ADHERENCE THERAPY FOR PEOPLE WITH PARKINSON'S DISEASE

By

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Abstract

Introduction: Medication non-adherence is prevalent in Parkinson's disease (PD). However, factors associated with non-adherence are unknown. Despite interventions to improve medication adherence being investigated in long-term conditions, few studies have focused on PD. Adherence Therapy (AT) is a novel, patient-centred approach to maximising adherence that has shown benefit in other chronic conditions.

Aim: To investigate the efficacy of AT for improving medication adherence and quality of Life (QoL) in people with PD.

Methods: To achieve the above aim I conducted a systematic review to identify factors associated with medication non-adherence, followed by a Cochrane systematic review on interventions for improving medication adherence in PD. I then tested the efficacy of AT in PD in a randomised controlled trial (RCT). Semi-structured interviews were used to explore patients' experiences of receiving AT.

Results: Mood disorders, cognition, poor symptom control/QoL, younger age/longer disease duration, regimen complexity/polypharmacy, risk taking

behaviours, poor knowledge of PD/education, lack of spouse/partner, low income, desire to maintain employment and gender were identified as factors associated with non-adherence in PD. Only one study previously investigated an intervention (didactic educational material) for improving medication adherence in PD, according to my Cochrane systematic review.

Seventy-six patients and 46 spouse/carers completed the RCT (CAAT-PARK). At week-12 follow-up the active treatment group significantly improved in adherence and QoL compared to the treatment as usual group. Thematic analysis of interviews from 10 patients and 3 spouse/carers suggested that positive effects and attributes of AT may be important for the success of AT. Furthermore, the findings suggested that the mechanism of AT may be bi-directional and associated with improved confidence and self-efficacy.

Conclusions: Adherence Therapy improved medication adherence and QoL in PD. A larger pragmatic trial to test the efficacy and cost effectiveness of Adherence Therapy with a control group placebo intervention is required. ISRCTN07830951

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List of Abbreviations

ADL	-	Activities of Daily Living
AE	-	Adverse Events
CENTRAL	-	Cochrane Central Register of Controlled Trials
CI	-	Confidence Intervals
COMT	-	Catechol-O-Methyl Transferase Inhibitors
CRF	-	Case Record Files
DDS	-	Dopamine Dysregulation Syndrome
DLB	-	Dementia with Lewy Bodies
DRT	-	Dopamine Replacement Therapy
HADS	-	Hospital Anxiety & Depression Scale
HBM	-	Health Belief Model
HIV	-	Human Immunodeficiency Virus
HRQoL	-	Health Related Quality of Life
H&Y	-	Hoehn & Yahr Scale
ICD	-	Impulse Control Disorder
ICH	-	The International Conference of Harmonisation
ICTRP	-	WHO International Clinical Trials Registry Platform
IMB	-	Information-Motivation-Behavioural Skills Theory
IQR	-	Inter Quartile Range
ISRCTN	-	International Standard Randomised Controlled Trial Number

ITT	-	Intension to Treat
LEDD	-	Levodopa Equivalent Daily Doses
MAO-B	-	Monoamine Oxidase-B-Inhibitors
MD	-	Mean Difference
MEMS	-	Medication Electronic Monitoring devises/caps
MeSH	-	Mapped Specific Subject Headings
MFE	-	Medicine For The Elderly Department
MMAS-4	-	Morisky Medication Adherence Scale 4 item
MMSE	-	Mini-Mental State Examination
MoCA	-	Montreal Cognitive Assessment Scale
MOOSE	-	Meta-analysis of Observational Studies in Epidemiology
MI	-	Motivational Interviewing
MPR	-	Medication Possession Ratio
MSA	-	Multiple Systems Atrophy
NICE	-	National Institute for Health and Clinical Excellence
NRR	-	UK National Research Register
NNT	-	Numbers Needed to Treat
NNUH	-	Norfolk and Norwich university Hospital
Non-IMPs	-	Non-Investigational Medicinal Products
NPF	-	National Parkinson's Foundation
OH	-	Orthostatic Hypotension
OR	-	Odds Ratio
PD	-	Parkinson's disease
PDD	-	Parkinson's disease Dementia
PMT	-	Protection Motivation Theory

PP	-	Per Protocol
PSP	-	Progressive Supranuclear Palsy
QALYs	-	Quality Adjusted Life Years
QoL	-	Quality of Life
REM	-	Rapid Eye Movement
SCT	-	Social-Cognitive Theory
SOPs	-	Standard Operating Procedures
STROBE	-	Strengthening the Reporting of Observational Studies
TPB	-	Theory of Planned Behaviour
TRA	-	Theory of Reasoned Action
TSC	-	Trial Steering Committee
TTM	-	Transtheoretical Model of Change
UK	-	United Kingdom
UPDRS	-	Unified Parkinson's disease Rating Scale
US	-	United States
USPSTF	-	US Preventive Services Task Force
WHO	-	World Health organization

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Parky's Time

"Parky is running around my brain what is he doing there

He whizzes round from dawn to dusk and doesn't seem to care

He makes my life quite hard to plan and leaves me feeling down

He twits my face this way and that and makes me wear a frown

Levodopa is the answer, so all the experts say

To put this right I have to take some medicine each day

Through studies made it has been proved it's most important to

Not just take them every day, but at the right time too.

My morning medications, starts off with good intent

The sequence that I follow, is time I think well spent

The importance of adherence, is there for all to see

It soothes the highs and the lows you see, and leaves me tremor free

It may be sometimes tiresome, for a clock to rule my day

But all in all it helps me live my life a better way"

Trial Participant: B181 (CRTU 052)

CHAPTER 1

The Necessity of This Work

Background
The Structure and Aim of This Thesis

1.1 Background

Parkinson's disease (PD) is a degenerative, neurological disorder that greatly impacts on Quality of Life (QoL). The diagnosis of PD is made based on four key symptoms: rigidity, bradykinesia (slowness of movement), postural instability and resting tremor (Hughes et al., 1992). Alongside motor dysfunction, many people with PD experience a wide variety of non-motor symptoms which can be both highly prevalent and problematic (Chaudhuri et al., 2006, Poewe, 2008).

The symptoms of PD are controllable, although management becomes considerably more complex as the condition progresses. Not only do slowness, rigidity and gait problems respond to treatment, but many non-motor symptoms can also be relieved by PD medications. Healthcare professionals responsible for managing PD have the potential to substantially improve the QoL of patients. Although not all symptoms of PD can be sufficiently managed, anti-parkinsonian medication affords the

patient an optimal QoL, allowing many individuals to remain in the mainstream of their lives for many years post diagnosis (Ahlskog, 2009).

Medication management for PD, however, is not straight forward and is complicated by a multitude of factors. There are various pharmaceutical formulations (drugs) available for use with the same therapeutic indications and overlapping pharmacodynamics. Many drugs can induce unique side effects, which may often be confused with the worsening symptoms of PD (Fahn, 1989). Despite a vast body of research, disparity remains in the literature concerning what is the best therapeutic approach to adopt at different stages of disease severity (Schapira, 2007). Furthermore, controversy between expert opinions regarding when to initiate certain treatments remains topical and continues to be a source of debate (Schapira and Obeso, 2006).

Obscuring management decisions further is the fact that PD is progressive, with new problems appearing over the course of the disease that can alter the therapeutic focus. This can result in continuous amendment of doses and class of medications used to control the symptoms. What's more, as PD is mainly a condition prevalent in older people, age related comorbidities add further to the burden on QoL. In light of the aforementioned factors, it is evident that successful medical management of a person with PD is a complex and on-going pursuit, particularly as the disease progresses.

As with all chronic diseases, adherence to medication is paramount for achieving effective symptom control; drugs do not have the desired therapeutic effect if they

are not taken as the prescriber intended (Rigby, 2007). However, reports from the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE) in the UK suggest that a third to half of all medications prescribed to people with long term conditions are not taken as recommended (WHO, 2003, NICE, 2009).

In PD more than half of people take two to four anti-parkinsonian medications three to four times daily (Leoni et al., 2002, Tan et al., 2005). This is because multiple drug classes are needed to adequately control symptoms as PD progresses (Schapira et al., 2009a). Adding further prescriptions often parallels dose escalation, resulting in complex polypharmacy (Kulkarni et al., 2008). Therefore, not surprisingly, medication adherence is poor in people with PD (Bainbridge and Ruscin, 2009).

