PBS), which is the publicly funded formulary in Australia. The standard use of Sifrol ® was further modified with the addition of the extended release (ER) formulation of pramipexole (Sifrol ER ®), which was added to the PBS in 2010. These dopamine agonists were added at a low dosage, such as Sifrol ER being introduced at a very low dose of 0.375 mg I mane and often maintained at this dosage until disease progression, at which stage it would be increased to 0.75 mg I mane and if required further increased to 1.5mg I mane.

Once either intolerance or disease progression was observed, the selegiline and dopamine agonist were retained but Sinemet ® was removed and replaced with combination L-dopa, carbidopa, entacapone in a ratio of 100:25:200) (Stalevo ®) at a dosage of either I b.d. or I t.d.s., depending on disease progression and the previous dosage of Sinemet, which may have been increased to I t.d.s. by this stage.

Other anti-Parkinsonian medications, such as benzhexol (Artane ®) 2 mg ½ b.d., building up to I b.d. may have been employed if the patient's main complaint was that of tremor, rather than bradykinesia or rigidity. Amantadine

(Symmetrel ®) could be used as adjunctive therapy and occasionally patients might be considered for Apomorphine delivered via pump. At this stage, no patients within this practice had undergone deep brain stimulation.

Assessment Methodology

A post-graduate public health scientist (J C-C), totally independent from the clinic, was introduced to the clinician, (RGB), by an internationally recognised health law expert, with specific interest in public health. The suggestion was for this scientist to undertake a work experience project, such as a clinical audit, to evaluate treatment paradigms within neurological practice.

The scientist was invited to undertake an independent audit of the efficacy, or otherwise, of the PD treatment algorithm, defined above. The scientist was given "unfettered" access to patients' records which had been diagnostically coded, thereby facilitating identification of patients who had been diagnosed with PD. The scientist was allowed to adopt whatever practice audit that seemed appropriate, without prejudice or favour, to compare the adopted treatment model for PD to expected outcomes based on scientific literature. No limitations were placed upon the audit method, so as to encourage the broadest possible patient evaluation, based upon open access to clinical records and limitless retrospective review of all available material.

The only limitation on methodology was to ensure rigorous maintenance of patient confidentiality, both within the process adopted for the audit and with any subsequent publication. All patients, within the practice, were identified by numerical order of presentation with an idiosyncratic, practice specific, assigned Medical Record Number (MRN) and that MRN was the only form of identification to be used.

Patient selection

Clinical records of currently active patient files, diagnostically coded for PD and seen within the last 5 years, were retrospectively reviewed by the scientist. Patient demographics were recorded, including diagnosis, patient biostatistics, treatment patterns, symptom progression and management parameters. Each patient's complete clinical record was reviewed to map treatment outcomes from the initial to the latest clinic consultation. Specific data to be extracted included: symptomatology and its progression; clinical signs per visit; time sequence between consultations; treatments prescribed; and response to treatment and adverse events. Records of 152 patients with PD were identified using the diagnostic coding. Of these, 40 patients had been treated for 5 or more years and were further analysed to provide sufficient period to determine disease progression and treatment analysis. These data were collected and registered in tabular form, using Microsoft Excel spread sheet, to provide descriptive epidemiology.

Results

The 152 PD patients comprised 88 males: 64 females at various stages of disease progression. Age range was 41-103 years (mean 72 years). Disease progression was idiosyncratic per patient but the treatment pattern confirmed the standardised approach of combination therapy as outlined above. Forty (40) patients were identified as attending the clinic for at least 5 years, 24 males and 16 females, treated between 5 and 20 years. The various drugs have been grouped into families. The number of drug's family was:

1. One drug family: L-Dopa (Sinemet 100/25 I b.d.or Madopar) for 3 patients treated between 6 and 10 years.
2. Two different drug's families: (Sinemet 100/25 I b.d. and Eldepryl 5 mg I b.d.) for 7 patients treated between 6 and 11 years.
3. More than half of the long-term patients (26) were treated with three or four medications, predominantly L-Dopa, MAO-B inhibitors, dopamine agonists and/or COMT inhibitors.
4. Four (4) of the 40 patients were on five different agents (Table 1, Figure 1).

