THE MANY FACES OF PARKINSON'S DISEASE: TOWARDS A MULTIFACETED APPROACH?

Marjolein A. van der Marck

The many faces of Parkinson's disease: towards a multifaceted approach?

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Methods	Controlled trial among 301 patients, comparing regions with this integrated model (n=150) with regions with usual care (n=151) over 8 months follow-up.
Results	Improvements on activities of daily living and quality of life, and tertiary health outcomes (e.g. non-motor symptoms). No differences in motor functioning, caregiver burden or costs.
Conclusions	Small positive effects on health outcomes, fueling the need for further research on how to organize team-based care in PD and design clinical trials to evaluate effectiveness.

INTRODUCTION

Partly based on

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This thesis focuses on the broad symptom complex of Parkinson's disease (PD). This multifaceted symptomatology markedly affects the quality of lives of affected individuals, as well as their caregivers, family members and friends. Not surprisingly, this complexity makes PD a very costly disease. The associated costs for society will rise further in the next decades because of a marked increase in the number of PD patients due to ageing of our population. Taken together, this enormous burden on health, coupled with the high healthcare costs and the rising numbers of PD patients, stress the importance of an optimally organized healthcare approach for Parkinson patients. Current medical management thus far relies mainly upon pharmacotherapy and – for a selected number of patients – on deep brain surgical approaches. This thesis addresses the possible merits of care offered by a multispecialty team that also includes allied health professionals, social workers, dieticians and nurse specialists, as a complementary approach to current medical management. We will address the many challenges associated with this relatively new but rapidly emerging field, including issues dealing with the organisation of multidisciplinary team-based approaches. This thesis concludes with a formative evaluation of a new approach towards comprehensive, integrated organisation of care that was studied in a large prospective controlled trial.

Parkinson's disease

Parkinson's disease (PD) is a chronic and invariably progressive neurodegenerative disorder (Box 1).

PD is typically known for its motor features, including tremor, bradykinesia, rigidity, postural instability and postural deformities.[1,2] However, although the diagnosis of PD is currently still founded on the presence of these motor symptoms, they actually represent only the tip of the iceberg.[3] Particularly in the last decade, attention is increasingly focused on a broad variety of non-motor symptoms that constitute an integral and crucial part of PD.[4] These include neuropsychiatric symptoms, sleep

Box 1 Parkinson's disease

The characteristics of Parkinson's disease (PD) were first described in 1817 by James Parkinson based on the observation of six cases, three of whom he only casually met in the street.[7] In his book '*An Essay on the Shaking Palsy*', he described the highly afflicting and complex nature of the disorder, with a variety of disabling motor and non-motor symptoms.

The symptoms observed in PD are caused to a large extent by degeneration of dopaminergic neurons in the substantia nigra, resulting in a neurotransmitter imbalance in the basal ganglia. These basal ganglia have an important role in motor performance, e.g. gait, balance, and speech. When approximately 80% of the neurotransmitter dopamine is lost, motor symptoms become evident. Several other areas within the brain and brain stem are also affected, including both dopaminergic and non-dopaminergic regions. The etiology and underlying pathogenic mechanism remains unclear and several mechanisms have been considered as contributing factors, including genetic and environmental factors, like pesticides. The diagnosis is based on clinical profile (leading to a possible or probable diagnosis of PD),[28] but post mortem observation remains needed to confirm a definite diagnosis of PD.[29] It is expected that these definitions will soon change, because of growing recognition that a variety of non-motor symptoms can precede the manifestation of overt motor symptoms.[30]

disorders, autonomic symptoms, gastrointestinal dysfunction and sensory symptoms.[5] Some of these symptoms, like olfactory deficits, sleep problems and constipation, can even be present in the "premotor" phase when motor symptoms have not yet appeared.[6] Almost all patients experience non-motor problems, and a high prevalence has been reported with on average 8 to 12 different non-motor symptoms per patient.[7-11] These non-motor features are an important issue from the patients' perspective,[12] and have a great negative impact on quality of life, which is in fact even greater than motor symptoms.[7, 8, 11]

Box 2 provides a comprehensive overview of all symptoms related to PD.

Box 2 Clinical profile of PD including motor symptoms and non-motor symptoms. [2,5]

Motor symptoms

- Classical motor symptoms (typically asymmetrical)
  - Resting tremor
  - Rigidity
  - Bradykinesia
  - Postural instability
- Other motor symptoms
  - Gait disturbances, including freezing of gait
  - Micrographia
  - Masked face
  - Dysphagia, contributing to drooling
  - Dysarthria
  - Flexed posture and other postural abnormalities

A wide range of non-motor symptoms including:

- Neuropsychiatric changes, e.g. depression, apathy, anxiety
- Cognitive impairments and dementia
- Autonomic symptoms, e.g. urogenital problems, sweating, orthostatic hypotension, sexual dysfunction
- Gastrointestinal dysfunction, e.g. dysphagia, choking, constipation
- Sensory symptoms, e.g. pain, reduced smell (hyposmia)
- Sleep disorders, e.g. Rapid eye movement (REM) sleep behavior disorder, excessive daytime somnolence, vivid dreaming
- Other symptoms, like fatigue, visual dysfunction, and weight changes

These many symptoms are understandably very disabling for PD patients and markedly influence their quality of life.[13] Indeed, compared to other chronic conditions like arthritis, diabetes, coronary heart disease or stroke, patients with PD score lower on both physical and mental levels of quality of life.[14] Due to the progressive nature of PD, patients constantly have to adapt to new impairments and to a gradual loss of motor and non-motor functioning during the course of the disease.

Because of this complex and multidimensional nature, PD also poses a significant challenge to medical specialists. This challenge relates not only to difficulties in correctly diagnosing this disorder, but also in the management of the wide variety of symptoms. Although the non-motor aspects are recognized as an important part of PD, these symptoms often remain unrecognized and are left untreated.[4,11] An additional challenge is the fact that PD is a highly variable disease across individuals, with a wide diversity in clinical presentation between individuals in terms of manifestation and progression of symptoms.[12] This great interindividual variation creates an even greater challenge to optimally treat the individual patient, particularly in this current era where patients increasingly demand a personalized approach with specific attention to their own, specific priorities.[15-17]

A multidimensional disorder

PD is a complex disorder with disabling features in various domains. Traditionally, treatment has been aimed to control the classical motor symptoms. Over the last years, more attention has been given to other symptoms, including the non-motor symptoms. This thesis focuses on an integral organisation of care for PD patients, to control the multiple motor and non-motor symptoms. The multidimensionality of PD will be illustrated by highlighting two common problems that are clinically relevant to patients but that have thus far received relatively little attention in daily clinical management of PD. These two symptoms include unintentional weight loss and falls, which are both examples of complications of PD that result from a complex interplay between both motor and non-motor problems. Both symptoms nicely demonstrate the urgent need for a broad and multispecialty approach in both the diagnosis and treatment. The first two sections of this thesis address the approach to each of these two specific symptoms (weight loss and falls). An evaluation of the integrative management of PD will be investigated in the third part of this thesis.

Nutritional problems

Unintentional weight loss is frequently reported by PD patients. It is a very relevant problem, as it can complicate the course of the disease and contribute to further morbidity and even mortality. Several symptoms in PD, both motor and non-motor, may influence energy balance and subsequently cause weight reduction. To allow for a timely detection and intervention, it is important to be aware of the underlying causes. In Chapter 2, we will review the diverse set of factors associated with PD that may all cause disturbances in energy balance. Since weight loss is not only common in PD, but also in other neurodegenerative disorders like Alzheimer's disease and Huntington's disease, these three major neurodegenerative disorders will be addressed in this review, to search for common denominators across these conditions. Several studies suggest that PD patients have a lower body weight compared to controls, but the scientific evidence remains inconsistent on this subject. For that reason, we will study the available literature on this topic, and also perform a meta-analysis to assess whether the Body Mass Index in PD patients is indeed different from that of controls (Chapter 3).

Fall prevention

Falls are common in PD patients and have serious health implications. Fall prevention is therefore needed in this population, but a comprehensive overview of all risk factors is lacking. In Chapter 4, we aim to create a set of fall prevention recommendations including all fall risk factors in PD patients. This overview may then serve two purposes: for use in currently daily clinical practice, as expert opinion pending further evidence; and as an active (but experimental) intervention in clinical trials, to obtain further evidence about (cost) effectiveness.

To evaluate whether fall prevention programs are indeed effective, a reliable and feasible tool to adequately monitor falls is required. Several tools have been developed to monitor falls, like questionnaires or falls diaries. However, these methods are often time-consuming and impractical, especially when used in large trials with long-lasting follow-up. We have therefore developed a computerized system to automatically follow-up fall incidents via telephone calls: the Falls Telephone. The reliability and user experiences of this automated Falls Telephone system to monitor falls will be evaluated in Chapter 5.

Towards a multifaceted approach?

Traditionally, healthcare interventions are provided in a relatively 'monodisciplinary' fashion, typically with one medical specialist who delivers the bulk of all care for PD patients. This is often a neurologist or geriatrician, who provides symptomatic treatment, primarily using dopaminergic medication. In Box 3, current medical management is described.

Box 3 Medical management of PD

To date, there is no cure for PD. Because of the marked dopamine reduction in the PD brain, treatment is mainly focused on dopamine replacement. The dopamine precursor levodopa is the most widely used approach to cover this loss. In addition, drugs have been developed that stimulate dopamine receptors or block the metabolism of dopamine, including dopamine agonists, COMT inhibitors, and MAO-B inhibitors.[31,32]

Levodopa is regarded as 'gold standard' treatment, which all patients eventually will require at some stage of the disease. Dopamine receptor agonists are also an effective way to compensate the reduction in central dopaminergic transmission. Such dopaminergic treatments are effective for most motor symptoms like rigidity and bradykinesia. However, other motor features, for example tremor, freezing episodes, postural instability, are not satisfactorily controlled or unresponsive to levodopa, or may even worsen due to dopaminergic treatment, as is the case for some elements of postural instability. Moreover, dopaminergic treatment typically has only limited effect for most non-motor symptoms and some of these may also worsen due to dopaminergic stimulation (e.g. orthostatic hypotension).[2,4] Another shortcoming of levodopa is the fact that chronic use is complicated by motor complications, including the 'wearing off' phenomenon, in which there is a shorter time of effect, unpredictable response fluctuations and involuntary movements (dyskinesias).[31] Surgical procedures, such as deep brain stimulation, can be considered when motor symptoms are insufficiently controlled with pharmacological treatment, mainly because side effects (response fluctuations) limit the ability to adequately dose dopaminergic treatment. However, these neurosurgical procedures are neither the complete answer: they are only suitable for a selected group of patients, and symptomatic effects will only be achieved for those symptoms that also responded to dopaminergic treatment prior to surgery. And, as with medication, symptoms may worsen again after surgery (because surgery does not cure the disease itself)[33], and because adverse events can occur, like worsening of gait and balance.[21]

Nonetheless, only a part of the symptoms respond well to dopaminergic stimulation, while others are insufficiently controlled or even worsen as a result of treatment.[2,4] Neurosurgical procedures can be considered, but these are only suitable for a selected group of patients. Taken together, current medical management is unable to satisfactorily control the multiple symptoms in PD, and this calls for a much broader approach. Indeed,

it is becoming increasingly clear that a single-clinician approach is insufficient to treat the entire symptom complex as seen in patients with PD. A team-oriented model, including both pharmacological and non-pharmacological interventions, seems preferable. Such a team approach may potentially involve a wide range of different health professionals, including physiotherapists, occupational therapists and speech-language therapists (indeed, over 20 different professional disciplines can offer potential value in the management of PD). Box 4 provides a comprehensive overview of disciplines that might be involved in PD care. These allied healthcare therapists can complement standard medical management as it is offered by the medical specialist. Over the past years, several forms of allied health therapy have developed into a more evidence-based profession, with growing evidence from good studies to support these interventions. This emerging evidence in the field of allied healthcare is reviewed in Chapter 6 of this thesis.

Box 4 Overview of disciplines (in alphabetical order) that may be involved in PD care.
The large number of professionals reflects the complexity of this condition. (*adapted from Bloem et al*.[19])

Discipline	Primary interest
Dietician	(Risk for) Weight loss and malnutrition Dietary advices related to medication or surgical procedures Dysphagia Constipation
General practitioner	Recognition of symptoms and side-effects of treatment, with subsequent referral to neurologist
Geriatrician	Elderly patients with complex set of comorbidities that need to be addressed, e.g. internal medicine, psychiatry, falls, or polypharmacy
Neurologist	Diagnosis, inventory of spectrum of symptoms and disease process Medical treatment, expert review of PD and management of complications Referral to other health professionals
Neuropsychologist	Changes in cognition, memory and behavior
Neurosurgeon	Surgical procedures
Occupational therapist	Cognitive impairments related to functional tasks Disabilities in activities of daily living, and safety and independence to perform these activities Support for family and caregivers to help patients perform activities of daily living
Ophthalmologist	Visual problems Oculomotor disorders, including vertical gaze palsy and diplopia
Parkinson's nurse specialist	Provide guidance, support and advice Education to patient and caregiver Observe symptoms and side-effects of medication Notify increased demands for care, with specific attention to cognitive, psychosocial, sexual and mood problems Close communication with neurologist, general practitioner and other healthcarers
Pharmacists	Check for medication interaction Enhance therapy adherence

Physiotherapist	Physical activity, general fitness, muscle strength Safety and functional independence, safe use of assistive devices Fear of falling, fear to move Restrictions in performing transfers (e.g. standing up from a chair, rolling over in bed) and walking (like freezing) Disorders of balance and postural control Prevent falling Motor learning and strategy training (e.g. breaking down activities)
Psychiatrist	Apathy, loss of taking initiative Behavioral problems Delirium Depression Anxiety, panic attacks
Psychologist	Stress of patient or caregiver Complex psychosocial problems Coping Problems with relationship Mood and anxiety disorders
Rehabilitation specialist	Observation and treatment of problems with activities of daily living, household activities, or participation Provide assistive devices Advice on job participation
Sexologist	Problems with sexual functioning
Sleep medical specialist	Diagnosis of complex sleep disorders. Treatment of sleep disorders, like insomnia, vivid dreaming and excessive daytime somnolence
Specialised elderly care physician	Daycare, short-stay or long-stay, regarding complex motor and non-motor pathology Palliative care Residential care
Speech-language therapist	Problems with speech or communication Swallowing disorders
Social worker	Psychosocial problems, e.g. coping or problems with daytime activities Caregiver burden (psychological and financial) Facilitate acquisition of services and inquiries, including legislation and regulation
Urologist	Urinary problems, e.g., incontinence and urgency, to exclude other causes besides PD Erection and ejaculation dysfunction
Complementary and alternative therapies	These therapies (e.g., nutritional supplements, massage therapy, acupuncture, homeopathy) are used commonly by PD patients

No standard template

Nowadays, a multifaceted approach is increasingly recognised as the optimal way to control a complex disorder like PD.[18-19] Importantly, this recognition is also shared by patients themselves.[15] Indeed, in current clinical practice, more different types of health professionals appear to become involved in PD care, but the effectiveness of their services in current clinical practice appears suboptimal.[20] One problem is that, despite overlapping treatment goals, the various different specialists typically work in isolation and parallel to one another, instead of

delivering an integrated approach. At present, PD centres worldwide increasingly implement team-based care in their clinical practice, but there is no standard template. Consequently, organisation of team-based care varies widely across different centres.[21] Even though there is a general feeling that these team-based approaches provide better care, the scientific evidence to support this feeling remains very limited, and the few trials published so far have showed inconsistent results.[22-25]

How to organise team care?

There are several ways to organise team-oriented models, varying from a relatively simple approach, where independent health professionals share their expertise, to a more complex and seamless continuum of care, based on consensus between all team members.[26] These models are illustrated in more detail in Box 5 and Box 6. As mentioned previously, there is currently no standard template for team-based PD care and it is unknown whether more complex organized models represent better care.

Box 5 Models of Team Healthcare Practice (Based on Boon H. *et al.*[26])

Parallel	•	independent health professionals
Consultative	•	independent health professionals who give expert advice to another
Collaborative	•	health professionals, normally working independent
	•	distribute information concerning a shared patient
Coordinated	•	team of health professionals working together
	•	coordination by case coordinator or manager via communication and sharing of patient records
Multidisciplinary	•	team of healthcare professionals working together
	•	each team member makes own decisions and recommendations
	•	team leader integrates recommendations and plans patient care
Interdisciplinary	•	team of healthcare professionals working together
	•	group decisions, usually based on consensus, facilitated by regular, face to face meetings
Integrative	•	interdisciplinary, non-hierarchical approach
	•	seamless continuum and shared decision making
	•	each professional and patient contributes with knowledge and skills
	•	patient centered care and support, treatment of whole person

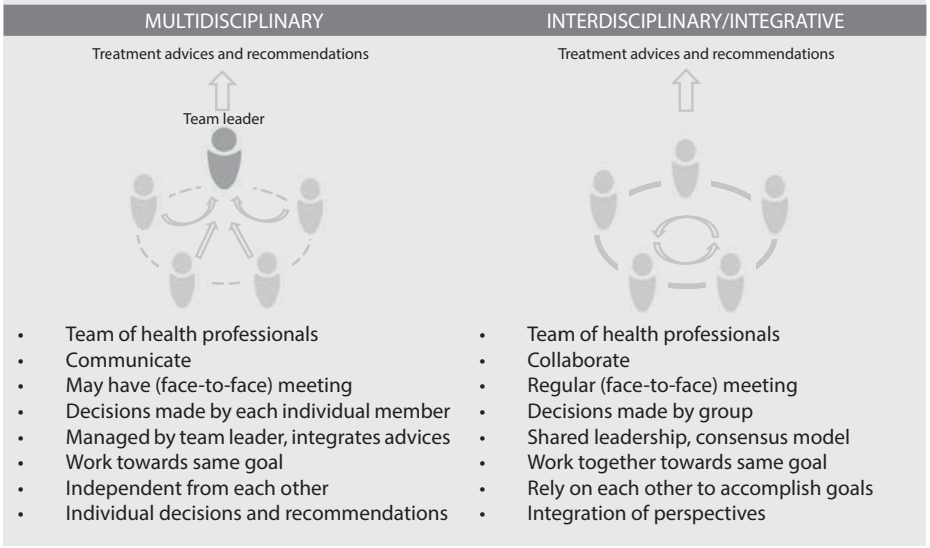
*Increased complexity**

** Increased complexity with growing number of determinants of health considered, diversity of outcomes and number of participants involved. Also, increased need for communication and synergy between participants, and importance of decision making by consensus. Growing emphasis on whole person and individualization of treatment, with an individually tailored approach.*

In this thesis, the organisation of two different approaches towards multispecialty team management is described and evaluated. These studies are among the first controlled trials that aim to evaluate the effectiveness of ongoing team care in PD. In Chapter 7, we describe an example of multidisciplinary care, featuring a movement disorders specialist supported

by PD nurses and a social worker, whose input is tailored to the patients' individual needs. In this chapter, we describe the results of a randomized controlled trial on the effects on health outcomes of this approach.

Box 6 Multidisciplinary versus Interdisciplinary/Integrative team care



The ultimate model: an integrated, comprehensive approach

With the wide variety of PD symptoms in mind, a comprehensive approach with involvement of professionals from various disciplines would appear preferable to treat PD. In Chapter 8, we examine the effectiveness of one specific example of a comprehensive model, namely an integrated approach of PD care as we deliver this at our centre in the Netherlands. This healthcare approach offers patients two complementary elements: a tailored assessment by an extensive team of health professionals, resulting in an integrated treatment advice based on consensus and shared decision-making. This treatment advice is subsequently carried out by dedicated allied health professionals working within the direct vicinity of the patients' homes, as part of specialised ParkinsonNet networks. These networks represent regional communities of closely collaborating allied health specialists, who are specifically trained to treat PD patients according to evidence-based guidelines. Besides increased PD expertise, these networks also aim to enhance interdisciplinary collaboration between specialists, to ultimately provide a seamless organization of care for those affected with PD.[27]

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WEIGHT LOSS IN NEURODEGENERATIVE DISORDERS

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Abstract

Unintended weight loss frequently complicates the course of many neurodegenerative disorders, and can contribute substantially to both morbidity and mortality. This will be illustrated here by reviewing the characteristics of unintended weight loss in the three major neurodegenerative disorders: Alzheimer's disease, Parkinson's disease and Huntington's disease. A common denominator of weight loss in these neurodegenerative disorders, is its typically complex pathophysiology. Timely recognition of the underlying pathophysiological process is of crucial importance, since a tailored treatment of weight loss can considerably improve the quality of life. This treatment is, primarily, comprised of a number of methods of increasing energy intake. Moreover, there are indications for defects in the systemic energy homeostasis and gastrointestinal function, which may also serve as therapeutic targets. However, the clinical merits of such interventions have yet to be demonstrated.

Introduction

Neurodegenerative disorders are traditionally associated with cognitive, psychiatric and motor impairments. However, what is much less appreciated is that the course of many neurodegenerative disorders can also be complicated by an unintended loss of body weight. Weight loss can contribute to both morbidity (e.g. because of increased risk of systemic infections and pressure sores) and mortality.[1-2] Moreover, recent findings suggest that changes in systemic metabolism could also directly influence the underlying neurodegenerative processes.[3-4] It is, therefore, crucial to be aware of the underlying causes of unintended weight loss, which will allow for timely detection, and tailored interventions directed at improving nutritional status and increasing body weight.

Here we first delineate the characteristics of unintended weight loss in neurodegenerative disorders, using Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) as representative and complementary examples. We will, subsequently, present a comprehensive model of the pathophysiology of weight loss in these disorders. Finally, we will use this model to highlight a number of possible implications for clinical management and patient care.

Characteristics of weight loss

Alzheimer's disease

AD is the most common cause of dementia and is characterized by the progressive loss of cognitive modalities. Weight loss in AD was already described by Alois Alzheimer in his original report from 1906.[5-6] Many epidemiological studies have since confirmed this initial observation. Weight loss is present in about 40% of AD patients, and can occur in all stages of the disease, even before a formal diagnosis has been made.[7-8] According to current diagnostic standards, weight loss is now considered a concomitant criterion for dementia.[9] A recent prospective follow-up study demonstrated that a decline in Body Mass Index (BMI) in older age is associated with both an increased risk of developing AD, and a faster rate of disease progression.[8] This may indicate a causal relationship, whereby weight loss aggravates the pathogenic processes that mediate AD. Conversely, the association may also arise when disease progression induces weight loss.[8] Age has a modifying effect on the relationship between body weight and the risk of dementia: being overweight in middle age (40-45 years) increases the risk of developing dementia later in life[10], while the relation between body weight and the risk of dementia in older age (65-75 yrs) appears to be U-shaped.[11] In even older age (≥ 76 years), a higher BMI is directly associated with a decreased risk of dementia.[11]

Parkinson's disease

The core motor symptoms of PD include bradykinesia, resting tremor, rigidity, and postural instability.[12] In addition, the disease is also frequently complicated by a variety of non-motor

symptoms, including dementia and depression.[13] Furthermore, numerous studies have revealed that patients with PD lose weight, and have a lower body weight when compared to matched control populations.[14] Weight loss in PD can be ascribed, primarily, to a loss of fat tissue.[14] A recent large-scale prospective study showed that weight loss in PD patients is a continuous, progressive process, which commences years before a formal diagnosis is made, and cannot be ascribed to a decreased energy intake.[15] However, analogous to AD, being overweight in middle age is an independent risk factor for developing PD later in life.[16]

Huntington's disease

HD is a hereditary, progressive, neurodegenerative disorder, characterized by motor, psychiatric, and cognitive disturbances.[17] The motor disturbances include chorea, dystonia, hypokinesia, and rigidity.[17] The disease is often accompanied by considerable weight loss, particularly in its final stages.[18-19] Many studies have demonstrated that HD patients are either underweight, or tend to lose weight during the course of their illness, eventually becoming cachectic.[20-22] Weight loss in HD is not associated with reduced intake due to anorexia, but rather with an increased appetite. [23-25] Although there are indications of a higher sedentary energy expenditure due to unwanted movements[26], these findings do not explain the lower BMI found in either asymptomatic gene-carriers[23-24] or HD patients who are in the early stages of the disease, when unwanted movements are absent or minimal.[20] Undernutrition is common in HD patients[19], and contributes to a higher rate of mortality.[27] Conversely, a higher body weight at the time of diagnosis is associated with slower disease progression.[28]

Pathophysiological mechanisms

Weight loss results from a prolonged disequilibrium between intake, digestion and absorption of energy from nutrients on the one hand, and energy expenditure on the other hand (Figure 1).

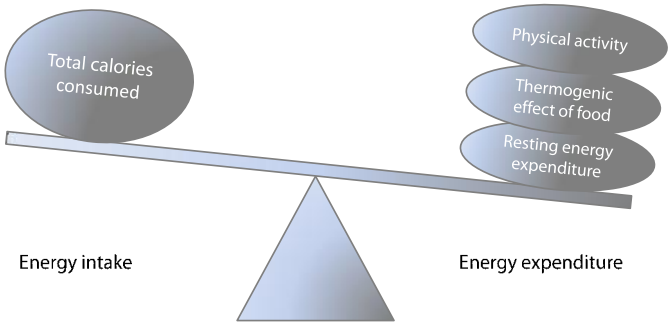

Figure 1 *Negative energy balance. Weight loss occurs when energy expenditure exceeds energy intake.*

Total daily energy expenditure is determined by the resting metabolic rate, the thermogenic effect of food, and the extent of physical activity and repair.[29] Through a process known as energy homeostasis, the central nervous system adjusts food intake in response to changing energy requirements, so as to promote stability in body weight over time.[30] Information regarding nutrient status and energy stores is communicated to the brain through diverse endocrine (e.g. leptin) and afferent neural signals where it is subsequently integrated with cognitive, visual, olfactory, and taste cues.[30-31]Accordingly, it should not come as a surprise that diseases of the central nervous system are often complicated by disturbed body weight regulation. Here, we will focus on weight loss in neurodegenerative disorders, the aetiology of which is complex and multifactorial. In this context, the factors which could disrupt energy balance can be divided into two groups: a) primary factors that are directly related to neuronal dysfunction and neurodegeneration, such as cognitive, psychiatric and motor disturbances, altered olfaction and gustation, and pathology of energy homeostatic centres in the brain, and b) secondary factors that are not directly attributable to neurodegenerative processes, but are, nevertheless, prevalent and can contribute to weight loss, such as side effects of medication, loss of autonomy, and a higher risk of co-morbidity (particularly infections like pneumonia and pressure sores).[32] The most important factors are summarized in Table 1. Although many of these factors could be involved in the pathogenesis of weight loss in all three of the major neurodegenerative disorders, some are of particular importance and, sometimes, unique to a specific disease (Table 1).

Table 1: Factors influencing energy balance

	Examples	Disorder	References
Factors influencing energy intake			
Cognitive disturbances	Neglect and agnosia (forgetting to eat), apraxia (difficulties with shopping and meal preparation), communication problems (desire to eat cannot be expressed)	AD	32,41
Psychiatric and behavioural disturbances	Depression (with vital features), afraid to eat, confusion, refusal to eat	AD, PD, HD	7,14,50,66
Motor disturbances	Wandering/pacing Tremor, tardive dyskinesias Rigidity, dystonia Chorea Dysphagia	AD PD PD, HD HD AD, PD, HD	50 51-52 26,51-52,54 26,86 57-59
Autonomic dysfunction	Swallowing difficulties	PD, HD	14,32
Sensory functions	Altered sense of smell and taste Reduced vision, hearing and tactile sense	AD, PD, HD AD	60 32
Orodental problems	Caries and reduced oral hygiene	AD, PD, HD	32,34

Age and social factors	Isolation/loneliness Poverty/ low social-economic position	AD, PD, HD	[34]
Decreased physical activity	Reduced appetite Muscle atrophy	AD AD, HD	[32] [23,44]
Pathology of brain energy homeostatic centres	Pathology of hypothalamus, brainstem (autonomic centres), mesial temporal cortex and mesocorticolimbic reward circuits	AD, PD, HD	[78-84]
Endocrine and metabolic abnormalities*	Reduction of endocrine and metabolic stimulants of energy intake	AD, PD, HD	[78-79,87]
Inflammatory abnormalities*	Anorexia due to increases in Il-1, Il-6, TNF-α	AD, PD, HD	[88-90]
Side effects of medication	Nausea, dry mouth, altered ability to smell and taste, reduced appetite, dysphagia, gastrointestinal dysfunction, dyskinesias, esophagitis, vomiting, tardive dyskinesias	AD, PD, HD	see Table 2
Factors influencing energy absorption			
Autonomic dysfunction	Slow stomach emptying, reduced absorption, constipation	PD	[58]
Side effects of medication	Gastrointestinal dysfunction, diarrhoea, vomiting	AD, PD, HD	see Table 2
Factors influencing energy expenditure			
Motor disturbances	Wandering/pacing Tremor, tardive dyskinesias Rigidity, dystonia Chorea	AD PD PD, HD HD	[44] [51-52] [26,51-52,54] [26,86]
Pathology of brain energy homeostatic centres	Hypermetabolic state due to pathology of hypothalamus, brainstem (autonomic centres), mesial temporal cortex	AD, PD, HD	
Endocrine and metabolic abnormalities*	Changes in: ACTH, cortisol, growth hormone, prolactin, TSH, T3, T4, testosterone and estrogen Glucose intolerance Abnormalities of fat and muscle tissue Increased resting energy expenditure ApoE4 genotype Loss of normal huntingtin function	AD, PD, HD AD, PD, HD HD PD, HD AD HD	[78-79,87,91-93] [94-96] [26,51-52,54] [97] [33]
Inflammatory abnormalities*	Procatabolic state due to increases in Il-1, Il-6, TNF-α	AD, PD, HD	[88-90]
Side effects of medication	Dyskinesias, lipolysis	AD, PD, HD	see Table 2

* For a large number of endocrine, metabolic and inflammatory changes an independent effect on weight loss has not been sufficiently investigated, although it has been suggested in a number of studies.
ACTH adrenocorticotropic hormone; *AD* Alzheimer's disease; *HD* Huntington's disease; *Il-1* interleukin-1; *Il-6* interleukin-6; *PD* Parkinson's disease; *T3* triiodothyronine; *T4* thyroxine; *TNF*-α tumor necrosis factor-α; *TSH* thyroid-stimulating hormone.

For example, a putative loss of function of the normal huntingtin protein may affect body weight regulation in HD.[33] An overview of commonly used drugs which may interfere with energy balance is presented in Table 2.

Table 2: Medication with a negative influence on energy balance

Side effects	Medication type
Anorexia	Cholinesterase inhibitors, NSAIDs, MAOIs
Nausea	Antibiotics, NSAIDs, levodopa, amantadine, dopamine agonists, MAOIs, toxic plasma levels of various drugs (e.g. digoxin, theophylline)
Altered sense of smell and taste	Anticholinergics, antibiotics
Gastrointestinal dysfunction (particularly constipation)	Benzodiazepines, opioids, anticholinergics, tetrabenazine, tricyclic antidepressants
Dyskinesias	Antipsychotics, tetrabenazine, levodopa
Dry mouth	Anticholinergics, amantadine, COMT inhibitors, MAOIs, tricyclic antidepressants
Esophagitis	Bisphosphonates
Dysphagia	Phenothiazines, neuroleptics
Diarrhoea	SSRIs, antibiotics, laxatives, COMT inhibitors
Lipolysis	Levodopa, dopamine agonists

Partly adapted from White H.K.[32] *COMT* catechol-o-methyltransferase; *MAOIs* monoamine oxidase inhibitors, *NSAIDs* non-steroidal anti-inflammatory drugs; *SSRIs* selective serotonin reuptake inhibitors.

Evaluation of weight loss and malnutrition

Periodical weighing of patients is a simple and efficient way to monitor body weight and nutritional status.[32] The following criteria could serve as a guide:[34]

- Does the patient have a low body weight? A BMI lower than 20 kg/m^2 indicates an increased risk of malnutrition. For people aged 65 years and over, 21 kg/m^2 is used as the cut-off point to compensate for age-related changes in body composition.[34]
- Has the patient lost weight unintentionally? Weight loss exceeding 5% in three months, or 10% in six months, is considered clinically relevant and indicates a greater risk of malnutrition.[35]
- Are there indications of decreased appetite or food intake (> 25% of food is not consumed in at least two out of three meals in the previous week)?[35]

Further examination is necessary when at least one of the above criteria is met. In addition, other instruments, such as the 'Malnutrition Universal Screening Tool'[36] and the 'Mini Nutritional Assessment'[37], are available for the systematic assessment of nutritional status. These two scales are easy to use, and have been validated in a variety of populations, although further corroboration is required in patients with neurodegenerative disorders[38-39] (see the accompanying websites[36-37] for further information).

Therapeutic strategies and implications for patient care

Timely recognition of the risk of malnutrition, and its underlying causes, is of crucial importance for adequate intervention. Formulation of extensive recommendations for the treatment of malnutrition and unintended weight loss in general, are beyond the scope of this article; excellent clinical guidelines can be found elsewhere[35,40] and are, generally, also applicable to neurodegenerative disorders. In this paper, we will limit ourselves to those aspects which are of specific importance to the treatment of malnutrition and weight loss in neurodegenerative disorders (Table 1).

Dementia and behavioural disturbances

Progressive dementia is an inherent feature of AD and HD and, to a lesser extent, PD. Getting patients with dementia to eat is generally a process of trial and error.[32] It is important that food is not only offered during mealtimes but also in between them. Most patients need constant supervision and simple instructions during meals. Finger foods could be utilised when patients are unable to use cutlery.[41] If appetite and vigilance are greater early in the day, it can be useful to increase the relative contributions of breakfast and lunch to the total daily energy supply.[41] Food intake can also be stimulated by simplifying the eating environment, such as by removal of potential distractions, the creation of a calm atmosphere, e.g. through soft background music[42], and by providing family style mealtimes.[43] Promoting physical activity can also stimulate appetite and, in addition, prevent muscle atrophy.[44]

Psychiatric disturbances

Depression is the most common psychiatric disturbance to complicate the course of the three major neurodegenerative disorders. Moreover, of all the psychiatric disturbances, depression has the greatest influence on energy balance.[45] Depression can lead to a decrease in appetite, and induce a cascade of neuroendocrine changes that can lead to weight loss over time.[45] Treatment of depression could thus have a positive effect on body weight. Although tricyclic antidepressants can induce weight gain, their side effects, such as constipation and a dry mouth, render these drugs less suitable when compared to selective serotonin reuptake inhibitors (SSRIs). The initial concern that SSRIs might promote weight loss in the elderly has never been substantiated.[46] and a number of them, particularly mirtazapine, are even associated with increased appetite and weight gain.[47] Although some SSRIs, such as fluoxetine, can induce weight loss in the short term, prolonged use (> ½ year) is associated with weight gain.[47] The effects of SSRIs on patients with dementia, both on depression and other outcome parameters, such as body weight, need further investigation. Furthermore, the application of neuroleptic medication for the treatment of psychosis in AD patients has been associated with weight gain.[48-49] While neuroleptic medication is also frequently used for treating psychosis in PD and HD (and for the suppression of choreatic movements in HD), the relation between

neuroleptics and body weight in PD and HD patients needs further investigation. In any event, serious side effects, such as extrapyramidal symptoms, place inherent limitations on the use of neuroleptics for the treatment of weight loss in neurodegenerative disorders.