Whilst not taking prescribed medication as recommended will result in ill managed symptoms in many chronic conditions, the ramifications of non-adherence in PD are acutely problematic (Grosset et al., 2005b, Kulkarni et al., 2008, Grosset, 2010). For example, sub-optimal medication adherence in PD can result in the 'wearing-off' of the treatment effect which can increase motor dysfunction (Grosset et al., 2005b, Kulkarni et al., 2008, Grosset, 2010). Researchers have shown sub-optimal medication adherence to be associated with poor symptom control, increased unplanned hospital visits for PD related problems and a poorer overall prognosis (Kulkarni et al., 2008).

Aside from sub-optimal medication taking, people may also over medicate on anti-parkinsonian therapy. This can result in severe motor complications such as peak dose motor fluctuations, dyskinesia (uncoordinated movements) and can even lead to psychosis (Lim et al., 2009, O'Sullivan et al., 2009). Although medication adherence is important in all chronic diseases, due to the intricate relationship between medication taking and both immediate and long-term symptom management, it is clear that sound adherence in PD is essential.

The reasons for non-adherence are likely to be multi-dimensional. Consequentially, there is a need for greater understanding of the factors that are associated with medication non-adherence in PD. With an increased understanding of why patients may not adequately adhere to medication regimens, an intervention that specifically aims to enhance adherence behaviour can be investigated. A targeted therapy that acknowledges factors associated with sub-optimal medication taking may result in overall improvement in rates of adherence. As various motor and non-motor symptoms of PD are sensitive to anti-parkinsonian therapies, improved medication adherence may enhance overall function. Consequentially, improved adherence to medication could theoretically benefit QoL.

1.2 The Aim & Structure of This Thesis

The main aim of the work presented in this thesis was to investigate the efficacy of an intervention for improving medication adherence in patients with PD. From this aim, several specific objectives were developed as presented below:

1. To identify from the existing literature which factors are associated with medication non-adherence in people with PD.

2. To identify from the literature which interventions have been investigated previously that aimed specifically to improve adherence to medication in PD.

3. To develop a novel intervention aimed at improving medication adherence in people with PD.

4. To investigate the efficacy of this novel intervention.

5. To evaluate patient acceptability and to investigate the potential underlying mechanism of the adherence enhancing intervention.

This thesis is presented in three parts. Part one contains Chapters 2, 3 and 4. In Chapter 2 I provide an introduction to PD, including an overview of the medication used to manage the common symptoms in both early and later stages of the disease. I then discuss the importance of medication adherence in PD, the prevalence of non-adherence and the associated consequences.

In Chapter 3 I present the rationale and findings of a systematic review identifying factors associated with medication non-adherence in people with PD. The development of a novel quality appraisal tool for assessing risk of bias is also discussed. Having highlighted factors associated with non-adherence in PD, in Chapter 4 I provide the rationale and findings of a Cochrane systematic review investigating interventions used to improve medication adherence in PD.

Part 2 commences with Chapter 5 where I discuss the common psychological theories of behaviour change. The underlying principles of, and the evidence base for, the disciplines of motivational interviewing and cognitive behavioural therapy are presented. I then conclude by introducing the therapy of interest in this thesis; that is, Adherence Therapy (AT) and by discussing its evidence base from the existing literature.

Chapter 6 outlines the justification and methodology for a randomised controlled trial investigating whether AT is beneficial for improving medication adherence and quality of life. The analyses undertaken and the ethical considerations relating to the conduct of the trial are then discussed. Part 3 starts with Chapter 7 where I present the quantitative findings of the RCT. In Chapter 8 I provide a detailed discussion of the findings.

In Chapter 9 I investigate the acceptability of, and proposed mechanism for, the AT intervention using a qualitative methodological approach. In Chapter 10 a detailed discussion of the findings is provided and the implications for practice and further research are considered.

This thesis concludes with Chapter 11. The findings of the Cochrane systematic review, presented in Chapter 4, are considered when the results of the clinical trial are added. The implications of the overall findings within this thesis are considered for both clinical practice and future research. The dissemination of the findings is also outlined.

Part 1

CHAPTER 2

Parkinson's Disease & Pharmacotherapy

Introduction
Parkinson's Disease & The Nigrostriatal Pathway
Prevalence and Cost of Parkinson's Disease
Symptoms of Parkinson's Disease
Pharmacotherapy for Parkinson's Disease
Treatment Regimens and Complexity in Parkinson's Disease
Medication Adherence
Summary: A Greater Understanding

2.1 Introduction

This chapter provides an outline of PD. Specifically, I summarise the underlying pathophysiology, characteristic symptoms, prevalence and the cost of PD. Following this I then highlight the typical anti-parkinsonian medications used to treat the symptoms of PD. In the final part of this chapter I discuss medication non-adherence and the associated consequences for people with PD.

2.2 Parkinson's Disease & The Nigrostriatal Pathway

The hallmark of PD is the progressive degeneration of the dopamine producing neurons within the substantia nigra (Jankovic, 2008). Microscopically, PD is characterised by the presence of Lewy bodies found within surviving nigral neurons. The protein alpha-synuclein, found in Lewy bodies, characterises PD aside from other forms of Parkinsonism (Ahlskog, 2009).

The nigrostriatal pathway is positioned centrally in the extrapyramidal (basal ganglia) motor control circuits (Ahlskog, 2009). Identifying that the nigrostriatal pathway is dopaminergic resulted in the discovery that replenishing dopamine with levodopa is a very effective treatment for PD (Ahlskog, 2009). Today levodopa remains the foundation of PD treatment and has been recognised as the most effective pharmacological intervention for symptom management (Schapira et al., 2009b).

2.3 Prevalence and Cost of Parkinson's Disease

2.3.1 Prevalence

Parkinson's disease is the second most prevalent neurodegenerative disorder after Alzheimer's disease (Mayeux et al., 1995, Bower et al., 1999, Nussbaum and Ellis, 2003) and is anticipated to impose an increasing social and economic burden on society as populations continue to age (De Lau and Breteler, 2006). A report by the National Parkinson Foundation (NPF) in the United States (US) suggested that PD affects an estimated four to six million worldwide (Oberdorf and Schmidt, 2010).

In the UK, PD is estimated to affect 100–180 people per 100,000 of the population and has an annual incidence of 4-20 per 100,000 (NICE, 2006). The incidence of the disease rises with increasing age (Findley, 2007, Findley et al., 2003). One in seven are diagnosed before 50 years of age, with a fivefold increase in diagnosis in those aged over 65 (Schrag et al., 2000a).

2.3.2 Cost of Parkinson's Disease

Due to an ageing population the prevalence of PD is forecast to increase substantially in the long term (De Lau and Breteler, 2006). This will result in immense financial dependency on healthcare organisations globally. Current costs are estimated to be $23 billion annually in the US alone and are projected to increase to $50 billion by 2040 (Oberdorf and Schmidt, 2010).

A cross-sectional study of the economic impact of PD on healthcare providers in the UK showed an estimated cost for care of approximately £450 million (Findley et al., 2003). However, this calculation was thought to be the most conservative scenario. Using current and future predicted prevalence rates, cost for healthcare analysis suggests expenditure will reach as high as £3.3 billion annually (Findley, 2007). Furthermore, the fiscal dependency for increased care in patients with PD rises exponentially with the progression of the disease. This is because people become increasingly medicated due to incapacitating motor and non-motor dysfunction.

Personalised one-to-one care may also be required for those who develop significant cognitive dysfunction, adding substantial costs for care (Oberdorf and Schmidt, 2010); researchers have shown cognitive impairment and dementia in PD greatly reduce QoL and can be more debilitating to patients and burdensome for carers than motor symptoms (Leroi et al., 2012). It is also well acknowledged that poor cognitive function is a key predictor of nursing home placement and mortality in people with PD (Hou and Lai, 2007, Liepelt et al., 2007).

In light of the reported prevalence's and findings from cost for healthcare analyses, it is essential that PD medication is closely managed to ensure that treatments are appropriate for each individual suffering from PD.