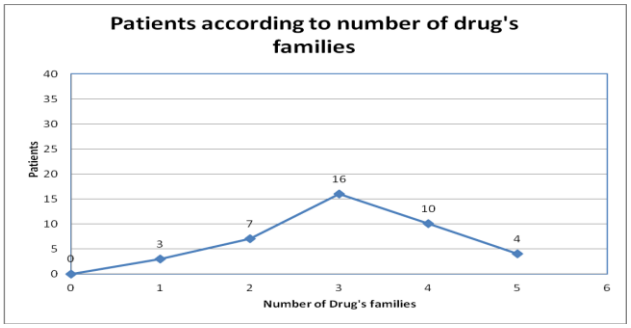

Figure 1: Number of patients according to drug's families.

Drug's families	Number of patients	Duration of consultation (year)
1	3	6 to 10
2	7	6 to 11
3	16	5 to 16
4	10	6 to 20
5	4	5 to 13

Table 1: Number of drug's families per patients.

Of the 152 patients, only 5 were restricted to a wheelchair and of the 40 long-term patients, only 1 was wheelchair-bound, the other 4 having been so restricted early in treatment, suggesting advanced disease at the time of presentation to the clinic (Table 2). The long-term patient who was wheelchair-bound had been treated for 7.7 years and the reason for reliance on a wheelchair was due to balance disturbance rather than rigidity, bradykinesia or tremor. This patient was treated with Sinemet 100/25 I b.d., Eldepryl 5 mg I b.d. and Pergolide (Permax) 0.25 mg I t.d.s. at her last visit.

Nine (9) of the 152 patients experienced dyskinesia of whom 6 (6/9, 67%) had been treated in excess of 5 years. Of those with dyskinesia, the involuntary movements fluctuated with changes in treatment and were only debilitating in a single patient who had been followed for 20 years.

Follow-up duration	Number of patients	Wheel chair	Dyskinesia
<1 Year	65	2	1
1 Year To 2 Years	22	2	0
2 To 5years	25	0	2
5 And Plus	40	1	6
Total	152	5	9

Table 2: Patients in wheelchair and/or presenting dyskinesia.

Discussion

This study was undertaken as an independent, public health clinical practice audit by a health scientist, rather than a doctor. This bypassed any pre-conceived notion as may exist amongst neurologists and movement disorder specialists. The scientist who conducted the study had "carte blanche" access to patient files and was encouraged to be as critical as is possible, of all that was reviewed. The aim of the project was to examine the efficacy of the algorithm adopted for early initiation of low dose polypharmacy for the treatment of PD and to evaluate this approach to patient management.

The majority of long term patients were taking between three and four anti-Parkinsonian agents (16 on three agents and 10 on four). They were essentially on combination with L-dopa (Sinemet ®); dopamine agonists (Parlodel ®) or Sifrol ®, (either standardised or extended release formulation); MAO-B inhibitor, selegiline (Eldepryl ®); and COMT inhibitors: entacapone (Comtan ®). (Table 1 and 2, Figure 1). Many studies, such as the clinical evidence-based guideline for the NHS in England, recommend levodopa, dopamine agonists and MAOB inhibitors as first choice option for initial pharmacotherapy in early PD [15]. It is the method adopted in this local study, although the number of anti-Parkinsonian agents prescribed stays lower than the medicines suggested in the national guideline for PD, given by the National Institute for Health and Clinical Excellence [15]. The guideline suggests eight different drugs families with the addition of the ones cited above, including: beta blockers, amantadine, anticholinergics and apomorphine [15]. The dosage of drugs, prescribed by the neurologist, in this local intervention, was for most of anti-Parkinsonian agents, smaller than the dosages observed in the published literature. An evidence-based review, of the treatment of PD with motor fluctuations and dyskinesia, suggests dopamine agonist: Sifrol ®.prescribed with a dose of 3-4mg per day [16] and as 0.5mg 3 times a day in a randomized controlled trial studying pramipexole (Sifrol ®.) as initial treatment [17]. In the treatment algorithm for PD, developed in this study, the dosage of Sifol ® remains lower than treatments observed in the literature. Typical treatment regimen, suggested by the National Parkinson Foundation, recommend Sinemet ® in a dosage of 150 – 1000 mg of levodopa total daily dose [18]. A dosage of 300mg daily of L-Dopa is also suggested in a trial comparing pramipexole to levodopa, as initial treatment [17]. Those regimens still prescribe dosage levels above the treatment algorithm adopted in this study, with a maximum dose of 300mg L-Dopa being the total daily dose. Additional medications were added to the treatment paradigm when the condition deteriorated and the duration of treatment extended beyond 10 years, suggesting that the approach which adopted three or four anti-Parkinsonian agents in low dosage provided an appropriate regimen, irrespective of that which appears within the guidelines (Figure 1, Tables 1 and 3).