Dyskinesias

Abnormal motor behaviour, such as excessive pacing, has been associated with weight loss in patients with AD.[50] However, in PD and HD patients, the relation between weight loss and motor disturbances, such as rigidity, tremor, dystonia and chorea, is still unclear. On the one hand, there are indications that dyskinesias could lead to a higher energy expenditure in both PD[51-53] and HD[26,54] patients, whereas on the other hand, the total daily energy expenditure in both PD and HD patients does not appear to be significantly different from that of matched control subjects.[26,55] This is probably explained by fewer spontaneous and voluntary movements.[26,55] Other findings that argue against the notion of dyskinesias being major determinants of weight loss in HD, are the lower BMIs, compared to controls, found in presymptomatic HD gene carriers and those patients who are at an early stage of the disease when motor disturbances are either absent or minimally present.[20,56] In addition, the weight gain that is often observed in PD patients after pallidotomy and deep brain stimulation in the subthalamic nucleus, is not associated with improvements in dyskinesia scores.[14,53] Therefore, it remains unclear whether reduced energy expenditure, due to improvement of the motor symptoms, could explain any weight gain after medical or surgical suppression of dyskinesias. However, dyskinesias can often impair food intake, particularly in PD patients with response fluctuations. A flexible feeding scheme adjusted to these response fluctuations may be helpful.[14] Furthermore, many AD, PD, and HD patients experience chewing and swallowing difficulties, which can further hamper energy intake.[57-59] Food intake can, therefore, be promoted by a combination of feeding assistance and optimal treatment of the motor impairments.[14]

Olfactory and gustatory disturbances

The sense of smell plays a considerable part in the perception of taste. Olfactory dysfunction, due to both structural and functional changes in the brain, has been reported in different neurodegenerative disorders.[60] It can occur early in the course of the disease in AD, PD, and HD.[60] A reduced ability to taste and smell may contribute to weight loss in these disorders. Therefore, it is particularly important to strive to maximize the smell and taste of food, for example by using aroma and flavour enhancers.[61]

Medication

The side effects of medication can interfere with energy balance on a number of different levels (Table 2).[32] In particular, commonly used drugs can cause many symptoms which could limit energy intake. Acetylcholinesterase inhibitors, which are the first option for treating cognitive symptoms in AD, have several potential adverse effects. These include

nausea, vomiting and anorexia, which can limit the intake and absorption of nutrients.[62-63] In addition, galantamine, an acetylcholinesterase inhibitor, has been associated with an increased incidence of weight loss.[64] Nausea and anorexia are also notable side effects of the dopaminergic medication that is widely used in the treatment of PD patients. Moreover, long-term dopaminergic therapy may increase lipolysis, as a consequence of increased growth hormone secretion[65], contributing to the loss of fat tissue reported in PD patients.[66-67] However, pramipexole, a dopamine receptor agonist, has been associated with weight gain in PD, presumably through a direct effect on the limbic D_3 receptors involved in feeding.[68] The use of neuroleptics is, generally, also associated with weight gain, although serious adverse effects limit their application (see above in the paragraph 'Psychiatric disturbances'). In HD patients, the effects on body weight of tetrabenazine, an antichoreic drug that selectively depletes central monoamines by reversibly binding to the type 2 vesicular monoamine transporter, are not well studied, although one study failed to find significant differences in weight change between patients on tetrabenazine and those on placebo.[69] On the other hand, a small-scale open-label study showed that HD patients taking creatine did not lose weight over two years of follow-up, suggesting that creatine supplementation may be effective for the treatment of weight loss in HD.[70] Thus, while some drugs, such as pramipexole in PD, and creatine in HD, appear promising for the treatment of weight loss in these disorders, large-scale clinical trials are needed to provide convincing evidence of their efficacy. Therefore, currently, no pharmacological interventions can be recommended for the treatment of weight loss in neurodegenerative disorders. Meanwhile, physicians and caregivers should be aware that patients with cognitive impairment may not be able to voice symptoms attributable to the side effects of commonly used drugs, such as nausea and anorexia.[32] In addition, patients who have a low body weight are at an increased risk of receiving higher cumulative doses of medication, with a proportional disruption of energy homeostasis attributable to side effects.[71] Therefore, in case of weight loss or low weight, all medication used should be checked and, if necessary, adjusted.

Nutritional supplements

Different studies have demonstrated that oral nutritional supplements can boost total daily energy intake, and stabilize or even increase body weight.[5,21,72-74] Therefore, energy-rich oral nutritional supplements can be applied in case of an increased risk of malnutrition. Daily energy requirements can be gauged based on estimates of physical activity level and resting energy expenditure, using predictive formulas like the Harris-Benedict and Schofield equations.[75] However, these equations have not been validated in patients with neurodegenerative disease, and should only be used as a guide, particularly because requirements are greater in people who are underweight.[76] As patients who need feeding assistance, and the elderly in general, are at an increased risk of developing micronutrient deficiencies, the routine use of vitamin and mineral supplements should also be considered.[32,77] The implementation of artificial

feeding is highly controversial.[5] Enteral feeding (nasogastric/gastrostomy feeding tubes) does not improve the prognosis in terms of survival, functional capacity, and susceptibility to pressure ulcers and infections.[5] However, transient artificial feeding should be considered for mildly affected patients in whom oral feeding is not possible in the short term.[5]

Defects in systemic energy homeostasis

In several neurodegenerative disorders, weight loss may occur despite adequate or even increased food intake. This suggests the involvement of other factors that may adversely affect systemic energy homeostasis, such as malabsorption, defects in energy homeostatic centres in the brain (particularly the hypothalamus and autonomic centres), and peripheral biochemical abnormalities, such as mitochondrial dysfunction.[58,78-84] Indeed, various components of systemic energy homeostasis in neurodegenerative disorders may be defective. For example, abnormalities have been described in gastrointestinal function, in peripheral tissues, such as muscle and fat, and in the different parts of the brain which are involved in the regulation of energy balance. [4,58,78-84] However, most of these findings stem from fundamental research of which the clinical relevance is still unclear. Further physiological studies on the relation between defects in the various components of systemic energy homeostasis and clinical symptoms are, therefore, warranted. Based on these studies, more effective therapeutic interventions could then be designed to target basal pathophysiological mechanisms.

Conclusion

Unintended weight loss frequently complicates the course of many neurodegenerative disorders. It is a clinically relevant problem since weight loss can contribute substantially to both morbidity and mortality. Timely recognition, and a multidisciplinary approach, could result in (cost)effective intervention, and prevent a variety of complications (e.g. infections), thereby eventually resulting in considerable improvements in the quality of life.[85] However, further studies on the (cost)effectiveness of the various types of intervention are necessary.

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1966 to February 2008. Two searches were performed, the first with the MeSH terms "weight loss" and "neurodegenerative diseases", and the second with the terms "weight loss" in combination with "Alzheimer disease", "Parkinson disease" or "Huntington disease". Articles were also identified through searches of the authors' own files.

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BODY MASS INDEX IN PARKINSON'S DISEASE: A META-ANALYSIS

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Abstract

Prior work suggested that patients with Parkinson's disease (PD) have a lower Body Mass Index (BMI) than controls, but evidence is inconclusive. We therefore conducted a meta-analysis on BMI in PD. We searched MEDLINE, EMBASE, Cinahl and Scopus to identify cohort studies on BMI in PD, published before February 2011. Studies that reported mean BMI for PD patients and healthy controls were eligible. Twelve studies were included, with a total of 871 patients and 736 controls (in three studies controls consisted of subjects from other published studies). Our primary aim was to assess differences in BMI between patients and controls; this was analyzed with random effects meta-analysis. Our secondary aim was to evaluate the relation with disease severity (Hoehn and Yahr stage) and disease duration, using random effects meta-regression. PD patients had a significantly lower BMI than controls (overall effect 1.73, 95% CI 1.11 – 2.35, P<0.001). Pooled data of seven studies showed that patients with Hoehn and Yahr stage 3 had a lower BMI than patients with stage 2 (3.9, 95% CI 0.1 – 7.7, P<0.05). Disease duration was not associated with BMI. Because a low body weight is associated with negative health effects and a poorer prognosis, monitoring weight and nutritional status should be part of PD management.

Introduction

Parkinson's disease (PD) was initially known mainly as a motor disorder, with tremor, bradykinesia and rigidity as dominant features. Later work underscored the importance of a wide range of non-motor symptoms, including neuropsychiatric, autonomic and gastrointestinal symptoms.[1-2] Both motor and non-motor symptoms may influence the energy balance.[3] Several studies suggested that PD patients have a lower Body Mass Index (BMI) compared to controls. This could have clinical implications, because a low body weight is associated with negative health outcomes.[4-5] However, differences between patients and controls were not statistically significant in all studies.[6-11] In fact, one uncontrolled study suggested that overweight or obesity may also be common in PD.[12] Our primary aim was to conduct a meta-analysis to examine whether BMI differs between PD patients and healthy controls. A secondary aim was to search for possible determinants of weight loss in PD.

Methods

A literature search was conducted to identify original studies that assessed BMI in PD patients in Medline (from 1948), EMBASE (from 1980), Cinahl (from 1982) and Scopus (from 2000). The search period ended in February 2011. The search strategy included a range of search terms for PD, body weight and body composition, which were entered both as thesaurus and as free text word (esupplement). Titles and abstracts were then reviewed to assess eligibility. In addition, reference lists of relevant articles were screened. Results were restricted to studies comparing PD patients with controls free of PD or atypical parkinsonism, meeting the following criteria: (a) patients diagnosed with PD; (b) mean BMI of PD patients and controls was presented or could be calculated; (c) body weight was actually measured and not just self-reported; (d) published as a full article (i.e. abstracts were excluded); and (e) published in English.

The study objective, study sample and mean BMI of patients and controls were extracted from all included studies. Possible determinants were very inconsistently reported, and only disease duration and disease severity were reported commonly enough to be extracted. Disease severity was expressed as Hoehn and Yahr stage (HY) [13] as this was the most widely reported scale.

Statistics

The primary outcome was the difference in BMI between PD patients and healthy controls. Random effects meta-analysis was used to compare these differences. For two[14-15] of the three studies [11,14-15] with an external control group obtained from existing population studies, the number of controls entered in the analysis were the same as the number of included patients in these studies. As secondary outcomes, the relationship between BMI and disease severity (expressed as HY stage) and disease duration was analyzed in a random effects meta-regression.

Table 1 Aim and definition of the study population of studies that reported the Body Mass Index (BMI) of patients with Parkinson's disease and healthy controls

Study	Aim	Patient definition	Controls definition
1. Yapa *et al*., 1989 [15]	Study nutritional status with various degrees of disability	Idiopathic PD patients	Age-matched predicted values from community surveys
2. Abbott *et al*., 1992 [16]	Examine nutritional status with particular emphasis on antioxidants	PD Patients, diagnosed before 60 years	Controls with routine screening of blood pressure and lipid profiles
3.Markus *et al*., 1993 [14]	Determine prevalence of undernutrition in PD and determinants	Patients with levodopa-responsive PD	Age and sex matched control values from elderly population
4. Beyer *et al*., 1995 [17]	Compare weight loss and body composition to predict nutritional risk	Free living PD patients	Free living age, sex and race matched controls
5. Coates and Bakheit, 1997 [8]	Identify prevalence of swallowing difficulties and relationship to nutritional status	PD patients	Spouses
6. Revilla *et al*., 1998 [7]	Compare body composition and study relationship with clinical disability	PD outpatient	Controls from Rheumatology clinic for nonspecific pain
7. Sato *et al*., 2001 [20]	Determine effects of physical state, bone mass and bone and calcium metabolism on the risk of hip fractures	Patients with PD	Age-matched healthy volunteers
8. Lorefalt *et al*.,2004,2006 [9,19]	Investigate determinants for weight loss (2004); Investigate food habits and intake of nutrients (2006)	Free living PD patients	Randomly selected sex and age matched, healthy controls
9. Uc *et al*.,2006 [11]	Examine change of body weight over years and determinants of weight loss	Consecutive patients with PD	Volunteers from longitudinal study on changes in body composition in elderly
10. Marczeweska *et al*., 2006 [10]	Investigate dietary habits, particularly protein intake	PD outpatients, attending a nutrition unit	Healthy spouses
11. Fernandez *et al*., 2007 [18]	Compare body composition and study associations among body composition parameters, bone mass and mineral metabolism	Consecutive PD patients	Controls with no history of fractures, concomitant disease or medication known to affect bone or mineral metabolism
12. Ragonese *et al*., 2008 [6]	Investigate relationship between PD and BMI changes during the time preceding the disease	Consecutive PD patients	Randomly selected gender and age matched controls, free of neurological diseases

Results

Search results

Our search strategy identified 2886 references, of which 14 met the selection criteria.[6-11,14-21] One study reported unusually high BMI values for patients and controls compared to other studies, which could have disproportionally influenced the results.[21] Therefore, this study was excluded from the analyses, but is addressed separately in the Discussion. Two articles reported the same population.[9,19] Hence, data from 12 studies were included. The objectives and definitions of patients and controls of these studies are specified in Table 1. In three studies, control data were obtained from studies in the elderly.[11,14-15] The other nine studies included their own control group. Objectives of the included studies varied widely, ranging from examining weight changes and body composition to studying risk factors for hip fracture (Table 1). Baseline characteristics and BMI are summarized in Table 2.

Cross-sectional data

Differences in BMI between patients and controls from the 12 included studies are presented in Figure 1. The studies reported the BMI of 871 patients and 736 controls (for those studies with their own control group). In all studies, the average BMI of PD patients was lower

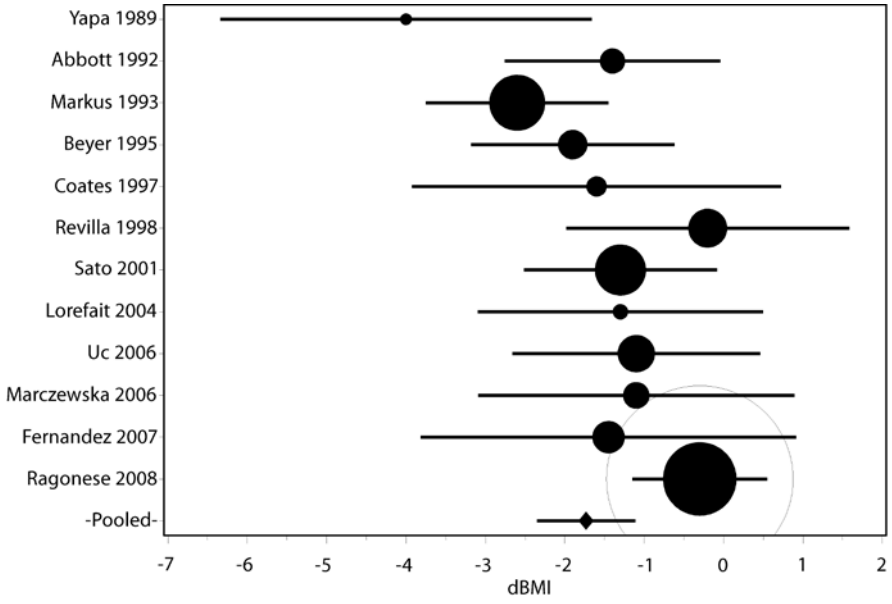

Figure 1 *Forest plot demonstrating the difference in Body Mass Index (BMI) between patients with Parkinson's disease and healthy controls, with the 95% confidence intervals of 12 studies. The magnitude of the circle size represents the sample size. Because of the large sample size of Ragonese et al., the circle size is adjusted and the original circle is indicated with a thin line.*

Table 2 Studies that reported the Body Mass Index (BMI) of patients with Parkinson's disease and healthy controls

Study	Patients (M/F)	Controls (M/F)	Patients Age (years)[a]	Controls Age (years)[a]	Disease severity[a]	Disease duration (yrs)[a]	BMI Patients[a]	BMI Controls[a]
1.	20 (9/11)	–	> 65 yrs	> 65 yrs	H&Y II (7),III (8), IV (2), V(3)	–	M 20.7 ± 3.5* F 21.3 ± 3.9*	M 24.2 ± 0.7 F 25.8 ± 0.8
2. **	45 (23/22)	41 (21/20)	62 ± 9 (44-83)	58 ± 9 (39-76)	–	–	<18 (9%) 18.0-20.0 (20%) 20.1-25.0 (51%) 25.1-30.0 (20%) >30.0 (0%)	<18 (0%), 18.0-20.0 (7%) 20.1-25.0 (72%) 25.1-30.0 (16%) >30.0(5%)
3. **	95 (53/42)	–	M 61.2 (39-77) F 62.4 (37-82)	–	H&Y M 3.0 (1-5) H&Y F 2.9 (1-5)	M 9.3 (0-30) F 8.9 (0-30)	M 23.0 ± 3.2 F 22.4 ± 4.6	M 25.4 F 25.2
4.	51	49	68 (45-86)	67(43-88)	H&Y II (28), III (12),IV (1)	8.8	24.4 ± 0.5[b]* (18 – 34)	26.3 ± 0.4[b] (20 – 33)
5.	48 (20/28)	21 (14/7)	69.9 (52-87)	68.1 (56-83)	Mean UPDRS score 1.4 ± 0.7	6.7 (1-24)	26.0 ± 4.9 M 26.1 ± 3.3 F 25.8 ± 6.6	27.6 ± 4.2 M 26.9 ± 4.2 F 28.1 ± 4.3
6.	52 (28/24)	80 (40/40)	M 63.1 ± 6.4 F 63.4 ± 5.3	M 62.8 ± 7.3 F 64.0 ± 5.3	H&Y 2.4 ± 0.8, UPDRS (total) 25.2 ± 13.1	5.9 ± 4.8	M 27.2 ± 3.9 F 25.3 ± 4.2	M 27.5 ± 2.0 F 25.4 ± 3.0
7.	104 (40/64); 18+F (2/16), 86 -F (38/48)	68 (30/38)	+F 73.9 ± 6.0 -F 70.7 ± 3.2	72.0 ± 3.1	H&Y +F 3.0 ± 0.5 H&Y -F 2.7 ± 0.6	+F 3.7 ± 3.5 -F 4.1 ± 3.5	+F 20 ± 3* -F 22 ± 4	23 ± 3
8.	26 (9/17)	26 (9/17)	74.0 ± 5.7	74.0 ± 4.5	UPDRS (motor) w-18.5 ± 10.3 w°14.0 ± 11.3	4.6 ± 3.9	24.7 ± 2.8 w- 24.3 ± 2.8 w° 25.9 ± 2.7	26.0 ± 3.6
9.	45(31/14)	78 (29/49)	72.9 ± 1.4[b]	72.8 ± 0.7[b]	H&Y 2.9 ± 0.2[b]	13.1 ± 0.8[b]	24.4 ± 0.6[b]	25.5 ± 0.5[b]
10.	45 (24/21)	45	65.6 ± 9.1	64.9 ± 9.1	66% H&Y 2.5 – 4, UPDRS (motor) 20.2 ± 9.8	10.6 ± 6.7	26.2 ± 3.7	27.3 ± 5.6

11.	22 (10/12)	88 (44/44)	67.3 ± 6.8 (57-79) M 67.4 ± 6.7 (58- 75) F 67.3 ± 7.2 (57-78)	M 67.1 ± 6.0 (57-79) F 66.4 ± 6.3 (58-77)	H&Y I (3), II (8), III (10), IV (1)	M 6.6 ± 5.6 F 6.7 ± 3.9	M 25.4 ± 2.0 (22.0-8.0) F 23.7 ± 4.9* (16.7-32.5)	M 25.8 ± 2.3 (21.0-29.6) F 26.1 ± 2.4 (20.8-30.0)
12.	318 (153/165)	318 (153/165)	66.9 (31-89) M 67.3 (34-89) F 67.5 (31-88)	67.4 (33-89) M 67.0 (37-89) F 67.8 (33-86)	–	5.9 (1-23) M 5.6 (1-19.7) F 6.3 (1-23)	26.0 (17.6-37.2) M 26.67 (18.4-37.1) F 25.3 (17.6-37.2)	26.3 (16.9-47.2) M 26.8 (20.6-40.8) F 25.78 (16.9-47.2)

PD Parkinson's disease; *M* male; *F* female; *BMI* Body Mass Index; *H&Y* Hoehn and Yahr stage; *-F* patients with no fracture; *+F* patients with fracture; w^- patients with weight loss; w^0 patients without weight loss.

* P<0.05 PD patients versus controls

** Differences between PD patients and controls were not tested in the original article

[a] Mean ± Standard deviation (range)

[b] Mean ± Standard error of the mean

compared to controls. Differences in BMI varied between -0.2 and -4. For the primary outcome, pooled data showed a significant difference of 1.73 in BMI between patients and controls (95% CI 1.11 – 2.35, P<0.001). Separate analysis of studies with their own control group again yielded a lower BMI for patients (1.0, 95%CI 0.37 – 1.63, P<0.01).

Longitudinal analyses

Two longitudinal studies on body weight in PD were included.[9-11] One study showed that after one year follow-up, body weight significantly decreased in patients (mean loss 1.8±SD 3.1 kilogram).[9] The other study examined changes in body weight before and up to on average 13 years after the clinical diagnosis in 49 patients. Body weight and BMI of patients were not changed in the pre-diagnostic phase, but significantly decreased after the diagnosis was made, with a mean change in BMI of 2.13 (with standard deviation 0.45).[11]

Determinants

Disease severity was reported in seven studies. The mean HY stage of individual studies covered only a small range, as the overwhelming majority of patients had HY stage 2, 2.5 or 3.[7,11,14-15,17-18,20] Pooled data showed that patients with HY stage 3 had a lower BMI than patients with HY stage 2 (3.9, 95% CI 0.1 – 7.7, P<0.05) (Figure 2). Disease duration was reported in ten studies. [6-8,10-11,14,17-20] There was no association between disease duration and BMI (0.02, 95% CI -0.44 – 0.48, n.s.).

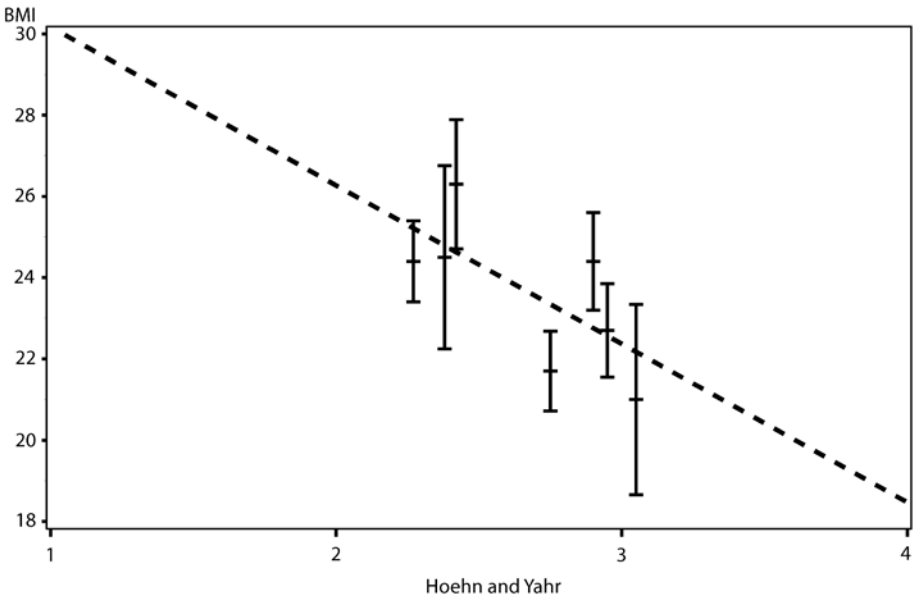

Figure 2 *Association between disease severity (Hoehn and Yahr stages) and Body Mass Index (BMI) (3.9, 95%CI 0.1 – 7.7, P < 0,05)*

Discussion

The main finding of this meta-analysis (which included 12 studies and a total of 871 patients) is that patients with PD have a lower BMI than controls. Only few potential determinants (disease duration and disease severity) were reported consistently enough to allow for further evaluation, and this analysis showed that a low body weight was more pronounced in patients with greater disease severity (HY stage 3 more than HY stage 2).

This is the first meta-analysis examining BMI in patients with PD. Several previous publications also suggested that patients have a lower body weight, but the results were inconsistent. By pooling the data of 12 studies, we now clearly show that patients have a lower BMI compared to healthy controls. One study [21] was excluded from the analysis because BMI in both patients and controls was unusually high, perhaps because of short stature in the test population, and this could have caused marked skewing of the data. However, this study was also consistent with the pattern seen in our meta-analysis, showing a lower BMI in patients compared to controls.[21] Converging evidence that body weight is reduced in PD also comes from studies that did not meet our inclusion criteria [22-25], e.g., those that did not specify how weight was measured or studies that merely relied upon self-report. Generally, these studies also found that BMI in PD patients was lower compared to controls. We found a pooled BMI reduction of -1.73 in PD patients, but the clinical relevance of this difference remains to be established. In the elderly, a reduction in BMI is generally associated with frailty, greater morbidity and higher mortality.[26-28] Whether this also applies to PD is currently unclear.

Our meta-analysis shows that BMI is on average lower in a PD population, but this does not imply that all individual patients are underweight. Clinicians should be aware that overweight may also occur in PD patients.[12] Additionally, it must be noted that a good BMI does not per se correspond with a good nutritional status. Even when weight is normal, patients may still be at risk for malnutrition.[29] Ideally, we would have liked to perform an additional analysis on the proportion of individual patients who are truly underweight. However, data were insufficiently reported to allow for such an analysis.

We also studied possible determinants of low BMI, but only few were reported sufficiently consistent to allow for a meta-analysis. Disease severity was reported in seven out of the 12 included studies. Pooled data showed that BMI decreased with greater disease severity (i.e. BMI was lower in HY stage 3 compared to HY stage 2), although the range of disease severity among patients included in this meta-analysis was fairly limited (most were between HY stages 2 and 3). Only one longitudinal study in our meta-analysis investigated this association, and showed that weight loss was more prominent and appeared to accelerate in advanced disease stages.[11] Weight changes have also been longitudinally examined in a large, prospective trial among 468 patients with PD.[30] This study showed that weight loss appears to be a

continuous process, that starts several years before the clinical diagnosis and persists thereafter. However, data on possible determinants of this weight loss were not assessed.[30] Other determinants than disease duration and disease severity were not consistently reported in the included studies. Ideally, we would have liked to assess the relative importance of well-known risk factors, such as dyskinesias[14], dysphagia[8] and hyposmia. Examining determinants that potentially contribute to weight loss could be a target for future research. In addition, causal relationships need further investigation. Disease progression is characterized by weight loss[31] and worsening of PD symptoms has been proposed as an independent predictor for this weight loss.[11] Alternatively, weight loss itself could be an important predictor of worsening of parkinsonism. Although the associations between pesticide exposures and the development of PD is still debated, increased plasma concentrations of organocholorine after weight loss have been suggested to contribute to worsening of symptoms.[32]

This meta-analysis was not without shortcomings. First, we have not assessed the quality of the individual studies included in our meta-analysis. A key source of potential bias in a meta-analysis is bias by limitations in the original studies, including the methodological quality of individual studies and the quality of reporting.[33] Currently, there is however no agreed 'gold standard' tool to evaluate the quality of observational epidemiological studies, which were included in our meta-analysis.[33] There is a need to agree on critical elements to assess quality and to develop appropriate evaluation tools[33], especially as different scales may reach different conclusions and influence the interpretation of meta-analytic studies.[34] Secondly, another potential limitation is the heterogeneity of patients and controls within the original studies. Nevertheless, despite this variety, the results of the individual studies consistently showed that BMI of PD patients was lower than BMI of controls.

What are the potential clinical implications of our findings? We would recommend to routinely record body weight and nutritional status as part of the management of PD. Previous research has shown that a substantial part of PD patients is at risk of malnutrition.[29,35] Hence, PD patients should be screened for under-nutrition and the Malnutrition Universal Screening Tool (MUST) may be considered as a useful early screening tool.[35] Dieticians might be considered as team member of the multidisciplinary Parkinson team, in order to monitor these patients and to provide nutritional interventions. In addition, much more work is needed to study the clinical implications of the observed weight differences. First, the clinical relevance of a low BMI in PD must be determined, and which magnitude of BMI reduction is associated with health risks. Second, it is necessary to examine possible predictors of weight changes and their relative importance. At present, there is no specific diet for patients with PD, and it is unknown whether dietary interventions (e.g. supplements, energy-dense products and protein redistribution) can influence the disease course and prognosis.[31,36] As a start, longitudinal studies now need to be performed to address these issues.

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CONSENSUS-BASED CLINICAL PRACTICE RECOMMENDATIONS FOR THE EXAMINATION AND MANAGEMENT OF FALLS IN PATIENTS WITH PARKINSON'S DISEASE

Based on

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Abstract

Falls in Parkinson's disease (PD) are common and frequently devastating. Falls prevention is an urgent priority, but there is no accepted program that specifically addresses the risk profile in PD. Therefore, we aimed to provide consensus-based clinical practice recommendations that systematically address potential fall risk factors in PD. We developed an overview of both generic (age-related) and PD-specific factors. For each factor, we specified: best method of ascertainment; disciplines that should be involved in assessment and treatment; and which interventions could be engaged. Using a web-based tool, we asked 27 clinically active professionals from multiple relevant disciplines to evaluate this overview. The revised version was subsequently reviewed by 12 experts. Risk factors and their associated interventions were included in the final set of recommendations when at least 66% of reviewing experts agreed. These recommendations included 31 risk factors. Nearly all required a multidisciplinary team approach, usually involving a neurologist and PD-nurse specialist. Finally, the expert panel proposed to first identify the specific fall type and to tailor screening and treatment accordingly. A routine evaluation of all risk factors remains reserved for high-risk patients without prior falls, or for patients with seemingly unexplained falls. In conclusion, this project produced a set of consensus-based clinical practice recommendations for the examination and management of falls in PD. These may be used in two ways: for pragmatic use in current clinical practice, pending further evidence; and as the active intervention in clinical trials, aiming to evaluate the effectiveness and cost-effectiveness of large scale implementation.

Introduction

Falls in patients with Parkinson's disease (PD) are common and often devastating. Prospective surveys have revealed high rates of falls that exceed those of the community-dwelling elderly. A meta-analysis concluded that the risk of sustaining a fall was considerably increased in moderately affected patients with PD as compared with healthy age-matched peers. Almost 50% of patients fell during a brief follow-up of only 3 months.[1]

Falls in PD are associated with a poor prognosis. Injuries are common, and patients with PD with hip fractures face high morbidity and mortality.[2] Minor injuries such as bruises or lacerations are even more common.[3] Moreover, the disease appears to become more severe and difficult to treat once falls are present, usually because of fall-related injuries and cognitive dysfunction, and overall survival of fallers is reduced.[4] Falls also commonly induce a fear of renewed falls,[3] which can lead to secondary immobilization and a reduction in general fitness, thereby increasing the risk of cardiovascular disease.[5] Lack of physical activity is also associated with constipation, pressure sores, insomnia and osteoporosis (which further increases fracture risk).[6] Immobility also deprives patients of their independence and social interactions. Not surprisingly, falls and mobility problems have been associated with poorer quality of life.[7-9] In addition, the economic burden of falls in PD is substantial, due to the relatively high cost of treatment of injuries and nursing home admissions.[10]

These potentially serious implications make the prevention of falls a high priority in the management of patients with PD. However, there is no accepted falls prevention program tailored specifically to the problems encountered in individual patients with PD. We therefore developed falls prevention recommendations specifically for PD, based on consensus among various health professionals and a smaller panel of experts on falls in PD. The starting point was based on the premise that falls in PD are typically multifactorial, resulting not only from various disease-specific mechanisms (e.g. freezing of gait),[11] but also from generic age-related risk factors.[12] Indeed, older patients with PD are not exempt from age-related processes or problems common to any geriatric population, such as complex co-morbidity or polypharmacy. Experience with the elderly suggests that optimal falls prevention requires a careful assessment of all potentially contributing risk factors, and this analysis should serve as a basis for subsequent interventions tailored to each of the identified risk factors.[12-14] We hypothesized that a similar multifaceted approach would be required for patients with PD. Here, we describe the development of the consensus-based clinical practice recommendations for the examination and reduction of falls, tailored to both generic and disease-specific risk factors in PD.

Methods

Development of concept recommendations

We first developed concept recommendations based on a literature search in PubMed using the following search terms: ((Parkinson's disease) OR (Parkinson disease)) AND risk factors AND ((accidental falls) OR (fall) OR (falling) AND ((fear of falling) OR (injuries) OR (fracture) OR (hip fracture) OR (fear of falling)) AND (fall prevention), supplemented with additional references by the panel members, generic guidelines,[15] PD-specific guidelines [16-17] and expert opinion. The resultant included 31 risk factors for falling, both generic (age-related) and PD-specific (Table 1). For each risk factor we outlined the following elements: background; method of ascertainment (i.e. how to verify the presence and severity of each risk factor); which disciplines should be involved in the assessment and treatment; the primarily responsible discipline; and suggestions for therapeutic interventions to reduce or eliminate the risk factor.

Multidisciplinary evaluation of the concept recommendations

The concept recommendations were presented via a web-based tool to a group of 27 professionals from multiple disciplines that were recruited from National Parkinson Foundation (NPF) centers (Figure 1).

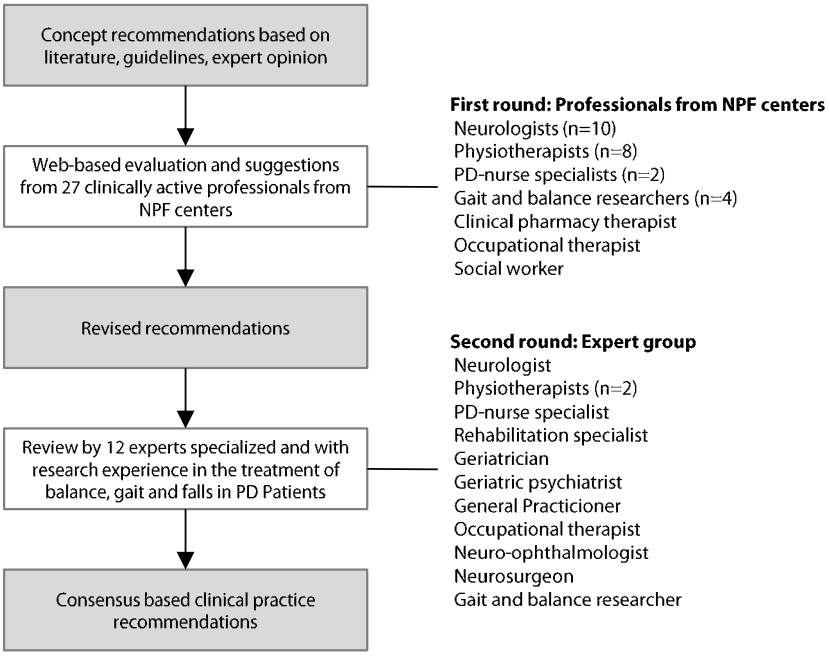

Figure 1 *Multidisciplinary evaluation of the falls prevention recommendations*

These professionals evaluated the recommendations, gave additional suggestions, and rated their level of expertise with each risk factor. If they rated their expertise as 'none' in any category, their scores were not considered. Subsequently, the revised recommendations were reviewed by 12 international experts from multiple relevant disciplines (Falls Task Force group; Figure 1). These experts were selected for their specialization and research experience in balance, gait and falls in PD. For each item, agreement between at least two-thirds of these experts was considered as consensus. Therapeutic interventions were scored on a 6-point scale, ranging from 0 (totally unimportant) to 5 (extremely important). Interventions with a mean evaluation score of >2 were included as final recommendations.

Implementation of the protocol in clinical practice

Two possible ways to implement the recommendations in clinical practice were offered to the panel of 12 experts. Option A was a 'One size fits all approach' where all patients should be reviewed for all risk factors, and be treated accordingly. This approach is comprehensive and ascertains that all risk factors will be addressed, but might lead to "over-care" in a subset of patients. Option B was the 'Fall type approach' where the first diagnostic step is to identify the specific fall type for each patient (e.g., falls that are always caused by freezing of gait, or falls that are consistently preceded by syncope). For those patients with a clear and identifiable fall pattern, the diagnostic and therapeutic approach could be limited to those specific risk factors and no unnecessary disciplines will be addressed. This provides a specialized approach, but carries the risk of under-treatment and missing of unidentified additional and possibly relevant risk factors. Each of the 12 experts of the Falls Task Force was given a choice between these two approaches, while underscoring the equipoise of the options.

Results

We identified 16 generic risk factors and 15 PD-specific risk factors (Table 1). All of these risk factors were recommended to be managed by a multidisciplinary team, except for visual impairment. Generic risk factors for falls in PD were recommended to be managed by the general practitioner, geriatrician, neurologist and PD nurse specialist. The neurologist, PD nurse specialist and physiotherapist were considered as the main disciplines to address PD-specific risk factors.[18-20] Caregivers were thought to have an important role in falls prevention, e.g. by assisting with implementing the recommended interventions. It is also necessary to consider the effect of falls on caregiver burden. The Falls Task Force unanimously preferred the 'Fall type approach' over the 'One size fits all approach'.