2.4 Symptoms of Parkinson's Disease

Parkinsonism implies the appearance of PD characteristics and is a broad term used to include other disorders like progressive supranuclear palsy (PSP), multiple systems atrophy (MSA), PD dementia (PDD) and dementia with Lewy bodies (DLB) (Albanese, 2003, Jankovic, 2008, Ahlskog, 2009). Prior to the diagnosis of PD patients may report non-specific symptoms: feelings of depression and/or anxiety, REM (rapid eye movement) sleep disorder, fibromyalgia and olfactory dysfunctions. It is not until PD progresses further that parkinsonian associated symptoms present (Albanese, 2003).

For many the onset of PD is insidious and people classically present with the cardinal signs and symptoms associated with the overarching phenomenon of Parkinsonism (Table 2.1). Additionally, a dysfunctional presence of thoracic flexion and freezing during gait have been proposed as characteristically prominent features in advanced Parkinsonism (Albanese, 2003, Jankovic, 2008).

Table 2. 1 - Symptoms of Parkinsonism

Symptom	Description
Bradykinesia	Slowed movements
Rigidity	Resistance as the examiner moves a relaxed limb
Gait	Shortened stride, reduced heel strike, shuffling
Resting tremor	Limbs, chin
Loss of automatic movements	Reduced animation; for example, facial masking, dampened arm swing when walking, gesturing when talking
Poor balance	Often not prominent in early PD

(Ahlskog, 2009)

Diagnostically the motor symptoms of PD characterise the disorder. However, non-motor symptoms are also significantly debilitating (Chaudhuri et al., 2004, Chaudhuri et al., 2006, Hou and Lai, 2007, Poewe, 2008, Chaudhuri and Martinez-Martin, 2008, Löhle et al., 2009, Park and Stacy, 2009). As many as 90% of people with PD are reported to experience non-motor manifestations throughout the disease course (Shulman et al., 2001).

Table 2.2 provides an outline of the non-motor symptoms of PD. As PD progresses non-motor symptoms start to become increasingly troublesome and multiple medications can be added (Hou and Lai, 2007). These can be in addition to drugs aimed at treating motor symptoms. For many people with PD this leads to increasing medication complexity and polypharmacy.

Table 2. 2 - Non-motor Symptoms of Parkinson's disease

Category of Non-motor symptom	Specific complaint
Neuropsychiatric	• Depression, apathy, anxiety, anhedonia, attention deficit, hallucinations. • Delusions, dementia, obsessive behaviour.
Sleep Disorders	• Restless legs, periodic limb movements, REM behaviour disorder. • Excessive daytime sleepiness, vivid dreaming, non-REM sleep movement disorder, insomnia.
Autonomic	• Bladder disturbance: urgency, nocturia and frequency, sweating, Orthostatic Hypotension (OH), falls related to OH, coat-hanger pain, sexual dysfunction, hypersexuality, erectile impotence.
Gastrointestinal	• Dribbling of saliva, ageusia, dysphagia/choking, reflux, vomiting, nausea, constipation, unsatisfactory voiding of bowl, bowl incontinence.
Sensory	• Pain, paraesthesia, olfactory disturbance
Other	• Fatigue, diplopia, blurred vision, seborrhoea, weight loss

Cognitive impairment is estimated to affect up to 85% of patients with PD if executive dysfunction is included (Aarsland and Kurz, 2010). Deficits include dysfunctional planning and organisation, visuospatial difficulties and impaired memory recall, amongst others (Dubois and Pillon, 1997, Hou and Lai, 2007). Even in early PD, subtle decline in cognitive function may be evident (Park and Stacy, 2009). As the disease progresses cognitive decline persists and PD patients

may develop dementia (PD dementia (PDD)) (Leroi et al., 2012). Aarsland & colleagues (2005) conducted a meta-analysis including a total of 1767 PD patients with a mean age of 73 years (range 70-76) and found the prevalence of dementia to be 30%. However, estimates suggest dementia affects 50% of PD patients who have had the disease for 15 years or more. It is likely therefore that in advanced PD treatment may be aimed at managing the consequences of dementing illness as opposed to treating motor symptoms which may have been the focus in earlier stages of PD (Dubois and Pillon, 1997, Bosboom et al., 2004, Ahlskog, 2009, Montine, 2010).

The remainder of this chapter focuses on two topics. First I outline the various pharmacological treatments used for the management of PD. I then discuss the issue of medication adherence and the consequences of non-adherence specifically in PD. Finally, I summarise the chapter by placing it within the context of the overall thesis.

2.5 Pharmacotherapy for Parkinson's Disease

Despite much research into strategies to inhibit PD progression, no treatment has yet been shown to offer promising neuroprotective properties (Suchowersky et al., 2006). Currently there is no encouraging evidence that any drug truly modifies the underlying pathophysiology of PD. Therefore, managing and controlling the symptoms of PD is the chief therapeutic goal of current treatment strategies; the aims of which are to keep patients engaged in society, remain ambulatory and

maximise QoL (Chaudhuri et al., 2006). Despite medications appearing to lack neuroprotective efficacy, drugs aimed at controlling the symptoms of PD can be substantially beneficial. Table 2.3 outlines the most common orally administered PD preparations.

Table 2. 3 - Oral Drug Preparations for Parkinson's disease

Classification	Drug Names		Preparations
	Generic	Brand	
Levodopa	Co-careldopa (carbidopa)*	Sinemet (tablet)	50mg/12.5mg Half Sinemet 100mg/25mg 100mg/10mg Sinemet CR 200mg/50mg 200mg/25mg
	Co-beneldopa (benserazide)*	Madopar (capsule)	50mg/12.5mg 100mg/25mg (dispersible tbl) 200mg/50mg 100mg/25mg CR** 100mg/25mg (dispersible tbl)
	Co-careldopa + Entacapone	Stalevo	50mg 70mg 100mg 125mg 150mg 200mg
Catechol-O-Methyl Transferase Inhibitors	Entacapone	Comtess	200mg
	Tolcapone	Tasmar	100mg
Monoamine Oxidase B Inhibitors	Rasagiline	Azilect	1mg
	Selegiline	Elderpryl (tbl or syrup)	5mg 10mg 10mg/5ml
	Selegiline	Zelapar	1.25mg
Dopamine Receptor Agonists (Non-ergot derived)	Pramipexole	Mirapexin	0.088 mg base/0.125 mg salt 0.18 mg base/0.25 mg salt 0.35 mg base/0.5 mg salt 0.7 mg base/1 mg salt
	Pramipexole	Mirapexin PR**	0.25 mg base/0.375 mg salt 0.52 mg base/0.75 mg salt 1.05 mg base/1.5 mg salt 1.57 mg base/2.25 mg salt 2.1 mg base/3.0 mg salt 2.62 mg base/3.75 mg salt 0.7 mg base/1 mg salt
	Ropinirole	Requip	0.25 mg 0.5mg 1mg 2mg 5mg
	Ropinirole	Requip XL**	2mg 4mg 8mg
Glutamate Antagonist	Amantadine	Symmetrel	100mg

* Dopa-decarboxylase inhibitor added to Levodopa in a ratio of 1:4 i.e. 4 parts Levodopa to one part inhibitor **CR (continuous release) drugs are complete doses that are released over a prolonged period. Often prescribed for overnight delivery of levodopa

2.5.1 Levodopa Therapy

Since its discovery more than fifty years ago, levodopa has been by far the most efficacious drug for managing the symptoms of PD (Schapira et al., 2009b). Levodopa is the amino acid precursor of dopamine and its administration has been shown to promptly raise dopamine concentrations in the nigrostriatal pathways, leading to increased QoL and overall life expectancy (Karlsen et al., 2000, Rajput, 2001, Schapira, 2007, Schapira et al., 2009b).

Following the diagnosis of PD careful consideration is required to establish the optimal dose of medication. Traditionally this has awaited the manifestation of significant motor symptoms and reduced QoL (Schapira and Obeso, 2006, Schapira et al., 2009b). However, evidence now suggests that early dopamine replacement therapy (DRT) offers long-term benefit to patients (Schapira and Obeso, 2006). It has been reported that the rate of clinical deterioration can be rapid within the first year post diagnosis of PD, with a significant decline of 8-10 points in the Unified Parkinson's Disease Rating Scale (typically considered large) observed in this short duration (Fahn et al., 2004). This suggests that early intervention with anti-parkinsonian therapies may offer worthwhile benefit for controlling PD symptoms in the long term.