Patients	Follow-up duration (year)	Treatment	Number of drugs	Number of family
1201	8 years 4 months	L_Dopa : Sinemet		
		Dopamine agonist (DA) Amandatine, Bromocriptine (Parlodel)	3	2
2049	20 Years	L_Dopa :Madopar , Levedopa		
		Dopamine agonist (DA): Pergolide (Permax),	5	4
		MAO-B Inhibitor: Selegeline (Eldeperyl)		
		COMT inhibitor: Entacapone (Comtan)		
2118	9 Years 8 Months	L_Dopa : Sinemet		
		Dopamine agonist (DA): Bromocriptine (Parlodel), Pergolide (Permax)	4	3
		MAO-B Inhibitor: Selegeline		
2308	6 Years 9 Mnoths	L_Dopa: Sinemet		
		Dopamine agonist (DA): Bromocriptine (Parlodel)	2	2
2313	7 Years 9 Months	L_Dopa: Sinemet		
		Dopamine agonist (DA°): Bromocriptine (Parlodel)	3	3
		MAO-B Inhibitor: Selegeline		
2378	5 Years 5 Months	L_Dopa: Sinemet		
		Dopamine agonist (DA): Bromocriptine (Parlodel)	3	3
		Anticholinergic: Benzhexol (Artane)		
2524	6 Years 9 Months	L_Dopa: Sinemet, Madopar		
3276	7 Years 1 Month	L_Dopa: Sinemet		
		Dopamine agonist (DA) Bromocriptine (Parlodel)	4	4
		MAO-B Inhibitor: Selegeline (Eldeperyl)		
		Anticholinergic: Congentin		
3525	11 Years 7 Months	L_Dopa: Sinemet		
		Dopamine agonist (DA): Bromocriptine (Parlodel)	4	4
		MAO-B Inhibitor : Eldepryl		
		COMT inhibitor: Tolcapone		
3743	13 Years	L_Dopa: Sinemet		
		DA: Parlodel	3	3
		MAOB Inhibitor: Eldepryl		
4297	10 Years 5 Months	L_Dopa: Sinemet		
		DA: Bromocriptine (parlodel)	4	4
		MAOB inhibitor : Eldepryl		
		COMT inhibitor: Tolcapone		
4606	6 Years 3 Months	L_dopa: Sinemet		
		DA: Parlodel	3	3
		MAOB inhibitor: Eldepryl		
4834	6 Years 2months	L_dopa: Sinemet		
		DA : Parlodel	3	3
		MAOB inhibitor: Eldepryl		
5323	12 Years 9 Months	L_Dopa : Sinemet, Madopar		
		Dopamine agonist (DA) : Bromocriptine (Parlodel)	6	5
		MAO-B Inhibitor: Eldepryl		
		COMT inhibitor: entacapone (Comtan)		
		Anticholinergic: Benzhexol(Artane)		
5651	6 Years 9 Months	L_Dopa: Sinemet		
		Dopamine agonist (DA): Pergolide (permax)	2	2
6990	11 Years 3 Months	L_Dopa : Sinemet		
		Dopamine agonist (DA) : Pergolide (Permax)	5	5