	Risk Factor	Background	Method of ascertainment	Who should be involved	Suggested intervention	Key references
Generic						
	Age	Fall risk increases with age	Interview patient; medical history taking	–	–	42
	Gender	Female gender is associated with an increased risk of falling		–	–	42
	(Sedative) medication	(Chronic) use of neuroleptics, antipsychotics, anticholinergics, antidepressants, anti-inflammatory drugs, sedatives and hypnotics, and benzodiazepines, in particular multiple benzodiazepines, increases risk of falls	Medical history taking Review of clinical notes	General practitioner[1] Neurologist Internist PD nurse specialist Geriatrician Rehabilitation specialist Clinical pharmacist**	Avoid interaction between medications with sedative effect Stop or minimize use of (multiple) benzodiazepines Lower dose as much as possible if stopping is impossible	5,42-44
	Polypharmacy	Use of ≥4 drugs, other than anti-Parkinson drugs, increases risk of falls	Medical history taking Review of clinical notes	General practitioner[1] Neurologist Internist PD nurse specialist Geriatrician Rehabilitation specialist Clinical pharmacist**	Reduce overall number of drugs Minimize drug interactions with negative outcome Consult geriatrician, general practitioner or internist	31,42,45-46
	Postural hypotension, orthostatic syncope, autonomic dysfunction	Orthostatic hypotension can lead to falls preceded by syncope	Medical history taking Record blood pressure in recumbent and standing position Tilt table testing if needed	General practitioner Neurologist[1] PD nurse specialist Geriatrician Clinical pharmacist**	Decrease hypotensive medication Increase dietary salt and fluid intake Raising the cranial end of the bed Frequent small meals Pressure stockings or abdominal band Anti-orthostatic maneuvers (if balance is good) Fludrocortisone* Midrodine* Decrease anti-Parkinson medication Domperidone* Physostigmine*	31,47-50
	Cardiac arrhythmia	Can lead to syncope and subsequent falls	Medical history taking ECG Holter ECG Provocative tests*	General practitioner[1] Geriatrician Cardiologist[1]	Tailored to specific cardiac pathology Refer to cardiologist	51

Arthrosis	Arthrosis may lead to inactivity of affected joints, which in turn predisposes patients to gait abnormalities and loss of bone mass, which commonly results in falls and fractures	Medical history taking Joint examination Muscle strength testing X-rays of affected joints	General practitioner[1] Neurologist Physiotherapist Rehabilitation specialist	Exercise therapy within limits set by joint capabilities Advise about load and load-bearing capacity Advise about orthopedic aids (when needed) Analgesic medication Cryotherapy (only for the knee; if necessary for shoulder**) Consult orthopedic surgeon or rheumatologist	16,52
Use of an assistive device	Proper use can reduce falls Incorrect use can worsen gait and increase risk of falling	Gait examination while using various different assistive devices	Physiotherapist[1] PD nurse specialist	Stimulation use of assistive device Train safe and adequate use of assistive device	53
Anxiety	Fear of renewed falls common, even after single falls Even more common in PD	Medical history taking FES-I questionnaire ABC-6 scale	General practitioner Neurologist PD nurse specialist[1] Physiotherapist Geriatrician Rehabilitation specialist Clinical pharmacist**	Balance confidence training Cognitive behavioral therapy Training program aimed at improvement of mobility Promote active lifestyle Prescribe anxiolytics*(note: possibly increased risk of falling as side-effect)	16,24,54-61
Weakness due to inactivity	Is associated with decreased functional independence, loss of mobility and increased risk for falls and injuries	Neurological examination	Neurologist Physiotherapist[1] General practitioner PD nurse specialist Geriatrician Rehabilitation specialist	Promote active lifestyle (including aerobic conditioning, strength and flexibility exercises) Muscle strengthening	16,62-66
Visual and ocular motor impairment	Several components of the visual and ocular motor system are compromised, e.g. impaired saccadic eye movements,; bradykinesia of the extraocular muscles; dopamine depletion of the retinal amacrine cells; diplopia; contrast sensitivity; blepharospasm.	Examination of vision and ocular motor control	Ophthalmologist[1] Neurologist	Refer to ophthalmologist Train use of auditory and tactile cueing techniques	31,42,67
Daily use of alcohol	Increased risk of falls with one or more alcoholic drinks on a daily basis	Medical history taking	General practitioner[1] Neurologist Internist PD nurse specialist Geriatrician Clinical pharmacist**	Education and advise	48

	Risk Factor	Background	Method of ascertainment	Who should be involved	Suggested intervention	Key references
	Environmental hazards	At home and in the community; examples include inadequate lighting, throw rugs, slippery floors, electrical or extension cords, uneven sidewalks, broken curbs, pets and footwear	Medical history taking Home visit by occupational therapist	Occupational therapist[1] PD nurse specialist Physiotherapist	Home visit with follow-up to monitor adherence	68-71
	Other co-morbidities**	High prevalence of common conditions in the elderly, e.g., vertigo, peripheral neuropathy, diabetes	Medical history taking Review of clinical notes	General practitioner Neurologist Clinical pharmacist**	Neurological examination (including full sensory examination) Treatment as appropriate (note possible drugs interactions)	23,42,72
	Depression**	Depression associated with increased risk of falls, but could also be caused in part by use of antidepressants	Screen for depression (e.g., HADS, BDI) Medical history taking	General practitioner Neurologist Neuropsychiatrist Clinical pharmacist**	Treatment of depression (note: possible increased risk of falling as side-effect of antidepressants)	42,44,73-74
	Osteoporosis**†	Increases risk of fractures	History of prior fractures Screen for risk factors for osteoporosis Examine spine (pain, shape) Measure bone density	General practitioner Geriatrician Clinical pharmacist**	Anti-osteoporotic treatment Promote physical activity and exercise	6
PD-specific						
	Fall history	Previous fall(s) predict falling	Medical history taking	General practitioner[1] Neurologist Physiotherapist	-	1,31,66,75
	Disease severity	Greater disease severity is associated with increased fall risk	Examination (UPDRS, H&Y)	Neurologist	-	31,59,75-80
	PD medication	Higher total doses of levodopa Use of dopamine agonists Anticholinergics	Medical history taking	General practitioner Neurologist[1] Clinical pharmacist**	Adjust dopaminergic medication; this could be a dose increase when falls are related to OFF events, but often also involves a dose reduction (e.g. when falls are related to violent dyskinesias, orthostatic hypotension, or delirium) Reduce anticholinergics	31,76

	Slow mobility	Decreased mobility is associated with an increased fall risk	Examine walking speed (e.g., TUG, 6 minute walking distance)	Physiotherapist[1] Neurologist Clinical pharmacist**	Increase dopaminergic medication Cueing strategies Strength training**	31,66,77,81-84
	Shuffling and small scaled gait	Increased risk of stumbling due to reduced step height	Medical history taking Gait examination, e.g. TUG, Tinetti mobility index Examine feet and footwear**	Neurologist PD nurse specialist Physiotherapist[1] Clinical pharmacist**	Increase dopaminergic medication Gait training by physiotherapist, including cueing techniques Assistive devices Training of muscle strength and trunk mobility	16,46,68-69
	Freezing of gait and festination	One of the most common causes of falls in parkinsonism	Detailed FOG questionnaires Specific tasks that typically elicit FOG episodes, in particular rapid 360 deg axial turning	Neurologist[1] PD nurse specialist Physiotherapist Geriatrician Clinical pharmacist**	Optimize dopaminergic medication: decrease dose for ON phase freezing, increase dose or add MAO inhibitor for OFF phase freezing Gait training using cues or cognitive movement strategies according to guideline Occupational therapy in home setting according to guideline; this includes optimizing the home environment (e.g. good lighting, creating larger spaces for turning)	16-17,31,47,77,85-88
	Posture	Stooped posture protects against backwards fall, but may worsen festination and forward falls	Neurological examination	Neurologist PD nurse specialist Physiotherapist[1] Geriatrician Rehabilitation specialist Clinical pharmacist**	Increase dopaminergic medication Physiotherapy according to evidence-based guideline Balance training Consider botulinum toxin injection if caused by trunk dystonia	16,27,31,89-90

	Risk Factor	Background	Method of ascertainment	Who should be involved	Suggested intervention	Key references
	Postural instability	Balance impairment	Examination of balance: pull test, push & release test, rising from a chair and sitting down, single leg stance, transfers Rating scales: Tinetti mobility index, Berg Balance Scale Examination during dual tasking** Vestibular evaluation**	Neurologist[1] PD nurse specialist Physiotherapist Clinical pharmacist**	Increase dopaminergic medication Adjustment of DBS parameters if needed Balance training (for example Tai Chi**) Muscle strengthening Home-based strategies** Train dealing with complex situation: dual tasking, centre of mass shift, turning strategies**	5,16,31,61,75,91-93
	Transfers	Falls during transfers, such as rising from a chair or bed	Examination of transfers, e.g. rising from a chair, getting in and out of bed Test for orthostatic hypotension	Neurologist PD nurse specialist Physiotherapist[1] Occupational therapist Clinical pharmacist**	In case of normal orthostatic situation: Transfer training using cues or cognitive movement strategies Adjust dopaminergic medication (see comments under PD medication above) In case of orthostatic hypotension: See above for generic measures. If needed: decrease dopaminergic medication	16,47,50-51
	Cognitive impairment	Frontal executive dysfunction associated with falls and freezing of gait	Medical history taking, including interview with caregiver Examination (MoCA, MMSE, FAB) Walking while talking**	Neurologist[1] PD nurse specialist Geriatrician Clinical pharmacist**	Avoid anticholinergics Reduce sedative medication Minimize hazardous behavior, including training or avoidance of multitasking In case of reckless behavior: supervised gait and transfers Cholinesterase inhibitors* Refer to neuropsychologist	31,94-98
	Axial rigidity	Reduces the ability to absorb impact of externally imposed perturbations	Neurological examination	Neurologist[1] PD nurse specialist Physiotherapist Geriatrician Clinical pharmacist**	Increase dopaminergic medication Flexibility exercises	99

	Dyskinesias	Balance impairment and large sways in centre of gravity caused by violent dyskinesias	Medical history taking Diary Neurological examination	Neurologist[1] PD nurse specialist Clinical pharmacist**	Optimize dopaminergic medication Amantadine* Consider continuous dopaminergic stimulation (DBS*, apomorphine** or intraduodenal levodopa) Education on safety strategies	47
	Long-term adverse effects of DBS of the subthalamic nuclei and GPi	Worsening of balance or gait (including freezing) as short-term postoperative effect, and as a delayed effect. Postoperative cognitive decline and impulsivity**	Medical history taking Detailed gait and balance examination	Neurologist[1] Neurosurgeon Physiotherapist Clinical pharmacist**	Consult neurologist or neurosurgeon: adjust stimulator settings Consult neurologist: adjust dopaminergic medication Refer to physiotherapist Refer to occupational therapist*	100-104
	Dual tasking**	Associated with falls, either as direct cause of falls or as marker of underlying vulnerability	Examine motor and cognitive dual tasking	Neurologist Physiotherapist Occupational therapist	Train use of dual tasks, or teach how to avoid dual tasks Cognitive movement strategies	16
	Urinary incontinence**	Nocturia associated with nighttime falls; also marker of frontal lobe dysfunction	Medical history taking	Urologist General practitioner Clinical pharmacist**	Pelvic floor muscle training for urge incontinence Reduce fluid intake in the evenings, in particular coffee and alcohol Bladder spasmolytics Desmopressin a.n. Optimize dopaminergic medication to reduce nighttime off periods Optimal lighting on Refer to urologist, treat underlying cause	105-106

ABC-6 scale Activities-specific Balance Confidence scale 6; *BDI* Beck Depression Inventory; *DBS* Deep Brain Stimulation; *ECG* Electro Cardio Gram; *FAB* Frontal Assessment Battery; *FES-I* Falls Efficacy Scale International; *FOG* Freezing of gait; *HADS* Hospital Anxiety and Depression Scale; *H&Y* Hoehn and Yahr; *MMSE* Mini Mental State Examination; *MoCA* Montreal Cognitive Assessment; *PD* Parkinson's disease; *TUG* Timed Up and Go test; *UPDRS* Unified Parkinson's Disease Rating Scale.
1 Primarily responsible discipline
*Recommendation based on consensus by four or less experts
**Additional to protocol as suggested by experts
† Included as a risk factor for fractures, not as a risk factor for falls.

Discussion

Our project yielded a comprehensive set of recommendations for the examination and possible reduction of falls for patients with PD, tailored to a combination of generic risk factors for older adults and PD-specific risk factors. These recommendations were based on a literature review plus consensus among both clinically active professionals (round 1) and an international expert panel (round 2), involving all relevant disciplines (medical, allied health and nursing). It should be seen as a clinical practice protocol based on expert opinion that supplements the existing formal guidelines. The recommendations offered here can be used to guide management decisions in current clinical practice. Furthermore, these recommendations can serve as active treatment in future intervention studies to determine the cost-effectiveness and feasibility of this approach. Finally, the present set of recommendations may serve to counter the common belief among older adults that falls cannot be prevented.[21] We will now discuss our findings, and briefly address several issues related to practical implementation of the current set of recommendations created to clinical practice.

Falls prevention is an important element of quality of care for elderly in general, as well as in PD management.[22-23] Recently, the American Academy of Neurology provided a core set of quality measures to guide treatment of PD. One of these quality measures includes the recommendation to query falls as part of diagnosis review and other regular visits.[22] The falls prevention recommendations included 31 risk factors, which underscores the complexity of falling problems in PD. Each risk factor alone can increase the risk of falls, but the fall risk markedly increases when multiple risk factors are present in a single individual.[15] For example, in older populations, the relative risk of falling increases from 8% when no risk factors are present, to 78% with four or more risk factors.[24] The complexity of falling problems in PD underscore the need for a multidisciplinary team approach, with a combined involvement of medical disciplines, allied health personnel and specialized nurses, each with specific roles. It was recommended that falls prevention programs in older adults utilize a multidisciplinary team approach.[25] A similar multidisciplinary team approach is widely felt to be optimal for patients with PD as well,[26] but to date there is no good evidence to support this recommendation, and further work remains necessary to demonstrate the merits of a multifaceted approach. Also, more research is needed on the effectiveness of the isolated elements to establish what specific part of the intervention package is effective. For instance, cueing strategies may have an indirect effect on falls via known influences on gait and mobility[27-29], but this is merely based on theory than direct evidence. Also, a recent Cochrane Review concluded that physiotherapy interventions had no effect on falls.[30] Additionally, although we included 31 potential factors, we concede that there may be other yet to be identified factors.

We concentrated on risk factors that were potentially modifiable. The best predictor of falls in PD is the presence of prior falls, but this is a risk factor that can no longer be reversed. A possibly modifiable marker of future falls is fear of falling,[1] although there are currently no established methods to reduce fear of falling in PD. In contrast, specific treatments are available for other risk factors. We will illustrate this for freezing of gait, which is increasingly recognized as an important cause of falls in PD.[11,31] Freezing of gait can be treated using adjustments in pharmacotherapy (usually an increase in dopaminergic medication),[10] delivery of individually tailored cueing strategies, according to evidence-based guidelines, and use of therapy and assistive devices.[27]

What group should receive the falls prevention recommendations? Pending further evidence, the Falls Task Force recommended a time-efficient strategy adjusted to specific individual risk profiles for those patients who report prior falls. For example, an important step in prior fallers is to ascertain whether or not falls were preceded by transient loss of consciousness.[32] A consistent pattern of falls caused by orthostatic syncope could obviate the need for a detailed assessment of all 31 risk factors. This strategy is defendable in terms of its short-term efficiency, and perhaps also optimizes compliance because interventions are linked to actually perceived problems. However, further work remains to determine the long-term outcome, as more falls may be prevented when all patients are consistently screened (and treated) for all risk factors. This certainly applies to patients without a clear fall pattern, who should be screened according to the entire protocol. It is important to note that even patients reporting no falls in the previous year should be eligible to receive the complete protocol, because the risk of falling is substantial in this population.[1] This suggestion also applies to older patients, and those with complex co-morbidity or polypharmacy. It is not possible to pinpoint patients with PD with a particular disease severity as being most likely to sustain falls, although fall risks appear highest in the 'intermediate' disease stages (Hoehn and Yahr stage 2.5 and 3) when patients develop gait disability and postural instability, but remain sufficiently active to be at risk of falling.[1,5]

Another issue is how frequently the protocol should be reviewed. PD is a progressive disease, and new risk factors will inevitably emerge over time. An annual review may be reasonable, though feasibility may be difficult as may be agreement on the viability of potential new factors.

We believe that optimal fall prevention also involves caregivers, although they are not specifically mentioned in the protocol. Caregivers can play a key role, e.g. by assisting patients in adopting recommendations and optimizing adherence to the falls prevention program. This could be important particularly for patients with cognitive decline. For example, caregivers can assist cognitively impaired patients in using external cues or applying cognitive move-

ment strategies.[33] In the elderly, a multifactorial falls prevention program with a patient-caregiver dyad was successful in a subgroup of patients with lower MMSE scores (27 or less), and living with a partner seemed to mediate this positive finding.[34] Additionally, it is necessary to consider the effect of falls on caregiver burden.[35]

This falls prevention protocol should serve to counter the common belief among older adults that falls cannot be prevented.[21] In older populations, active participation of patients and their caregivers is essential, but this recommendation is extra challenging for complex, multifactorial interventions as proposed here.[36] Implementation of fall prevention strategies should therefore be embedded within a positive approach, including emphasis on a positive self-identity (e.g., increased independence, better confidence, more active role)[21] and a focus on health and independence, rather than falls.[37] In addition, theories of health behavior, like the health belief model or self-efficacy theories, could be used. Recommendations are best tailored to the individual lifestyle, and patients should have an active role in implementing the fall prevention program.[21] Follow-up is also needed to ascertain that patients actually adhere to the recommendations.

A word of caution regarding the development process is necessary. We selected two sequential panels to offer feedback on a concept procedure of recommendations that was drafted based upon an extensive literature review. Participation in either of the two panels was by invitation and this could have introduced a bias. However, it should be pointed out that we succeeded in generating two multidisciplinary panels with representatives of all relevant disciplines, although some professionals were more heavily represented than others. The two panels were complementary, the first being pragmatically oriented, the second being driven by experts with state-of-the-art knowledge. The literature search was comprehensive and included generic and PD-specific guidelines. [15-17,23,38-41] We acknowledge that the division into generic versus disease-specific risk factors was to some extent arbitrary for some of these factors, as these commonly occur in both PD and with ageing (an example is cognitive impairment). Indeed, our sole motivation for making this distinction was to ascertain that the set of recommendations would be comprehensive, and that generic factors would not be overseen in this population with its own specific risk factors. As such, our recommendations underscore just how many different risk factors can be involved, and how complex it is to prevent falls in patients with PD.

Although not infallible, we believe that the present fall prevention recommendations are an adequate reflection of the current evidence and expert opinion in the field. We acknowledge that these recommendations are based largely on expert opinion and smaller research studies (partially done in elderly populations without PD), and that it is not yet based on large randomized controlled trials in PD, fueling the need for further research. The recommendations

can be considered for use in current clinical practice in three different ways: as a 'one size fits all' strategy to postpone or perhaps even prevent the very first fall in prior non-fallers; as a 'one size fits all' strategy to diminish the risk of further falls in patients with unclear fall patterns; and as a dedicated falls prevention strategy in patients with a consistent and specific fall pattern. Further research is now needed to test the effectiveness of the individual components and also the cost-effectiveness and feasibility of this falls strategy approach.

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EVALUATION OF THE 'FALLS TELEPHONE': AN AUTOMATED SYSTEM FOR ENDURING ASSESSMENT OF FALLS

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Abstract

Objectives To evaluate the reliability and user experiences of an automated telephone system to monitor falls during a prolonged period of time.

Design Prospective cohort study.

Setting Four neurological outpatient clinics in The Netherlands.

Participants We included 119 community-dwelling, non-demented patients with Parkinson's disease, because falls are common in this population.

Measurements We obtained clinical and demographic data. The Falls Telephone is a computerized telephone system, through which subjects can enter the number of falls during a previous period. During a follow-up period of one to forty weekly calls, 2465 calls were made. In total, 173 "no-fall" entries and 115 "fall" entries were verified by personal telephone interviews. User experiences were evaluated in 90 of the 119 participating patients, using structured telephone interviews.

Results All "no-fall" entries and 78% of "fall" entries were confirmed to be correct. Sensitivity to detect falls was 100% and specificity was 87%. Users regarded the Falls Telephone as a convenient tool to monitor falls.

Conclusion The Falls Telephone is a convenient and reliable instrument to monitor falls. The automated system has a high specificity, obviating the need for time-consuming personal follow-up calls in the majority of non-fallers. As such, the Falls Telephone lends itself well for data collection in large trials with prolonged follow-up in patients with Parkinson's disease.

Introduction

Falls are common in the elderly. The morbidity of falls is considerable because of fall-related injuries and loss of independence. Moreover, mortality rates are increased among fallers.[1] There is a pressing need for development of tools that can reliably detect falls over long periods, for example to evaluate the effect of fall prevention strategies.[2] Frequently used outcomes include the number of fallers and fall rates.[3] There are several approaches to obtain these data, e.g. via personal or telephone interviews, questionnaires, or diaries. However, these methods are resource-intensive, especially within large and long-lasting trials. To address this, we have developed an automated system to monitor falls by telephone. This "Falls Telephone" is comparable with automated telephone systems used previously for other purposes, e.g. for management of diabetes care[4-5], health promotion[6] or as a reminder for medication intake.[7] The Falls Telephone automatically makes periodic phone calls at an investigator-defined interval, allowing participants to enter the number of falls experienced in the preceding period.

Here, we describe our first evaluation of the Falls Telephone. We piloted the system in patients with Parkinson's disease (PD) because of their high fall rates.[8] A meta-analysis showed that, even during a brief follow-up of three months, 46% of PD patients fell at least once.[9] These fall rates make people with PD a good test population, with a substantial proportion of both fallers and non-fallers, allowing for tests of specificity and sensitivity.

Methods

Participants

Patients were part of a trial on the cost-effectiveness of multidisciplinary care for PD patients (ClinicalTrials.gov identifier NCT00518791). Main inclusion criteria were idiopathic PD, Hoehn and Yahr stage[10] ≤4, Mini-Mental State Examination[11] ≥24 and living independently in the community. We included 119 non-demented PD patients (77 men, 65%; mean age 67.6 years (range 43.4 – 81.1); mean disease duration 6.3 years (range 0.8 – 21); mean Unified Parkinson's Disease Rating Scale motor score (Part III)[12] of 23.6 (SD 10.6).

Falls Telephone

The Falls Telephone is a computerized system that automatically contacts patients by telephone using pre-recorded messages. The system was developed by a software company specialized in communication (ASK Community Systems, Rotterdam, The Netherlands).

First, the system has to be activated via a website. After logging on, name and telephone number of the patient are entered as well as the day of the week on which the Falls Telephone starts calling. Then, the Falls Telephone automatically calls at the pre-specified day and time. Patients are asked to start the procedure and confirm that they are the requested person by dialing '1'. Every call then starts with a brief explanatory introduction. Patients then need to

enter the number of falls via the touch-tone keypad. They are asked to enter this number twice as a verification step. When the entry is correct, the system calls again at the next scheduled day and time. Otherwise, the system will call again on the same day or on the subsequent day, until the telephone call has been completed successfully. The outline of the telephone call is shown in Table 1. The frequency of the calls is adjustable, according to the needs of the investigator. Other parameters which can be tailored include the day and time of calling, as well as the frequency of a repeated call on a single day (in case of no response).The software company provides the automated telephone calls. The system requires that the patient has a telephone device with dual-tone multi-frequency (DTMF) signals. Both home telephones (analogue telephony, ISDN and VOIP) and cell phones can be used. Entered data are automatically stored within a MySQL database, which is accessible through the internet using a standard web browser. After logging on, data can easily be exported by the researcher on any computer at any time.

Table 1 The digitally recorded introduction and instructions that were asked by the Falls Telephone during weekly telephone calls (translated from Dutch).

Start	Good day. You're being called because a healthcare professional requires information from you. Please press 1 to continue. "1"→Introduction "Other number" → Replay message (maximum 3 times, otherwise disconnect) "No number" → Disconnected
Introduction	You are called by the Falls Telephone of the IMPACT study from the Radboud University Nijmegen Medical Centre in cooperation with your own hospital. You are a participant of this study and therefore we would like to ask you a question. Please indicate how many times you have fallen in the past week. To overcome mistakes, you are asked to indicate the number of falls twice. You can now dial the number of falls in the previous week. "Number dialed"' → Verification "No number dialed" → Introduction
Verification	Please dial the number of falls in the past week once more. "Same number dialed" → Closure "Different number dialed"→ (maximum 3 times, otherwise disconnect) The entered number differs from your previous entry, please try again. You can now dial the number of falls in the previous week. "Number dialed" → Verification "No number dialed" → Introduction
Disconnected	You were called by request of a healthcare professional. We could not reach you and will try again at a later time. Disconnected; patient will be called again.
Closure	Thank you for your participation. The telephone connection will now be disconnected.

For this study, the Falls Telephone called weekly on workdays, between 11 a.m. and 8 p.m. with time intervals of three hours, until the telephone call had been completed successfully. Patients were asked to enter the number of falls sustained in the preceding week. At the outset of the study, all patients received a letter with instructions about the Falls Telephone, as well a definition of a fall. A fall was defined as "an unexpected event in which the participants come to rest on the ground, floor, or lower level".[2] In addition, the procedure was explained in person by a research-assistant.

Evaluation

All 119 patients used the Falls Telephone for a given period (varying per patient from one to forty weeks). Entries were verified through personal telephone interviews, within two weeks after the week in which the entry was made. During these interviews, patients were asked to confirm the entry and to confirm whether the reported number of falls represented their actual number of falls in the previous week.

Personal telephone interviews took place at several time points. First, all 119 patients were contacted when they had been using the Falls Telephone for several weeks. We then evaluated if the system was working properly (e.g. no technical problems) and verified their latest entry. Second, 90 patients were interviewed for user experiences with the system (see below). During these interviews we also evaluated their entries in the preceding week. Third, all "fall" entries were, whenever possible, evaluated by personal telephone interviews. This approach yielded a total of 288 entries that were verified, including 173 "no-fall" entries given by 109 patients, and 115 "fall" entries given by 46 patients. Hence, some patients were interviewed to confirm a "no-fall" entry as well as a "fall" entry.

To evaluate user experiences, a sample of 90 patients was randomly selected from our study population and interviewed by telephone. These interviews included questions on clarity of the instructions and the feasibility of the system. Patients were also asked for any encountered problems, suggestions for possible improvements, and their overall satisfaction on a 10 point-scale (1: very poor; 10: excellent). We also discussed several alternative ascertainment methods, such as a falls calendar, fortnightly postcards and a falls hotline (i.e. patients call the hotline themselves when a fall has occurred), in light of their current experience with the Falls Telephone. For each of the different ascertainment methods, patients were asked if they were willing to use that particular system to monitor their falls for prolonged periods of time.

Costs

We estimated the expenses needed to weekly monitor falls using (1) the Falls Telephone, (2) fall diaries and (3) personal telephone interviews. Personnel costs were based on an hourly salary of $27, and on the following amounts of time needed: Falls Telephone, 10 minutes once-only to activate the system for each patient and to export individual data at the end of the study, 10 minutes to verify each "fall" entry and 10 minutes weekly to export data from

all patients; Diaries, 20 minutes per diary to send, check for response, telephone follow-ups when diaries are not returned and entering the data in the database; Interviews, 25 minutes per week per patient for the interview, repeated attempts to contact patients and data entry. Operational costs were based on the following estimations. Falls Telephone: $5360 to set up the system and $51 per patient per year, including telephone costs for weekly calls. Fall diaries: $1.17 per fall diary.

Statistical analysis

Descriptive statistics were used for patient characteristics. Means were calculated for continuous variables and percentages were used for categorical variables. In order to take into account that some telephone calls were made by the same patients, a random effects model was used to estimate sensitivity and specificity, with patient as random factor.

Ethical Considerations

The trial from which patients were selected was approved by the Medical Ethical Committee. Use of the Falls Telephone was an integral part of this trial. All patients gave informed consent for participation.

Results

A total of 2465 telephone calls were completed successfully. On 2332 occasions patients indicated that they had not fallen in the preceding week. Fall incidents were reported during 133 calls by 49 patients (41.2%). These calls concerned 105 "single fall events", 11 times "two falls events" and 17 times "three or more falls", with a maximum number of 12 falls in the preceding week. The mean number of successfully completed telephone calls was 20.7 per patient (range 1 – 40).

Reliability

All "no-fall" entries (n=173) were confirmed as non-falls. Among the "fall" entries, 115 were verified and 90 (78%) were confirmed as actual falls. An overview of the fall and no-fall entries and the verification data is shown in Figure 1. Explanations for misclassification (n=25) were dialing the incorrect number (n=12) and scoring a 'near fall' as an actual fall (n=2). Incorrect entry was not confirmed in nine cases, as patients said they had dialed a different number than the number stored in the database. Data entry was not remembered in two cases.

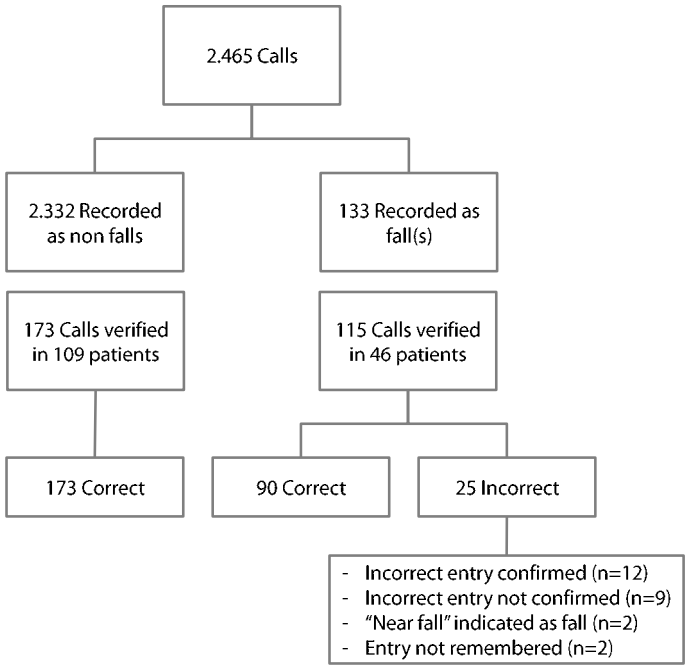

Figure 1 *Overview of total number of calls made by the Falls Telephone, indicated falls and non-falls and the reliability of the verified data.*

Frequent falls (more than one fall per week, verified in 25 calls) had been entered reliably in 24 calls. In one case the reported value was underestimated (three falls had been entered, instead of the actual five fall incidents). The other incorrect "fall" entries (n=24) were all single fall events. The comparison of fall data obtained via the Falls Telephone and personal telephone interviews is presented in Table 2. The sensitivity of the Falls Telephone to detect a fall was 100% (CI 96% - 100%), and the specificity was 87% (CI 82% - 92%).

Table 2 Comparison of fall data obtained using the Falls Telephone and personal telephone interviews

Falls Telephone	Personal telephone interviews		
	Fall	No-fall	Total
Recorded as fall	90	25	115
Recorded as no-fall	0	173	173
Total	90	198	288

User experiences

The clarity of the instructions was rated positively by almost all patients (99%, n=89). The majority of patients (94%, n=85) did not experience the weekly calls as a burden. The Falls Telephone was perceived as an attractive system to record falls by 96% (n=86) of the patients. The use of alternative methods was less often scored as an attractive system: a fall calendar by 50% (n=45), postcards by 31% (n=28) and a falls "hotline" by 30% (n=27). Overall, patients were pleased with the Falls Telephone and the mean overall rating was 8.3 (range 6-10). Issues raised were that the Falls Telephone could not be used due to technical restrictions of the phone (n=2) and the system did not ring long enough for patients to answer the telephone on time (n=1). Four patients experienced problems while using the Falls Telephone, two of them mainly when they started using the system. One patient did not trust the system and therefore did not answer the telephone calls. The following improvements were suggested (all mentioned once): dialing the number of falls just once (instead of twice), shorten the introduction, exclude holidays and Sundays, call monthly instead of weekly, allow more time to dial the number, and to use a telephone hotline in the beginning of the disease (because falls are very rare in this stage), with a switch to the Falls Telephone in later disease stages when falling becomes more prevalent. One patient indicated that the voice could be more cheerful.

Costs

Costs were estimated for a fictive trial with 50 participants and one-year follow-up. Based on approximately 5% of the Falls Telephone entries as "fall" entry (which needs to be verified by telephone), this would amount to the following costs estimations, for various methods. Falls Telephone: $8,954 (operational costs $7,910, personnel costs $1,044), fall diaries: $26,442 (operational costs $3,042, personnel costs $23,400) and personal telephone interviews: $29,250 (personnel costs).

Discussion

Several methods are available to monitor falls, both prospectively and retrospectively.[3] Comparisons between calendars, postcards, interviews or questionnaires show varying percentages of sensitivity (31%-97%) and specificity (91%-99%).[13-14] However, comparisons of these sensitivity and specificity levels across techniques is difficult because of methodological differences (e.g. duration of the recall intervals over which falls were assessed). Prospective data collection has been recommended to avoid recall bias[2], but the optimal way to monitor falls remains unknown.[13] Our Falls Telephone is sensitive (100%), but less specific (87%). The great strength of the Falls Telephone is that persons can reliably indicate when they have not fallen, so this obviates the need for a time-consuming and labor-intensive personal follow-up in the large majority of non-fallers. Conversely, patients who indicate having fallen need to

be called by the researcher to verify if the reported fall represents an actual fall event. For the current study, this implied that a relatively small proportion of all telephone calls (133 out of 2465 calls) needed to be verified to reliably estimate fall rates. In addition, this verification call can be used to obtain more details about the fall events, such as specific circumstances or the consequences of the fall.

The Falls Telephone is likely to save costs. Estimations based on a fictive trial (involving 50 patients with weekly fall monitoring and one year follow-up) showed that the Falls Telephone will save about $17,500 compared to falls diaries, and even more when compared to personal interviews. Once the application has been installed, the system automatically runs at relatively low costs. Personnel expenses are much less for the Falls Telephone because most patients (i.e. those who have not fallen) do not have to be called. The cost savings in favor of the Falls Telephone will become increasingly larger with more participants, or with prolonged follow-up.

Our study demonstrates a good agreement between the automated Falls Telephone and a structured interview. We acknowledge that a structured interview (regarded in this study as the gold standard) is not infallible, as patients may have forgotten some of their falls by the time of the personal interview. However, simultaneously using alternative monitoring tools such as calendars or fall cards was not possible because this could have resulted in response enhancement for both methods.

The system scored high on patient satisfaction. Most patients regarded the Falls Telephone as an attractive system to monitor falls for prolonged periods of time. Alternative methods, such as calendars, postcards or a falls hotline, were found to be less appealing. Only a few patients were disturbed by the use of the Falls Telephone, while the majority of patients were not burdened by the weekly calls. Although most telephone devices meet the requirements of the Falls Telephone system, some patients may experience problems due to technical restrictions of their phone. For those patients who are unable or unwilling to use the Falls Telephone, alternative methods can be used to collect falls data.
Another technical restriction was the fact that the Falls Telephone did not provide information about unsuccessful calls for the investigators. In a new release of the Falls Telephone, the call history information will be made visible for a regular user of the system.

Another future improvement of the Falls Telephone is to include a reminder of the fall definition. When patients started using the Falls Telephone, they received a letter with instructions (how to use the system, and a definition of falls). In the present study, subjects were not reminded of this fall definition during the automated telephone calls. Providing a reminder of this definition in the pre-recorded message can simply be implemented by adding just a

single sentence. One advantage is that fewer patients will mistake a 'near fall' as a fall incident. If desired by the investigators, a definition of near falls can also be added, so these can be recorded as well. Such reminders would be particularly helpful in trials with a long follow-up. Additionally, future studies should evaluate whether automated calls must be made weekly, or whether less frequent calls would be sufficient to obtain a reliable estimate of falls.

We evaluated the Falls Telephone in a group of PD patients, because of their high fall rates.[9] We suspect that the Falls Telephone also holds promise for other populations with a high risk of falling, but this needs to be demonstrated in future work. A particular challenge will be to test this new approach in patients with cognitive impairment: they have a clearly increased risk of falling[15], but may have more difficulty remembering the instructions and recalling their number of falls. On the other hand, all other methods of ascertainment are also threatened by cognitive decline in the study population, and the Falls Telephone may represent a good alternative for spouses or other carers, allowing them to enter the fall rates. Our present study population only included non-demented patients with PD, so additional studies need to address the feasibility and reliability of the Falls Telephone in elderly populations with varying degrees of cognitive impairment.

Conclusion

The Falls Telephone is a convenient instrument to monitor falls, not only for patients but also for researchers. Combined with personal interviews to verify the accuracy and details of reported falls, the system is a useful and reliable tool to collect fall rates, especially in large and long-lasting trials.

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MULTIDISCIPLINARY CARE FOR PATIENTS WITH PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder with a complex phenotype, featuring a wide variety of both motor and non-motor symptoms. Current medical management is usually monodisciplinary, with an emphasis on drug treatment, sometimes supplemented with deep brain surgery. Despite optimal medical management, most patients become progressively disabled. Allied health care may provide complementary benefits to PD patients, even for symptoms that are resistant to pharmacotherapy or surgery. This notion is increasingly supported by scientific evidence. In addition, the role of allied health care is now documented in recent clinical practice guidelines that are available for physiotherapy, occupational therapy and speech-language therapy. Unfortunately, adequate delivery of allied health care is threatened by the insufficient expertise among most therapists, and the generally low patient volumes for each individual therapist. Moreover, most allied health interventions are used in isolation, with insufficient collaboration and communication with other disciplines involved in the care for PD patients. Clinical experience suggests that optimal management requires a multidisciplinary approach, with multifactorial health plans tailored to the needs of each individual patient. Although the merits of specific allied health care interventions have been scientifically proven for other chronic disorders, only few studies have tried to provide a scientific basis for a multidisciplinary care approach in PD. The few studies published so far were not yet convincing. We conclude by providing recommendations for current multidisciplinary care in PD, while highlighting the need for future clinical trials to evaluate the cost-effectiveness of a multidisciplinary team approach.

Introduction

Parkinson's disease is a chronic and progressive neurodegenerative disorder with a complex and diverse phenotype. Clinically discernable motor features include varied combinations of resting tremor, akinesia, rigidity, gait impairment and postural instability. In addition, most patients also experience a wide variety of non-motor symptoms, including neuropsychiatric complaints (depression, anxiety or cognitive decline), sleep disorders, autonomic dysfunction and sensory problems. These non-motor symptoms have a major impact on the quality of life and are an important source of disability.