2.5.2 Levodopa Response

Early in the course of PD the therapeutic response to levodopa is typically constant; that is, patients are not usually susceptible to response fluctuations (Ahlskog and Muenter, 2001). Some patients can take doses later than the prescribed time or even

completely miss doses without noticing a substantial decline in symptom control. This phenomenon has been referred to as the long-duration levodopa response and may partly explain medication underuse in early PD (Lopez et al., 2001).

After a few years some of the benefit offered by levodopa starts to become time locked. Patients may note 20-60 minutes post drug administration that their symptoms improve. However, the therapeutic response often declines after a few hours and people with PD may start to feel their symptoms return sooner than they once did. For example, patients commonly report slowing-up during gait and feeling progressively more rigid. This is referred to as the short-duration response which is reported to represent the underpinning for the 'wearing-off' phenomenon in PD (Lopez et al., 2001, Sesar et al., 2011). Once this starts to occur levodopa regimens almost certainly require modification. Doses can be increased or more doses can be added so that the time between each dose is reduced. Adjunctive medications can also be used, however this further complicates the medication regimen (Ahlskog, 2009).

2.5.3 Dopamine Receptor Agonists

Dopamine receptor agonists imitate the action of the neurotransmitter dopamine by stimulating dopamine receptors at the post synaptic membrane (Lim et al., 2009). Drugs from this classification do not require enzymatic conversion or a specific transport system to cross the blood-brain barrier, making their successful uptake simpler than levodopa preparations (Gerlach et al., 2003). The main orally

administered dopamine agonists are pramipexole (Mirapexin) and ropinirole (Requip).

In contrast to levodopa, the principal benefit of dopamine receptor agonists is that they have a longer duration of action. The half-life of levodopa is only around ninety minutes (Yeh et al., 1989). In contrast, the half-life of pramipexole is substantially longer (8-12 hours) and is around 6 hours for ropinirole (Kvernmo et al., 2006). The prolonged-release formulation of ropinirole, pramipexole MR and the rotigotine transdermal patch each deliver a reasonably constant 24-hour supply which aims to keep dopaminergic tone stable (Pfeiffer, 2005).

In advanced PD levodopa conversion and storage is limited, as is the regulation of synaptic dopamine concentrations. Often in later disease stages functioning nigral cells (i.e. cells still able to convert levodopa to dopamine) are lacking. What's more, loss of receptor cells at the post synaptic membrane can also be substantial. Consequentially, what dopamine is readily available may become redundant. Due to this the motor response to levodopa can be erratic and pulsatile and in time some patients will experience significant response fluctuations and dyskinesias (Péchevis et al., 2005, Grosset, 2008). In this scenario, longer acting dopamine receptor agonists may be of benefit (Ahlskog, 2009).

There are however limitations to the use of dopamine agonists, such as incomplete receptor agonism. Dopamine receptors are divided into five types: D1-D5. The main motor effects of dopamine have been primarily attributed to D1 and D2 receptor stimulation (Ahlskog, 2009) which are greatly expressed in striatal

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regions. However, all three dopamine agonists mentioned have specific affinity to D3 receptor cells. Ropinirole and pramipexole for example have a 100-fold affinity to D3 than D2 receptors (Gerlach et al., 2003). Rotigotine has around a 20-fold greater predilection to D3 than D2 (Jenner, 2005). Neither pramipexole nor ropinirole have however demonstrated affinity to D1 receptors (Gerlach et al., 2003) and the affinity of the transdermal patch to D1 receptor site stimulation is 100-fold less than it is for D3 (Jenner, 2005). This continuum of receptor cell stimulation offers two clinically relevant implications when comparing dopamine agonist efficacy to that of levodopa:

(1) Agonists offer reduced capacity for improving motor control than dopamine generated from levodopa because of the specificity and affinity to certain receptors;

(2) There is greater potential for patients developing behavioural problems as a result of D3 receptor stimulation (Joyce, 2001).

2.5.4 Monoamine Oxidase-B Inhibitors

Monoamine oxidase (MAO) enzymatically degrades monoamines such as dopamine within the brain tissue. Inhibiting the activity of MAO type-B thus increases brain dopamine concentrations, potentially improving PD symptoms (Henchcliffe et al., 2005, Fernandez and Chen, 2007a, Fernandez and Chen, 2007b). The therapeutic indication for the use of MAO-B inhibitors (selegiline and rasagiline) is still a source of debate. Whilst evidence shows that they do improve

the clinical symptoms of PD, they appear to do so only moderately (Ives et al., 2004).

2.5.5 Catechol-O-Methyltransferase Inhibitors

As highlighted earlier in Table 2.3, levodopa is mostly prescribed in a ratio of one to four. For example, one part dopa-decarboxylase inhibitor (25mg carbidopa) may be prescribed with four parts levodopa (100mg) to produce Sinemet (125mg). The added carbidopa aims to prevent conversion of levodopa to dopamine outside of the central nervous system in an attempt to optimise brain dopamine concentrations. However, despite the addition of the dopa-decarboxylase inhibitor, levodopa can still be metabolised in the periphery by the enzymatic activity of Catechol-O-Methyltransferase (COMT) (Bonifati and Meco, 1999, Männistö and Kaakkola, 1999). As COMT can reduce the availability of levodopa, one of two COMT inhibitors may also be prescribed: entacopone (Comtess) and tolcapone (Tasmar). Inhibiting COMT helps to reduce the quantity of levodopa metabolised peripherally and thus helps to lengthen the therapeutic effect of levodopa.

2.5.6 N-Methyl-D-Aspartate (NMDA) Glutamate Antagonist

Amantadine has been used to treat PD for almost as long as levodopa. Originally the therapeutic indication was for the treatment of early parkinsonism. However, when prescribed today it is mainly used to combat levodopa induced dyskinesias (Metman et al., 1998, Metman et al., 1999). Although amantadine is proposed to attenuate levodopa induced dyskinesias without worsening PD symptoms (Metman

et al., 1999), findings from a Cochrane systematic review did not support this claim (Crosby et al., 2003).

2.5.7 Anticholinergics

Anticholinergics drugs were the first medications to be routinely prescribed to treat PD. One of the most commonly administered anticholinergics is trihexyphenidyl (Broflex). Drugs from this classification can reduce resting tremor in some PD patients but do little to combat bradykinesia, gait problems or other motor and non-motor symptoms of PD. Given their vast side effect profile and limited therapeutic benefits, most often a more efficacious anti-parkinsonian agent is prescribed in place of an anticholinergic drug (Ahlskog, 2009).

2.6 Treatment Complexity in Parkinson's Disease

2.6.1 Early Treatment

Optimum medication management typically allows people who are newly diagnosed with PD to remain active in all aspects of their lives. When symptoms impede on working commitments, reduce social interaction, or result in sedentary lifestyles initiating treatment is necessary. The natural progression of PD confers less drug efficacy and more disability later in the disease course (Apaydin et al., 2002). There is no evidence that the best drug response can be saved for later years. By deferring treatment and accepting early disability, the patient may be sacrificing good years of life for no therapeutic gain (Ahlskog, 2009).

The pharmacological management of PD is complex. Dopaminergic drugs like levodopa, MAO-B inhibitors and dopamine receptor agonists are the main therapeutic options and represent usual first line treatment strategies (NICE, 2006, Schapira and Obeso, 2006, Schapira, 2007). All of these drugs have supporting clinical data to justify their therapeutic use (Goetz et al., 2005, Pahwa et al., 2006). Typically younger individuals are treated with an MAO-B inhibitor (once daily), especially if symptoms are mild, or a dopamine receptor agonist (three daily doses) as first line intervention. Older individuals ($\geq$75 years), especially those with or at risk of cognitive impairment, may be treated with levodopa as first line therapy (Schapira et al., 2009b, Schapira, 2007). Figure 2.1 shows a decision pathway for initiating PD treatment.