		MAO-B Inhibitor: Eldepryl		
		COMT inhibitor: entacapone (Comtan)		
		Anticholinergic: Benzhexol (Artane)		
7372	13 Years 6 months	L_Dopa: Sinemet, Stalevo		
		Dopamine agonist (DA) : cabergoline (Cabaser)	4	3
		MAO-B Inhibitor: Eldepryl		
7658	7 Years 8 Months	L_Dopa : Sinemet	4	4
		Dopamine agonist (DA) : Pergolide (Permax)		
		MAO-B Inhibitor: Eldepryl		
		COMT inhibitor: entacapone (Comtan)		
7806	6 Years 6months	L_Dopa: Sinemet, Madopar		
		MAO-B Inhibitor: Eldepryl	6	4
		COMT inhibitor: entacapone (Comtan)		
		Anticholinergic: Artane, Congentin		
7966	7 Years 8 Months	L_Dopa: Sinemet		
		DA: Pergolide (Permax)	3	3
		MAOB Inhibitor: Eldepryl		
8033	7 Years	L_Dopa: Sinemet		
		MAOB Inhibitor: Eldepryl	3	3
		COMT inhibitor: entacapone (Comtan)		
8065	8 Years 4 Months	L_Dopa: Sinemet,		
		MAO-B Inhibitor: Eldepryl	4	4
		COMT inhibitor: entacapone (Comtan)		
		DA: Pergolide (Permax)		
9162	16years 10months	L_Dopa: Sinemet, Stalevo		
		MAO-B Inhibitor: Eldepryl	6	3
		DA: Cabergolide (cabaser) Sifrol, Symmetrel		
9188	7 Years 10months	L_Dopa: Sinemet		
		MAO-B Inhibitor: Eldepryl	3	3
		Anticholinergic: Artane		
8586	7 Years	L_Dopa: Sinemet		
		MAO-B Inhibitor: Eldepryl	5	5
		Anticholinergic: Artane		
		DA: Pergolide (Permax)		
		COMT inhibitor: entacapone (Comtan)		
9225	5years	L_Dopa: Sinemet		
		MAO-B Inhibitor: Eldepryl	6	5
		Anticholinergic: Artane		
		DA: Pergolide (Permax), Bromocriptine (Parlodel)		
		COMT inhibitor: entacapone (Comtan)		
7732	13 Years	L_Dopa: Sinemet, Stalevo		
		MAO-B Inhibitor: Eldepryl	4	3”
		DA: Sifrol		
9580	7 Years	L_Dopa: Sinemet		
10913	11 Years	L_Dopa: Sinemet,, Stalevo		
		MAO-B Inhibitor: Eldepryl	6	4
		DA: Sifrol, cabergoline (Cabaser)		
		Anticholinergic: Artane		
11234	11 Years	L_Dopa: Sinemet,, Stalevo		
		MAO-B Inhibitor: Eldepryl	6	4
		DA: Sifrol, cabergoline (Cabaser)		
		Anticholinergic: Artane		

11252	11 Years	L_Dopa: Sinemet, Stalevo		
		MAO-B Inhibitor: Eldepryl	3	2
11284	11 Years	L_Dopa: Sinemet, Stalevo		
		MAO-B Inhibitor: Eldepryl	4	3
		DA: Sifrol,		
11300	10 Years	L_Dopa: Sinemet		
		MAO-B Inhibitor: Eldepryl	2	2
11302	10 Years	L_Dopa: Sinemet, Madopar		
		MAO-B Inhibitor: Eldepryl	4	3
		Anticholinergic: Artane		
11737	8 Years	L_Dopa: Sinemet, Stalevo	7	4
		MAO-B Inhibitor: Eldepryl		
		COMT inhibitor: entacapone (Comtan)		
		DA: Sifrol, Permax, Amandatine		
11835	10 Years	L_Dopa: Sinemet,		
11934	9years	L_Dopa: Sinemet,		
		MAO-B Inhibitor: Eldepryl	3	3
		DA: Sifrol		
12059	7 Years	L_Dopa: Sinemet,		
		MAO-B Inhibitor: Eldepryl	3	3
		DA: Cabaser		
12096	7 Years	L_Dopa: Sinemet,		
		MAO-B Inhibitor: Eldepryl	2	2
12258	9 Years	L_Dopa: Sinemet, Stalevo		
		MAO-B Inhibitor: Eldepryl	3	2

Table 3: Treatment algorithm of patients classified per drug's families.

Among the 40 long-term patients, only one had major difficulties with walking and required a wheelchair for mobilisation, equivalent to 2.5% of patients requiring a wheelchair. Six (6) of the 40 patients (15%) demonstrated 'on/off phenomenon' [19], manifested by dyskinesia. Six patients who demonstrated dyskinesia were followed between 6 and 20 years, all of whom were coping well, according to data entries in their clinical records.