Current medical management

The current therapeutic approach of PD is often 'monodisciplinary', i.e. only one medical discipline is involved in the care for patients. In most cases this is the medical specialist (neurologist or geriatrician) who focuses on minimising motor symptoms and reducing disease severity. Therapy is based primarily on symptomatic treatment with dopaminergic medication, and this is usually effective in reducing the classical motor features. However, there are drawbacks to current pharmacotherapy in PD. First, even levodopa is unable to sufficiently alleviate all motor symptoms. For example, ON-period freezing, falling and postural instability are usually not very responsive to dopaminergic treatment. Second, only few non-motor symptoms are responsive to dopaminergic treatment. Some non-motor symptoms may actually worsen due to dopaminergic therapy, including e.g. orthostatic hypotension or hallucinations in PD. Third, long-term use of dopaminergic treatment is complicated by development of dose-limiting response fluctuations, including sometimes disabling dyskinesias. Deep brain surgery can be considered when motor symptoms can no longer be controlled satisfactorily with drug treatment. These surgical procedures are suitable for only a selected group of patients, and the symptomatic effects do not exceed those obtained with dopaminergic therapy. Hence, pharmacotherapy and neurosurgery alone are insufficient to meet the entire symptom complex of PD.

Allied health care

Allied health care may complement these standard medical treatments, both in terms of focus, treatment goals and working mechanisms (Table 1).

Allied health care includes physiotherapy (PT), occupational therapy (OT) and speech-language therapy (SLT), as well as treatment by dieticians, social workers or sexologists. While the neurologist determines disease severity and optimizes medical treatment to reduce symptoms, allied health therapists aim to minimize the impact of the disease process s and improve the patient's participation in everyday activities. The underlying working mechanism is also different. Both pharmacotherapy and neurosurgery aim to correct nigrostriatal dysfunction in PD. In contrast, allied health therapists try to bypass the defective basal ganglia

Table 1 Differences between medical management (pharmacotherapy and deep brain surgery) and allied health care

	Medical management	Allied health care
Focus	Disease process	Impact of disease process on daily functioning
Treatment goals	Reduce symptoms Minimise disease severity	Reduce disability due to motor and non-motor symptoms Improve participation in roles and activities in daily life Improve level of activities
Working mechanism	Correct nigrostriatal dysfunction	Support compensatory (movement) strategies
Scientific evidence	Moderate to strong	Limited (occupational therapy) to moderate or strong (physiotherapy, speech therapy)

by engaging alternative neural circuitries that are still intact (cortical pathways and sensory systems). This generic principle can be applied to support a broad variety of motor functions, such as increasing the stride length while walking, or phonating louder when talking. There are three motor strategies that are specific for patients with hypokinetic-rigid features and that can be applied for both PT, OT and SLT: (a) avoiding multitasking during daily activities, by instructing patients to focus on the primary task at hand; (b) using cues to initiate and maintain movements during activities; and (c) dividing complex movements into a series of simpler components of the overall task, such that each component now needs to be executed independently and sequentially.[1]

Support for the possible merits of allied health care long came from mere clinical experience. Here we will discuss how allied health care is increasingly developing into an evidence-based profession.

Physiotherapy

The therapeutic arsenal of physiotherapy in PD is outlined in an evidence-based guideline for clinical practice.[1] This guideline has been adopted by the Association of Physiotherapists in Parkinson's Disease Europe (APDDE) and is available online (http://www.appde.eu). The guideline incorporates all available scientific evidence, and is supplemented with expert opinion. Among the 39 recommendations for clinical practice, there were several strong recommendations (i.e. based on randomized trials of good methodological quality): application of cueing strategies to improve gait, application of cognitive movement strategies to improve transfers (e.g. turning around in bed, and rising from a chair), and exercise therapy to improve balance (mainly strength and balance training).

An update of the guideline appeared in 2008.[2] New findings included the notion that cueing strategies improved not only undisturbed gait, but also gait while performing a secondary motor task. In addition, cues were found to be helpful for improving posture, transfers (performance of sit to stand), and the confidence to carry out functional activities without falling. Another relevant finding was that cueing strategies, although effective in the short term, had no long-term effects (as determined at 6-weeks of follow-up). [3] However, cueing strategies may be more effective under real life circumstances when cues are needed most. There was also new evidence for exercise therapy: high-force eccentric resistance training of the lower extremities improved physical capacity, as reflected by improvements in stair descent, walking distance and muscle volume.[4] A meta-analysis provided a strong recommendation that exercise therapy can improve physical capacity (strength, balance), gait speed and health-related quality of life.[5] Two treadmill training studies provided supporting evidence that exercise therapy can improve gait parameters, lower extremity tasks and well-being.[6-7] Finally, one hour of Tango classes improved both balance (Berg Balance Score) and gait (backward stride length).[8] This 'Tango study' also illustrates the challenge to scientifically identify the most effective component of such mixed and complex interventions: the music can act as an auditory cue, the consecutive steps of the dance can act as a movement strategy, and the activity itself can act as an exercise.

Occupational therapy

PT and OT are closely related, but the treatment goals are different. PT aims to improve daily functioning by enhancing basic skills such as gait or transfers. In contrast, OT focuses on being able to use these skills, enabling patients to engage in meaningful roles and activities in the domains of self care, productivity and leisure activities. OT interventions can focus on changing person-related factors, on adopting the actual activities themselves, and on tackling the environment where the activities are being performed.

In 2008, an evidence-based guideline for OT in PD was published in the Netherlands (translation into English is underway).[9] A total of 31 recommendations were made, covering referral, assessment techniques and treatment. Good scientific evidence for the effectiveness of OT in PD is lacking, hence recommendations were made based on indirect evidence obtained from PT. Specifically, the assumption was made that PD-specific compensatory strategies (shown previously to enhance basic skills) are also effective in optimizing activity performance. Additional indirect evidence was obtained from published experience with effective OT interventions for other chronic conditions (e.g. dementia and multiple sclerosis), whenever these interventions were felt to be relevant for PD.

Important elements of the guidelines are the focus on encouraging self-management skills and addressing the needs of caregivers on issues related to activities and participation.

Another recommended OT intervention is coaching the patient in carefully planning daily and weekly routines, while considering factors such as energy level, medication effects and speed of task performance. A daily or weekly activity plan may also provide a structure for patients with problems in initiating or planning activities. To optimize the use of motor or cognitive strategies and activity performance, the occupational therapist can advise the patient and caregiver about alternative equipment or changes to the physical environment.

The guideline also highlighted the need for well-designed intervention trials. No large scale OT intervention trials have been published since appearance of the guideline, but some relevant articles have been published. These articles concern the possible contribution of OT in self-management in PD[10], the use of assistive devices and mobility aids in PD[11], and approaches to optimize hand function in PD.[12] A pilot RCT in the UK supports the feasibility of evaluating OT in a randomised clinical trial.[13] In the Netherlands, an RCT has started this year to evaluate the impact of a 10-week OT intervention according to clinical practice guidelines.

Speech and language therapy

In 2008, an evidence-based guideline for SLT in PD was published in the Netherlands.[9] This guideline provides 60 recommendations that can assist speech-language therapists in clinical decision making, during both assessment and treatment. The treatment goals can be bundled into three main domains: speech impairment (hypokinetic dysarthria), swallowing disorders, and drooling. The recommendations are graded from strong (n=2), moderately strong (n=41) to weak (remainder). The two strong recommendations were made in the domain of speech. One recommendation is to limit dysarthria assessment in PD to establishing whether or not patients are indicated for specific intensive treatment (Lee Silverman Voice Treatment –LSVT- or Pitch Limiting Voice Treatment - PLVT).[14-15] The other strong recommendation is to treat patients with an indication with PLVT or LSVT at least three times a week for at least four weeks[14], the highest treatment intensity that is currently realistic, at least for Dutch SLTs. Patients with severe hypokinetic dysarthria or mixed dysarthria (resulting from atypical parkinsonism) can profit from the same approach, but results are obviously limited.

Other work showed that videophone-delivered speech therapy can be cost-effective.[16] In the field of drooling there is new evidence that botulinum toxin injections can trim down saliva production, without improving swallowing physiology.[17] In the field of dysphagia, a small pilot study demonstrated that the daily use of effortful swallowing (assisted with biofeedback) for two weeks was helpful in reducing dysphagia in PD.[18] Another small study showed that expiratory muscle strength training can reduce aspiration while swallowing in PD.[19] Although evidence is still limited, it seems that high-energy treatments are not only effective in improving voice quality and intelligibility in PD[20], but also in improving swallowing and maybe also saliva control.

Drawbacks to current allied health care

Allied health care as it is currently used is not without shortcomings. More good quality randomized trials are needed to demonstrate the effectiveness of allied health care interventions. Furthermore, more work is needed to show if allied health approaches can be applied universally in all patients, or whether certain subgroups are less suitable for receiving these treatments. For example, the presence of cognitive impairment can interfere with the aforementioned treatment strategies, because patients may be unable to understand the recommendations or fail to memorise their new movement strategies. Patients with cognitive impairment may also fail to appreciate the risks of walking disturbances or dysphagia. Hence, therapy should also focus on safety aspects. The caregivers should be involved whenever possible, because they can support the patient by applying the newly acquired strategies while performing daily activities.

Another problem is that allied health care interventions are typically used in isolation, despite partially overlapping treatment strategies and partially complementary goals. In current clinical practice, most health professionals are unfamiliar with the potential treatment options offered by other professionals.[21] For example, LSVT is such an intensive training that less emphasis on other treatments during those four weeks is highly advisable.

Multidisciplinary treatment of PD

Given the complexity of PD, a multidisciplinary approach would appear to be preferable. Indeed, allied health care interventions are effective for only part of the complex symptom spectrum in PD. A multidisciplinary team approach, combining pharmacological and non-pharmacological therapies, thus seems necessary to obtain optimal therapeutic efficacy. For this reason (and also increasingly driven by patient foundations), specialized PD centres have begun to implement integrated and multidisciplinary health care programs within their clinical practice. The UK-based NICE guideline also recommends regular access to a broad range of medical and allied health professionals. An obvious question is: who should be part of the team? There is no evidence whatsoever that has addressed this question, and our impression (based on discussions with colleagues) is that a considerable variation exists in team constitution across different treatment centres, depending on issues such as availability of expertise and funding. It is not known which clinical structure or team involvement is most effective, and the NICE guidelines give no recommendations as to how to organize the multidisciplinary care.

Theoretically speaking, multidisciplinary care teams for PD patients could include a wide range of different professionals, including medical specialists (neurologist, neurosurgeon, psychiatrist, geriatrician, urologist), specialised PD nurse specialists and allied health professionals (at least PT, OT and SLT). In addition, dieticians, social workers, sexologists

and clinical neuropsychologists can be included in the team. Important elements of inter-professional team work are, among others, shared goal setting and shared contribution to treatment plans, effective communication and appropriate referrals to other team members. These aspects should all be incorporated when organizing multidisciplinary care for PD patients. Professionals should work according to evidence-based guidelines, when these are available. The goals should be defined not only around disease severity and symptoms, but should also consider mobility, independence and relationships. Importantly, the treatment plan should address the individual needs of each patient. In our Parkinson Centre Nijmegen, we routinely invite our patients to prioritize their own 'top five' complaints, and we have been struck by the wide variety in priorities set by different patients. Because this prioritization is done before the actual visit to our centre, we can adjust the team constellation according the unique needs of each patient. This client-centered approach improves the quality of care, while reducing the amount of redundant attention to issues that are less relevant for patients.

The treatment plan is incomplete without engaging the immediate caregiver, family and friends. Many caregivers have a crucial role in assisting more severely affected patients in using cues or cognitive movement strategies. Caregivers may also benefit from OT, by improving their ability to cope with complex situations and to gain more competence in supporting the patient. Moreover, an optimal multidisciplinary approach also addresses the needs of the caregivers. When the caregiver collapses, patients may lose their independence, and must resort to much more expensive assisted care.

Evidence for multidisciplinary care in PD (and beyond)

Multidisciplinary care is used increasingly, but the question arises how well founded this approach is. Scientific evidence on the effectiveness of multidisciplinary care in PD is limited. Positive effects on health, disability, quality of life and well-being have been reported in several uncontrolled studies that used a pre-test versus post-test design.[22-25] Only few studies used a controlled design to evaluate the effectiveness of multidisciplinary care in PD.[26-27] One crossover RCT evaluated a multidisciplinary intervention that featured individualised PT, OT, SLT, specialized nursing, access to a social services care manager, and group educational support.[27-28] Improvements for patients and their caregivers were found directly after the program (using a pre-post test design), but these had disappeared after six months of follow-up. A recent RCT evaluated the effect of group education combined with personal rehabilitation delivered by a multidisciplinary team, including a specialized movement disorder neurologist, PT, OT, dietician, psychologist and a nurse.[29] Positive effects were found for quality of life, activities of daily living (UPDRS II) and motor scores (UPDRSIII) at eight weeks after the intervention.

Given this limited availability of good quality research, we resorted to published evidence that supported the merits of multidisciplinary care for other chronic neurological or even non-neurological disorders. Generally speaking, some trends have been found towards positive effects of integrated care programs in the chronically ill.[30] In addition to positive effects for patients, team work may also improve process outcomes, such as compliance and adherence to guidelines, and lead to a higher degree of work satisfaction.

Future trials

Although sound scientific evidence is available for certain allied health care interventions, the evidence for an integrated multidisciplinary approach is still limited. Clearly, more work is needed to substantiate the general feeling that multidisciplinary care improves the quality of care and leads to a better outcome for patients. Research is needed to provide a more thorough basis for multidisciplinary care in PD (in case of positive findings), or to a critical reappraisal of this costly and time-consuming intervention (in case of negative findings). There is also a need to determine which specific elements should be part of the multidisciplinary approach, and whether a 'one size fits all' treatment is as good as an individually tailored approach. Even positive findings need to be weighed against the undoubtedly higher costs associated with multidisciplinary care: how much is the society willing to spend on quality of life for PD patients and their families? In the Netherlands, we are currently performing a large cluster controlled trial (the IMPACT study) to evaluate the effectiveness and costs of integrated, multidisciplinary care in PD, as compared to usual - i.e. largely monodisciplinary - care. Hopefully, the results of this trial and other studies will contribute to a better quality of care for PD patients and their families.

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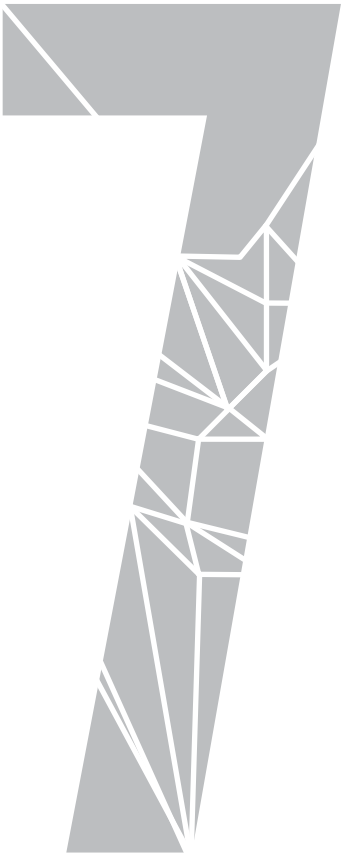

EFFECTIVENESS OF MULTIDISCIPLINARY CARE IN PARKINSON'S DISEASE

7.1 The Parkinson's disease multidisciplinary package

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Physicians caring for patients with Parkinson's disease (PD) often use many therapies simultaneously, including medications, dietary recommendations, physical therapy, social support strategies, and for some patients, surgery. In most cases, the implementation of this multifaceted care involves a team of experts, including movement disorder specialists, trained nurses, and social workers. Whereas this type of approach may be available in movement disorder specialty centers, the same integrated care is less feasible for general neurologists. Randomized clinical trials focus on the study of individual components of this overall care model, but the overall "package" of integrated multidisciplinary care has not been previously evaluated.

In this issue of Movement Disorders, van der Marck and colleagues conducted a randomized clinical trial to study the impact on quality of life and other functional measures in PD patients receiving multidisciplinary specialty care or general neurological care.[1] *(Chapter 7.2) The results favor the multidisciplinary approach, with improvements in quality of life and UPDRS, depression, and psychosocial functional scores. In a brief discussion of effect size, the authors argue that the observed differences have clinical pertinence. There is no health economic analysis to provide readers with a measure of societal cost for the relative difference. A substantive cost difference can be inferred, however, in that no patient in the general neurologist care group accessed a social worker or a PD specialty nurse, whereas in the multidisciplinary group, 69% consulted with social workers and 86% accessed a specialty nurse, with 59% receiving care from both. Because the movement disorder specialist was only part of the multidisciplinary team, the specific importance of the higher level of PD expertise cannot be dissected. Further, it is clear that those in the multidisciplinary group received more attention and time focused on them, so it not possible to attribute the favorable outcomes specifically to better expertise. Had neighbors or friends phoned the patients or visited them at the same level as the professionals, would the patients have done equally well?*

The article, even with these limitations, is an important contribution because scientists and clinicians increasingly recognize that PD is a disease composed of motor and nonmotor impairments. In fact, the latter components often become the predominant issues as the disease advances. Having this article as a starting point offers a first entry into the evidence base of comprehensive health models and presents international colleagues with a number of ideas for future protocols and studies.

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7.2 Effectiveness of multidisciplinary care for Parkinson's disease: a randomized controlled trial

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Abstract

Background

Multidisciplinary care is considered an optimal model to manage Parkinson's disease (PD), but supporting evidence is limited. We performed a randomized controlled trial to establish whether a multidisciplinary/specialist team offers better outcomes compared to stand-alone care from a general neurologist.

Methods

Patients with PD were randomly allocated to an intervention group (care from a movement disorders specialist, PD nurses and social worker) or a control group (care from general neurologists). Both interventions lasted 8 months. Clinicians and researchers were blinded for group allocation. The primary outcome was the change in quality of life (Parkinson's Disease Questionnaire, PDQ-39) from baseline to 8 months. Other outcomes were Unified Parkinson's Disease Rating Scale (UPDRS), depression (Montgomery-Asberg Depression Scale, MADRS), psychosocial functioning (Scales for Outcomes in Parkinson's disease-Psychosocial, SCOPA-PS) and caregiver strain (Caregiver Strain Index, CSI). Group differences were analyzed using analysis of covariance adjusted for baseline values and presence of response fluctuations.

Results

122 patients were randomized and 100 completed the study (intervention n=51, control n=49). Compared to controls, the intervention group improved significantly on PDQ-39 (difference 3.4, 95%CI 0.5 – 6.2) and UPDRS motor scores (4.1, 95%CI 0.8 – 7.3). UPDRS total score (5.6, 95%CI 0.9 – 10.3), MADRS (3.7, 95%CI 1.4 – 5.9) and SCOPA-PS (2.1, 95%CI 0.5 – 3.7) also improved significantly.

Conclusions

This randomized controlled trial gives credence to a multidisciplinary/specialist team approach. We interpret these positive findings cautiously due to the limitations in study design. Further research is required to assess teams involving additional disciplines, and to evaluate cost-effectiveness of integrated approaches.

Introduction

Parkinson's disease (PD) is a progressive and disabling disorder.[1-2] A multidisciplinary team approach is widely felt to offer better control of PD than pharmacotherapy alone.[3-5] However, evidence supporting this approach remains limited, and previous randomized controlled trials (RCTs) did not show robust and sustained findings.[6-9] Here, we report the results of an RCT to establish whether a multidisciplinary/specialist team approach (involving a movement disorders specialist, PD nurses and PD social worker) offers better outcomes compared to stand-alone care by a general neurologist.

Methods

The study was designed as a single-blind RCT comparing two arms: an intervention group (IG), with care delivered by a multidisciplinary/specialist team (movement disorders specialist, PD nurses and social worker) and a control group (CG), with care delivered by a general neurologist. The trial was conducted between June 2002 and January 2005 and was approved by the Markham Stouffville Hospital Research Ethics Committee. Written informed consent was obtained from all participants.

Participants

Patients were referred to the Centre for Movement Disorders (Markham, Ontario) for multidisciplinary management of their PD. The reason for referral varied widely and did not necessarily involve complex or advanced patients. Due to limitations in the number of movement disorders specialists in Ontario, it is common for PD patients to be seen initially by a general neurologist and then referred to a sub-specialist. The intervention Centre had a single movement disorder neurologist (MG) during the study. No other neurologists worked in the Centre. The general neurologist continued to be involved until the first visit by the movement disorder neurologist.

Administrative staff at the Centre, not involved in the study, booked the initial assessment appointment with the patient with a wait time of approximately eight months as part of the standard processing of new patients. This wait time was typical for new patients referred to the Centre at the time of this study. After accepting their initial appointment, consecutive patients were contacted by telephone by research assistants and screened to discuss their potential involvement. A screening assessment was offered to patients who passed the initial telephone screen. This screening assessment was conducted by movement disorders fellows who were part of the research staff for this study and did not participate in the clinical care of any recruited patient. At the screening assessment, inclusion criteria were evaluated, including a clinical diagnosis of PD according to the UK Brain Bank criteria,[10] ability to complete the study questionnaires, written informed consent and presence of a caregiver who also participated in the study. Exclusion criteria included dementia (Mini-Mental State Examination <24)

and current treatment by a movement disorders specialist. We also determined the presence of response fluctuations (wearing-off or dyskinesias, assessed with the Unified Parkinson's Disease Rating Scale (UPDRS)).

Randomization, blinding and study design

Patients meeting the inclusion criteria were randomly assigned to the IG or CG. Randomization allocation was computer generated. There was a 1:1 randomization to the intervention or control group, stratified by presence of response fluctuations. Research assistants without clinical or research involvement in the trial assigned patients with sealed envelopes and organized visits and data-entry. The research staff who performed the screening, baseline and follow-up assessments were unaware of group identity. The clinical team providing care were not aware if patients participated in the study.

After randomization, patients in the IG were rescheduled for a clinical neurological examination by the movement disorders specialist within three weeks from the screening visit, rather than waiting for their original appointment (typically 8 months later). Patients in the CG received usual care from general neurologists who did not have nursing or social work staff. Usual care was determined by the general neurologist; there was no standard approach to the frequency of visits or other interventions. The general neurologists were not aware of patients' participation. Patients in both groups were asked to not share their study involvement with any treating clinician. No formal power calculation was made, but we strived to include 100 patients. Patients who unblinded their participation were dropped from the study and replaced randomly to reach the target of 100 patients who completed the study. This occurred only sporadically (one IG patient).

Intervention

The intervention is described in detail in the Addendum. This included ongoing individually tailored care from the movement disorders specialist, supported by PD nurse and social worker within the same physical location. Visits to the movement disorders neurologist were scheduled at baseline, 4 months and 8 months. Additionally, patients were offered to see the social worker for psychosocial issues and homecare issues, and the PD nurse for changes in symptoms, medication issues or other PD-related questions. Control patients were followed by the general neurologist outside the Centre who was associated with their care before referral. Intervention patients saw the movement disorders neurologist at the Centre.

Outcomes

Baseline and follow-up assessments were performed by trained movement disorders fellows and physiotherapists who were not involved in patient care and who were unaware of group allocation. The primary outcome was change from baseline to 8 months in quality of life,

assessed with the Parkinson's Disease Questionnaire (PDQ-39).[11-12] The secondary outcome was change from baseline to 8 months in the UPDRS part III (motor section). Motor ratings were not performed in a pre-specified time with respect to the patient's medication response. Tertiary outcomes included UPDRS total score, depression (Montgomery-Asberg Depression Scale, MADRS), psychosocial functioning (Scales for Outcomes in Parkinson's disease-Psychosocial, SCOPA-PS) and caregiver strain (Caregiver Strain Index, CSI). Daily medication use was converted to levodopa equivalent dose.[13] Outcomes were assessed at baseline, 4 months and 8 months.

Statistical analyses

Changes from baseline to 8 months were analyzed for all outcome measures. Differences in changes between groups were examined with analysis of covariance (ANCOVA), with baseline value of the variable and presence of response fluctuations as covariates. In a secondary analysis, the possible impact of disease duration and age were evaluated by including these variables in the analyses. Results with $P<0.05$ (two-sided) were considered statistically significant.

Results

Study population

159 patients were screened, 122 were eligible to participate and were randomly assigned to IG or CG (Figure 1). Twenty-two patients dropped out due to withdrawal of consent, unblinding of the clinical team, incorrect diagnosis or having received the clinical neurology assessment before baseline assessment. In total, 100 patients completed the study, including 51 patients in IG and 49 in CG (Table 1). Baseline characteristics and baseline scores for the outcomes were comparable between the groups, except for higher CSI scores in IG.

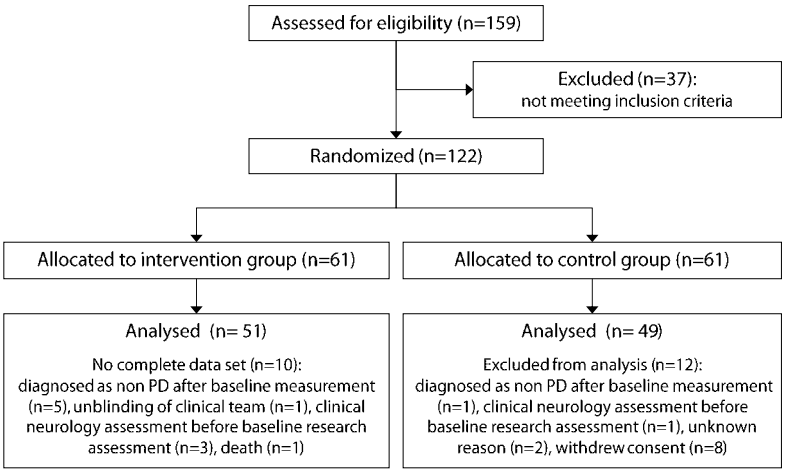

Figure 1 *Enrollment and patient flow.*

Table 1 Participants characteristics at baseline

Variable	Intervention group Mean (SD) (n=51)	Control group Mean (SD) (n= 49)
Age (yrs)	65.9 (8.5)	68.1 (8.8)
Men (%)	59	57
Disease duration (yrs)	4.6 (3.9)	3.7 (3.5)
Patients with response fluctuations (%)	27.4	28.6
PDQ-39 index score	22.2 (14.4)	19.1 (12.4)
Mobility	26.6 (25.0)	23.4 (21.8)
Activities of daily living	26.6 (21.0)	22.2 (19.4)
Emotional well-being	25.7 (18.4)	21.4 (17.0)
Stigma	18.8 (19.8)	15.1 (15.2)
Social support	8.2 (12.3)	6.5 (14.7)
Cognition	20.2 (17.0)	21.7 (16.4)
Communication	21.1 (21.2)	15.3 (15.7)
Pain	30.9 (22.0)	27.2 (20.3)
UPDRS III	22.6 (14.4)	21.7 (11.3)
UPDRS total	39.0 (23.1)	36.0 (18.1)
MADRS	10.1 (7.5)	8.2 (6.7)
SCOPA-PS	10.6 (7.0)	9.2 (6.6)
CSI	18.3 (12.3)	14.1 (10.6)
Daily levodopa equivalent dose (mg)	413 (247)	431 (289)
Medication, used by (%)		
Levodopa	67%	71%
Dopamine agonist	24%	29%
COMT inhibitor	6%	2%
MAO B blocker	2%	0%
Anticholinergic	10%	0%
Amantadine	10%	8%

COMT catechol -O-methyl transferase; *CSI* Caregiver Strain Index; *MADRS* Montgomery-Asberg Depression Scale; *MAO B* monoamine oxidase beta; *PDQ-39* Parkinson's Disease Questionnaire; *SCOPA-PS* Scales for Outcomes in Parkinson's disease-Psychosocial; *SD* standard deviation; *UPDRS* Unified Parkinson's Disease Rating Scale (III, motor part).

Intervention

All IG patients visited the movement disorders specialist three times. PD nurses were engaged by 86% of patients, the social worker by 69% of patients, and both professionals by 59% of patients. PD nurses were mainly contacted by telephone (84% of 160 contacts), whereas the majority of social worker contacts was an office visit (72% of 46 contacts). In contrast, no CG patient visited a PD nurse or social worker during the study period.

Efficacy

The PDQ-39 improved from 22.2±14.4 at baseline to 19.7±14.2 at eight months for IG, but worsened from 19.1±12.4 at baseline to 20.2±13.4 at eight months for CG (Table 2).

Table 2 Health outcomes change (8 months – baseline) and differences between groups

	Intervention Group Mean (SD)	Control Group Mean (SD)	Estimated difference (95%CI)
Primary outcome			
PDQ-39 index score (n=98)	-2.5 (5.8)	1.4 (8.6)	3.4 (0.5 to 6.2)
Mobility	-3.8 (9.4)	3.8 (16.2)	7.1 (1.9 to 12.3)
Activities of daily living	-2.9 (14.0)	3.3 (14.2)	5.1 (-0.5 to 10.6)
Emotional well-being	-4.7 (11.2)	2.0 (13.8)	5.4 (0.7 to 9.9)
Stigma	-2.0 (13.9)	1.1 (14.4)	1.8 (-3.4 to 6.9)
Social support	0.0 (11.5)	2.1 (11.7)	1.6 (-2.7 to 5.9)
Cognition	-0.4 (12.5)	1.9 (13.7)	-1.1 (-6.1 to 3.9)
Communication	-3.8 (10.3)	0.0 (13.2)	2.2 (-2.3 to 6.7)
Bodily discomfort	-2.6 (18.4)	1.1 (18.8)	1.9 (-4.8 to 8.5)
Secondary outcome			
UPDRS III (n=100)	-2.7 (8.7)	1.6 (9.3)	4.1 (0.8 to 7.3)
Tertiary outcome			
UPDRS total (n=100)	-4.4 (13.4)	2.0 (12.4)	5.6 (0.9 to 10.3)
SCOPA-PS (n=100)	-1.8 (4.4)	0.7 (4.7)	2.1 (0.5 to 3.7)
MADRS (n=99)	-4.1 (6.6)	0.4 (6.6)	3.7 (1.4 to 5.9)
CSI (n=97)	-0.7 (7.7)	1.4 (5.1)	1.5 (-1.2 to 4.2)
Daily levodopa equivalent dose (mg)	42.1 (158.4)	95.4 (208.7)	18.5% (-1% to 41%)

CI Confidence interval; *CSI* Caregiver Strain Index; *MADRS* Montgomery-Asberg Depression Scale; *PDQ-39* Parkinson's Disease Questionnaire; *SCOPA-PS* Scales for Outcomes in Parkinson's disease-Psychosocial; *SD* Standard deviation *UPDRS* Unified Parkinson's Disease Rating Scale (III, motor part).

These changes differed significantly between IG and CG (3.4, 95% CI 0.5–6.2). Separate analysis for the eight PDQ-39 domains showed that IG patients significantly improved on mobility scores (7.1, 95% CI 1.9–12.3) and emotional well-being scores (5.4, 95% CI 0.7–9.9) compared to CG patients. There were no group differences on the other domains (Table 2). The secondary outcome (UPDRS III) improved from baseline to eight months in the IG, but deteriorated in the CG. These changes differed significantly between both groups (4.1, 95% CI 0.8-7.3). Tertiary outcomes that improved significantly in the IG included UPDRS total scores (5.6, 95% CI 0.9 – 10.3), SCOPA-PS (2.1, 95% CI 0.5 – 3.7) and MADRS (3.7, 95% CI 1.4 – 5.9) (Table 2). CSI scores did not differ between IG and CG (1.5, 95% CI -1.2 – 4.2). Additional analyses with age and disease duration incorporated as covariates did not change the results.

Levodopa equivalent dose

During follow-up, the levodopa equivalent dose increased more in CG compared to IG (difference 18.5%, 95% CI -1% – 41%). Additional adjustment for levodopa equivalent dose did not change the greater improvement in PDQ-39 scores for the IG compared to the CG (estimated difference in improvement 3.7, 95% CI 0.2 – 7.3).

Discussion

These results show that an individually tailored multidisciplinary/specialist team intervention, with involvement of a movement disorders specialist, PD nurses and social worker, improved both primary (PDQ-39) and secondary (UPDRS-III) outcome measures, as compared to management by a general neurologist alone. Several tertiary outcomes (UPDRS total, SCOPA-PS, MADRS) also improved during the 8-month intervention period. As such, this is one of the first RCTs that gives credence to a multidisciplinary/specialist team approach. However, we will interpret these positive findings cautiously, given the complexity of the intervention, and in light of several methodological imperfections.

Effect size

Did the effects of this multidisciplinary/specialist team intervention have any clinical relevance? For quality of life (primary outcome), our results showed an improvement of 3.4 points on the PDQ-39 summary index for the team approach. Such an improvement will be clinically meaningful to patients.[14] By comparison, the effect of deep brain stimulation on quality of life compared to optimal medication is about 7.0 points, based on four trials.[15] Comparison with our trial is difficult, e.g. because stimulation is given to more severely affected patients, and because quality of life at baseline is lower. However, this comparison suggests that a multidisciplinary team approach may offer a fairly substantial effect, compared with an invasive and highly effective intervention like deep brain stimulation.

We also found greater improvement in motor functioning for the team approach, as assessed with UPDRS part III (4 points difference in favor of IG). This improvement falls within the range of effect sizes reported in several clinical trials of dopaminergic medication.[16] Although direct comparisons with drug trials are difficult, the observed change in motor functioning appears clinically relevant for patients.[17] Although the motor assessments were not performed in a pre-specified "on" or "off" time, it is unlikely that this altered our findings since only 28% of patients in both groups had response fluctuations.

With respect to the IG, we do not know other studies that evaluated a similar group of patients in a prospective controlled study with a similar type of intervention that could act as comparison. Our CG essentially reflected usual care and natural disease progression. Compared to natural disease progression studies and to the control arms in open label studies, our CG globally behaved the way we expected them to[18-22], suggesting we included representative patients.

In general, integrated care programmes for the chronically ill seem to have a positive effect on quality of care, but comparisons are difficult due to the heterogeneity of interventions and outcomes used.[23] Thus far, the evidence on multidisciplinary rehabilitation in PD remains

limited and failed to reveal consistent benefits.[3,5] The literature to support multidisciplinary involvement in other chronic neurological disorders is also variable. For example, the evidence to support multidisciplinary inpatient stroke units is robust, showing beneficial effects on survival and independence.[24-25] For dementia, collaborative primary care involving an advanced practice nurse working together with families with dementia has shown improvements in behavioural and psychological symptoms.[26] However, other studies showed that coordinated care in memory clinics had no positive effects on health outcomes in dementia patients.[27-29]

Components of the multifactorial intervention

Compared to single interventions like drugs, evaluation of multidisciplinary care poses scientific challenges due to the complex nature of the intervention, with several interconnecting components.[30] Here, we evaluated the merits of a team intervention as the sum of its parts. Our study was not designed to evaluate the contributions of the different members of the multidisciplinary/specialist team. However, it is important to consider which component of our multifactorial intervention might have contributed to the observed benefits. One important element was the movement disorders specialist who treated all IG patients, whereas all CG patients were treated by general neurologists. Because the multidisciplinary team included a movement disorders specialist, we cannot be certain if the group difference in outcome was due to the "team" aspect or the "specialist" aspect of the intervention. A retrospective analysis of Medicare claims in the United States suggested that neurologist's care of PD patients is associated with better clinical outcomes (fewer hip fractures) and greater survival, compared to primary care without neurologist, although a causal relationship could not be proven.[31] In our study, patients in both arms received neurologist care, but for the IG the neurologist was a specialist in movement disorders who perhaps offered better care than a general neurologist. Interviews and surveys have clarified that patients greatly value the dedicated expertise of a movement disorders specialist,[32-33] so patient expectations may have played a role. Moreover, PD experts may yield better outcomes because of improved diagnosis, better counseling, and dedicated treatment for specific complications of PD.

The team intervention also included access to PD nurses and a social worker. PD nurses are closely involved in several aspects of care, including counseling, coping with PD and social concerns. However, evidence for the effectiveness of nursing care alone for PD patients remains limited and inconclusive.[34] Perhaps nursing care is more effective when delivered as part of an integrated team approach. The treatment goals of social workers aim at psychosocial issues, helping patients to link to community services that are not offered to patients on site. The nature of these services of PD nurses and social workers corresponds with the improvements observed on the tertiary outcome measures relating to emotional and psychosocial functioning. Finally, the multidisciplinary/specialist team that we evaluated

could also have included additional disciplines, such as physiotherapy or speech-language therapy, which are increasingly becoming evidence-based treatments for PD.[35-37] Future work should investigate their possible added value to the multidisciplinary team approach.

Recently, the American Academy of Neurology provided a core set of quality measures to guide clinicians in their management of PD.[38] These quality measures recommend focusing on 10 topics as part of the clinical assessment, and most measures focus on non-motor symptoms. This emphasizes the need for a team-oriented approach to manage the broad range of PD-related symptoms, as these cannot easily by managed by one discipline.