Two studies showed that although the use of levodopa improved the Unified PD Rating Scale by 3-5 points more than a corresponding agonist, motor control was still considered satisfactory by patients and clinicians when treated with the agonist alone (Rascol et al., 2000). Additionally, researchers have shown MAO-B inhibitors are useful as monotherapy in early disease or as adjuvant therapy in later stages of PD (Fernandez and Chen, 2007a, Fernandez and Chen, 2007b). It is well acknowledged, however, that MAO-B inhibitors are not as effective as levodopa or dopamine agonists for the management of PD and thus their therapeutic indications are limited (Ives et al., 2004).
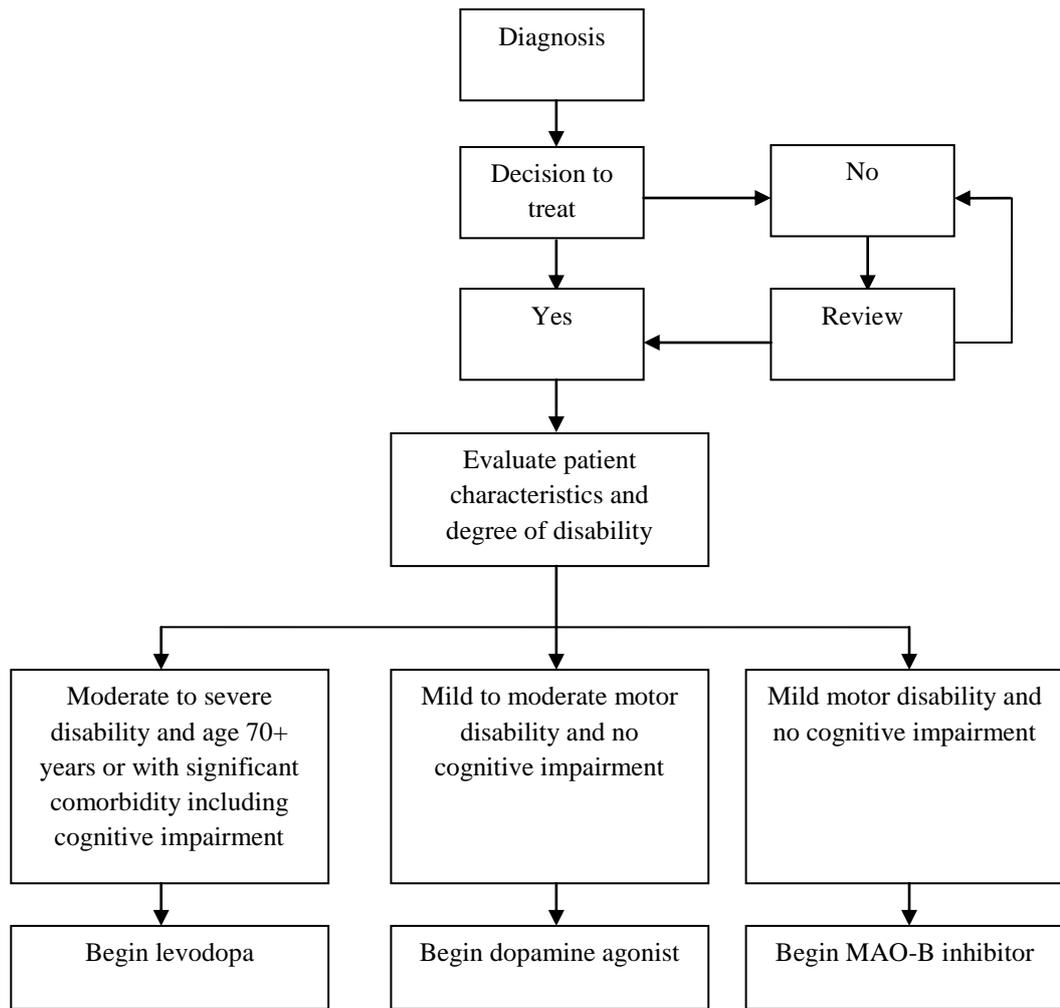
(Schapira, 2007)

Figure 2. 1 - Decision Pathway for Initiating Parkinson's disease Treatment

2.6.2 Advancing Treatment

As PD progresses, controlling symptoms becomes considerably more challenging. Researchers have shown that more than half of people with PD take two to four anti-parkinsonian medications three to four times daily (Leoni et al., 2002, Tan et al., 2005). This is because multiple drug classes are required as PD progresses (Rascol et al., 2000, Holloway et al., 2004, Bainbridge and Ruscin, 2009, Schapira et al., 2009a). Long-term follow-up studies indicate that of the PD patients who began receiving a dopamine agonist, approximately half at three years and two-thirds at five years required levodopa supplementation (Rascol et al., 2000, Holloway et al., 2004).

As levodopa is added, treatment regimens become more complex. The transition from MAO-B inhibitor or dopamine agonist to levodopa marks a significant juncture in PD treatment when considering the specificity of dose timing. A patient previously managed with an MAO-B inhibitor is likely to have only taken one tablet daily. Although a dopamine agonist may have been prescribed in three daily doses to manage symptoms, comparable to levodopa when initiated, the considerably longer half-life of agonists affords the patient a greater time window in which medication needs to be taken. A patient can be more flexible with the time of dosing with little or no ill effect. This phenomenon also stands true for levodopa in the initial years of treatment when the long-duration response predominates. As some patients may be able to omit doses without detrimental consequences to function, this may partly explain medication non-adherence in early PD.

However, as the half-life of levodopa is only around 90-120 minutes (Yeh et al., 1989), patients with advanced PD will require a more stringent dosing schedule to maintain steady plasma concentrations and desired therapeutic benefit (Ahlskog, 2009, Schapira et al., 2009b).

Occasionally people with long standing PD will experience responses to therapy lasting only 1-2 hours, reflecting the plasma half-life of levodopa (Yeh et al., 1989). By five years of active levodopa treatment, approximately 40 per cent with PD report experiencing the short-duration response and this becomes increasingly more likely and debilitating over subsequent years (Ahlskog and Muenter, 2001, Rascol et al., 2000). At this juncture, one strategy is to add a further dose to shorten the time interval between each pill taken (Ahlskog, 2009). This however starts to add significant regimen complexity. Around this time, and as PD continues to progress, some patients also begin to experience debilitating motor fluctuations and dyskinesias resulting from long-term use of dopaminergic therapy.

In addition to adding further doses, each drug prescribed may have different dosing schedules, which can complicate treatment regimens (Leoni et al., 2002). COMT inhibitors can supplement levodopa but this approach adds further complexity if given as a separate tablet.

With advancing disease the therapeutic window narrows and becomes dependent on more frequent dosing to maintain the treatment effect (Grosset et al., 2005b, Schapira et al., 2009b). Some people with advanced PD can take as many as ten doses a day in attempt to control symptom fluctuation (Schapira, 2007,

Valldeoriola et al., 2010). Dyskinesias (involuntary movements) associated with long-term levodopa use may also require remediation in later PD. This adds even greater treatment complexity to a population already potentially highly medicated (Schapira et al., 2009b, Valldeoriola et al., 2010). Additionally, specific non-motor complications may necessitate further drug use which adds to the polypharmacy in PD (Chaudhuri et al., 2006, Bainbridge and Ruscin, 2009).

Whilst medication use may be consistent in many chronic illnesses, it is evident that in PD treatment strategies can change in order to address a patient's progressive symptom manifestation. Such amendments to treatment can add considerable complexity and this may make accurate pill taking challenging for even the most cognitively able individuals.

2.7 Medication Adherence

The effectiveness of prescribed drugs depends not only on the efficacy of the medications, but also on adherence to the therapeutic regimen. Adherence is defined by the World Health Organisation (WHO, 2003) as:

"the extent to which a person's behaviour – taking medication, following diet,
and/or executing lifestyle changes, corresponds with agreed recommendations
from a health care provider".

Adherence to medication is paramount for achieving optimal therapeutic benefit. Using medication appropriately is dependent on two factors: ability and motivation (Horne, 2000). Most of the early research on adherence focussed on a patient's ability to take medication. As a result, non-adherence was assumed to be unintentional (e.g. forgetfulness and poor understanding), or a physical ailment (e.g. poor eyesight or lack of dexterity). These factors are unquestionably important. However, it is also being increasingly acknowledged that non-adherence to medication may result from a decision to avoid medication or to use it in a manner inconsistent with the prescriber's instructions (Horne and Weinman, 1999, Horne, 2000). Previously such behaviour may have been viewed as disobedient. However, a new view of health has emerged in which patients are encouraged to take a more active role in their healthcare and more specifically in decisions about their treatment (Barber, 1995).