Levedopa has long been the gold standard for symptomatic efficacy in PD treatment, although long-term treatment with L-dopa is often complicated by the development of various unwanted motor responses, together with drug-induced dyskinesias [20]. Dyskinesias are manifested by involuntary muscular movements. Several studies have shown that, after 5 years of levodopa use, most of the patient present motor response oscillations [21,22,23]. Such untoward effects are reported in approximately one third of patients with more than 2 years exposure to L-dopa [24], with the frequency of dyskinesias reported to range between 30 and 80% [25,26]. This was not the case in the present study as, among the 40 long-term patients, only 15% reported dyskinesia, with 9/152 (5.9% of the overall 152 patients demonstrating dyskinesia). The majority of patients were able to move well, not requiring a wheelchair, which was only needed by one of the long-term patient sample.

Five (5) of the 152 patients were wheelchair restricted (3.3%), of whom 4 were at this stage before attending the clinic, thus not reflecting upon the treatment algorithm adopted by the neurologist. Of the 5 patients using wheelchairs, all could lift themselves out of the wheelchair without difficulty and were well animated. Only 1 patient, of the 40 long-term patients, (2.5%) was wheelchair bound. Those results are far removed from those reported in a cross study of late stages of PD [27]. In the cross study, severe akinetic symmetric Parkinsonism was present in most of the 50 patients studied and most of them were wheelchair bound. Severe postural instability and freezing of gait, causing frequent falls and fractures, were observed which was not the case with the current audit.

Most of the studies of L-dopa treatment affirm that after a few years of same, the motor complications appear to become more prominent if the treatment is started early in the disease process [28]. All of the 40 long-term patients, reported in this study, had commenced early treatment with L-dopa for between 5 and 20 years and

continued to have a good quality of life and were coping well with their PD.

Contrary to well-accepted guidelines, early initiation and long-term treatment with L-dopa did not impede quality of life of these patients. The data collected at each consultation permitted an independent assessor to monitor the evolution and progress of the disease process and the impact of that disease and its treatment upon patient well-being. Through symptoms and signs, observed and documented at each consultation, it was apparent that the treatment had considerable benefit for improvement in quality of life and this was on a long-term basis, despite its early initiation.

This study represents a clinical audit of real "coalface" outpatient neurological practice with inherent limitations, such as the absence of standardised evaluative tools, to allow full comparison with "research based" clinical study design which often relies on the UPDRS. It is argued that this approach far better mirrors that which occurs in everyday neurological practice. This is particularly relevant when acknowledging that the person conducting the audit was totally independent and unbiased by practice considerations and hence was conducting an open and unbiased critical appraisal which was the mandated public health requirement of the study. Being a long-term, retrospective study, there is no predetermined "control" group to provide a contemporaneous comparator, thus making reliance on published data a requisite to assess the efficacy of the adopted paradigm. The absence of usage of such evaluative tools, such as the UPDRS, does diminish objective assessment, although the scientist was trained in public health and was not biased by predetermined expectations. The study offers an independent evaluation of a particular protocol for the treatment of patients with PD and demonstrated that, despite accepted guidelines, in several studies of PD patients, this approach has proven efficacy both in the short term and in the long-term management of such patients.

PD is a chronic, degenerative disease associated with progressively worsening quality of life, either related to disease progression or treatment consequences [29]. This study demonstrates that it is not necessary to be restricted, within the parameters of published protocols, and, while there continues to be an absence of cure, in the long-term management of PD, this approach appears beneficial for patient well-being. Among the patients observed in this series of cases, treated at an early stage of disease with low dose L-dopa for long periods, very few patients' demonstrated motor complications, as might be expected from review of the literature [21-26,30] and a high majority reported good quality of life. L-dopa remains the gold standard for symptomatic treatment of PD and this study illustrates that an alternative management paradigm may prove equally efficient and efficacious.

Conclusion

The findings of this audit reinforce the clinical approach adopted, and defined above, as well as the need to critically appraise what one does, particularly if that which is done is contrary to published guidelines. It affirms the benefit of using an independent scientist to critically conduct an unbiased audit of clinical practice, especially if there is an absence of standardised evaluative tools (such as the UPDRS). This study validates the integrity of a clinical appraisal and the treatment algorithm reported and offers supportive evidence favouring the early commencement of treatment with L-dopa for PD and maintenance of low dose therapy with polypharmacy.

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