Shortcomings and future perspectives

This study was not without shortcomings. First, we were unable to perform an intention-to-treat analysis, because we acquired no data in dropouts. Hence, we were restricted to perform a case-controlled analysis with only subjects who completed the study. Future work needs to take this into account. Second, it is possible that the observed differences were caused by more neurological services being provided to the IG compared to the CG. It was not possible to determine the number of neurological services received in the CG, and this should be addressed in future studies. In addition, the exact nature of the intervention should be addressed further. Data on the number of visits and telephone contacts with the team members were reported, but we did not report the topics that were addressed. Third, the study results cannot automatically be generalized due to a possible selection bias in referrals to the participating centre. The reason for referral to a movement disorder specialist varies widely and does not necessarily involve complex patients or advanced patients. Nevertheless, it is conceivable that referrals were for more complex patients, or for patients that were more interested in specialized care. However, such selective referral to a specialized centre reflects everyday clinical practice worldwide, and as such our trial does inform the current management of PD in many specialized centers. Fourth, most patients had relatively early stage PD, as only 28% had experienced response fluctuations. Therefore, our findings cannot be extrapolated to patients with more advanced disease. Fifth, this RCT was conducted as a single-blind study. Awareness of treatment allocation among patients might have induced a placebo effect in favor of the intervention. In PD drug treatment studies, placebo effects commonly taper off during a 3-6 month study, although placebo effects can persist for longer periods of time. In our study, the efficacy was present in the primary and secondary outcomes throughout the 8-month observation, but a placebo effect cannot be excluded. Double-blind RCTs are required to better untangle placebo effects from real effects of the intervention, but are difficult to perform with this type of study. Finally, our results were limited to an 8-month follow-up. More research is needed to establish the potential long-term effects of multidisciplinary care, including a cost-effectiveness assessment. A multidisciplinary team approach is a far more complex and less homogenous intervention than, for example, a single

dose drug intervention. This is a generic challenge for studies in this new emerging field. To explore the impact of a team, a next step might be to perform an RCT on a general neurologist plus a team versus a general neurologist alone. Studying a movement disorders specialist plus a team versus a movement disorders specialist risks the possibility of a ceiling effect. In view of the shortage of movement disorders specialists,[33] a solution could be to surround a general neurologist with PD nurses and social workers, reserving movement disorders specialists to patients beyond the care of such a team. Additionally, more research is needed to refine the most effective elements of multidisciplinary interventions. A further challenge is to extend the intervention with additional disciplines, e.g., physiotherapists or occupational therapists, to establish the relative importance of each discipline within such a team approach, and to evaluate their merits in different settings.

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ADDENDUM

Intervention

The intervention included individually tailored care from a single movement disorders specialist (MG) supplemented with support, teaching and assistance from Parkinson's disease (PD) nurses and a PD social worker. Visits to the movement disorders neurologist were scheduled at baseline, 4 months and 8 months. Supplementary appointments were determined by the patients' needs. At the initial clinical appointment each patient was offered to meet with the social worker. In addition to performing a psychosocial assessment, the social worker oriented patients as to the role of the paramedical healthcare professionals in the multidisciplinary/specialist team. The patients were given more detailed information about the potential for telephone support before the next scheduled visit and were given information as to who they should contact for different situations. Patients were instructed to contact the social worker for psychosocial issues and if there were issues related to access to local government provided services including homecare in addition to educational services provided by the local Parkinson's Society. Patients were also instructed to contact the nursing staff if they had a change in their PD symptoms, issues with their PD medications or if they had other questions relating to their PD. They were informed that the team members would communicate with the neurologist and get back to the patient with a plan to address their issues. If they requested an earlier appointment with the neurologist before the next scheduled appointment, this was discussed with the neurologist as part of daily meetings and a decision of how to manage the issue was then made by the neurologist. In addition to telephone support, patients were offered meetings with the paramedical staff during their office visits as determined by the movement disorders specialist to enhance their PD management. The intervention, both in the frequency of visits and the topics addressed, was tailored to the patient's individual needs.

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INTEGRATED MULTIDISCIPLINARY CARE IN PARKINSON'S DISEASE

8

8.1 Challenges of multidisciplinary care in Parkinson's disease

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Despite advances in the treatment of Parkinson's disease, many patients develop serious complications that are unresponsive to pharmacological and surgical manipulation of dopaminergic neurotransmission.[1] As a result, several studies have assessed the value of rehabilitation in Parkinson's disease, particularly through a multidisciplinary approach.[2-4] Such studies typically suggest a slight benefit from this approach, yet they do not satisfy current standards of evidence-based practice.[5]

In The Lancet Neurology, Marjolein van der Marck and colleagues[6] (Chapter 8.2) begin to address this gap in the evidence with the Integrated Multidisciplinary care for Parkinson's disease: a Controlled Trial (IMPACT) study by taking the question one step further: how effective is multidisciplinary care within the setting of a modern health-care system? A superficial review of the study might conclude that its results are negative: the slight benefits of the treatment on activities of daily living and quality of life were wiped out when the analysis was corrected for asymmetries in severity between the intervention and control groups. However, the greater importance of this study lies in the lessons learned while addressing the challenges of implementing a multidisciplinary care model within a modern health-care system, and of assessing the effectiveness of such implementation.

To answer the question of how to implement multidisciplinary care within a health-care system, the IMPACT investigators adopted a hybrid approach, with initial multidisciplinary assessments at an expert centre yielding recommendations for therapy that were subsequently outsourced to providers participating in ParkinsonNet, a network of community-based collaborating allied health professionals with specialised Parkinson's disease training. The investigators included 150 patients in the intervention group and used a geographically separate control group of 151 patients who received standard care as prescribed by their neurologists. One out of three patients in the intervention group declined the intervention, and many of the patients who agreed did not consistently comply with recommendations. Conversely, more than half of the patients in the control group did receive rehabilitative treatments as part of standard care, which, not least because of the previous efforts of the investigators of this study,[7] is already at a very high level in the Netherlands.

What can be learned from the apparent failure of multidisciplinary care in this implementation model? The investigators point out three weak links in their design that might have frustrated their efforts to provide high-quality conclusive evidence: the heterogeneous, customised nature of the administered treatments; the absence of selection of patients to whom the intervention was offered; and the hybrid nature of the multidisciplinary intervention.

On the basis of assessments, customised treatment recommendations were provided by the multidisciplinary team for each patient in the intervention group. The investigators postulate that a

more standardised prescription across patients might be easier to assess, even if it might result in excessive care for some patients. Besides cost concerns, such an approach could erode effect size by not showing an effect in patients for whom an effect was not expected or needed. The customised approach would more likely enhance compliance; after all, multidisciplinary care is under investigation, and heterogeneity of treatments is part of its nature.

Apart from some general inclusion and exclusion criteria, allcomers were offered participation to the trial, irrespective of the perceived need for intervention. The investigators propose that restricting multidisciplinary care to those with the highest need might result in better compliance. Notably, the study population included generally mildly affected individuals (about three-quarters of the intervention group were at Hoehn and Yahr stage 2·5 or lower). Conceivably, less severely affected individuals are less likely to have a short-term benefit from the intervention, because most of their symptoms are responsive to pharmacological treatment; extending this argument, a statistical correction for the asymmetry in severity between groups does not take into account the possibility that the relation between disease severity and effect size might be non-linear. Therefore, the same study might have yielded different results in Hoehn and Yahr stages 3 and 4, when patients might have more robust short-term benefits. The intervention could even be linked to a specific need, and relevant outcome measures could be targeted.

This approach would increase the heterogeneity of the administered treatments; however, to reiterate, the concept of the multidisciplinary care rather than any specific treatment is under investigation. In implementing the intervention within the health-care system, patients were offered assessments and treatment recommendations at the expert centre, whereas administration of the treatments was outsourced to the community. The investigators suggest that it might be preferable to complete the recommended treatments at the expert centre, which would preserve and ensure the interdisciplinary dimension of the multidisciplinary model. One of the strongest arguments in support of multidisciplinary care is that communication between disciplines has a synergistic positive effect on outcomes.[8] Spatial proximity removes barriers that could compromise such communication. Conversely, such requirement might adversely affect patient recruitment and retention by adding more barriers (eg, distance to travel, need for lodging).

The investigators ought to be applauded for including cost-effectiveness and caregiver burden analyses in their study. The absence of an adverse economic effect of multidisciplinary care emphasises the need for further study: if outcomes can be improved at no higher cost, this model should not be dismissed without further study and high-quality evidence. Future studies of multidisciplinary care could examine new short-term outcome measures for assessing effectiveness, investigate long-term benefits of this approach and relevant long-term outcome measures (eg, falls resulting in injury, admission to an institution, and survival), devise support services to reduce caregiver stress, and assess the role of recurrent interventions, among other things. The study

by the IMPACT investigators[6] has launched the discussion on the place of multidisciplinary care within a changing health-care environment. The lessons learned will inform future research of this care model, not only in Parkinson's disease, but also in other chronic progressive diseases.

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8.2 Integrated multidisciplinary care in Parkinson's disease: a non-randomised, controlled trial (IMPACT)

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Abstract

Background A multidisciplinary approach is thought to be the best way to manage the motor and non-motor symptoms of Parkinson's disease, but how such care should be delivered is unknown. To address this gap in knowledge, we assessed the effectiveness of an integrated multidisciplinary approach compared with usual care.

Methods We recruited patients for our non-randomised controlled trial from six community hospitals in the Netherlands (two in regions where the integrated care intervention was available and four in control regions that administered usual care). Eligible patients were those with Parkinson's disease, aged 20–80 years, and without severe cognitive impairment or comorbidity. Patients in the intervention group were offered an individually tailored comprehensive assessment in an expert tertiary referral centre and subsequent referrals to a regional network of allied health professionals specialised in Parkinson's disease. Primary outcomes were activities of daily living (Academic Medical Center linear disability score [ALDS]) and quality of life (Parkinson's disease quality of life questionnaire [PDQL]) measured at 4, 6, and 8 months. Secondary outcomes included motor functioning (unified Parkinson's disease rating scale, part III [UPDRS III], at 4 months), caregiver burden (belastungsfragebogen Parkinson angehörigen-kurzversion [BELA-A-k] at 4 and 8 months), and costs (during whole study period). Primary analysis was by intention to treat and included scores over 4, 6, and 8 months, with correction for baseline score. The trial is registered at Clinicaltrials.gov, number NCT00518791.

Findings We recruited 301 patients (150 patients in the intervention group and 151 in the control group) between August, 2007, and December, 2009, of whom 285 completed follow-up (last follow-up was July, 2010). 101 (67%) patients in the intervention group visited the expert centre; 49 (33%) opted not to visit the expert centre. The average ALDS score from months 4, 6, and 8, with correction for baseline score, was greater in the intervention group than in the control group (difference 1·3 points, 95% CI -2·1 to 2·8; corresponding raw logit score difference 0·1, 95% CI 0·003 to 0·2) as was the average PDQL score (difference 3·0 points, 0·4 to 5·6). Secondary analysis with correction for baseline disease severity showed no differences between groups for ALDS (difference 0·9 points, 95% CI –0·6 to 2·4; corresponding raw logit 0·1, –0·02 to 0·3) or PDQL (difference 1·7 points, –1·2 to 4·6). Secondary outcomes did not differ between groups (UPDRS III score difference 0·6 points, 95% CI –1·4 to 2·6; BELA-A-k score difference 0·8 points, –0·2 to 1·8; cost difference €742, –€489 to €1950).

Interpretation This integrated care approach offered only small benefits to patients with Parkinson's disease, and these disappeared after correction for baseline disease severity. These results suggest that different approaches are needed to achieve more substantial health benefits.

Introduction

Parkinson's disease is increasingly recognised as a multidimensional disorder. In addition to classic motor symptoms, patients have a wide variety of non-motor symptoms that substantially affect quality of life but often remain unrecognised and untreated.[1] Moreover, most non-motor features do not respond satisfactorily to dopaminergic drugs, and some might even get worse, such as orthostatic hypotension and cognitive function.[1] Therefore, the possible benefits of non-pharmacological interventions are generating interest. A multidisciplinary approach combining pharmacological treatment with non-pharmacological interventions to manage a complex disorder such as Parkinson's disease might be beneficial.[2] Despite the shortage of evidence for effectiveness,[3] guidelines recommend regular access to a broad range of medical and allied health-care professionals.[4-5] Indeed, many centres deliver integrated and multidisciplinary care for patients with Parkinson's disease.[2,6] However, a standard template for multidisciplinary care in Parkinson's disease does not exist, and guidelines do not clarify how a team approach should be organised and structured. We developed an integrated model to organise care for patients with Parkinson's disease, with two complementary elements: an individually tailored assessment by a multidisciplinary team that defines a comprehensive treatment plan (including advice on drug treatment and recommendations for non-pharmacological interventions); and subsequent implementation of this plan within a network of specifically trained allied health professionals, supervised by the referring neurologist.[7] To assess the effectiveness of this model, we designed Integrated Multidisciplinary care for Parkinson's disease: a Controlled Trial (IMPACT) to compare outcomes in patients with Parkinson's disease who had access to this model of care with those in patients receiving standard care.

Methods

Study design and participants

We recruited patients for this non-randomised, controlled trial from neurological outpatient clinics in six community hospitals in the Netherlands—two in a region where the intervention was available (intervention region), and four in regions where it was not (control regions; appendix). The control regions were geographically separated from the intervention region. Inclusion criteria were having Parkinson's disease (diagnosed by a neurologist according to UK Brain Bank criteria),[8] being aged 20–80 years, living independently in the community, being able to complete questionnaires, having no severe cognitive impairment (mini-mental state examination ≥24), having no severe comorbidity that interfered with daily functioning, and having a planned routine follow-up consultation with the treating neurologist. Exclusion criteria were having atypical parkinsonian syndromes, being wheelchair bound (Hoehn and Yahr [HY] stage 5), having other neurological disorders, intending to have a deep brain stimulation procedure within the intervention period, and having a previous assessment at the expert centre in the intervention region. Signed informed consent from each patient was

obtained at the start of the research assessment. The study protocol was submitted for review to the medical ethics committee of the Radboud University Nijmegen Medical Centre, but they declared that formal judgment was not required.

Randomisation and masking

The type of intervention did not allow for randomisation, because the integrated organisation of care was confined to one specific region were the tertiary expert centre and allied health-care networks were available. Therefore, we compared patients recruited from hospitals within the intervention region (containing the integrated care model) with those recruited from the control regions, where this infrastructure of care was absent. Patients and caregivers were masked to differences in organisation of care between the intervention and control regions. The research staff was responsible for all research activities, but had no role in the multidisciplinary assessment or treatment of patients. The clinical team was masked to trial participation and was not involved in any research activities related to the outcome measures; they assessed patients at the centre. Treatment was administered by regional therapists. The patients' own neurologists were aware that patients were invited to participate in the trial and of the differences between the regions, but were not told whether patients had accepted or declined participation. The Parkinson's disease nurses in the two community hospitals in the intervention region were aware of participation in the trial and of the differences between the two regions. The Parkinson's disease nurses in the control regions were not involved in trial activities, but might have been aware that patients had been invited to participate in the trial.

Procedures

In the intervention region, organisation of care was integrated by combining the services of an expert tertiary referral centre for Parkinson's disease (the Parkinson Centre of the Radboud University Nijmegen Medical Centre) with those of ParkinsonNet - a regional network of health-care providers who specialise in treating and managing patients with Parkinson's disease. A detailed description of the multidisciplinary assessment in the expert centre is provided in the appendix. All patients were assessed at baseline, and about two weeks later met their own neurologist for a routine follow-up visit. Participants in control regions received their usual care. By contrast, after the baseline assessment and visit to the neurologist, patients in the intervention group then met the Parkinson's disease nurse of their local hospital who offered them an optional visit to the expert centre. This visit was scheduled immediately for participants who consented. Otherwise, usual care was continued. After the multidisciplinary assessment in the expert centre, patients were followed up by the same nurse. When patients in the intervention group visited the expert centre they received an individually tailored 3-day assessment by a multidisciplinary team of medical and allied health-care professionals. These consultations were followed by an integrated face-to-face meeting of all team members and a treatment plan, created on the basis of consensus building between all of the medical and

allied health-care professionals, was discussed subsequently with the patient and caregiver. This plan included medical advice for the referring neurologist plus referrals to allied health professionals (physiotherapists, occupational therapists, and speechlanguage therapists) working in the ParkinsonNet network. Key elements included dedicated training of all professionals, treatment according to evidence-based guidelines, structuring of referral processes, and optimisation of communication between specialists.[7]

Table 1 Similarities and differences in healthcare between the intervention and control regions

	Intervention region	Control regions
Expert assessment in tertiary movement disorders centre	Yes	No
ParkinsonNet network of allied health-care professionals who specialise in Parkinson's disease (physiotherapists, occupational therapists and speech-language therapists)	Yes	No
Community neurologists	Yes	Yes
Community-based allied health-care professionals without ParkinsonNet training	Yes	Yes
Medical specialists (other than neurologist; see table 3)	Yes	Yes

The expert centre and ParkinsonNet services were accessible to patients in the intervention region, but not to patients in control regions (Table1). This approach in the intervention region fits the conceptual framework of an integrative model of team health-care practice.[9] The organisation of care in control regions was not changed by the investigators; professionals working in the control regions were free to change their care services as they saw fit. In both groups, health professionals could initiate any assessment or treatment that they thought to be appropriate. After the initial baseline assessment, all patients were assessed at 2, 4, 6, and 8 months (Figure1). Meetings were scheduled with trained research assistants at baseline and 4 months. Questionnaires that could be completed by patients were sent to the patients' homes. Participating caregivers completed questionnaires at baseline, 4 months, and 8 months.

The primary outcomes were activities of daily living and quality of life; differences between groups over 4, 6, and 8 months were analysed. Activities of daily living were assessed with the Academic Medical Centre linear disability score (ALDS).[10-14] The ALDS is a generic item bank that quantifies functional status by the ability to undertake activities of daily life using an item response theory framework. The item bank includes activities hierarchically ordered

from relatively easy to difficult. Based on item parameters for each of these activities and algorithms, ALDS logits are calculated. These logits are used in the analysis and transformed to ALDS scores to make the results easier to interpret. For this study, 30 activities of daily living were selected and the maximum ALDS score was 90. Higher scores suggest a better functional status. Quality of life was assessed with the Parkinson's disease quality of life questionnaire (PDQL).[15-16] This disease-specific assessment contains 37 items allocated to four subscales: parkinsonian symptoms (14 items), systemic symptoms (seven items), emotional functioning (nine items), and social functioning (seven items). The overall score ranges from 37 to 185, with higher scores suggesting a better quality of life.

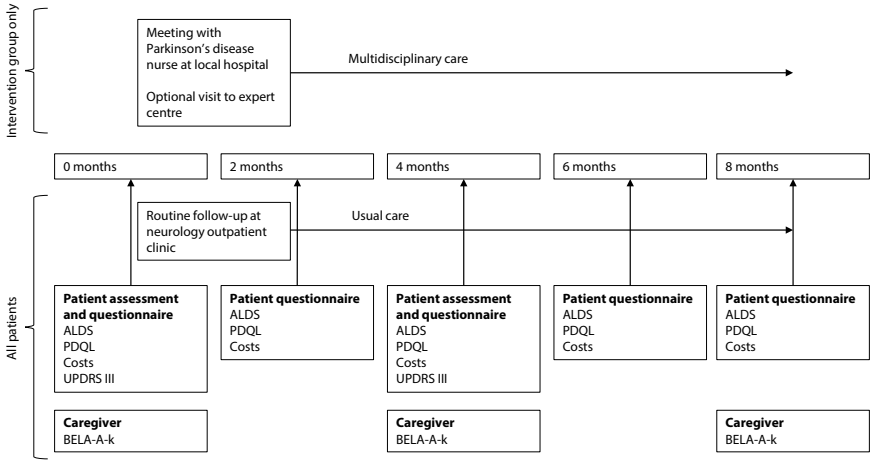

Figure 1 *Study design. Informed consent was obtained at baseline (0 months). Costs refer to total health-care costs, assessed by questionnaires about health-care use completed by patients.*
ALDS Academic Medical Centre linear disability score; *BELA-A-k* belastungsfragebogen Parkinson angehörigen-kurzversion; *PDQL* Parkinson's disease quality of life questionnaire; *UPDRS III* unified Parkinson's disease rating scale, part III.

Secondary health outcomes were changes in motor functioning - measured by the unified Parkinson's disease rating scale, part III (UPDRS III), a motor assessment scored by trained research assistants[17] - and caregiver burden - measured by the "bothered by" subscale of belastungsfragebogen Parkinson angehörigen - kurzversion (BELA-A-k), a questionnaire for measuring caregivers' psychosocial problems caused by caring for an individual with Parkinson's disease.[18] Health-care costs were estimated from a societal perspective with a detailed questionnaire completed by patients at baseline, 2, 4, 6, and 8 months, each covering their health-care use over the previous 2 months. We then used this data to calculate total costs on the basis of microcosting (appendix).[19-20]

Tertiary endpoints included changes in generic quality of life (36-item short-form health survey, version 2 [SF-36v2]), depression and anxiety (hospital anxiety and depression scale

[HADS]), fear of falling (falls efficacy scale–international [FES-I]), freezing of gait (freezing of gait questionnaire), ability to undertake activities of daily living (self-assessment Parkinson's disease disability scale [SPDDS]), and overall wellbeing (measured with a 100-point visual analogue scale), all measured at baseline, 4 months, and 8 months; non-motor symptoms (non-motor symptoms [NMS] scale), treatment-related motor and non-motor complications (UPDRS IV), activity limitations (patientspecific index for physiotherapy in Parkinson's disease [PSI-PD]), balance (single leg stance), turning, and the Parkinson activity scale, measured at baseline and 4 months; fall frequency (monitored weekly with the Falls Telephone);[21] and a questionnaire on quality of care (not standardised) measured at 4 months. For caregivers, tertiary health outcomes were depression (HADS) and quality of life (SF-36v2), measured at baseline, 4 months, and 8 months, and their view on the patients' ALDS. Because the entire proposed assessment proved too cumbersome and tiring for study participants, the Berg balance scale and caregivers' views on patients' memory (memory assessment clinic rating scale) were assessed at baseline but left out during follow-up assessments.

Statistical analyses

We estimated that a sample size of about 300 patients was needed to detect a difference of 2 points in ALDS scores, with 80% power and 5% significance (two-sided), assuming a standard deviation of 9 and a correlation of 0·7 between the measurements.[14] We assessed primary outcomes by a random effects repeated measures analysis whereby ALDS and PDQL scores measured at 4, 6, and 8 months were compared between groups. Because the ALDS has been developed within the framework of item response theory, the analyses were based on the original units of measurements (logits).[22] We analysed scores from months 4–8 using a linear mixed model, with random factor patient and fixed factors treatment, baseline value, assessment time (4, 6, and 8 months), and the interaction of assessment time and treatment. We included patients with at least one measure at 4, 6, or 8 months in the analysis of health outcomes. Other variables were analysed similarly. We analysed health-care costs over the 8 months with correction for baseline costs over the 2 months preceding study participation. As the costs data were highly skewed, with some outlying values, we used the bootstrap procedure to generate 1000 new samples from the data; we calculated the confidence interval on the basis of these samples.The primary analysis was by intention to treat. After completion of enrolment we noticed that some baseline characteristics differed between the intervention and control groups. Therefore, we did secondary analyses according to UPDRS III score, disease duration, HY stage, NMS score, and daily levodopa equivalent dose (mg). Not all patients in the intervention group opted for the multidisciplinary assessment in the expert centre. Therefore, we did a secondary post-hoc per-protocol analysis for the primary outcomes, comparing patients who had actually received the expert multidisciplinary assessment with patients in the control group. The trial is registered at Clinicaltrials.gov, number NCT00518791.

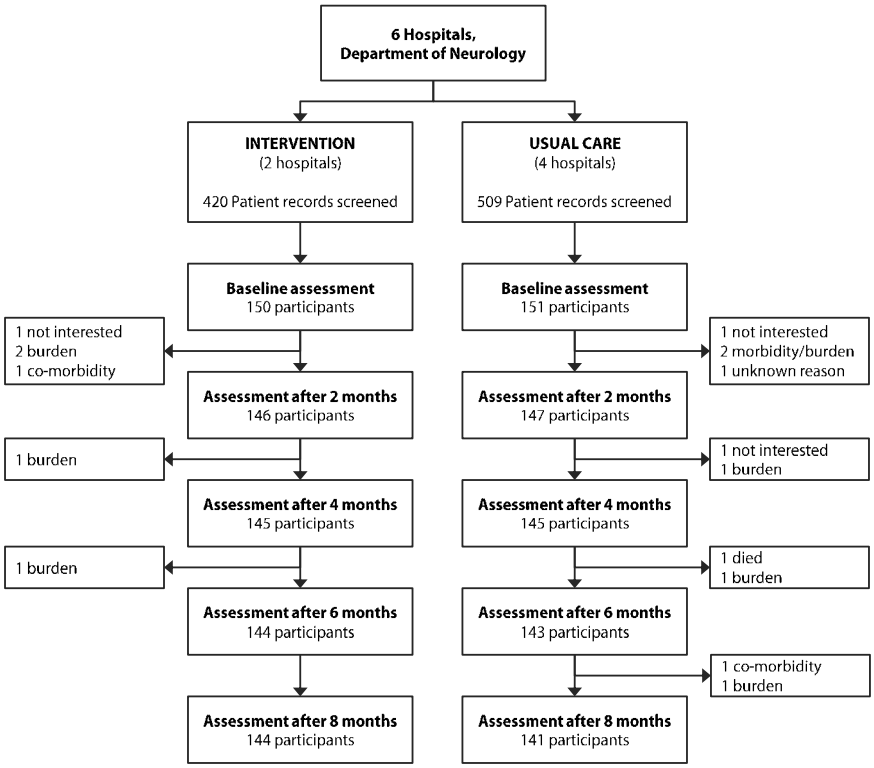

Figure 2 *Recruitment and dropout. Burden refers to patients who either found involvement in the study a burden, or whose Parkinson's disease become too much of a burden for them to continue.*

Results

We recruited 301 patients (150 patients in the intervention group and 151 in the control group) between August, 2007, and December, 2009, of whom 285 completed follow-up (5% dropout rate; figure2). The final follow-up measurement took place in July, 2010. Of the 150 participants in the intervention group, 101 (67%) received a multidisciplinary assessment. 49 (33%) patients opted not to visit the expert centre. Reasons to decline included lack of perceived benefit or an anticipated burden of having to attend the 3-day assessment. 196 caregivers participated: 102 in the intervention group (31 [30%] were men, and the mean age was 64·0 [SD 9·3] years) and 94 in the control group (32 [34%] men, mean age 65·6 [9·8] years). At baseline, patients in the intervention group were younger, and had shorter disease duration and less disease severity (lower UPDRS motor scores) than did patients in the control group (Table 2).

Table 2 Baseline characteristics

	Intervention group (n=150)	Control group (n=151)
Age (years)	66·5 (8·2)	69·3 (7·6)
Men	96 (64%)	92 (61%)
Time since diagnosis (years)	5·8 (4·2)	6·8 (4·8)
Modified Hoehn and Yahr stage*		
HY 1	28 (19%)	33 (22%)
HY 1.5	6 (4%)	5 (3%)
HY 2	65 (43%)	38 (25%)
HY 2.5	22 (15%)	9 (6%)
HY 3	24 (16%)	60 (40%)
HY4	2 (1%)	4 (2,6%)
UPDRS III, motor scores (0-108)*	25·6 (11·1)	32·6 (12·1)
Daily levodopa equivalent dose (mg)	494 (402)	580 (305)

Data are mean (SD) or number (%). UPDRS III unified Parkinson's disease rating scale part III; *HY* Hoehn and Yahr.
**Data for HY stage and UPDRS III were not obtained in three patients in the intervention group and two patients in the control group because these patients refused to be examined.*

An overview of consultations during the expert assessment and subsequent referrals is presented in the appendix. 90 patients were referred to one or more regional allied health-care professionals, resulting in 271 referrals. These referrals were not always implemented; 197 (73%) referrals led to consultations. Seven (8%) of the 90 referred patients had no resultant consultations. Referrals that included a recommendation to start a new treatment resulted in a consultation in 41 (98%) of 42 patients referred to physiotherapy, 37 (74%) of 50 referred to occupational therapy, and 24 (65%) of 37 referred to speech-language therapy. Assessment of health-care use showed that patients in both groups were treated by several health professionals (Table 3), therefore, control patients also received some multidisciplinary care.

Both primary endpoints showed small improvements in favour of the intervention. At 4–8 months, average ALDS score was 1·3 points greater (95% CI -2·1 to 2·8; corresponding raw logit score difference of 0·1, 0·003 to 0·2) in the intervention group than in the control group (p=0·045), and PDQL score was 3·0 points (0·4 to 5·6) greater in the intervention group than in the control group (p=0·03; Table 4; appendix).

UPDRS III and BELA-A-k scores did not differ between groups (Table 4), apart from the partner bonding subscale of BELA-A-k, which was significantly greater (indicating a greater burden) in the intervention group compared with the control group (appendix). Data for tertiary endpoints are presented in the appendix. We noted significant improvements in the interven-

Table 3 Overview of consultations by medical specialists and allied health professionals during the 8-month study period. These numbers are based on self-reported healthcare and include all evaluations by healthcare professionals, i.e. both single treatment sessions and prolonged treatments (multiple sessions).

Health professional	Intervention group (n=150)	Control group (n=151)
Neurologist	142 (95%)	135 (89%)
PD nurse	93 (62%)	43 (28%)
Physiotherapist	120 (80%)	92 (61%)
Occupational therapist	64 (43%)	8 (5%)
Speech-language therapist	49 (33%)	13 (9%)
Psychologist	25 (17%)	3 (2%)
Psychiatrist	13 (9%)	2 (1%)
Social worker	29 (19%)	2 (1%)
Dietician	14 (9%)	9 (6%)
Rehabilitation specialist	11 (7%)	12(8%)
Sexologist	16 (11%)	0 (0%)
Sleep specialist	1 (1%)	0 (0%)
Geriatrician	3 (2%)	1 (1%)
Nursing home specialist	1 (1%)	1 (1%)
Other specialist (e.g. cardiologist, urologist, internist)	54 (36%)	62 (41%)

tion group compared with the control group in: anxiety and depression (HADS); activities of daily living (SPDDS); non-motor symptoms (total NMS scale score); SF-36 role limitations due to physical health, role limitations due to emotional problems, and vitality; and perceived general health (visual analogue scale). Quality-of-care scores were better in the intervention group, but overall satisfaction was not different from the control group. Changes in levodopa equivalent doses during the 8 month follow-up were similar between groups (difference of -1%, 95% CI -26 to 32).

Secondary analysis with additional correction for overall disease severity removed the group differences for both primary outcomes (Table 4).

The post-hoc per-protocol analysis showed that the difference in the ALDS score at 4-8 months in the intervention group compared with the control group was the same as that in the intention-to-treat analysis (1·3 points, corresponding raw logit score difference of 0·1, 95% CI -0·01 to 0·3), but the per-protocol analysis showed a greater difference in PDQL score between groups (difference 3·6 points, 0·7 to 6·5) than in the intention-to-treat analysis.

The mean average health-care costs per patient during the 8 month follow-up were €4478 (SD €5544; range €0-37 031) in the intervention group and €5601 (SD €12 260; range €0-135 357) in the control group. Based on bootstrapping analysis, this difference was not significant

Table 4 Primary and secondary outcomes

	Intervention group		Control group		Primary analysis[1]	Secondary analysis[2]
	n	Mean (SD)	n	Mean (SD)	Estimated difference (95%CI)	Estimated difference (95%CI)
Primary outcomes						
ALDS						
Baseline	148	79·2 (11·5)	151	79·8 (10·0)		
Average 4, 6 and 8 months	144	80·8 (7·7)	145	79·5 (10·1)	1·3 (-2·1 to 2·8)†	0·9 (-0·6 to 2·4)†
PDQL						
Baseline	148	139·0 (23·2)	150	141·3 (23·8)		
Average 4, 6 and 8 months	144	142·2 (23·6)	145	140·7 (25·5)	3·0 (0·4 to 5·6)	1·7 (-1·2 to 4·6)
Secondary outcomes						
UPDRS III						
Baseline	147	25·6 (11·1)	149	32·6 (12·1)		
4 months	135	28·4 (11·6)	140	32·9 (11·5)	0·6 (-1·4 to 2·6)	0·3 (-1·8 to 2·4)
BELA-A-k (Bothered by)						
Baseline	101	7·0 (7·3)	94	5·7 (7·5)		
Average 4, 6 and 8 months	94	6·8 (7·0)	90	5·2 (5·6)	0·8 (-0·2 to 1·8)	1·2 (0·04 to 0·2)

ALDS Academic Medical Centre linear disability score; *PDQL* Parkinson's disease quality of life questionnaire; *UPDRS III* Unified Parkinson's Disease Rating Scale motor part; *BELA-A-k* Belastungsfragebogen Parkinson Angehörigen-kurzversion, Bothered By subscale.

[1] Primary analysis with correction for baseline scores for each outcome. [2] Baseline values of UPDRS III, Hoehn and Yahr stage, disease duration, non-motor symptoms score, and daily levodopa use (mg) added as covariates to the primary analysis as an overall measure for disease severity. †Corresponding estimated diff erence according to original measurement units (logits) were 0•1 (95% CI 0•003 to 0•2) for the primary analysis and 0•1 (-0•02to 0•3) for the secondary analysis.

(mean difference €1123, 95% CI -€844 to €3568). Including baseline costs as covariates did not change the significance (mean difference €742, 95% CI -€489 to €1950). Exclusion of outliers did not affect the results.

Discussion

Parkinson's disease is increasingly acknowledged as a multidimensional disorder, with disabling symptoms in physical, emotional, and cognitive domains.[1,4,23] Because of this complexity, many specialised Parkinson's disease clinics worldwide use a multidisciplinary team approach, because this approach is felt to offer the best management of Parkinson's disease.[2,6,24-25] However, this assumption is supported by only a small amount of inconclusive scientific evidence.[3,26] Here, we assessed one specific integrative multidisciplinary approach with two complementary components: expert review in a tertiary movement disorders clinic and subsequent health-care delivery within a regional professional network. Compared with usual care, this approach offered significant improvements for the primary outcomes (activities of daily living and quality of life), but the effect sizes were small and unlikely to be clinically relevant. Moreover, these small effects disappeared after correction for differences in baseline disease severity (controls were more severely affected). Better matching for baseline disease severity could have been achieved with a randomised study design, but this was impractical because the integrated organisation of care was confined to one region where the expert centre and professional network were available; randomisation within this region would have been at risk of contamination, because control patients could have gained access to specialised allied health treatment offered by the regional professional network.

Larger improvements were unlikely to have been missed because of use of insufficiently sensitive outcomes. Large previous trials in Parkinson's disease also used quality of life and activities of daily living as primary outcomes,[22,27-30] with some using ALDS and PDQL scores to measure outcomes. The intervention that we examined was heterogeneous, including an individually tailored multidisciplinary assessment aimed at both motor and non-motor symptoms of Parkinson's disease. This heterogeneity precluded use of a primary outcome that reflected the intervention more closely (eg, gait speed for those who received physiotherapy). Therefore, we selected activities of daily living and quality of life as overarching outcomes.

We noted no effect on secondary outcomes (motor functioning and overall caregiver burden). We were particularly interested in caregiver burden because many patients receive support from their family members, and providing this support can be a substantial burden.[31-32] Although overall caregiver burden did not differ between groups, our results suggest a higher caregiver burden in the intervention group for the partner bonding subscale of BELA-A-k. This paradoxical effect needs to be researched further. The tertiary outcomes showed improvements in various domains, including anxiety, depression, and total NMS scale scores in patients. These non-motor symptoms represent an important target in the management of Parkinson's disease.[1,33-34] However, the benefits for these non-motor symptoms were small and unlikely to be clinically relevant.

We did an economic evaluation from a societal perspective, providing a comprehensive overview of direct and indirect health-care costs. These costs in our Dutch study population fell within the range of costs estimates from six different countries.[35] Our data are consistent with previously reported cost estimates for a Parkinson's disease cohort (n=699) in the Netherlands that participated in an effectiveness study of physiotherapy.[20] The economic evaluation showed that, although the integrated multidisciplinary intervention was complex and more intensive than the care in the control regions, the average costs during the 8 month follow-up were similar in both study groups.

Several factors might have masked larger benefits for the intervention group. First, usual care in the Netherlands often includes a multidisciplinary approach,[36] which might have meant that the contrast in care between groups was small. Indeed, many control patients received some form of allied health care. Moreover, control patients received treatment by a neurologist working in a community hospital, and neurologist care is an important determinant of better clinical outcomes.[37] Usual care in the Netherlands might achieve acceptable results that improved only incrementally with the more intensive integrated care tested in our study. Second, the contrast between both groups was diluted further because the health plan - recommended by the expert centre - was not fully implemented by the community professionals.

Only 73% of all recommended interventions were delivered to intervention patients, and some patients did not receive any follow-up. Delivery of the health plan was left at the discretion of the community neurologist, local Parkinson's disease nurse, and community therapists and we acknowledge this factor as a shortcoming of our approach. A better alternative-used by Parkinson's disease centres in, for example, Tel Aviv (Israel), Toronto (Canada), and Melbourne (Australia)[38-39]-is to incorporate the assessment plus the tailored intervention within one centre, supervised by one case manager for each patient. Third, our primary analysis was based on an intention-to-treat principle. However, only two-thirds of the patients in the intervention group visited the expert centre. The improvement in quality of life was somewhat larger in the per-protocol analysis-excluding patients who did not have a multidisciplinary assessment-suggesting that patients who visited the expert centre benefited more. However, this post-hoc analysis should be interpreted cautiously. Finally, we might not have included patients who were most likely to benefit. Multidisciplinary rehabilitation seems to be most beneficial for patients with higher perceived needs.[40] Conceivably, patients with advanced disease and many disabilities benefit most from multidisciplinary interventions. Yet, in our trial and in previous studies,[39,41] severely affected patients were largely underrepresented. For mildly affected patients, a less comprehensive approach might be more appropriate, and cause less stress to caregivers.