In PD pharmacological management is essential for managing symptoms and maximising QoL. Sound medication adherence therefore cannot be over emphasised (Rigby, 2007). This is especially relevant as motor function becomes progressively worse, requiring increasingly intricate medication regimes to manage symptoms (Davis et al., 2010). Furthermore, as non-motor symptoms have been reported by patients and carers to be more negatively impactful than motor complaints in PD (Martinez-Martin et al., 2011), adequately adhering to prescribed regimens is likely to be important for maximising health related quality of life (HRQoL). However, in spite of the identified importance of medication adherence, non-adherence to treatment is a problem in PD as the next part of this chapter outlines.

2.7.1 Prevalence of Non-adherence in Parkinson's Disease

Researchers propose that a third to half of all medicines prescribed to people with long-term conditions are not taken as recommended (Haynes et al., 2002b, WHO, 2003, NICE, 2009). Despite recognising that non-adherence is prevalent in many chronic conditions, it has only recently been acknowledged that people with PD do not take prescribed medication as intended (Grosset et al., 2005b, Bainbridge and Ruscin, 2009, Grosset, 2010).

Dutton et al (1993) were one of the first research groups to identify that elderly people with PD were under-medicating. Soon after Copeland and colleagues (1994) found that many blood samples taken from PD patients were below the lower levodopa concentration limit, indicating poor medication adherence. Additionally, five samples were shown to be above the therapeutic range and understandably dyskinesia was common in this group of patients. Despite medication having the potential to optimise QoL in PD, these early studies suggest that medication non-adherence is prevalent.

More recently researchers have highlighted the prevalence of medication non-adherence in PD using a variety of assessment strategies. Leopold and colleagues (2004) used Medication Electronic Monitoring caps (MEMS), the reported gold standard method, to show that only 10% of PD patients fully adhered to treatment.

A further study identified that 20% of patients with PD were under users of anti-parkinsonian medication (Grosset et al., 2005a). In addition, patients who satisfactorily adhered to medication (average total pill taking > 80%) all showed

28

substantial problems with dose timing adherence (number of doses taken at the correct time interval). Furthermore, findings revealed that 56% of patients were more likely to take once-daily drugs on time than drugs that had to be taken more frequently, where as few as 3% adhered satisfactorily (Grosset et al., 2005a). Kulkarni and colleagues (2008) conducted a retrospective longitudinal cohort study in people with PD and found the prevalence of sub-optimal adherence to be 67%.

Collectively these findings indicate that medication non-adherence is a significant problem in people with PD. Specifically, findings to date have revealed that dose timing is poor, even in PD patients with overall satisfactory adherence (those taking greater than 80% of their prescribed dose).

2.7.2 Consequences of Non-adherence in Parkinson's Disease

The consequences of non-adherence to medication in PD can be substantial and should be considered from various perspectives. For the patient, medication does not work if it is not taken as the prescriber intended. However, assumptions by clinicians that non-adherence is a passive process; that is, forgetfulness or resulting from impaired cognition, may be too simplistic and it should be recognised that medication taking behaviour is more complex (Grosset, 2010). Active consideration may in some cases be significant. For example, discontinuing treatment due to perceived side effects, either accurate or fallacious; medication sparing based on the belief of loss of efficacy over time (i.e. becoming immune or unresponsive to treatment); or fear of long-term complications such as peak dose

dyskinesias and response fluctuations are all proposed reasons why a patient with PD may not adhere to treatment (Bainbridge and Ruscin, 2009, Grosset, 2010).

Patients with PD should take their medication as prescribed for numerous reasons. Firstly, sudden withdrawal of dopaminergic drugs can result in suppression of central dopamine transmission and thus trigger the neuroleptic malignant syndrome, which may lead to fatality (Mizuno et al., 2003). Secondly, one major theory for the genesis of motor fluctuations is that erratic, pulsatile dopaminergic stimulation is contributory (Juncos et al., 1989, Rascol et al., 2000, Grosset et al., 2005a). Sporadic dopamine levels in blood plasma, partly from inadequate timing of medication taking, correlate with alternating high and low levels in the brain. Such erratic stimulation (the so called peak and trough effect) is proposed to result in motor fluctuations (Bezard et al., 2001).

Researchers evaluating the effect of reduced pill intake in PD showed that non-adherence was associated with the 'wearing off' of the treatment effect (Kulkarni et al., 2008). This was shown to result in motor fluctuations and increased risk of worsening symptoms compared to medication adherent individuals. Furthermore, poor adherence to treatment was associated with more unplanned hospital admissions for PD related problems and an overall poorer prognosis (Kulkarni et al., 2008).

Interestingly, and perhaps unique to PD, non-adherence to medication is not specific to sub-optimal pill intake. Patients may also non-adhere by over medicating. Excessive intake of dopaminergic agents was prevalent in 10% of

patients diagnosed with PD at a younger age (Grosset et al., 2005a). The consequences of over medicating can be substantial and include severe medication induced dyskinesia, behavioural disturbances and potentially even psychosis (Merims and Giladi, 2008, O'Sullivan et al., 2009).

Medication non-adherence in PD also has serious consequences for other parties involved. From the perspective of family members, their relative's health is deteriorating leading to poor QoL and increasing care requirements. This can place significant burden on the spouse/carer which can greatly affect their health and QoL. For treating clinicians, future management decisions are based on the premise that the patient is correctly taking the intended treatments. Dose escalation, adjunctive therapy use and, in some cases, diagnostic reconsideration may all result from seeing a patient in clinic who apparently has had a poor response to therapy (Bainbridge and Ruscin, 2009, Grosset, 2010).

Poor drug management in PD is not confined to patients living in the community but is also an acknowledged problem in secondary care. Parkinson's UK launched a "Get it on time" campaign aiming to ensure people admitted to hospital receive medication at their individual time. Such a campaign emphasises the critical relationship between medication non-adherence and functional deterioration in PD and helps illuminate the importance of ensuring patients adhere to their medication dosing as intended.

2.8 Summary: A Greater Understanding

The symptoms of PD can be extremely debilitating in all aspects of life. What is considered a small complaint by one individual may be significantly troublesome and impactful to another. However, as stated earlier in this thesis, many of the symptoms of PD are treatable to varying extents. Healthcare professionals therefore have the ability to improve the QoL of many people with PD for several years. Unlike decades previous, today's arsenal of pharmacological agents is more substantial with clinicians having many treatment options available that can be tailored to the patient's specific needs.

Despite this, however, it is clear from the evidence that some people with PD are not taking their prescribed anti-parkinsonian medication in accordance with medical advice. Furthermore, it is evident that non-adherence to medication in PD results in many people experiencing a 'wearing off' of their treatments therapeutic effect. This has been shown to negatively impact on function and QoL. It is therefore essential for clinicians to be able to identify non-adherent PD patients. With a greater knowledge of who is likely to non-adhere to prescribed medication, targeted interventions can be provided in attempt to improve adherence and thus maximise the therapeutic effect of prescribed treatment.

In the next section of this thesis I present the rationale, methods, results and discussion of two systematic reviews. In Chapter 3 I provide the findings of a systematic review identifying what factors are associated with medication non-adherence specifically in PD. In Chapter 4 I present the findings of a Cochrane

systematic review on interventions used to enhance medication adherence in people

with PD.

CHAPTER 3

Factors Affecting Medication Non-adherence in Parkinson's Disease

Background
Study Design
Risk of Bias/Internal Validity
Findings
Discussion

3.1 Background

As highlighted in Chapter 2, to achieve optimum symptom control in chronic conditions medication adherence is imperative. Despite this, the World Health Organization (2003) report that as much as half of all medications prescribed for long-term conditions are not taken as intended. Therefore, it is not surprising that medication adherence is poor in PD.

Leopold et al (2004) reported as few as 10% of a PD cohort showed full adherence. Kulkarni et al (2008) found the prevalence of poor adherence ranged between 60% and 70% when followed over 5-years while Grosset et al (2005a) reported complete medication adherence in as few as 3% of PD patients. These findings are concerning when placed in a clinical context. Kulkarni and colleagues (2008)

showed that poor medication adherence increased the risk of worsening symptoms compared to medication adherent people with PD. As PD treatments are self-administered, there is a need for greater understanding of why people do not take their prescribed medications as intended. This theoretical knowledge could help to better understand how best to improve medication adherence in people with PD.

Pharmacological based interventions such as simplifying drug regimens and non-pharmacological approaches such as provision of educational material have been advocated to address non-adherence in PD (Bainbridge and Ruscin, 2009, Grosset and Grosset, 2007). However, whilst these interventions may be beneficial in other chronic conditions, such approaches in a PD population are theoretical because the current evidence on why medication non-adherence develops specifically in PD is limited.

Regardless of the various theories, it remains unclear which factors are associated with non-adherence specifically in PD. The identification of such factors may allow healthcare professionals to identify potentially non-adherent individuals. With this knowledge, the development of targeted interventions to counteract or prevent non-adherence may be possible and could prove beneficial. This is both in terms of symptom management and the clinicians' understanding of a patient's treatment response and disease progression.

In the next part of this chapter I outline the processes used to identify which factors are associated with medication non-adherence in people with PD.

3.2 Study Design

I used the systematic review approach to identify literature relating to medication non-adherence in PD.

3.2.1 Search Methods

To ensure that both quantitative and qualitative evidence was identified, I performed a systematic search of online databases in April 2011. The five databases searched were Medline (Ovid, 1948), EMBASE (Ovid, 1980), AMED (Ovid, 1985), PsycINFO (Ovid, 1806) and CINAHL (EbscoH, 1982). In January 2012 I updated the search to capture more recently published articles. I also conducted a supplementary hand search of bibliographies of extracted articles and reviews to acquire records not identified electronically. Next I outline the search strategy for the systematic review.

3.2.2 Search Terms

Before conducting the systematic search I reviewed the key words and search strings used by the authors of related articles with the aim of developing a comprehensive set of search terms. When relevant key words were identified I added these to the search string. This practice continued until I was satisfied that I had the key words required to conduct a comprehensive search of the topic. The terms 'Parkinson's disease' and 'Parkinsonism' were combined with keywords relating to non-adherence: 'non-adherence', 'non-compliance', 'influencing

factors', 'caregiver compliance', 'sub-optimal', 'determinants', 'drug adherence', 'therapy adherence', 'drug compliance', 'denial psychology' and 'therapy compliance'. To make the search strategy more comprehensive, I mapped key terms to database specific subject headings (MeSH). I then 'exploded' each MeSH term to include all relevant sub-categories. Truncations and Boolean operators (e.g. 'and', 'or') were used where necessary to broaden the search window. Exact search strings can be seen in Appendix 1.

3.2.3 Selection Criteria

Once identified records had been imported into the Endnote reference manager and duplicated items had been removed, I proceeded by reviewing all relevant titles and abstracts for potential study inclusion. Full text articles were obtained either where abstracts appeared relevant or when insufficient information was provided from which an adequate assessment of relevance could be made from the abstract alone. Studies meeting the following criteria were included:

(1)   English language

(2)   Full-article publication available (accessed directly or requested from the study authors)

(3)   Idiopathic PD population (iPD) (defined by the authors).

(4)   All age ranges and duration of anti-parkinsonian treatments.

(5)   Presented either quantitative or qualitative data on factors associated with medication non-adherence.

3.2.4 Data Extraction

Having identified potentially eligible records, the full text of each article was reviewed for potential inclusion in the systematic review. I developed a concise, standardised data extraction table (Table 3.1) to acquire information relevant to the review from each included study. Extracted data were checked twice for accuracy. Relevant study information was tabulated focusing on study design, methodological characteristics, included participants and the analytical methods used. Extracted data for each included study can be seen in Appendix 2.

Table 3. 1 - Data Extraction Table

Study Design What was the study design? What were the aims and objectives?
Participants What was the sample size? Were participant demographics reported and how were they collected? How were participants recruited and from where? Was there specific inclusion/exclusion criteria?
Measurement Tools/Outcomes What was the primary outcome? Was adherence to medication assessed? If so, what method or instruments were used? How was the instrument administered and by whom?
Statistical Analysis What analysis was used to determine factors that influence/are associated with medication adherence? Were covariates identified and included in the analysis?
Results What were the response rates? What were the main reported determinants of non-adherence to medication in PD?

In the next section of this Chapter I will describe the procedure used to assess the risk of bias of the studies included in this systematic review.

3.3 Risk of Bias/Internal Validity

3.3.1 Terminology

Bias is defined as the risk of systematic error, or deviation from the truth, when interpreting the findings or inferences of a study. The term 'risk of bias' is interchangeable with internal validity, which is often defined as the extent to which the design and conduct of a study are likely to have prevented bias (Higgins and Green, 2009).

Despite the risk of bias assessment being a key phase when conducting a systematic review, the specific term used varies substantially across review groups and specialities. A common alternative term to risk of bias is quality assessment. However, the meaning of quality can vary greatly. For example, one source defines quality as:

"The extent to which all aspects of a study's design and conduct can be shown to protect against systematic bias, non-systematic bias and inferential error."

(Lohr, 2004)

In the US the Preventive Services Task Force (USPSTF), an independent panel that systematically reviews evidence of effectiveness, equates quality with internal

validity and classifies individual studies first according to a hierarchy of study design and then by individual study criteria. In contrast the Cochrane Collaboration argues for a wider use of the phrase risk of bias instead of quality, reasoning that:

"An emphasis on risk of bias overcomes ambiguity between the quality of reporting and the quality of the underlying study's methodology."

(Higgins and Green, 2009)

Due to the inconsistency and potential confusion of the term 'quality', I will refer to validity assessment as 'risk of bias assessment' throughout the remainder of this thesis. In the next section of this thesis I describe the development of the appraisal tool that I used for the current systematic review.

3.3.2 Development of the Risk of Bias Appraisal Tool

I developed a specific, novel appraisal tool to assess the risk of bias of the studies included in this systematic review. To comprehensively assess the studies I sought to evaluate the impact of bias, confounding and statistical chance on the study findings. Having identified the effect of these risks of bias, I aimed to assess their individual and combined impact on the interpretability of each study's findings.

Prior to developing the appraisal tool I systematically reviewed existing quality indicator scales and checklists. Medline (Ovid, 1948), EMBASE (Ovid, 1980), AMED (Ovid, 1985), PsycINFO (Ovid, 1806) and CINAHL (EbscoH, 1982) were

searched using pre-defined search terms. The following terms/key words were exploded and then combined in each respective database:

'bias', 'confounding', 'chance', 'internal validity', 'threats to validity', 'validity', 'reliability', 'appraisal' were combined by 'OR' during the search. This was then combined by 'AND' with the results of the following search string:

'data collection', 'epidemiology', 'observational study', 'questionnaires', 'scales', 'checklists', 'indexes', 'assessments', 'tools', 'instruments'.

Many of the appraisal tools identified appeared to replicate published reporting guidelines such as the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (Von Elm et al., 2007) and MOOSE statements (Meta-analysis of Observational Studies in Epidemiology) (Stroup et al., 2000). These statements were developed for use by authors to ensure a high standard of reporting, not for assessing methodological rigor.

Many tools focused on whether authors clearly reported the methodological steps undertaken, instead of providing guidance on how to assess the risk of bias in what was reported. For example, many tools asked whether participant recruitment was described by study authors without providing guidance on whether the methods used to screen and recruit participants were prone to selection bias.

I also reviewed the 47 scales and 51 checklists identified by Shamliyan and colleagues (2010) in a systematic review of tools to assess the quality of

observational studies. In comparison to the appraisal tools identified in my independent search, many tools identified by Shamliyan and colleagues (2010) also failed to differentiate between poor reporting and risk of bias.

To this end, I designed a novel, generic use quality indicator tool with the view to detect risk of bias (threats to internal validity) in non-interventional studies (Table 3.2).

Having assessed the methodological performance of each included study using this novel appraisal tool, I was able to create a risk of bias (Threats to Validity) table highlighting the methodological strengths and limitations of each study included in the review.