Panel: Research in context

Systematic review

We searched PubMed until Feb 8, 2013, for trials published in English that had the following search terms in the title: "Parkinson disease", "Parkinson's disease", "Parkinsonian disorders", or "parkinsonism" combined with "multidisciplinary", "interdisciplinary", "integrated", "integrated delivery of healthcare", "patient care team", "team approach", or "rehabilitation". We identified four reports[42-45] on multidisciplinary interventions with pre-test–post-test designs, without control groups, and four randomised controlled trials (RCTs).[39-41,46-47]

Interpretation

The published work on multidisciplinary and team care in Parkinson's disease is heterogeneous, in terms of the types of interventions that have been assessed (both the nature and length of the tested intervention), outcomes used, types of interventions (pre-test–post-test design, crossover studies, randomised trials), and duration of follow-up. Our study is unique in terms of sample size (to the best of our knowledge, the largest study in this specialty thus far), comprehensiveness of the team in the expert centre, and low dropout rate. Moreover, we have assessed a new integrated care approach, consisting of a comprehensive assessment by a multidisciplinary team (part of a specialised movement disorders centre), with subsequent treatment by specialised health professionals working in a regional network. Health outcomes focused not only on patients but also on caregivers. We also included an economic evaluation. Our primary outcomes showed benefits in favour of the intervention group, but the effects were too small to be clinically relevant, and were partly attributable to baseline differences. Our study is well timed, in view of societal developments towards delivery of more multidisciplinary care, despite a shortage of supporting evidence. Our results issue caution against overzealous implementation of multidisciplinary interventions, pending further evidence. The heterogeneity of designs, interventions, outcomes, and follow-up complicates a direct comparison with previous studies. Our trial also confronted us with challenges in assessment of this integrated care approach, because several interconnecting components had to be tested, and it was difficult to keep the control intervention stable. Our study offers important lessons about the complexity of designing and assessing a multidisciplinary concept. Overall, our findings and those of previous studies support further development of well designed clinical trials to obtain more knowledge and scientific evidence on how to organise team-oriented care in Parkinson's disease.

Only a few previous trials used controlled designs, with inconsistent results.[2-3,26] Most trials studied the effectiveness of multidisciplinary rehabilitation programmes (Table 5; panel).[40-41,46-47] One Canadian randomised controlled trial closely resembles our trial, both in the study design and the intervention, and both trials assessed ongoing care for 8 months.[39] Specifically, patients received specialised team care by a movement disorders specialist, a Parkinson's disease nurse, and a social worker. This approach positively affected quality of life, motor functioning, depression, and psychosocial functioning. This study and ours have several key differences, including the team size (small team with only three disciplines in the Canadian trial vs a comprehensive approach with up to 13 disciplines in our study), the collaboration structure (informal meetings and hierarchal structure vs regular team meetings with mutual decision making), and the settings (one expert tertiary centre vs a tertiary centre combined with community treatment). Our study is also larger (n=301) than the Canadian trial (n=122). Additionally, usual care in the Canadian trial (where treatment involved only a general neurologist) differs substantially from that in the Netherlands (where many patients receive allied health interventions). The Canadian study included only patients who had been referred to the expert centre because of a perceived need for extra care, whereas we offered the intervention to all patients in the entire region. This difference between the studies might partly explain the difference in outcome, because about a third of patients in each group

Table 5 Previous studies of multidisciplinary interventions for Parkinson's disease

	Design	Number of recruited or randomized patients*	Intervention	Findings
Carne *et al*, 2005 [42]	Pre-test–post-test, no control group	43	Ongoing multidisciplinary care for 1 year follow-up (mean follow-up 12.2 months [range 8-16 months])	Improvements in motor function over 1 year identified on medical records
Carne *et al*, 2005 [43]	Pre-test–post-test, no control group	49	Ongoing multidisciplinary care for 1–3 years (divided into three groups according to timing of most recent follow-up: 12±4 months, 24±4 months, and 36±4 months)	Improvements in motor function over 1-3 years identified on medical records and based on descriptive statistics
Ellis *et al*, 2008 [44]	Pre-test–post-test, no control group	68	Multidisciplinary rehabilitation during hospital stay (mean 20.8 days)	Immediate positive effects on functional status, transfer from a sitting to a standing position, walking ability, and the effect of symptoms on upper-extremity function.
Trend *et al*, 2002 [45]	Pre-test–post-test, no control group	137	Multidisciplinary rehabilitation including individual treatment and group educational support for 6 weeks	Immediate positive effects on: mobility and gait; voice, articulation and speech; depression; and health-related quality of life
Guo *et al*, 2009 [46]	Randomised, single-blinded (neurologists), controlled trial with a pre-test-post-test quasi-experimental design	44	Group education and personal rehabilitation for 8 weeks	Improvement in bodily discomfort at 4 weeks (pre-test–post-test); immediate improvement in quality of life, motor function, activities of daily living, and mood at 8 weeks compared with control group

	Design	Number of recruited or randomized patients	Intervention	Findings
Wade *et al*, 2003 [41]	Randomised, single-blinded (research assessors) controlled trial, crossover pre-test–post-test design	144 (7 duplicates)	Multidisciplinary rehabilitation including individual treatment and group educational support for 6 weeks	Deterioration in disability, physical limitations, general health, health-related quality of life, and carer strain at 24 weeks (pretest–post-test; n=86); decreased scores of mental and general health at 24 weeks compared with the control group (n=94)
Tickel-Degnen *et al*, 2010 [40]	Randomised, single-blinded (evaluator) controlled trial	117	Multidisciplinary rehabilitation (18 or 27 h) for 6 weeks	More patients in the rehabilitation group had improved quality of life compared with patients without rehabilitation, directly after the intervention and at 6 months
White *et al*, 2009 [47]	Randomised, single-blinded (examiners) controlled trial	116	Multidisciplinary rehabilitation (18 or 27 h) for 6 weeks	No immediate effects on walking activity and endurance
Van der Marck *et al*, 2013 [39]	Randomised, single-blinded (clinical and research team) controlled trial	122	Ongoing care by a multidisciplinary specialist team (movement disorders specialist, Parkinson's disease nurse, and social worker) for 8 months, compared with care by a general neurologist only	Benefits for quality of life, motor functioning, depression, and psychosocial functioning over 8 months

**Number of patients actually analysed differed in some studies from the number recruited or randomized*

in our trial were in the early stages of Parkinson's disease (HY stage 1-1·5) and might have been less likely to improve than patients with more advanced Parkinson's disease. Finally, our patients were masked to treatment assignment, which might also explain why we observed smaller benefits in the intervention group than did the Canadian trial.

Our trial identified several weak links in the tested intervention, raising suggestions as to how to optimise team-based management of Parkinson's disease. First, care was tailored to each patient's individual needs, but this creates a heterogeneous intervention that is difficult to assess. Future studies could test a standard set of interventions for each patient, although this approach might lead to excessive care for some. Second, we offered the expert screening to all patients in the intervention region because we had no a-priori grounds to restrict the treatment to any specific subgroup. However, a third of eligible patients declined to visit the expert centre, partly because they perceived it as having no benefit. This suggests that a multidisciplinary intervention should not be offered routinely to all patients, but reserved for patients with the highest need. Indeed, the Canadian trial, which focused on patients who had been specifically referred to an expert centre, reported greater beneficial effects after multidisciplinary treatment.[39] A third limitation was that the expert centre offered expert advice but responsibility for the actual treatment was outsourced to the community team who were left free to modify the treatment plan. Our analysis showed undertreatment in the intervention group, in which not all patients received the recommended treatments from specialised community therapists. This finding suggests that expert centres should take responsibility for chronic care, either by delivering the actual interventions, or by coordinating community care with individual case managers.

We conclude that the integrated approach assessed in this study offered only a small benefit compared with multidisciplinary usual care delivered in the Netherlands. We assessed an integrated intervention that seemed ideal in theory, but we encountered challenges with respect to the applicability and feasibility of this model in the healthcare system. As such, our study extends beyond the question of effectiveness, because it highlights challenges that come with the assessment of a complex multidisciplinary intervention, in the face of the realities of a changing healthcare system. Our results fuel the need for development of improved interventions. The evidence supporting the merits of isolated allied healthcare interventions is growing,[48-50] but more work is needed to investigate how these separate interventions are best bundled into a multidisciplinary approach. Finally, future studies should assess how patients and caregivers could engage in the discussion on how to optimise Parkinson's disease care, because this research will help us to explain why many patients declined the intervention in our study, to develop real patient-centred care, and to identify which patients are likely to benefit most.

Contributors

BRB and MM obtained funding. BRB, MM, MAvdM, GFB, EMH, and WM developed the study concept, design, and protocol. MAvdM coordinated the trial, and, together with MM and BRB, oversaw data collection, data cleaning, merging of datasets, and preparations of extracts for analysis. GFB led the analysis. BRB, MM, MAvdM, GFB, and SO contributed to interpretation of findings and preparation of the report. All authors approved the final version.

IMPACT study group members

All authors were members of the IMPACT study group, which also included Henk-Willem Nijmeijer and Theo J Tacke (Ziekenhuis Groep Twente, Almelo, Netherlands); Okke L G F Sinnige (Medisch Centrum Leeuwarden, Leeuwarden, Netherlands); and Jack N Wessel (Wilhelmina Ziekenhuis Assen, Assen, Netherlands).

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Supplementary Appendix

Methods

Recruitment participants and hospitals

Study coordination took place at the Parkinson Centre Nijmegen of the Radboud University Nijmegen Medical Centre. Participants were recruited from the neurological outpatient clinic of six hospitals. Two hospitals were selected as the intervention region as they were in the direct referral area of the Parkinson Centre Nijmegen and as regional ParkinsonNet networks were already present. The control regions were selected based on the following criteria: 1) comparable with intervention hospitals with regard to the number of neurologists and number of hospital beds, and 2) absence of a ParkinsonNet network or a comparable organisation for comprehensive multidisciplinary care. Healthcare records of all patients with PD within the participating hospitals were screened to identify eligible participants. Eligible patients received a written invitation to participate. Responders were telephonically contacted by the research team to further assess eligibility and schedule the baseline assessment in the two weeks prior to their routine follow-up consultation with their neurologists.

Intervention

Individually tailored assessment

At the Parkinson Centre Nijmegen, patients received an individually tailored 3-day assessment by a team of specifically trained health professionals, including movement disorders specialists, PD nurse specialists, social workers, physiotherapists, occupational therapists, speech therapists, sleep specialists, dieticians, sexologists, neuropsychologists, neuropsychiatrists, rehabilitation specialist, and geriatricians. The team consisted of permanent team members and several professionals whose input was tailored to the needs and priorities indicated by the patients. Initially, the permanent team included the movement disorders specialist, PD nurse specialists and physiotherapist. The social worker instead of the physiotherapist was part of the permanent team for fourteen patients. The needs and priorities of the patients were obtained via a comprehensive questionnaire including all possible problem areas in PD, which was sent to patients prior to their visit. At the end of the questionnaire, patients were asked to indicate which symptoms and disabilities particularly needed clinical attention. Caregivers were asked to accompany the patient during the assessment. The individual assessment took place during two consecutive days that were separated by a week, followed by a multidisciplinary meeting at the third day.

Integrated treatment

Based on the consultations and a multidisciplinary meeting with all team members involved, an integrated treatment advice was written and subsequently discussed with the patient and their caregivers. This advice included referrals to health professionals working in the patients'

direct vicinity, including referrals to allied health therapists within the ParkinsonNet networks. Initially, this concept was designed for cooperating physiotherapists.[7] At the time of the study, the ParkinsonNet networks included community neurologists, physiotherapists, occupational therapists and speech-language therapists. These networks were implemented in the intervention region from 2004[51] and were accessible to all patients in the intervention group, even if they were not enrolled in the study or did not receive the multidisciplinary assessment in the Parkinson Centre Nijmegen.

Quality of care

Quality of care for Parkinson's disease was assessed with a self-developed questionnaire. This questionnaire included questions on integration of care, the possibility to ask questions and satisfaction with obtained answers and information (n=4); questions related to the communication and referral process between health professionals and their involvement and expertise (n=6); attention to PD specific problems including medication, sleep, depression and mood, constipation, urinary problems, balance and fall risk, speak and swallowing, driving ability, cognition, intimacy and sexuality, and work and leisure time (n=11). Answers were based on a 5 point Likertscale. Attention to specific PD problems was reported on a 4 point scale with an additional option to state that there were no problems with that specific topic. Overall satisfaction of all healthcare received was reported on a 10 point-scale (1: very poor; 10: excellent). All questions related to PD care that was received over the preceding six months.

Economic evaluation

Data on the patients' healthcare use were obtained via detailed questionnaires, which also allowed for an evaluation on the extent to which the treatment referrals were implemented in daily care. These questionnaires were completed by patients at baseline, 2, 4, 6 and 8 months, each covering the preceding 8 weeks, and included the following categories of healthcare costs: PD medication, consultation of medical professionals and allied health therapists, day-hospital rehabilitation, admission to hospital, home-care from paid services, informal care, and productivity loss for paid and unpaid labour. Costs were calculated by multiplying volumes of resources by standardized cost prices based on the Dutch guidelines for economic evaluation in healthcare.[19] Costs for medication were valued according to the formal Dutch reference for costs of medication[52] plus purchase costs.[19] Informal care was valued based on standardized prices[19], with a maximum of 8 hours per day, equalling a workday. Missing data were approached as if no costs were made. This analyses was chosen as the most simple and realistic approach. Two other imputation methods, namely imputation by series mean and multiple imputations, were used. All analyses had similar results.

Results

Table 1 Overview of consultations to the different health professionals during the multidisciplinary assessment in the expert centre, the number of patients who were referred to community health professionals for treatment, and the number of patients who reported an actual consultation to these health professionals during the 8-month follow-up of the study

Health professional	Consultations in expert centre	Number of patients referred for treatment	Number of patients who received actual consultation by a community professional
Movement Disorders specialist	101	n.a.	n.a.
Physiotherapist	98	70	69
Occupational therapist	86	52	39
Social worker	72	8	4
Speech therapist	71	38	25
Parkinson's disease nurse specialist	63	49	35
Sexologist	25	5	0
Psychiatrist, psychologist	26	36*	23
Sleep consultant	11	10	2
Dietician	11	1	0
Rehabilitation specialist	1	2	0

* The number of patients referred outnumbers the number of consultations in the expert centre, because the social worker also referred patients to the psychiatrist and psychologist.
N.a. not applicable, patients own neurologist continued treatment

Table 2 Scores of primary and secondary outcome measures

					Primary analysis[1]	Secondary analysis[2]
		Intervention group		Control group	Estimated difference (95%CI)	Estimated difference (95%CI)
	n	Mean (SD)	n	Mean (SD)		
ALDS						
Baseline	148	79·2 (11·5)	151	79·8 (10·0)		
4 months	142	81·6 (7·2)	145	79·5 (10·4)		
6 months	140	81·1 (8·0)	143	79·6 (10·6)		
8 months	140	79·7 (10·6)	141	79·5 (10·7)		
Average 4 to 8 months	144	80·8 (7·7)	145	79·5 (10·1)	1·3 (-2·1 to 2·8)†	0·9 (-0·6 to 2·4)†
PDQL						
Baseline	148	139·0 (23·2)	150	141·3 (23·8)		
4 months	142	143·7 (22·7)	145	141·8 (26·2)		
6 months	140	141·2 (24·7)	143	140·2 (25·5)		
8 months	140	141·6 (25·6)	140	140·1 (27·2)		
Average 4 to 8 months	144	142·2 (23·6)	145	140·7 (25·5)	3·0 (0·4 to 5·6)	1·7 (-1·2 to 4·6)
UPDRS III						
Baseline	147	25·6 (11·1)	149	32·6 (12·1)		
4 months	135	28·4 (11·6)	140	32·9 (11·5)	0·6 (-1·4 to 2·6)	0·3 (-1·8 to 2·4)
BELA-A-k (Bothered by)						
Baseline	101	7·0 (7·3)	94	5·7 (7·5)		
4 months	81	6·2 (6·5)	90	5·0 (5·3)		
8 months	91	7·1 (7·4)	85	5·3 (6·2)		
Average 4 to 8 months	94	6·8 (7·0)	90	5·2 (5·6)	0·8 (-0·2 to 1·8)	1·2 (0·04 to 0·2)

ALDS Academic Medical Centre linear disability score; *PDQL* Parkinson's Disease Quality of Life questionnaire; *UPDRS III* Unified Parkinson's Disease Rating Scale motor part; *BELA-A-k* Belastungsfragebogen Parkinson Angehörigen-kurzversion, Bothered By subscale.

[1] Primary analysis with correction for baseline score

[2] Baseline scores of UPDRS III, Hoehn and Yahr stage, disease duration, Non Motor Symptoms score and daily levodopa use (mg) added as covariates to the primary analysis as overall measure of baseline disease severity

† Corresponding estimated diff erence according to original measurement units (logits) were 0·1 (95% CI 0·003 to 0·2) for the primary analysis and 0·1 (–0·02to 0·3) for the secondary analysis.

Table 3 Primary and secondary health outcomes with summary index and subscale scores

	Intervention group		Control group		Estimated difference (95%CI)
	n	Mean (SD)	n	Mean (SD)	
Primary health outcomes					
ALDS					
Baseline	148	79·2 (11·5)	151	79·8 (10·0)	
Mean 4 to 8 months	144	80·9 (7·7)	145	79·5 (10·1)	1·3 (-2·1 to 2·8)†*
PDQL					
Summary index					
Baseline	148	139·0 (23·2)	150	141·3 (23·8)	
Mean 4 to 8 months	144	142·3 (23·6)	145	140·3 (25·5)	3·0 (0·4 - 5·6)*
Parkinsonian symptoms					
Baseline	148	51·1 (9·5)	150	52·3 (9·3)	
Mean 4 to 8 months	144	52·6 (9·3)	145	52·2 (9·5)	1·0 (-0·1 - 2·1)
Social functioning					
Baseline	148	27·3 (5·5)	151	27·7 (5·8)	
Mean 4 to 8 months	144	27·4 (5·7)	148	27·2 (6·2)	0·31 (-0·4 - 1·0)
Systemic symptoms					
Baseline	148	25·5 (4·7)	151	25·9 (5·2)	
Mean 4 to 8 months	144	26·0 (4·7)	145	25·9 (5·2)	0·31 (-0·3 - 1·0)
Emotional functioning					
Baseline	148	35·1 (6·2)	151	35·4 (6·4)	
Mean 4 to 8 months	144	36·4 (5·9)	145	35·1 (6·7)	1·3 (0·5 - 2·1)*
Secondary health outcomes					
UPDRS III					
Baseline	147	25·6 (11·1)	149	32·6 (12·1)	
Mean 4 months	135	28·4 (11·6)	140	32·9 (11·5)	0·6 (-1·4 to 2·6)
BELA-A-k (Bothered By)					
Baseline	101	7·0 (7·3)	94	5·7 (7·5)	
Average 4 to 8 months	94	6·8 (7·0)	90	5·2 (5·6)	0·8 (-0·2 to 1·8)
Achievement capability/ physical symptoms					
Baseline	101	1·8 (2·3)	94	1·4 (2·3)	
Average 4 to 8 months	94	1·7 (2·2)	90	1·3 (1·8)	0·1 (-0·2 to 0·5)
Fear/ emotional symptoms					
Baseline	101	2·6 (2·8)	94	2·1 (2·7)	
Average 4 to 8 months	94	2·4 (2·5)	90	1·9 (2·0)	0·3 (-0·1 to 0·7)
Social functioning					
Baseline	102	1·4 (1·9)	94	1·0 (1·6)	
Average 4 to 8 months	94	1·4 (1·8)	90	1·0 (1·3)	0·1 (-0·2 to 0·4)
Partner-bonding/family					
Baseline	102	1·3 (1·7)	94	1·3 (1·8)	
Average 4 to 8 months	94	1·3 (1·5)	90	1·0 (1·3)	0·3 (0·1 to 0·6)*

ALDS Academic Medical Centre linear disability score; *PDQL* Parkinson's Disease Quality of Life questionnaire; *UPDRS III* Unified Parkinson's Disease Rating Scale motor part; *BELA-A-k* Belastungsfragebogen Parkinson Angehörigen - kurzversion, Bothered By subscale.

* Statistically significant, p<0.05

† These values correspond with original measurements units (logits) of 0·1 (95%CI 0·003 to 0·2)

Table 4 Tertiary health outcomes

	Intervention group		Control group		Estimated difference (95%CI)
	n	Mean (SD)	n	Mean (SD)	
HADS Anxiety					
Baseline	145	6·1 (4·0)	151	4·9 (3·5)	
Average 4 to 8 months	141	4·9 (3·5)	144	4·9 (3·3)	-0·7 (-1·3 to -0·2)*
HADS Depression					
Baseline	145	5·4 (3·8)	151	4·9 (3·6)	
Average 4 to 8 months	141	4·7 (3·4)	144	5·0 (3·6)	-0·5 (-1·0 to -0·1)*
FES-I					
Baseline	136	25·9 (9·3)	151	25·2 (8·8)	
Average 4 to 8 months	141	25·7 (9·4)	143	26·5 (9·8)	-1·2 (-2·4 to 0·1)
FOGQ					
Baseline	138	6·0 (4·7)	151	6·0 (5·3)	
Average 4 to 8 months	141	5·8 (4·7)	144	6·4 (5·2)	-0·3 (-0·9 to 0·2)
SPDDS					
Baseline	149	38·2 (11·1)	151	36·7 (11·1)	
Average 4 to 8 months	141	37·4 (11·4)	144	38·1 (12·8)	-1·5 (-2·9 to -0·1)*
NMS Scale					
Baseline	146	47·3 (38·7)	145	35·7 (35·6)	
Average 4 to 8 months	138	37·6 (36·5)	140	38·9 (38·5)	-9·8 (-15·8 to -3·7)*
Cardiovascular					
Baseline	146	1·5 (3·2)	145	0·9 (2·3)	
Average 4 to 8 months	138	0·6 (1·9)	140	0·8 (2·4)	-0·3 (-0·8 to 0·2)
Sleep/fatigue					
Baseline	146	11·1 (11·1)	145	7·2 (9·1)	
Average 4 to 8 months	138	7·8 (9·5)	140	7·6 (9·1)	-1·5 (-3·3 to 0·4)
Mood/cognition					
Baseline	146	6·2 (11·3)	145	3·1 (7·6)	
Average 4 to 8 months	138	4·7 (9·3)	140	4·1 (8·9)	-1·0 (-2·9 to 0·9)
Perceptual problems					
Baseline	146	0·9 (3·2)	145	1·2 (3·1)	
Average 4 to 8 months	138	1·0 (3·8)	140	1·2 (3·1)	0·08 (-0·5 – 0·6)
Attention/memory					
Baseline	146	5·2 (7·1)	145	4·3 (7·2)	
Average 4 to 8 months	138	4·4 (6·8)	140	4·4 (7·1)	-0·3 (-1·6 to 1·0)
Gastrointestinal					
Baseline	146	4·8 (6·7)	145	4·2 (6·3)	
Average 4 to 8 months	138	4·2 (7·1)	140	5·1 (7·3)	-1.4 (-2·6 to - 0·1)*
Urinary					
Baseline	146	9·2 (10·9)	145	7·6 (10·1)	
Average 4 to 8 months	138	7·9 (10·5)	140	9·0 (10·1)	-2·4 (-4·3 to - 0·6)*
Sexual function					
Baseline	146	3·3 (6·0)	145	2·0 (4·3)	
Average 4 to 8 months	138	2·4 (5·7)	140	1·5 (2·7)	0·5 (-0·5 to 1·6)
Miscellaneous					
Baseline	146	5·3 (7·8)	145	5·2 (7·3)	
Average 4 to 8 months	138	4·7 (6·7)	140	5·4 (7·7)	-0·7 (-2·1 to 0·7)

	Intervention group		Control group		Estimated difference (95%CI)
	n	Mean (SD)	n	Mean (SD)	
UPDRS IV					
Baseline	148	2·6 (2·5)	150	2·4 (2·2)	
Average 4 to 8 months	137	2·1 (2·1)	139	2·4 (2·1)	0·4 (- 0·8 to 0·06)
SF-36					
Physical functioning					
Baseline	149	61·6 (24·3)	150	61·7 (25·5)	
Average 4 to 8 months	141	62·7 (24·5)	144	60·8 (25·7)	1·6 (-1·4 to 4·5)
Role physical					
Baseline	148	51·6 (24·3)	150	56·6 (25·9)	
Average 4 to 8 months	141	54·8 (23·9)	144	54·7 (25·2)	4·1 (0·3 to 7·9)*
Role emotional					
Baseline	148	70·6 (27·0)	150	72·6 (26·9)	
Average 4 to 8 months	141	70·6 (23·0)	144	66·7 (24·4)	4·7 (0·7 to 8·6)*
Vitality					
Baseline	149	56·3 (17·8)	150	60·4 (19·2)	
Average 4 to 8 months	141	58·2 (17·4)	144	58·6 (19·2)	2·7 (0·02 to 5·4)*
Mental Health					
Baseline	149	69·8 (17·6)	150	72·4 (16·7)	
Average 4 to 8 months	141	71·1 (16·3)	144	71·8 (17·6)	1·3 (-1·1 to 3·7)
Social functioning					
Baseline	149	73·8 (24·2)	150	77·8 (21·3)	
Average 4 to 8 months	141	74·9 (21·1)	144	75·6 (20·6)	1·8 (-1·7 to 5·4)
Pain					
Baseline	149	70·9 (24·1)	150	72·3 (24·6)	
Average 4 to 8 months	141	71·4 (22·6)	144	72·9 (22·7)	-0·9 (-4·7 to 2·8)
General health perception					
Baseline	149	50·2 (16·3)	151	50·7 (18·4)	
Average 4 to 8 months	141	51·6 (16·6)	144	50·4 (18·3)	1·5 (-1·2 to 4·2)
Health transition					
Baseline	149	60·7 (19·6)	151	54·5 (22·4)	
Average 4 to 8 months	141	57·6 (21·2)	144	59·2 (17·4)	-3·6 (-7·6 to 0·3)
VAS general health					
Baseline	149	68·2 (13·9)	150	71·0 (14·5)	
Average 4 to 8 months	141	69·0 (12·4)	144	67·4 (13·9)	3·1 (0·8 to 5·4)*
PSI-PD					
Baseline	138	53·4 (17·9)	136	53·9 (17·3)	
4 months	128	53·8 (18·5)	130	57·2 (18·7)	-3·3 (-5·3 to -1·2)
Single leg stance					
Baseline	149	16·1 (11·4)	148	13·0 (11·6)	
4 months	138	16·6 (11·0)	138	13·5 (10·9)	1·5 (-0·7 to 3·6)
PAS					
Baseline	123	50·8 (5·7)	108	47·9 (5·0)	
4 months	123	49·1 (6·5)	108	48·9 (5·4)	-1·3 (-2·4 to -0·3)
Turning 360^0 (seconds)					
Normal speed: left					
Baseline	129	5·4 (5·5)	138	4·8 (1·8)	
4 months	133	4·8 (2·6)	132	4·3 (1·7)	0·3 (-0·15 to 0·73)

	Intervention group		Control group		Estimated difference (95%CI)
	n	Mean (SD)	n	Mean (SD)	
Normal speed: right					
Baseline	129	5·5 (5·7)	137	4·6 (2·0)	
4 months	133	4·8 (3·5)	132	4·3 (1·7)	0·17 (-0·27 to 0·61)
Increased speed: left					
Baseline	129	3·9 (5·1)	137	3·7 (3·9)	
4 months	129	3·5 (3·0)	128	3·1 (1·3)	0·19 (-0·94 to 0·47)
Increased speed: right					
Baseline	129	4·1 (5·8)	137	3·3 (1·5)	
4 months	129	3·5 (2·8)	128	3·1 (1·2)	0·08 (-0·20 to 0·36)
Quality of care#					
Questionnaire score					
4 months	127	70·7 (13·5)	141	65·6 (13·9)	-5·0 (-8·3 to - 1·7)
Overall satisfaction					
4 months	126	7·6 (1·0)	138	7·4 (1·3)	-0·2 (-0·5 to 0·1)
Care costs (€)					
Baseline†	150	850 (1174)	151	1347 (2733)	
Over 8 months studyperiod	150	4478 (5546)	151	5601 (12258)	742 (- 489 to 1950)
CAREGIVER HEALTH MEASURES					
HADS Anxiety					
Baseline	102	4·8 (3·6)	94	4·0 (3·2)	
Average 4 to 8 months	94	4·7 (3·3)	90	4·0 (2·7)	0·2 (-0·4 to 0·7)
HADS Depression					
Baseline	102	2·9 (3·1)	94	2·7 (3·1)	
Average 4 to 8 months	94	3·1 (3·0)	90	2·8 (2·5)	0·1 (-0·3 to 0·6)
SF-36					
Physical functioning					
Baseline	102	82·6 (20·3)	94	80·5 (22·6)	
Average 4 to 8 months	94	81·7 (21·3)	90	81·2 (21·1)	-0·3 (-3·4 to 2·9)
Role physical					
Baseline	102	75·7 (26·7)	94	71·5 (25·1)	
Average 4 to 8 months	94	73·4 (21·9)	90	70·3 (24·0)	0·5 (-3·8 to 4·2)
Role emotional					
Baseline	102	78·0 (25·9)	94	81·0 (21·2)	
Average 4 to 8 months	94	79·3 (20·4)	90	79·6 (20·9)	0·9 (-3·7 to 5·5)
Vitality					
Baseline	102	66·1 (16·8)	94	67·9 (16·9)	
Average 4 to 8 months	94	67·0 (14·7)	90	68·1 (15·8)	0·6 (-2·2 to 3·4)
Mental Health					
Baseline	102	73·6 (17·3)	94	78·5 (15·3)	
Average 4 to 8 months	94	74·1 (15·7)	90	79·1 (13·3)	-1·6 (-4·3 to 1·1)
Social functioning					
Baseline	102	85·5 (17·9)	94	85·5 (19·1)	
Average 4 to 8 months	94	85·4 (17·8)	90	85·0 (16·5)	0·5 (-3·3 to 4·3)
Pain					
Baseline	102	79·5 (22·8)	94	79·8 (20·5)	
Average 4 to 8 months	94	79·6 (22·4)	90	79·5 (19·5)	0·09 (-3·8 to 4·0)

	Intervention group		Control group		Estimated difference (95%CI)
	n	Mean (SD)	n	Mean (SD)	
General health perception					
Baseline	102	65·9 (18·6)	94	66·9 (20·0)	
Average 4 to 8 months	94	65·4 (18·3)	90	66·9 (19·0)	0·5 (-2·7 to 3·7)
Health transition					
Baseline	100	52·5 (15·7)	94	55·6 (15·6)	
Average 4 to 8 months	94	51·1 (15·3)	90	54·2 (10·8)	-1·5 (-4·9 to 1·8)
Caregivers view on patients' ADL					
Baseline	102	78·7 (10·6)	94	78·7 (11·8)	
Average 4 to 8 months	94	79·8 (9·8)	90	78·2 (12·9)	1·2 (-0·4 to 2·8)§

HADS Hospital Anxiety and Depression Scale; *FES-I* Falls Efficacy Scale-International; *FOGQ* Freezing Of Gait Questionnaire; *SPDDS* Self-assessment Parkinson's Disease Disability Scale; *NMS Scale* Non-Motor Symptoms Scale; *UPDRS IV* Unified Parkinson's Disease Rating Scale, Complications of therapy; *SF-36* Short-Form 36; *VAS* Visual Analogue Scale; *PSI-PD* Patient Specific Index for Parkinson's Disease, *ALDS* Academic Medical Centre linear disability score.
* Statistically significant, p<0.05
# Measured at 4 months only; analysed with independent sample t-test
† over 8 weeks for enrolment
§These values correspond with original measurements units (logits) of 0·10 (95%CI -0·05 to 0·24, p = 0·18)

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SUMMARY

PD is progressive and disabling disorder, which is typically accompanied by a range of motor and non-motor features. This broad symptom complex, combined with a highly variable individual presentation and progression of the disease, poses a significant treatment challenge to medical specialists. This thesis aimed to cover the broad symptom complex in a structured way, covering the spectrum from identification of individual symptoms to an integrated treatment approach. The multidimensional nature of PD was illustrated by addressing unintentional weight loss and falls. This complexity of PD calls for team-based care, but it is unknown how this team approach should be organised to offer optimal care for PD patients and their caregivers. Therefore, we also addressed the effectiveness of allied health care interventions and two different organisations of team-oriented models in this thesis.

Weight loss

Chapter 2 and 3 addressed unintentional weight loss, which is common among PD patients. The work described in these chapters showed the complexity of weight loss by summing the various causes, and by providing evidence that PD patients have a lower Body Mass Index (BMI) when compared to controls.

In **Chapter 2**, we reviewed the various potential causes of unintentional weight loss in PD. This review showed that various symptoms might lead to different levels in energy balance, i.e. reduced energy intake, reduced intestinal energy absorption and increased energy expenditure. The factors that are co-responsible for unintentional weight loss in PD include not only those that are directly related to neuronal dysfunction and neurodegeneration (like motor disturbances, altered olfaction and cognitive problems), but also secondary factors that are not directly attributable to the neurodegenerative processes itself, but which are nevertheless common, like nausea and other side effects of medication. Because weight loss and low body weight are associated with increased morbidity and mortality, timely detection of weight changes is important for adequate intervention. We addressed some therapeutic strategies and implications for better patient care, for example to improve food intake by offering food more frequently in between meals, and the use of flavour enhancers. Also, changes can be made to the medication regime in order to reduce potential adverse effects. Moreover, nutritional supplements may be used to ensure adequate intake. Overall, a team approach seems warranted in light of the complexity and multifactorial nature of unintentional weight loss in PD. This complexity is not unique for PD, but applies to other neurodegenerative disorders as well. This was also illustrated in this chapter by reviewing the pathophysiology underlying three different major neurological disorders (PD, Alzheimer's disease and Huntington's disease), summing both common (i.e. generic across conditions) and disease-specific features for each of these three conditions.

Unintentional weight loss in PD is caused by a complex interplay of multiple contributing factors. For an adequate intervention, timely detection is important, and a multispecialty team will be required to tackle all causative factors.

A meta-analysis on the literature on body weight in PD patients and controls

Weight loss is frequently described in PD. There is, however, a controversy whether patients have a lower body weight than controls since differences described in the literature were not always statistically significant. Therefore, we performed a meta-analysis to establish if PD patients indeed weighted less compared to controls (**Chapter 3**). In addition, we looked at possible determinants. After a literature search, 12 studies were included that met our inclusion criteria. These combined data showed that patients with PD have a significantly lower BMI of 1.73 (95%CI 1.11-2.35) compared to controls. Hoehn & Yahr (HY) stage was reported in seven studies and pooled data showed a relation with BMI. Patients with HY stage 3 had a significantly lower BMI compared to patients with HY stage 2 (3.9, 95%CI 0.1 - 7.7). Other determinants were inconsistently reported, and did not allow further analysis.

Patients with PD weight significantly less than controls. Disease severity appears to be one of the determinants of weight loss.

Falls prevention

The complexity of PD was further illustrated by providing a comprehensive overview of fall risk factors. Falls are a common and devastating consequence in PD, fuelling the need for falls prevention in this population. Therefore, consensus-based clinical practice recommendations for prevention of falls in PD was presented in **Chapter 4**. We developed a set of concept recommendations which was evaluated during two rounds. First, it was evaluated by 27 clinically active professionals from multiple specialties, and subsequently by 12 falls experts in the field, also from several disciplines. For each risk factor, the following items were evaluated: best method of ascertainment; disciplines that should be involved in the assessment and treatment; and which interventions could be engaged. Risk factors and their associated interventions were included in the final set of recommendations when at least 66% of the reviewing experts agreed. The final overview provided a summary of 31 risk factors to be considered by healthcare teams. These included generic risk factors, like age, side-effects of medication and postural hypotension, and disease-specific risk factors, such as slow mobility, freezing of gait and postural instability. Almost all risk factors required a multispecialty team approach for management, with important roles for the neurologist and PD-nurse specialist. Finally, the expert panel opted for a tailored approach to first identify the specific fall type and to adapt screening and treatment accordingly, over a one-size-fits-all approach including all risk factors for each patient. A routine evaluation of all risk factors remains reserved for high-risk patients without prior falls, or for patients with seemingly unexplained falls.

We developed clinical practice recommendations for the management of falls in PD. Falls prevention in PD is complex, because the risk of falls in this population includes both generic, age-related as well as disease-specific risk factors. Therefore, a multispecialty team approach is required that should preferably be tailored to each patient's individual risk factors.

A new system to monitor fall events: the Falls Telephone

When evaluating the prevalence of falls and effectiveness of falls prevention programs, accurate information about the occurrence fall events is needed. In **Chapter 5** we described the evaluation of an automated telephone system for fall monitoring that could provide a low-cost method for tracking falls for longitudinal studies. This so called "Falls Telephone" consists of a computerized system that automatically makes periodic phone calls (done at an investigator-defined interval), allowing participants to enter the number of falls experienced in the preceding period. We designed an evaluation study to determine the sensitivity, specificity and acceptability of the Falls Telephone, using a set-up where the patients were called at weekly intervals. 119 community-dwelling, non-demented PD patients were followed for one to 40 weeks (mean 20.7 calls per patient). In total, 2465 calls were made. Of these, 173 "no- fall" entries and 115 "fall" entries were verified by personal telephone interviews. We verified whether entries were correctly stored, and whether the reported number of falls represented their actual number of falls in the previous week. All "no-fall" entries and 78% of "fall" entries were confirmed to be correct. Sensitivity to detect falls was 100% and specificity was 87%. With this high specificity, the Falls Telephone obviates the need for time-consuming and costly personal follow-up calls in the majority of non-fallers. Also, user experiences were evaluated in a subgroup of 90 patients during telephonically interviews with questions on several aspects of the usability. We also discussed several alternative ascertainment methods that are frequently used to monitor falls events, such as a falls calendar, fortnightly postcards and a falls hotline, in light of their experience with the Falls Telephone. Findings showed that users regarded the Falls Telephone as a convenient and attractive tool to monitor falls. In addition, cost estimates were provided. Based on a fictive trial of 50 subjects with weekly calls over a one year follow-up, the Falls Telephone was estimated to likely save costs, mainly on personnel requirements.

The Falls Telephone offers an effective, convenient and reliable tool way to monitor falls in population-based studies in patients with PD, and possibly also for other disorders complicated by falls.

Team-based care

The multidimensional nature of PD and the shortcomings of current medical management to adequately control all symptoms call for a broad approach with input from multiple disciplines, as opposed to the single-clinician management which is still the dominant approach for many patients. A team-oriented approach is increasingly regarded as the optimal model to treat a complex disorder like PD. Yet, there is no standard template on how to organize such an approach and there is only limited scientific evidence to support this widespread positive perspective of team-oriented models. **Chapter 6, 7, and 8** focused on the advantages of complementary interventions beyond current medical management.

The scientific evidence to support the merits of individual allied healthcare interventions in PD and multidisciplinary approaches was summarized in Chapter 6. These interventions include physiotherapy, occupational therapy, and speech-language therapy. Allied healthcare can complement current medical management in terms of focus (impact on daily functioning rather than the primary disease process), treatment goal (improve participation in everyday activities), and working mechanism (try to bypass the defective basal ganglia by engaging alternative neural circuitries that are still intact). Nowadays, there is increasing evidence to support the effectiveness of these professions when delivered as a monodisciplinary intervention: class II for both physiotherapy and speech-language therapy, and class III for occupational therapy.[1-3] Despite overlapping treatment goals, allied health carers and medical specialists often work isolated from each other. A team approach, in which multiple disciplines work together, is widely suggested to represent the optimal treatment approach, in light of the broad symptom complex in PD. So far, however, there is only limited scientific evidence to support this contention, and only a few controlled trials have thus far evaluated team-based interventions in PD.

> The scientific evidence for isolated allied healthcare interventions is growing. Preferably, these specialists should work together as a team, instead of working parallel to one another. Although there is a general feeling that such a multispecialty team approach is important and may offer benefits, so far there is only limited research on this topic to support this positive perspective of a team-oriented approach.

A multidisciplinary specialised team approach

In **Chapter 7**, we described the evaluation of a multidisciplinary team model, defined as specialised care by a movement disorders specialist, PD nurse and social worker, whose input was tailored to the patients' individual needs. We studied the effectiveness of this multidisciplinary care approach (intervention group, n=51) through a single-blind randomized controlled trial (RCT) with a waiting list control group (n=49) that received care from a neurologist only. After 8 months, there were improvements in the group randomized to the multidisciplinary team. Subjects in the intervention group improved on quality of

life (PDQ-39, difference 3.4, 95%CI 0.5 – 6.2) and motor scores (UPDRS III, 4.1, 95%CI 0.8 – 7.3) compared to the control group. Also, total UPDRS (5.6, 95%CI 0.9 – 10.3), measures of depressive symptoms (MADRAS, 3.7, 95%CI 1.4 – 5.9) and psychosocial function (SCOPA-PS, 2.1, 95%CI 0.5 – 3.7) were improved in the intervention group. Caregiver burden (CSI) was not different between groups (1.5, 95%CI -1.2 – 4.2). This is one of the first RCTs that gives credence to a multidisciplinary/specialist team approach.

In a single-blind randomized controlled trial, we offer new evidence that specialised care by a multidisciplinary team – consisting of a movement disorders specialist, PD nurse and social worker – offers benefits in several health-related domains (quality of life, motor scores, depression and psychosocial functioning). This is one of the first RCTs that gives credence to a multidisciplinary/specialist team approach.

Towards an integrated model of PD care

Chapter 8 described a large controlled trial aiming to evaluate the effectiveness of an integrated organisation of care. This healthcare model included two complementary elements: (a) an individualized assessment within an expert centre, resulting in set of treatment advices that should next be implemented within (b) regional networks of collaborating allied health professionals. Patients were offered a three-day assessment by a comprehensive team, whose input was tailored to the patient's own needs and priorities (identified by patients before their actual visit to our center, using a comprehensive screening questionnaire). The disciplines included movement disorders specialist, PD nurse specialist, social worker, physiotherapist, occupational therapist, speech therapist, sleep specialist, dietician, sexologist, neuropsychologist, neuropsychiatrist, rehabilitation specialist, and geriatrician. During an integrated meeting (attended by all health professional involved in the assessment of a particular patient), treatment advices were developed. This advice could be implemented by specialised therapists within the patient's vicinity, under supervision of the patient's own neurologist. These specialised allied health professionals (physiotherapists, occupational therapists, and speech-language therapists) worked within regional ParkinsonNet networks.[4-5] Key elements of these networks included specific training, treatment according to evidence-based guidelines, structuring of referral process, and optimization of communication and collaboration between specialists.

We designed a controlled trial comparing intervention region (with the integrated care model; n=150 PD patients) with control regions (usual care; n=151 patients). Effectiveness was evaluated over a 4 to 8 month period after baseline assessment. The primary outcomes, activities of daily living and quality of life, were significantly improved (ALDS 1.3, corresponding with raw logit 0.1, 95%CI 0.003 – 0.2; PDQL 3.0, 95%CI 0.4 – 5.6). These effects were, however, small and disappeared after correction for disease severity at baseline. Secondary outcomes, which were motor scores (UPDRS III) and caregiver burden (BELA-A-k), did not change. A

range of tertiary health outcomes, including non-motor symptoms, anxiety and depression and perceived general health, showed consistent but small improvements. Costs data from a societal perspective did not show statistical differences between the groups over the 8 months follow-up (mean difference €742, 95%CI -€489 – €1950).

In a large controlled trial (the IMPACT study), we showed that an integrated organisation of PD care, including an expert centre complemented by regional networks of specialised therapists, offered only small benefits. Moreover, these improvements disappeared after correction for baseline severity. This trial does not provide evidence that the specific integrative specialised approach tested here offers a more effective model of PD healthcare over usual multispecialty care. One possible explanation is that, while we performed the trial, usual care gradually changed in the Netherlands and also became more multispecialty, thereby diluting the contrast between the study arms.

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GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Partly based on

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Parkinson's disease (PD) poses a significant challenge to medical specialists with respect to both the diagnosis and treatment, due to the wide variety of motor and non-motor symptoms that typically present in patients with PD. Despite this complexity, PD is a treatable disease, and there is more to management than solely drugs. This thesis focused on the multifaceted nature of PD, describing the road from individual symptoms towards team-oriented care approaches. We underscore that such a team approach should also include non-pharmacological interventions, to control the broad symptom complex. It is evident that PD requires expert care delivered by a multispecialty team, and in this thesis, we illustrate this for two specific topics: unintentional weight loss; and fall prevention. Indeed, to optimally treat the various domains affected by PD, a multidisciplinary approach with access to expert care has been recommended by professional guidelines.[1-2] Quality indicators of PD care also emphasize the importance of a broad approach to manage PD.[3-4] A recent Task force of the American Academy of Neurology has provided a core set of quality measures that should guide clinicians in the management of patients with PD, and most of these indicators focus on the non-motor manifestations.[4]

In this thesis, we have described our experience with two types of organisation of team healthcare in two different centres. These two approaches have been evaluated in two different trials, aiming to identify evidence for their effectiveness on a range of health outcomes. Here, we will discuss some of the lessons that we have learned about multifaceted management in PD. These will be addressed below by means of the following three themes: (1) the organisation of care, (2) clinical effectiveness, and (3) challenges to clinical research on multifaceted interventions.

What's in a name? Multispecialty vs multidisciplinary vs multifaceted

Throughout this thesis different words are used, including multispecialty, multidisciplinary and multifaceted. In this discussion, the following definitions are used: by "multispecialty" we mean that multiple health professionals from multiple disciplines are involved. "Multidisciplinary" care is commonly used to describe such a multispecialty approach. Yet, as we adhere to the terminology of Boon *et al.*[5], we interpret the term "multidisciplinary" care as one of the models to organise team collaboration. Although distinctions are made between organisations of healthcare, the terminology is often used interchangeably and many synonyms are used to describe team approaches (e.g., multiprofessional, interprofessional and transdisciplinary care).[6] Moreover, we use "multifaceted" care to indicate the broader approach to manage PD with several elements of care, independent of whether this is provided by one or multiple disciplines.

I. Organisation of care

Although care provided by multiple specialists appears to be the optimal treatment for a complex disorder such as PD, there is no standard template to organise such a team-oriented approach. As a result, the organisation of these team-based approaches differs widely across different Parkinson centres worldwide.[7] Indeed, the two approaches[8-9] that we presented in this thesis shared common elements (e.g., multispecialty, PD expertise, tailored care), but also differed in many ways regarding the actual implementation of care. Table 1 provides an overview of the design of healthcare teams from these two different models. Here, we will discuss some of these elements in more detail.

Table 1 Similarities and differences of the two multispecialty team interventions

	Guttman trial[8] (Chapter 7)	IMPACT trial[9] (Chapter 8)
Disciplines	Relatively small team: • movement disorders specialist • PD nurse • social worker	Comprehensive team: • movement disorders specialist • PD nurse specialist • social worker • physiotherapist • occupational therapist • speech-language therapist • sleep specialist • dietician • sexologist • neuropsychologist • neuropsychiatrist • rehabilitation specialist • geriatrician
Organisation of team work	Multidisciplinary model, hierarchically structured with daily contact between team members	Integrative model with two components: (1) an expert centre, that used consensus and shared decision-making during regular integrated team meetings; and (2) regional networks facilitating collaboration between community healthcare providers
Individually tailored	Consultation by movement disorders specialist, complemented with individually tailored input of PD nurse and social worker	Individually tailored intervention, with movement disorders, PD nurse and physiotherapist as standard team members supplemented by optional input of other team members; Needs and priorities ranked by patient
Setting and implementation of treatment	Expert centre; outpatient clinical service. General neurologist no longer involved	Expert centre and community networks; outpatient clinical service. Treatment by community neurologist and local healthcare providers outside centre
Usual care (Comparator/ control arm)	General neurologist; Access to allied health therapists, but lack of expertise	Predominantly the general neurologist, sometimes supported by PD nurse; Access to allied healthcare, but inadequate referrals and lack of expertise[53]

Team formation

No standard template

As described previously, PD comprises a complex set of motor and non-motor symptoms (Box 2, Chapter 1). Guidelines recommend that patients should be referred and have access to a wide range of therapists.[1-2] Indeed, over twenty healthcare professionals might be involved in PD care to optimally treat this broad symptom complex (Box 4, Chapter 1 Introduction).[1] There is, however, no standard list of disciplines that should be involved in PD care, and it is not known which combination of team members is best, nor what the relative contribution of each specialist within a team can be. Keeping the heterogeneity of symptoms and individual priorities among PD patients in mind, an individually tailored team arrangement seems preferable over a "one size fits all" approach.

A broad team for a complex disorder

In the last few years, the non-motor symptoms have increasingly been acknowledged as a significant component of the PD phenotype. These non-motor symptoms are very common, even in early stages of the disease.[10] Nevertheless, despite their high prevalence, these non-motor symptoms mostly remain unrecognised and untreated.[11-12] The NMS (Non Motor Symptom) Questionnaire[13] and Scale[14] might be helpful instruments for clinicians to better identify these non-motor symptoms. and to select the appropriate team members accordingly. Multispecialty teams should include a wide range of medical specialists. In general, the neurologist and specialised nurse are identified by both professionals and patients as key contributors to optimal PD care.[1,15-17] These two disciplines were also considered as the most important profession that could contribute to fall prevention (Chapter 4). Indeed, regular access to neurologists is recommended by clinical guidelines as a part of good PD management, [1-2,15] and these neurologists should preferably be specialised in movement disorders.[15-16,18-19] Also, regular access to PD nurse specialists is recommended, and their involvement may offer additional support to patients and their informal carers.[1-2] A range of other health professionals can complement medical management, each contributing their own specialty care (see Box 4 in Chapter 1 for a list of healthcare providers that might be involved in PD care). In fact, regular access to physiotherapy, occupational therapy and speech-language therapy is also recommended by professional guidelines.[2] An even broader approach should be considered for patients with needs in several other domains, including depression, sleep problems and psychosocial functioning.[20-22] A multispecialty assessment is also recommended to manage weight and nutritional issues in PD (Box 1), and for fall prevention programmes (Box 2).

Current evidence on 'monodisciplinary' interventions

The scientific evidence to support the merits of 'monodisciplinary' interventions is increasing and several clinical practice guidelines are currently available (Chapter 6).[23] The number of trials on the effectiveness of physiotherapy has increased rapidly over the years[24] and the

BOX 1 Monitoring weight and nutritional status

We showed that PD patients weigh less than controls (Chapter 3) and that various nutrition-related symptoms are present in PD (Chapter 2). Additionally, it has been shown that malnutrition is frequent in this population and that a substantial part of PD patients are at risk for malnutrition, with prevalence exceeding numbers seen in the general population.[79-81]

Screening
We recommend routinely recording body weight and nutritional status as part of the management of PD. It should be noted that PD is characterised by a gradual decline in body weight, which might be missed by conventional instruments (e.g. MUST, SNAQ) that are primarily aimed at determining weight changes due to acute illness. Dieticians should ideally be included as member of the multispecialty Parkinson team to monitor (and treat) these patients.

Treatment by multispecialty team
Both PD and the treatment result carry the risk of inducing or worsening weight loss and malnutrition. This warrants a multispecialty approach by a team of PD specialists.[82-84] Obviously, dieticians will have an important role, for example by providing nutritional interventions.[85] Neurologists should be aware of weight changes as daily levodopa dose per kg body weight (rather than the absolute daily intake) has been shown to represent a significant factor for dyskinesias.[86-87] A range of other specialists, including occupational therapists, speech-language therapists, PD nurses, and general practitioners, might be part of the team approach to weight loss and malnutrition as well.[85]

Recommendations for clinical practice
Recently, a best practice guideline has been developed in the Netherlands for nutritional care in PD.[85] Although a broad range of nutritional risk factors have been identified, the effectiveness of nutritional interventions and their influence on the course of PD remains unknown and requires future investigation.[82,88] While awaiting more evidence, the guideline can now be implemented in clinical practice as a first step to harmonize treatment and to offer professionals some guidance to shape their intervention. As indicated above, all PD patients should be monitored regularly for changes in body weight and nutritional status. Accordingly, energy and nutritional deficiencies should be treated, as well as symptoms and side effects that cause these changes. Although residential patients are less often represented or even not included in PD nutrition research, this vulnerable population should not be overlooked in clinical care.

efficacy of physiotherapy has been shown in trials with short-term follow-up (i.e. less than three months).[25] More well-designed trials are needed, focusing especially on the long-term effectiveness of these physiotherapeutic interventions.[25] Although the evidence is also increasing for speech-language therapy, there is still insufficient evidence on the efficacy of speech-language therapy to conclusively support or refute the efficacy of therapy for speech problems in PD.[26-27] Good scientific evidence to support occupational therapy in PD is lacking so far[28], but research is on the way. The effectiveness of occupational therapy based on the Dutch guideline is currently being investigated in an RCT (the OTiP study).[29] PD nurses are closely involved in several aspects of care, including counselling, coping with PD and social concerns. However, the evidence for the effectiveness of nursing care alone for PD patients also remains limited and inconclusive so far.[30] Hence, there is a need for further and more intensive scientific research on these and other 'monodisciplinary' interventions, given the scarcity of high quality evidence to date.[1,31]

BOX 2 Multifactorial fall prevention

Falls are a common and devastating consequence in PD, fuelling the need for fall prevention in this population. Based on the literature, guidelines and expert opinion, we developed an overview of recommendations for the examination and management of falls in patients with Parkinson's disease including an overview of all generic and disease-specific fall risk factors in PD (Chapter 4).

Screening
Our set of recommendations provides insight into the complex nature of falls in PD, with a wide range of generic and PD-specific risk factors. For each risk factor, assessment methods were provided. We recommend to routinely query falls and to screen for fall risk factors as part of everyday PD management.

Treatment by multispecialty team
In light of the complexity of falls in PD, a multispecialty approach is likely needed to adequately screen for falls and to implement fall prevention strategies. Neurologists and PD nurses are the key professions within the falls prevention team, together with general practitioners and geriatricians (to tackle the generic risk factors) as well as physiotherapists (to address the PD-specific factors). A range of other health specialists might also be involved, including rehabilitation specialists, occupational therapists and clinical pharmacists.[89]

Recommendations for clinical practice
While awaiting further evidence on fall prevention strategies in PD populations, the clinical practice recommendations can now be implemented as part of PD management. An individually tailored approach is preferred to systematically address the many fall risk factors for each patient. Follow-up is needed to ascertain that patients actually adhere to the recommendations. Furthermore, routine monitoring will be necessary to detect changes in risk profile when the disease progresses. Our Falls Telephone (Chapter 5) might serve as an easy and reliable tool to monitor fall incidents. This automated system has already been used in PD populations (IMPACT trial[9], Parkfit study[90]), and is suitable for monitoring fall incidents among frail older persons.[91]

Patient and their carers as team members

Effective team-based care comes with the recognition that patients as well as their informal caregivers should be actively involved as part of the healthcare team.[2,7,32] It is important to incorporate the experiences and expectations of patients as a meaningful part of the treatment plan. All multidisciplinary team interventions tested so far have largely been driven by professionals. However, there is increasing evidence that active involvement of patients helps to improve the quality of care and may reduce healthcare costs.[33-35] PD patients wish to be more actively involved in self-management,[36] and evaluating whether and how these patients in various disease stages can achieve this is an interesting challenge.

Types of collaboration between members of healthcare teams

There are various ways to implement a team approach (Box 5, Chapter 1 Introduction). These range from relatively simple models in which professionals work independently from each other. At best, the individual professionals have incidental consultations with colleagues to share expert advices at an individual case level. We reasoned that a more formalised and complex approach of teamwork would be more efficient and effective. Based on the commu-

nication and collaboration between the various team members, three different concepts can be distinguished: multidisciplinary care, interdisciplinary care and integrative care. *Multidisciplinary* care involves multiple health professionals who are each responsible for a specific patient care need. This model can be extended to the *interdisciplinary* team approach, in which team members work collaboratively through regular face-to-face meetings and make group decisions. The *integrative* model of care is characterised by a shared, synergistically charged plan of care guided by consensus building in which each health professional contributes with his or her knowledge and skills and engages patients as team members.[5]

The optimal model?

Integrative models are considered to be the most complex, in terms of number of participants involved, in terms of number of health determinants that are to be addressed, in terms of an increased need for communication and synergy, and in terms of emphasis on the individual patient as a whole. However, integrative models do not by definition represent the optimal model for organising healthcare. In fact, it is still unclear which type of healthcare delivery offers the greatest benefits to PD patients. In the Guttman trial (Chapter 7), we showed that a multidisciplinary care approach offered improved outcomes compared to stand-alone care from a neurologist. Whether more complex organisations of team healthcare (e.g. interdisciplinary or integrated approaches) would result in even better outcomes, remains to be established. In fact, we evaluated an integrated model of care in the IMPACT trial (Chapter 8). This theoretically represents an optimal organisation to shape team collaboration that extends into the community. However, we were unable to show that this approach was a lot more effective, as this approach resulted in only minor health benefits over and beyond usual care in the Netherlands. We will offer several explanations for this limited effectiveness below.

Integration of health professionals

Based on interviews with patients and carers in the Parkinson Centre Nijmegen we know that besides PD expertise, involvement of multiple health providers and collaboration between these professionals are the most important elements of our expert centre (unpublished data*). Nevertheless, in current healthcare, patients still identify a lack of collaboration between health professionals.[36] Indeed, integrated healthcare is complex in terms of coordination, and it is also often challenging to integrate the priorities of patients and their families with the needs of health professionals.[32] Collaboration between health professionals is not self-evident: connecting professionals does not necessarily entail improved teamwork among disciplines.[17] Although team-based care is underlined as a core element of the ParkinsonNet networks, health professionals are not always aware who participates in the individual patient healthcare team. Despite various implementations to encourage communication (e.g. by

* *Unpublished data from interviews with patients (n=10) and carers (n=9) before the implementation of the expert centre to identify needs and desires; and interviews with patients (n=38) and carers (n=35) six months after they visited the expert centre.*

structured referral, regular meetings, and web-based communities)[37] information exchange between team members can still be improved significantly.[17] Perhaps other initiatives (like an online conference table with access for the patient, caregiver and all professionals within their individual healthcare team, as is being used in geriatric care) [38] could be implemented to overcome this problem and to increase patient-centeredness of care.

At what stage should team-oriented care be delivered?

The current therapeutic approach of PD is often 'monodisciplinary' with one medical specialist (mostly neurologist or geriatrician) who focuses on accurately diagnosing PD and on optimizing medical treatment.[23] The clinical diagnosis of PD is based on the presence of motor symptoms.[39-40] Nevertheless, it has become evident that some non-motor features, like obstipation, olfactory dysfunction and sleep disorders, can precede the development of the defining motor signs.[41-42] Therefore, suggestions have been made to redefine PD, including a 'premotor' stage to describe these early PD stages, when motor symptoms have not yet appeared.[41-44] The presence of these non-motor symptoms in the early stages calls for a broader approach than just a single specialist defining PD on the motor symptoms. A multispecialty team approach from diagnosis onwards should be effected to adequately treat the wide variety of symptoms at these early stages.

Early versus late disease

Overall, a team approach appears preferable throughout all stages of the disease. With advanced disease, the number of non-motor symptoms increases[45] (although non-motor symptoms are remarkably common even in de novo patients)[10] and long-term treatment complications become prevalent, including response fluctuations and the development of dyskinesia.[40] The impact of illness also varies among stages: a study comparing early versus late PD patients showed that the most prevalent complaints in early stages were slowness, tremor, stiffness, pain and loss of smell/taste, whereas patients in the later stages ranked fluctuating response to medications, mood changes and drooling as their top problems.[46]

Tailored to individual preferences

The variability in the perception of most troublesome symptoms across individual patients highlights the importance of providing interventions tailored to the patients' individual needs and preferences for care. Such a patient-centred approach represents a crucial element of quality of care.[47] Patient-centeredness comes with the recognition that care is delivered with the patient's needs and preferences in mind. Although this remains a rather new field in patient care and research, evidence is accumulating that empowering patients via self-management support and shared-decision-making results in improved self-efficacy, better health-related quality of life, greater treatment compliance and higher patient satisfaction (reviewed in reference Van der Marck *et al*.[7]).

Targeting the right patient

In most studies, including the two trials described in this thesis, severely affected patients were largely underrepresented.[9,48-51] These patients, in particular, might benefit most from a comprehensive assessment because they are faced with an increasing number of disabilities. A recent survey in nursing homes has shown that residents in these facilities are faced with great disability, caused by severe motor and non-motor handicaps.[52] In fact, baseline attributes have been linked to effectiveness, such that multidisciplinary rehabilitation seemed most beneficial for those patients with higher perceived needs.[51] However, it remains to be established whether patients in the advanced stages of PD might still benefit from a comprehensive team approach. The disabilities that become prevalent in later stages, such as response fluctuations to medication, might just obviate the need for specific care in an expert centre. For mildly affected patients with a limited number of disabilities, a less comprehensive team might be more appropriate. In such cases, access to regional care provided by specialised therapists might already be sufficient to alleviate the disease burden for these patients with less complex needs.

Setting

One expert centre versus networks

The interventions described in this thesis also differed with respect to the actual implementation of treatment. In the IMPACT trial (Chapter 8), treatment was provided by outpatient services. Here, the actual delivery of healthcare interventions as recommended by the expert centre was outsourced to community professionals. Whether or not treatments were actually delivered and how well this was performed, was outside our control and was left at the discretion of the community neurologist, local Parkinson nurse and community therapists. In fact, post-hoc analyses showed that only a proportion of all recommended interventions had actually been delivered to the intervention patients. Overall, 73% of referrals had resulted in an actual treatment visit, but this percentage varied widely between individual disciplines. Referrals for some disciplines were hardly or even not implemented (e.g., sleep consultant, sexologists) whereas referral to other disciplines showed actual implementation for over 65% of referrals (this included occupational therapists, speech-language therapists, and PD nurses). Treatment compliance was best for physiotherapy, with an almost full implementation of recommended referrals. Conversely, some patients never received any follow-up, and this is worrisome. An alternative and perhaps better approach might be to incorporate the tailored evaluation plus the intervention within one centre, similar to the approach described in the Guttman trial (Chapter 7). This may offer a more seamless organisation of care because assessment and treatment are delivered by the same team. However, such a centred approach might not always be feasible, for example due to the high number of patients that have to be screened and treated. Additionally, PD patients often experience difficulties in their mobility that could hamper their travel to healthcare professionals outside their own region. This

might be particularly important for intensive treatments that require multiple consultations (like PLVT training by the speech-language therapist) or regular visits for longer periods of time (such as weekly physiotherapy visits). The regional networks of the ParkinsonNet concept of care were therefore designed to offer patients good care within the vicinity of their own home, making specialised healthcare easily accessible without need for much travelling.

The ParkinsonNet concept: specialised regional network care

The initial idea to develop ParkinsonNet networks was motivated by research showing that referrals to allied healthcare were suboptimal (i.e. not all patients with a clear need for treatment were being referred, while others without indication received chronic weekly treatments), combined with lack of PD-specific expertise among health providers.[53] This lack of expertise was at the time caused in part by the absence of evidence-based treatment guidelines, and also by the fact that allied health therapists treated only a small number of patients annually (and this precluded development of adequate expertise). Most of these shortcomings have now been tackled. Specifically, PD specific knowledge, adherence to guideline recommendations, and patient volume per therapist are increased.[53] The quality of care has indeed been improved within these professional ParkinsonNet networks.[54] However, the current concept of hospital-based expert evaluation followed by treatment in the community is not infallible. For example, supervision of care by a single case manager or transition coach for each patient might have helped to improve the coordination of care between these two complementary elements. Lack of coordination and supervision across the entire healthcare chain might explain why many treatment recommendations were never followed. We acknowledge that this was a shortcoming of our study design in the IMPACT trial. Also, the current extension of the regional networks with other therapists might improve the actual uptake of referrals, and we are currently implementing an alternative approach where Parkinson nurses assume the role of personal coaches who supervise the entire treatment trajectory.

The number of health professionals included within the ParkinsonNet networks is still increasing. Initially, the ParkinsonNet concept started with just physiotherapists, but this has meanwhile expanded and over the years multiple other professions have been engaged. At the time of the IMPACT trial, the networks also included neurologists, occupational therapists and speech-language therapists. Currently, PD nurses, dieticians, psychologists and sexologists are also included as regular team members and the networks have reached full national coverage in the Netherlands.[37] This expansion might facilitate the implementation of referrals to specialised allied health therapists. For example, specialised sexologists were not involved at the time of the IMPACT trial, which might be one of the reasons that referrals to this discipline did not result in actual consultation after the assessment in the expert centre.

II. Effectiveness

Both trials described in this thesis evaluated the clinical effectiveness of team organisation of care by PD specialists, whose input was tailored to the patients' individual needs (Table 2 provides an overview of the research designs of our two trials). In the Guttman trial (Chapter 7), movement disorders specialists provided treatment supported by a PD nurse and a social worker. This approach was shown to positively affect quality of life, motor functioning, depression, and psychosocial functioning. No effects were found on caregiver burden. In the IMPACT trial (Chapter 8), the movement disorders specialist collaborated with a broad range of disciplines, resulting in consensus-based treatment recommendations for regional therapists. Consistent, but small improvements were found in several domains, including quality of life, activities of daily living, non-motor symptoms, depression and anxiety. No effects were shown on motor functioning and caregiver burden.

Interpretation of the results

The results of the Guttman trial give credence to a multidisciplinary specialist care over usual stand-alone care from a general neurologist. The improvements on the primary and secondary outcomes, quality of life (assessed by PDQ-39) and motor functioning (assessed by UPDRS III), were not only statistically significant, the effect sizes also represented clinically relevant improvements for the patients.[49] The results of the IMPACT trial also pointed towards effectiveness of the intervention, with statistically significant effects on both primary outcomes (activities of daily living, assessed by the ALDS; quality of life, assessed by the PDQL) and a range of tertiary outcomes. However, the improvements were only small and unlikely to be clinically relevant. Moreover, the effects might have been partly explained by differences at baseline, since the differences disappeared after correction for baseline disease severity. Taken together, we concluded that usual care was not convincingly outweighed by the more intensive integrated care model tested in this IMPACT trial. In both trials, caregiver burden was included as one of the outcome measures. The results jointly suggested a higher caregiver burden in the intervention groups, and this confirms the experience gained in an earlier trial.[48]

Possible explanations

The two trials each evaluated a different team in which collaboration was differently organised, each at a different setting, with a different research design and with partially different outcome measures. The results of both trials were in favour of multispecialty expertise care, but the Guttman trial showed more robust effects, while only small improvements were shown in the IMPACT trial. We will address some perspectives as possible explanations for these different results.

One explanation might be the difference in the number of team members involved and the selection of adequate outcome measures that fit the intervention. In the Guttman trial, three

disciplines were involved, the movement disorders specialist, PD nurse and social worker. The outcome measures (that rated emotional and psychosocial functioning) might have corresponded better with the actual content of delivered healthcare by the PD nurse and social worker. Conversely, in the IMPACT trial, we opted for a wide-ranging approach with access to a team of 13 health professionals. The input of these disciplines was tailored to each patient's individual needs, resulting in an enormous variety of arrangements of care that complicated the choice of more specific outcomes measures. A larger number of disciplines might also induce a barrier for collaboration between multiple disciplines.[36]

Another difference between the trials was the inclusion process. In the Guttman trial, patients were already referred to multidisciplinary/specialist care before they were randomly assigned to immediate care or the control group, who visited the centre after the 8-month study period. In the IMPACT trial, patients were first included in the study. Subsequently, those patients who lived in the intervention region, were referred to the expert centre. It is conceivable that refer-

Table 2 Overview of research design

	Guttman trial[8] (Chapter 7)	IMPACT trial[9] (Chapter 8)
Recruitment	Patients were referred to the expert centre for a team assessment before inclusion in the trial	Patients were offered team assessment in the expert centre after inclusion in the trial
Design	Randomised Controlled Trial: randomised after inclusion in the trial to immediate intervention or usual care/waiting list	Controlled Trial: intervention region (integrated model) versus control regions (usual care)
Blinded	Patients: no Medical team: yes Research staff: yes	Patients: yes Medical team: yes Research staff: no
Data analyses	No data on drop-outs collected	Intention-To-Treat (ITT)
Outcome measurements	Primary: quality of life (PDQ-39) Secondary: motor and total UPDRS scores, depression (MADRS), psychosocial functioning (SCOPA-PS) Caregiver burden (CSI)	Primary: activities of daily living (ALDS) and quality of life (PDQL) Secondary: UPDRS motor scores, economical evaluation. Range of other outcome measures including non-motor symptoms (NMS Scale), depression (HADS), general quality of life (SF-36, VAS) Caregiver burden (BELA-A-k; SF-36, HADS)
Process evaluation	Partly: within expert centre	Yes

ALDS AMC Linear Disability Score; *BELA-A-k* Belastungsfragebogen Parkinson Angehörigen-kurzversion; *CSI* Caregiver Strain Index; *HADS* Hospital and Anxiety Scale; *MADRS* Montgomery-Asberg Depression Scale; *NMS Scale* Non-motor symptoms scale; *PDQ-39* Parkinson's Disease Questionnaire; *PDQL* Parkinson's Disease Quality of Life questionnaire; *SCOPA-PS* Scales for Outcomes in Parkinson's disease-Psychosocial; *SF-36* Short Form 36; *UPDRS* Unified Parkinson's Disease Rating Scale; *VAS* Visual Analogue Scale.

rals in the Guttman trial were made for more complex patients or patients that were more interested in specialised care. Indeed, a sizeable minority of patients (33%) in the IMPACT trial declined to be referred to the expert centre, presumably because they were mildly affected and anticipated only little gain.

Blinding was another factor that differed between the studies. Patients were not blinded to group assignment in the Guttman trial, and this might have contributed to a larger influence due to a placebo effect. In contrast, patients in the IMPACT trial were not informed about the differences between the regions.

Additionally, it is important to understand the setting in which the research was performed. In the Netherlands, usual care already involves multiple healthcare professionals. For example, two analyses of usual care in the Netherlands showed that many patients already receive some form of multidisciplinary care, including in particular physiotherapy (57% to 62.5% of patients), but to a lesser extent also e.g. occupational therapy (8.5% of patients) or speech-language therapy (14.4% of patients).[53,55] Consequently, in the IMPACT trial, we compared a formal organisation of team care with a less formally structured collaboration between healthcare professionals. The contrast of the intervention in the IMPACT trial over usual care was therefore only limited, while this approach might have resulted in larger effects when implemented in different settings, for example in countries were allied healthcare therapy is not part of usual care. In the Guttman trial, we compared a team approach by PD specialists with stand-alone care by a general neurologist who did not have access to support from PD nurses or social workers. We would probably not have seen the same results if we had implemented this approach in the Netherlands, as many neurologists in usual Dutch healthcare are already supported by PD nurses.

Interestingly, both models did not decrease caregiver load. In fact, the results even suggested a higher caregiver burden, extending earlier experience.[48] Many patients receive support from their family members throughout daily life. Intensifying the care process by applying new treatment strategies and organising extra referrals also impacts on the daily activities of both the patient and the caregivers. This can cause a considerable burden for these carers.[56-57] The results might also have resulted from a lack of attention for the specific problems that these carers experience themselves. For this reason, we have recently initiated dedicated consultations for the spouses or other immediate caregivers, who are offered the opportunity to visit our social worker of PD nurse specialist without the patient being present. Specific attention to the problems experienced by caregivers is also part of standard care in other PD centres. For example, the Tel Aviv Movement Disorders Unit runs a caregivers' clinic for those who need personal counselling on how to take care of their own difficulties to cope with the burden of taking care for their family member with PD.[7]

Evidence from previous studies

In PD, positive effects on health, disability, quality of life and well-being of multispecialty team interventions have been reported in several uncontrolled studies that used a pre-test versus post-test design.[58-62] Besides our two trials, only a few trials using controlled designs have been published previously, and the results on the effectiveness of team management have been inconsistent.[23,63-65] A synopsis of the controlled trials published so far (including our two trials) is provided in Table 3. Two earlier trials (Guo *et al*., Trend *et al*.) showed marked improvements in patients' outcome following multidisciplinary interventions. [50,62] However, these trials only described the immediate effects following short-lived interventions (6 to 8 weeks). One of these trials[62] was designed as a long-term study (Wade *et al*.), but the follow-up data after six months (i.e., about four months after completion of the six-week treatment) showed no sustained effects. In fact, deterioration was noticed for several outcomes compared to baseline and to controls.[48] Another study by Tickle-Degnen *et al*. also involved a six-month follow-up. Directly after the intervention and after six months, more patients in the rehabilitation group experienced an improved quality of life compared to patients without rehabilitation.[51] However, the group difference declined with time, suggesting that the benefits were short-lived.[51] These findings, as well as the fact that PD is a progressive condition, suggest a need for continuing treatment to obtain more sustained benefits. In fact, the trials in this thesis evaluated the effects of prolonged care by a multidisciplinary team for a period of eight months. A longer follow-up may still be relevant for health outcomes and cost-effectiveness. Future trials should therefore investigate whether the effects found in our trials are also persistent and how care can best be reinforced to sustain effects as the disease progresses.

Heterogeneity in design, intervention and outcomes

The summary of trials in Table 3 clearly reflects the large variability in research design, nature of the multispecialty intervention and choice of outcome measures. This heterogeneity makes it difficult to compare studies. Just like our trials, previous studies were also complicated by methodological difficulties, including loss of follow-up data, and potential bias due to study design, blinding and selection methods.[48,50-51] In fact, there are many methodological challenges when evaluating complex approaches like multispecialty care in PD, which we will further address in the following part of this Discussion.

Study	Design	Intervention and duration	Team members (alphabetical order)	Study duration	Outcome measurements
Wade *et al.*,2003[48] (n=144, 7 duplicate patients)	RCT, including pre-post test design - Early vs late intervention - Blinding: assessor	6-weeks individual training and group activities.	Occupational therapist Physiotherapist PD nurse Speech-language therapist Access and referral to social services care manager, neurologist, psychologist	6 months after study entry	PD Disability questionnaire, PDQ-39, SF-36, EQ5D, stand-walk test, NHPT, HADS, UPDRS speech items Carers: CSI and EQ5D
Lindskov *et al.*, 2007[77] (n=97)	Controlled design with waiting list	6-week educational program with weekly 2-hour session	Dental hygienist Dietician Nurse Occupational therapist Physician Physiotherapist Psychologist Social worker Speech therapist	10 weeks	SF-12
Guo *et al.*,2009[50] (n=44)	RCT, including pre-post test design - Intervention vs usual care (late intervention) - Blinding: assessor	8- weeks of group education with personal rehabilitation.	Dietician Movement disorders specialist Nurse Occupational therapist Physiotherapist Psychologist	4 weeks (pre-post test design) 8 weeks (RCT)	PDQ-39, UPDRSII and III, SEADL, Zung SDS, PMS
Tickle-Degnen *et al.*, 2010[51] (n=117)	RCT - 3 groups: (1) no rehabilitation, (2) 18 hours (3) 27 hours - Blinding: assessor	6-weeks of group sessions and (for group 3 only) individualised self-management rehabilitation. Attentional control social sessions (9 hours) for group 2.	Occupational therapist Physiotherapist Speech-language therapist	6 weeks, 2 months, 6 months	PDQ-39 Walking activity and endurance (by White *et al.*in same population)[78]

Study	Design	Intervention and duration	Team members (alphabetical order)	Study duration	Outcome measurements
Van der Marck *et al*. 2013[8] (n=120)	RCT - Intervention vs usual care (late intervention) - Blinding: care and research team	Ongoing care, individualised assessment and treatment in expert centre	Movement disorder specialist PD nurse Social worker	8 months	PDQ-39, UPDRS III, UPDRS total, MADRS, SCOPA-PS Caregiver: CSI
Van der Marck *et al*, 2013[9] (n=301)	Controlled trial - Intervention vs control regions (usual care) - Blinding: patients and care team	Ongoing care, individualised assessment in expert centre with referral to specialised local therapists for treatment	Dietician Movement disorders specialist Occupational therapist Physiotherapist PD nurse Psychiatrist, psychologist Rehabilitation specialist Sexologist Sleep consultant Speech-language therapist Social worker	8 months	ALDS, PDQL,UPDRS III, health care costs, NMS Scale, HADS, falls, FES-I, FOGQ, SPDDS, UPDRS IV, SF-36, overall well-being (VAS), quality of care Caregiver: BELA-A-k, HADS, SF-36

ALDS AMC Linear Disability Score; *BELA-A-k* Belastungsfragebogen Parkinson Angehörigen-kurzversion; *CSI* Caregiver Strain Index; *EQ-5d* EuroQuol 5d; *FES-I* Falls Efficacy Scale – International; *FOGQ* Freezing of Gait Questionnaire; *HADS* Hospital and Anxiety Scale; *MADRS* Montgomery-Asberg Depression Rating Scale; *NHPT* Nine Hole Peg Test; *NMS* Non Motor Symptom; *PD* Parkinson's Disease; *PDQ-39* Parkinson's Disease Questionnaire; *PDQL* Parkinson's Disease Quality of Life questionnaire; *PMS* Patient's Mood Status; *RCT* Randomised Controlled Trial; *SCOPA-PS* SCales for Outcomes in Parkinson's disease-PsychoSocial questionnaire; *SEADL* Schwab and England Activities of Daily Living; *SF -12* Short Form-12; *SF-36* Short Form 36; *SPDDS* Self-assessment Parkinson's Disease Disability Scale; *UPDRS* Unified Parkinson's Disease Rating Scale (part II is Activities of Daily Living, Part III is Motor Score, Part IV Complications of therapy);*VAS* Visual Analogue Scale;*Zung SDS* Zung-Self-rating Depression Scale;

III. Challenges to clinical research on multifaceted care

Complex interventions, like our multispecialty approaches, represent an emerging field that poses significant challenges to the scientific evaluation. In addition to the practical and methodological difficulties that all studies have to overcome, these interventions are increasingly challenging due to multiple active and interacting components.[66-67] We also faced methodological and practical difficulties while designing and implementing our trials. We will address some of the lessons we have learned.

Variability in intervention and control care

It was not possible to apply the same standardisation as in single intervention studies (like drugs trials), as there was no uniformity of care in the intervention or control group. Drugs trials are simpler in design, because a certain drug is provided at a specific dose, frequency and treatment duration. Here, however, we were faced with a much more complex and variable design: a variety of disciplines were involved, which provided a diverse set of therapies at a variable intensity, frequency, and duration of treatment. In addition, our multispecialty approaches were delivered in a tailored fashion, based on each patient's individual needs. This complexity was further increased by the choice of control intervention. Pharmacological trials often include a placebo or 'gold standard' treatment. Yet, 'usual care' in PD does not include such a straightforward control. This even occurred in the IMPACT trial (Chapter 8), as many control patients received allied health treatment in the community, and this may have masked greater benefits for the intervention patients in this trial. Other variables that increased the complexity of our team-based approaches included the skill mix among all healthcare professionals involved and the inclusion of different clusters of care as controls.

Study design

Randomised controlled designs are regarded as the highest level of evidence and the gold standard for clinical trials. However, due to the complexity of integrated interventions as described above, a randomised design is not always feasible. For example, in the IMPACT trial, a better matching for baseline disease severity could have been achieved using a fully randomised design within a single participating region, but this was impossible because of a risk of contamination. Specifically, if we had randomised within a single region, control patients could have gained access to specialised allied health treatment offered by the regional professional networks. In the Guttman trial (Chapter 7), we did use a randomised design to evaluate the effectiveness of the intervention. Nevertheless, this trial had other methodological constraints. For example, no data on drop-outs were gathered and therefore an intention-to-treat analysis could not be performed.

Choice of outcome measures

Another difficulty in this particular area of research is the choice of outcome measures. Our interventions were aimed at a range of both motor and non-motor symptoms of PD, and were indivually tailored, i.e the menu of interventions varied considerably across individual patients. This makes it very difficult to assess the effectiveness of such a multifaceted and individually tailored approach using one overarching outcome that applies equally well to each study participant. More specific outcome measurements that reflect the actual intervention more closely (e.g. gait speed for those that received physiotherapy) might be more suitable for capturing the effect. However, these were impossible to select as overall outcome measurements in our trials since each patient received an individually tailored set of interventions that differed enormously across individuals. Also, the focus of one primary outcome will not be sufficient to determine the full extent of treatment effects and individual improvements of complex healthcare. Perhaps, a better alternative would be to include a combination of multiple outcome measures.[32,68] Additionally, mixed methods designs, including both quantitative and qualitative methods, might offer a more suitable methodology to evaluate complex healthcare interventions. These mixed designs might also improve the fit between research on the one hand, and participants and clinical practice on the other. Bridging this gap might positively affect inclusion rates and the translation of research results into clinical practice. Also, the use of complementary qualitative data will be valuable in explaining differences between expected and observed results that are left undetected by quantitative methods, for example by identification of barriers that hampered uptake or adherence to interventions under study.[69] Frequently, outcomes are chosen from the researchers' perspective. However, it might be a better alternative to select outcomes from the participants' perspectives as well, because patients may have different views about what an important or meaningful outcome is. [32,68-70]

Process evaluation

Ideally, process evaluations should be included as an integral element of clinical trials.[71-72] This is particularly true for the evaluation of complex interventions like multifactorial fall prevention programmes.[73] These evaluations might be useful for exploring the actual implementation of the interventions and might explain discrepancies between expected and observed effects. In the IMPACT trial, the process evaluation provided transparency about the healthcare interventions that were delivered, indicating that both patient groups received care by multiple disciplines. In addition, it showed that some patients were not interested in the comprehensive assessment at our expert centre. Without our process evaluation we would not have had such a robust description of the actual delivery of the intervention, which ultimately helped us to explain the limited contrast between the groups.

Multispecialty team care

There is no standard template or model to design multispecialty care for PD. There are many aspects that have to be considered while organising such a team approach, including which disciplines need be involved and how many therapists (e.g. a small versus a comprehensive team); how the various team members should collaborate (whether this should be organised as incidental consultation of experts who work independently, or towards more formalized and complex approaches based on shared decision making); at what stage (early versus late, or tailored to patients' needs); and whether care should be delivered integrally by one centre or via collaboration with community-based networks.

Multispecialty team approaches are not only complex to design, these models also offer significant challenges for the scientific evaluation due to the complex nature of these interventions with multiple active and interacting components. The scientific evaluations of team care in PD are thus far inconsistent, but do generally point towards possible benefits of multispecialty interventions. However, there are only a limited number of controlled trials, and comparison between these studies is difficult because of the wide heterogeneity across studies, with varying team members, differences in duration and intensity of the interventions, as well as differences in outcome measures that have been used.

Pending further evidence, we feel that the complex nature of PD (with a diverse set of motor and non-motor symptoms) plus the evidence presented in this thesis warrant a judicious application of a multispecialty approach to optimally manage the complexity of PD.

Conclusion: Towards a multifaceted approach!

The work included in this thesis describes the multidimensional nature of PD and provides the basis for a multifaceted approach in the management of this broad symptom complex. A team-oriented approach including pharmacological and non-pharmacological interventions provided by multiple disciplines appears to be warranted, and we offer some new insights into the actual effectiveness of various care models. There is increasing scientific support for the use of allied healthcare interventions as a complementary approach to standard medical management. The possible clinical implications of allied healthcare interventions were illustrated in this thesis for physiotherapy, occupational therapy and speech-language therapy. Although multispecialty approaches are increasingly acknowledged as representing the optimal management of the motor and non-motor symptoms in PD, there is no known standard or best template for organising these team models of healthcare. We described two large, controlled trials on the effectiveness of two different types of organisation that were implemented in two different settings. The results underlined previous positive experiences and pointed in favour of team/specialist intervention. These trials did not, however, offer the final answer on how to optimally design team-based care in PD management, but instead provided an initial inventory of the scientific evidence of comprehensive healthcare models in PD. Fortunately, further research on the effectiveness of multispecialty team interventions in PD is currently underway.[74-76] This is a new, emerging and exciting field that offers challenges to both clinical practice and scientific research, and which offers hopes for PD patients who crave for better treatments of this often debilitating disease.

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SAMENVATTING

De ziekte van Parkinson is een invaliderende aandoening, waarbij een scala van motorische en niet-motorische symptomen voorkomt. Dit brede palet aan symptomen, gecombineerd met het individuele ziektebeeld en ziektebeloop, maakt de behandeling van deze aandoening tot een complexe uitdaging voor medisch specialisten. Het centrale thema van dit proefschrift is de complexiteit van de ziekte van Parkinson. Eerst hebben we deze complexiteit geschetst aan de hand van twee symptomen van de ziekte: ongewenst gewichtsverlies en valpreventie. Vervolgens hebben we de integrale behandeling van het gehele ziektebeeld met de vele verschillende symptomen besproken. De complexiteit bij de ziekte van Parkinson vraagt om een teamgerichte aanpak, waarbij verschillende zorgverleners samenwerken. Echter, het is nog niet bekend wat de meest optimale organisatie van teamzorg is voor Parkinsonpatiënten en hun mantelzorgers. Daarom hebben we binnen dit proefschrift ook gekeken naar de effectiviteit van paramedische zorg bij de ziekte van Parkinson en de effectiviteit van twee verschillende vormen van organisatie van teamsamenwerking.

Een progressieve, neurodegeneratieve aandoening

De ziekte van Parkinson is een neurodegeneratieve aandoening. Dit houdt in dat er een afbraakproces plaatsvindt in verschillende delen van de hersenen. Hierdoor is er een tekort aan dopamine, een stof die in bepaalde hersendelen noodzakelijk is voor het overbrengen van zenuwimpulsen. Door dit tekort is de zenuwbesturing van het lichaam, waaronder de aansturing van de spieren, aangedaan. Parkinson is een progressieve aandoening, wat inhoudt dat de schade in de hersenen gedurende de ziekte toeneemt.

Gewichtsverlies

Hoofdstuk 2 en 3 hebben betrekking op ongewenst gewichtsverlies. Ongewenst gewichtsverlies is een veel voorkomend probleem bij Parkinsonpatiënten. Deze twee hoofdstukken beschrijven zowel de complexiteit van dit gewichtsverlies, middels een opsomming van de verschillende oorzaken, als de evidentie dat Parkinsonpatiënten een lagere Body Mass Index (BMI) hebben vergeleken met controlepersonen.

Hoofdstuk 2 betreft een review van de literatuur naar de verschillende mogelijke factoren van ongewenst gewichtsverlies bij de ziekte van Parkinson. Deze review liet zien dat verschillende Parkinsonsymptomen de energiebalans kunnen verstoren, met als resultaat een verminderde inname, verminderde absorptie of verhoogd energieverbruik. De factoren die ongewenst gewichtsverlies bij de ziekte van Parkinson veroorzaken zijn niet alleen de factoren die rechtstreeks betrekking hebben op het ziekteproces in de hersenen bij Parkinson (zoals motorische problemen, verminderde reuk en cognitieve problemen), maar ook secundaire factoren die vaak voorkomen maar niet direct gerelateerd zijn aan het neurodegeneratieve proces (zoals misselijkheid en andere bijwerkingen van medicatie). Omdat gewichtsverlies en een laag lichaamsgewicht geassocieerd zijn met een verhoogd risico op ziekte en sterfte, is het belangrijk gewichtsveranderingen tijdig te herkennen om adequaat te kunnen

behandelen. Hiertoe hebben we in dit hoofdstuk ook enkele therapeutische mogelijkheden en aanbevelingen beschreven, waaronder het frequent aanbieden van voeding tussen de maaltijden door en het gebruik van smaakversterkers om de voedingsinname te verbeteren. Daarnaast kunnen aanpassingen in de medicatie zinvol zijn om mogelijke bijwerkingen met een negatieve invloed op de energiebalans te beperken. Ook kunnen voedingssupplementen voorgeschreven worden om te zorgen voor een adequate inname. De complexiteit en de vele oorzaken van ongewenst gewichtsverlies bij de ziekte van Parkinson vragen samenwerking tussen zorgverleners. Deze complexiteit is echter niet uniek voor Parkinson, maar is ook te zien bij andere neurodegeneratieve aandoeningen. Dit hebben we geïllustreerd aan de hand van de onderliggende pathofysiologie van ongewenst gewichtsverlies bij de drie meest voorkomende neurologische aandoeningen – de ziekte van Parkinson, de ziekte van Alzheimer en de ziekte van Huntington - door zowel de gemeenschappelijke, generieke factoren als de ziektespecifieke factoren voor deze drie aandoeningen te beschrijven.

Ongewenst gewichtsverlies bij de ziekte van Parkinson wordt veroorzaakt door een complexe interactie van verschillende factoren. Voor adequate behandeling is een tijdige herkenning belangrijk en inbreng vanuit verschillende disciplines.

Meta-analyse van de literatuur over lichaamsgewicht van Parkinsonpatiënten en controlepersonen

Ongewenst gewichtsverlies bij Parkinsonpatiënten is veelvuldig beschreven. Het is echter niet geheel duidelijk of patiënten een lager gewicht hebben dan controlepersonen, aangezien deze verschillen in de literatuur niet altijd statistisch significant waren. Daarom hebben we een meta-analyse uitgevoerd om vast te stellen of Parkinsonpatiënten inderdaad een lager gewicht hebben vergeleken met controlepersonen (**Hoofdstuk 3**). Daarnaast hebben we gekeken naar mogelijke determinanten. Na een literatuuronderzoek hebben we 12 studies geïncludeerd die aan onze inclusiecriteria voldeden. Deze studies tezamen lieten zien dat Parkinsonpatiënten een lagere BMI hebben van 1.73 (95% betrouwbaarheidsinterval 1.11 tot 2.35) vergeleken met controles. Ziekte-ernst was gerapporteerd in zeven studies (deze ziekte-ernst is uitgedrukt in Hoehn & Yahr (HY) stadium; hoe lager het HY stadium des te minder gevorderd de ziekte is). De gepoolde dataset van deze zeven studies toonde een relatie met BMI: patiënten met HY stadium 3 hadden een significant lagere BMI dan patiënten met een HY stadium 2 (3.9, 95% betrouwbaarheidsinterval 0.1 tot 7.7). Analyses met andere determinanten konden niet uitgevoerd worden omdat de waardes inconsistent gerapporteerd waren binnen de verschillende studies.

Patiënten met de ziekte van Parkinson hebben een lager gewicht dan controlepersonen. Ziekte-ernst is één van de mogelijke determinanten van gewichtsverlies.

Valpreventie

De complexiteit van de ziekte van Parkinson wordt in dit proefschrift ook geïllustreerd aan de hand van de valrisicofactoren die bij deze aandoening voorkomen. Valincidenten zijn een veelvoorkomend en relevant probleem bij Parkinson, waardoor valpreventie noodzakelijk is. **Hoofdstuk 4** geeft een uitgebreid overzicht van de valrisicofactoren bij de ziekte van Parkinson met aanbevelingen om deze te onderzoeken en te behandelen. Dit overzicht is gebaseerd op consensus. Eerst hebben we een concept ontwikkeld, dat vervolgens geëvalueerd is tijdens twee rondes. Tijdens de eerste ronde werd het overzicht geëvalueerd door 27 professionals vanuit verschillende disciplines, die allen actief betrokken zijn bij de klinische zorg van deze patiëntengroep. Vervolgens hebben 12 experts op het gebied van vallen bij de ziekte van Parkinson, eveneens vanuit verschillende disciplines, het overzicht beoordeeld. Voor iedere risicofactor hebben zij de volgende items beoordeeld: de methode voor diagnostiek; disciplines die betrokken moeten zijn bij diagnostiek en behandeling; en welke interventies ingezet kunnen worden. Deze items en de risicofactoren werden opgenomen binnen het definitieve overzicht van aanbevlingen als tenminste 66% van de beoordelende experts instemde. De uiteindelijke versie omvat 31 valrisicofactoren. Dit zijn zowel generieke factoren (o.a. leeftijd, bijwerkingen van medicatie en posturale hypotensie) als Parkinson-specifieke factoren (zoals verminderde mobiliteit, loopproblemen en houdingsinstabiliteit). Voor bijna alle risicofactoren geldt dat een multidisciplinaire samenwerking nodig is voor valpreventie, waarbij de neuroloog en de Parkinsonverpleegkundige een centrale rol vervullen.

Het expertpanel gaf de voorkeur aan een individueel toegespitste benadering (waarbij eerst gekeken wordt naar een specifiek valtype, en screening en behandeling hierop aanpast worden), boven een 'one-size-fits-all' benadering (waarbij alle riscofactoren bij iedere patiënt onderzocht worden). Regelmatige beoordeling van alle valrisicofactoren blijft voorbehouden aan risicopatiënten zonder eerdere valincidenten, of voor patiënten met een onverklaarbare oorzaak van vallen.

Op consensus gebaseerde aanbevelingen zijn nu beschikbaar voor de screening en behandeling van vallen bij de ziekte van Parkinson, welke gericht zijn op de klinische praktijk. Valpreventie bij de ziekte van Parkinson is complex omdat zowel generieke, leeftijd gerelateerde factoren als ziektespecifieke risicofactoren bij kunnen dragen. Vandaar dat een multidisciplinaire benadering nodig is en de behandeling aangepast zou moeten worden aan de persoonlijke risicofactoren van de individuele patiënt.

Een nieuw systeem om valincidenten bij te houden: de Valtelefoon

Om de prevalentie van vallen en de effectiviteit van valpreventieprogramma's te evalueren is nauwkeurige informatie nodig over het aantal valincidenten. In **hoofdstuk 5** hebben we de evaluatie beschreven van een geautomatiseerd telefoonsysteem dat valincidenten registreert. Zo'n systeem kan een voordelige methode zijn om vallen binnen longitudinale studies

bij te houden. Deze zogeheten "Valtelefoon" werkt als volgt: een computergestuurd systeem neemt - met een door de onderzoeker vastgestelde frequentie - automatisch telefonisch contact met deelnemers op, waarbij de deelnemer het aantal valincidenten over een voorafgaande periode intoetst op de telefoon.

De sensitiviteit, specificiteit en gebruikerservaringen van deze Valtelefoon hebben we bepaald middels een evaluatiestudie. Hierbij belde het systeem met wekelijkse intervallen. 119 Parkinsonpatiënten (niet dementerend, zelfstandig wonend) werden gevolgd gedurende 1 tot 40 weken (gemiddeld 20,7 telefoongesprekken per patiënt). In totaal vonden er 2465 automatische telefoongesprekken plaats. Van deze gesprekken is de invoer van 173 'geen val' meldingen en 115 'val' meldingen geverifieerd middels persoonlijke telefonische interviews door de onderzoeker. Tijdens dit interview controleerden we of de invoer correct doorgekomen was binnen het systeem en of het ingetoetste aantal overeen kwam met het daadwerkelijk aantal vallen in de voorafgaande week. Alle 'geen val' meldingen werden bevestigd en 78% van de 'val' meldingen. De sensitiviteit van het systeem om vallen te detecteren was 100% en de specificiteit was 87%. Door deze hoge specificiteit kan de Valtelefoon tijdsintensieve en kostbare persoonlijke follow-up vervangen voor de 'niet-vallers'. Ook hebben we gebruikerservaringen geëvalueerd in een subgroep van 90 patiënten middels telefonische interviews. Hierbij hebben we vragen gesteld over verschillende aspecten rondom gebruiksvriendelijkheid van het systeem en mogelijke alternatieve methodes besproken die vaak gebruikt worden om vallen te registreren, waaronder een valkalender, tweewekelijkse valkaarten, en een 'val-hotline'. De resultaten toonden aan dat de gebruikers de Valtelefoon beoordeelden als een eenvoudig en gebruiksvriendelijk systeem om vallen te kunnen registreren. Daarnaast hebben we inschattingen van de kosten van het systeem gegeven. Uitgaande van een fictieve studie van 50 personen met wekelijkse intervallen gedurende een jaar zou de Valtelefoon kosten kunnen besparen, voornamelijk op personele inzet.

De Valtelefoon biedt een effectief, gebruiksvriendelijk en betrouwbaar systeem om valincidenten bij te houden in populatiestudies met patiënten met de ziekte van Parkinson, en mogelijk ook voor andere aandoeningen waarbij vallen voorkomen.

Teamsamenwerking binnen de zorg

Het complexe karakter van de ziekte van Parkinson en de beperkingen van de huidige medische zorg om alle symptomen voldoende onder controle te houden, vragen om een bredere benadering vanuit verschillende disciplines boven een behandeling door één enkele specialist. Een teamgerichte aanpak wordt steeds meer beschouwd als het optimale model om een complexe aandoening als Parkinson te behandelen. Er is alleen nog geen standaardmodel dat aangeeft hoe zo'n bredere aanpak dan georganiseerd moet worden. Ook is er maar weinig

wetenschappelijk bewijs om te onderbouwen dat teamzorg beter is. De **hoofdstukken 6, 7 en 8** zijn toegespitst op de voordelen van een bredere aanpak met aanvullende interventies naast reguliere medische behandeling.

Het wetenschappelijke bewijs voor paramedische behandelingen (fysiotherapie, logopedie en ergotherapie) en multidisciplinaire behandelingen bij de ziekte van Parkinson was samengevat in **hoofdstuk 6**. Paramedische zorg biedt een toegevoegde waarde naast medische zorg, door een andere insteek op focus, doel en werkingsmechanisme: paramedici kijken naar de invloed van de symptomen op het dagelijks functioneren van de patiënt in plaats van naar het primaire ziekteproces; het doel van de behandeling is het verbeteren van de participatie tijdens alledaagse activiteiten in plaats van het verminderen van symptomen met medicatie; en het werkingsmechanisme is anders aangezien paramedische zorg de beschadigde basale ganglia omzeilt en gebruik maakt van de alternatieve netwerken in de hersenen die nog intact zijn. Tegenwoordig is er steeds meer bewijs voor de effectiviteit van fysiotherapie, logopedie en ergotherapie als afzonderlijke, 'monodisciplinaire' behandeling (klasse II bewijs voor fysiotherapie en logopedie en klasse III bewijs voor ergotherapie).

Ondanks het feit dat paramedici en medisch specialisten overlappende behandeldoelen hebben, werken ze veelal afzonderlijk van elkaar. Een teambenadering, waarbij verschillende disciplines samenwerken, biedt waarschijnlijk de meest optimale behandeling voor het brede palet aan symptomen dat de ziekte van Parkinson kenmerkt. Echter, tot nu toe is er maar weinig wetenschappelijk bewijs en zijn er slechts enkele gecontroleerde studies die behandeling door een team van zorgverleners bij de ziekte van Parkinson geëvalueerd hebben.

Het wetenschappelijke bewijs voor afzonderlijke, 'monodisciplinaire' paramedische behandelingen neemt toe. Samenwerking tussen specialisten is waarschijnlijk effectiever dan wanneer iedere specialist afzonderlijk te werk gaat. Ondanks het feit dat er een algemeen gevoel heerst dat een dergelijke multidisciplinaire aanpak nodig is en voordelen biedt, is er tot nu toe slechts weinig onderzoek gedaan om deze gedachte te onderbouwen.

Verschillende soorten van samenwerking

Zorgverleners kunnen op verschillende manieren samenwerken, varierend van het uitwisselen van kennis en adviezen op basis van een indivudele patient tot het leveren van teamsamenwerking, waarbij alle zorgverleners hun kennis inbrengen tijdens gezamenlijke bijeenkomsten en samen tot een behandeladvies komen.

Binnen teamsamenwerking is er nog onderscheid te maken tussen multidisciplinair, interdiscipinair en een integrale aanpak. Bij *multidisciplinaire* samenwerking zijn verschillende zorgverleners betrokken, die ieder hun eigen deel van de behandeling waarnemen. Deze vorm van zorg kan uitgebreid worden naar *interdisciplinaire* zorg, waarbij er regelmatig overleg en bijeenkomsten plaatsvinden en er vanuit de groep beslissingen genomen worden. Het *integrale* model van zorg is gebaseerd op een gezamenlijk opgesteld behandelplan dat vanuit consensus van de verschillende teamleden ontstaat. Hieraan draagt iedere zorgverlener bij met zijn/haar expertise en wordt ook de patient betrokken binnen het team.

Een gespecialiseerde teambehandeling met meerdere disciplines

Hoofdstuk 7 beschrijft de evaluatie van een multidisciplinair team model. De interventie bestond uit gespecialiseerde zorg verleend door een bewegingsstoornissenspecialist, Parkinsonverpleegkundige en maatschappelijk werker, wiens inbreng toegespitst was op de individuele behoeftes van de patiënt. We onderzochten de effectiviteit van deze multidisciplinaire behandeling (interventiegroep, n=51) middels een eenzijdig geblindeerd, gerandomiseerd onderzoek met een controlegroep (n=49, wachtlijst) waarin patiënten zorg van een algemene neuroloog ontvingen.

Na 8 maanden verbeterden de patiënten in de groep die multidisciplinaire zorg ontving. Deze groep verbeterde op kwaliteit van leven (PDQ-39, verschil 3.4, 95% betrouwbaarheidsinterval 0.5 tot 6.2) en motor score (UPDRS III, 4.1, 95% betrouwbaarheidsinterval 0.8 tot 7.3) in vergelijking met patiënten in de controlegroep. Ook waren er verbeteringen in totale UPDRS score (5.6, 95% betrouwbaarheidsinterval 0.9 tot 10.3), depressie (MADRAS, 3.7, 95% betrouwbaarheidsinterval 1.4 tot 5.9) en psychosociaal functioneren (SCOPA-PS, 2.1, 95% betrouwbaarheidsinterval 0.5 tot 3.7). De belasting voor de mantelzorgers (gemeten met de CSI) was niet verschillend tussen de groepen (1.5, 95% betrouwbaarheidsinterval -1.2 tot 4.2). Dit is een van de eerste gerandomiseerde gecontroleerde onderzoeken die meerwaarde voor multidisciplinaire/gespecialiseerde behandeling aantoont.

> Gespecialiseerde zorg van een multidisciplinair team bestaande uit een specialist in bewegingsstoornissen, Parkinsonverpleegkundige en maatschappelijk werker biedt meerwaarde op verschillende domeinen (kwaliteit van leven, motorisch functioneren, depressie en psychosociaal functioneren).

Richting een geïntegreerd model van Parkinsonzorg

Hoofdstuk 8 beschrijft een omvangrijk onderzoek met een gecontroleerd design. Het doel van dit onderzoek was het evalueren van de effectiviteit van een integrale organisatie van teamzorg. Dit zorgmodel omvatte twee complementaire delen: (a) een beoordeling in een expertisecentrum waarbij behandeladviezen gegeven worden, die geïmplementeerd kunnen worden in (b) regionale netwerken van samenwerkende paramedici. Patiënten werden uitgenodigd voor een driedaagse screening door een team van zorgverleners, wiens inbreng toegespitst was op de individuele behoeftes en prioriteiten van de patiënt. Verschillende disciplines waren betrokken: specialisten in bewegingsstoornissen, Parkinsonverpleegkundigen, maatschappelijk werker, fysiotherapeuten, ergotherapeuten, logopedisten, slaapspecialisten, diëtisten, seksuologen, neuropsychologen, neuropsychiaters, revalidatieartsen en geriaters. De behandeladviezen werden tijdens een gezamenlijke bijeenkomst opgesteld. Deze adviezen konden in de eigen leefomgeving van de patiënt geïmplementeerd worden door gespecialiseerde paramedici (fysiotherapeuten, ergotherapeuten en logopedisten) die samenwerken binnen regionale ParkinsonNet netwerken. De belangrijkste elementen van

deze netwerken zijn specifieke training, behandeling volgens evidence-based richtlijnen, structurering van verwijsprocessen en optimalisatie van onderlinge communicatie en samenwerking tussen de verschillende specialisten.

We hebben een gecontroleerd onderzoek opgezet, waarbij een interventieregio met het hierboven beschreven zorgmodel (n=150) vergeleken werd met reguliere zorg in controleregio's (n=151). De effectiviteit hebben we geëvalueerd over een periode van 4 tot 8 maanden na de startmeting. De primaire uitkomstmaten, activiteiten van dagelijks leven en kwaliteit van leven, waren significant verbeterd (ALDS 1.3, gelijk aan een verschil in logit van 0.1, 95% betrouwbaarheidsinterval 0.003 tot 0.2; PDQL 3.0, 95% betrouwbaarheidsinterval 0.4 tot 5.6). Deze verbeteringen waren echter klein en waren niet langer aanwezig als gecorrigeerd werd voor ziekte-ernst tijdens de startmeting. Er was geen verandering in motorische score (UPDRSIII) en mantelzorgerbelasting (BELA-A-k) als secundaire uitkomstmaten. Een scala aan tertiaire gezondheidsmaten, waaronder niet-motorische symptomen, angst en depressie, en algemene gezondheidsperceptie, lieten ook positieve, maar kleine verbeteringen zien. De kosten van zorg (meegenomen vanuit het maatschappelijke perspectief) lieten geen statistisch significant verschil zien tussen de groepen over de 8 maanden studieperiode (gemiddeld verschil €742, 95% betrouwbaarheidsinterval -€489 tot €1950).

Een integrale organisatie van Parkinsonzorg, met een expertise centrum en regionale netwerken van gespecialiseerde therapeuten, bood weinig meerwaarde. Naast het feit dat de verbeteringen klein waren, verdwenen de effecten na correctie voor ziekte-ernst bij aanvang van de studie. Deze studie levert daarom geen onomstotelijk bewijs dat de integrale organisatie van zorg die wij geëvalueerd hebben meer te bieden heeft dan reguliere zorg door verschillende therapeuten.

DANKWOORD

LIST OF PUBLICATIONS

ABOUT THE AUTHOR

DISSERTATIONS OF THE PARKINSON CENTRE NIJMEGEN

Dankwoord

BEDANKT ALLEMAAL!

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List of publications (* listed in this thesis)

* **MA van der Marck**, PhCM Klok, MS Okun, N Giladi, M Munneke, BR Bloem. Consensus-based clinical practice recommendations for the examination and management of falls in patients with Parkinson's disease. *Parkinsonism and Related Disorders* (accepted)

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Curriculum vitae

Marjolein Astrid van der Marck was born on the 25th of June 1982 in Eindhoven, the Netherlands. In 2000, she finished secondary school at the St Joris College in Eindhoven and received her VWO diploma. She started her university training in Human Nutrition and Health at the Wageningen University and Research centre that same year. There, she conducted research on several topics, including the role of curcuma in the treatment of colorectal cancer (BSc degree); the evaluation of a web-based counseling tool as part of a tailored support program to lower fat intake in patients with elevated cardiovascular risk; and the effects of structurally different lipid emulsions in parenteral nutrition on the immune system (MSc degree). She completed her master dissertation internship at the Dietetic department of the University Hospital Maastricht, with research on weight changes after deep brain stimulation in patients with Parkinson's disease.

In October 2005, Marjolein received her Master of Science degree (specialization in Clinical Nutrition) and, at the same day, she was appointed as a PhD student at the department of Neurology of the Radboud University Medical Center. Initially, she started working on the development of ParkinsonWeb (a website to inform patients on Parkinson's disease and to facilitate communication between health professionals). Then, she began her work on the evaluation of the Parkinson Centre Nijmegen, including interviews with patients and informal caregivers, development of evaluation questionnaires and database, an open-label study, and the work which has been described in this thesis, including the IMPACT trial. During her PhD project she attended several (international) conferences and followed several courses and workshops, including academic writing, scientific journalism, presenting, and biometrics. Furthermore, she presented her research at conferences in the field of movement disorders and Parkinson's disease, where one of posters was also selected for a Guided Poster Tour (MDS 2009 Paris Congress).

From 2012, Marjolein is appointed as a postdoctoral fellow in research on Alzheimer's disease at the department of Geriatrics of the Radboud University Medical Center, including medication research, development of a guideline, and organization of dementia care. She is also a member of the ESPEN Development Guidelines Group on nutrition in neurodegenerative disorders.

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Curriculum vitae

Marjolein Astrid van der Marck werd op 25 juni 1982 geboren in Eindhoven. In 2000 behaalde zij haar VWO diploma aan het St Joris college in Eindhoven. Aansluitend volgde zij aan de Wageningen Universiteit de opleiding Voeding en Gezondheid. Binnen de opleiding voerde zij verschillende onderzoeken uit, onder andere naar kurkuma in de behandeling van darmkanker (BSc fase); de evaluatie van een website als onderdeel van een persoonlijk programma voor patiënten met een verhoogd risico op hart- en vaatziektes te helpen hun vetinname te verlagen; en de effecten van verschillende vetten in parenterale voeding op het immuunsysteem (MSc fase). Marjolein koos voor de afstudeerrichting Klinische Voeding. Tijdens haar stage aan de afdeling Diëtetiek van het Academisch Ziekenhuis Maastricht verrichtte zij onderzoek naar gewichtsveranderingen bij patiënten met de ziekte van Parkinson die een operatie ondergingen voor een diepe hersenstimulatie.

In Oktober 2005 rondde zij de Master of Science opleiding met succes af en werd op dezelfde dag aangenomen op de afdeling Neurologie van het Radboudumc als promovenda. Binnen deze functie heeft zij ParkinsonWeb opgezet (een website als informatievoorziening voor de patient en als communicatiemiddel voor zorgverleners) en deed zij onderzoek rondom de evaluatie van het Parkinson Centrum Nijmegen, waaronder interviews met patiënten en mantelzorgers, het ontwikkelen van evaluatievragenlijsten en databases, een eerste pilot studie, en het onderzoek zoals beschreven in dit proefschrift (o.a. de IMPACT studie). Tijdens haar promotietraject heeft Marjolein verschillende cursussen en workshops gevolgd (o.a. wetenschappelijk schrijven, wetenschapsjournalistiek, presenteren, en biometrie) en heeft ze haar werk op verschillende congressen gepresenteerd, waar één van haar onderzoeken geselecteerd was voor een 'Guided Poster Tour' (MDS congres, Parijs, 2009).

Vanaf 2012 werkt Marjolein als postdoc en projectleider bij onderzoek op de afdeling Geriatrie van het Radboudumc, waaronder geneesmiddelenonderzoek, richtlijnontwikkeling en organisatie van zorg. Daarnaast is zij lid van de ESPEN richtlijn ontwikkelingsgroep over voeding bij neurodegeneratieve aandoeningen.

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  Radboud University Nijmegen, 10 January 2014

THE MANY FACES OF PARKINSON'S DISEASE: TOWARDS A MULTIFACETED APPROACH?

The work included in this thesis describes the multidimensional nature of Parkinson's disease and provides the basis for a multifaceted approach in the management of this broad symptom complex. A team-oriented approach, including multiple professional disciplines as well as patients themselves, seems warranted to optimally manage all motor and non-motor symptoms, as illustrated in this thesis. Furthermore, we evaluated two different types of organisations of multispecialty team care, and offer new scientific evidence to support comprehensive health care models in Parkinson's disease.