Table 3. 2 - Tool to Appraise Risk of Bias in Non-Interventional Studies

Quality Criteria	Threat to Validity	Source of Threats to Validity	Identification & Evaluation:
Representativeness of population: cases and controls	Selection Bias (misclassification bias)	Diagnosis inaccuracy	Were eligibility criteria used? Were inclusion/exclusion criteria specified? How were these determined and used?
	Selection Bias	Source and method for sampling	Was screening adequate or bias? Where were participants accessed? Is this representative of the population?
	Chance	Sample size	How was the sample size determined? Was this sample target reached?
	Confounding	Demographics/characteristics of participants	Comparability of control to cases: disease severity, duration, medication profile, comorbidity?
Quality of measurement and outcome	Detection Bias (misclassification bias)	Validity/reliability (systematic bias/errors) - Instrumentation (e.g. calibration)	Are measurement tools valid? Has reliability been determined? Does the instrument have cut-offs or do the authors determine this? Is this consistent?
	Detection Bias	Measurement biases: - Self-report - Recall - Observer/ interviewer	What efforts have been made to minimise measurement biases? Are measurement biases acknowledged and reported?
Appropriate statistical methods and result interpretation	Detection Bias (Information bias)	Follow-up period time	Were follow-up periods the same for cases and controls?
	Detection Bias (Unmasked bias)	Blinded analysis	Was data collection/analysis masked where necessary?
	Chance	Analysis: - Study power & probability value - Sub-analysis power - Confounders - Effect Modification**	Did authors conduct appropriate analysis? Was adjustment performed for identified confounders? What was used to control for known effect modifiers and confounders? I.e. randomisation, matching, restriction (exclusion), stratification, multivariate analysis. Could significance be a result of chance?
	Attrition Bias	- Missing data	Was missing data discussed and dealt with appropriately?
Conflict of interest	Reporting Bias	Investigator bias, funding bias	Were conflicts of interest disclosed? Who funded the research? Could this explain findings?

3.4 Findings

The five databases searched yielded a total of 1880 records. An additional six records were identified through targeted hand searching of reference lists. Figure 3.1 shows the PRISMA diagram depicting the stages of study identification. After discarding duplicates and reviewing abstracts of identified records, 46 articles were suitable for full text retrieval. Of them, six articles met the study inclusion criteria: Leopold et al. (2004), Grosset et al. (2005a), Evans et al. (2005), Banks and Lawrence (2006), Grosset et al. (2009), Valldeoriola et al. (2010). A further study by Drey & colleagues (2012) was later added to the list of included papers providing a total of seven records. This article had not been published at the time of the initial search and therefore it was not originally identified.

3.4.1 Summary of Studies

The characteristics of the seven included studies are presented in Table 3.3. The systematic review included a total of 787 PD patients. Five of the studies were observational in design of which four were cross-sectional surveys (Leopold et al., 2004, Grosset et al., 2005a, Grosset et al., 2009, Valldeoriola et al., 2010) and one was a case-controlled study (Evans et al., 2005). Of the remaining two studies one was a postal survey which encompassed one-to-one patient interviews (Banks and Lawrence, 2006) and the other was an exploratory qualitative study using semi-structured interviews (Drey et al., 2012).

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┌─────────────────────────┐    ┌─────────────────────────┐
│ Potentially relevant    │    │ Additional records      │
│ records identified      │    │ identified through hand │
│ through electronic      │    │ searching:              │
│ database search:        │    │ n = 6                   │
│ n = 1880                │    │                         │
└─────────────────────────┘    └─────────────────────────┘

┌─────────────────────────┐
│ Number of duplicates    │
│ removed:                │
│ n = 188                 │
└─────────────────────────┘

┌─────────────────────────┐    ┌─────────────────────────┐
│ Number of records       │    │ Number of records       │
│ screened:               │    │ excluded:               │
│ n = 1698                │    │ n = 1652                │
└─────────────────────────┘    └─────────────────────────┘

┌─────────────────────────┐    ┌─────────────────────────────────────┐
│ Number of full-text     │    │ Number of full-text articles        │
│ records retrieved for   │    │ excluded with reasons: n=40         │
│ detailed evaluation:    │    │  -  Article not in English (n=1)    │
│ n = 46                  │    │  -  Abstract only available (n=1)   │
└─────────────────────────┘    │  -  No data provided on factors     │
                                │     influencing non-adherence (n=8) │
┌─────────────────────────┐    │  -  No reference to medication      │
│ Total number of records │    │     non-adherence (n=5)             │
│ included in systematic  │    │  -  No assessment of adherence (n=3)│
│ synthesis:              │    │  -  Non-adherence to functional     │
│ n = 7                   │    │     activity and exercise (n=1)     │
│ (n= 6 from database     │    │  -  Review papers on adherence      │
│ search & n=1 later      │    │     (n=10)                          │
│ added)                  │    │  -  Pathogenesis of Dopamine        │
└─────────────────────────┘    │     Dysregulation Syndrome review   │
                                │     (n=1)                           │
                                │  -  No reference to PD (n=9)        │
                                │  -  Commentary (n=1)                │
                                └─────────────────────────────────────┘
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Identification · Screening · Eligibility · Included

Figure 3. 1 - PRISMA Flow Diagram of Study Identification

Table 3. 3 - Characteristics of Included Studies

Article	Study Design	Study Aims	Source of Participants	Participant Characteristics			Adherence Assessment	Identified Factors for Non-adherence
				Intervention/ study group	Control or comparison group	n=		
Evans et al (2005)	Case-control	Identify predisposing factors to DDS in people with PD	Outpatients attending a specialist PD clinic	Dopamine dysregulation syndrome n=25	Patients without identified DDS n=100	125	n/a	Novelty Seeking Depression Alcohol intake Age of PD onset
Grosset et al (2005a)	Cross-sectional survey	Compare medication intake and characteristics of patients according to medication intake	Outpatient movement disorder clinics	All participants given MEMs device.	n/a	54	Electronic Event Monitoring (MEMS)	Younger age Depression Poor quality of life More daily tablets
Valldeoriola et al (2010)	Cross-sectional survey	Determine demographic, social and clinical aspects modifying therapy adherence	Multiple academic tertiary and secondary hospitals in Spain	All participants assessed by MMAS-4	n/a	418	Physician subject assessment & Morisky-4 scale	Low knowledge of PD Poor clinical control No spouse or partner low income Cognitive Impairment Psychiatric symptoms
Leopold et al (2004)	Cross-sectional survey	To report on drug use in PD using MEMS.	PD and movement disorder clinic.	All participants given MEMs devise.	n/a	39	MEMS	Gender (females less accurate at reporting miss-timed doses) Level of education

Banks and Lawrence (2006)	Postal survey	Explore the impact of PD on employment from the perspective of the PD patients.	Identified through the PD Society.	339 returned questionnaire.	n/a	24	n/a	Maintaining employment – adjustment of dosing
Grosset et al (2009)	Cross-sectional survey	To define the pattern of therapy adherence, to assess factors associated with non-adherence.	Large Multi-centre (8 centres in 5 countries)	All assessed with MEMS for adherence.	n/a	112	MEMS	Higher motor impairment assessed by UPDRS and PDQ-39 motor sub-score. Timing adherence associated with total tablets, disease duration and age. Complexity of regimens
Drey et al (2012)	Exploratory qualitative study with semi-structured interviews	To identify how people with PD adhere to prescribed medication, and what are the antecedents of non-adherence to antiparkinsonian medication.	A specialist PD clinic in an unnamed National Health Service hospital in England.	All participants (9 males and 6 females) interviewed	n/a	15	Self-report	All participants demonstrated at least one type of non-adherent behaviour. - Forgetfulness - Minor, deliberate amendment of doses - Major, deliberate non-adherence - often over-use of mediation.

Four of the seven studies recruited from single-centre clinics (Leopold et al., 2004, Grosset et al., 2005a, Evans et al., 2005, Drey et al., 2012). One recruited from secondary and tertiary care hospitals across Spain (Valldeoriola et al., 2010), whilst one multi-centre study identified PD patients from eight centres across five European countries: France, Germany, Italy, Spain and the UK (Grosset et al., 2009). The seventh study recruited from the PD Society register, nurse specialist clinics and the PD Society magazine in the UK (Banks and Lawrence, 2006).

The mean age of the participants in this review was 62 years (range 44 – 74 years) with a mean disease duration of 7.4 years (range < 1 year – 17 years) and a mean Hoehn & Yahr (H&Y) score of 2.2 (a widely used clinical rating scale which defines broad categories of motor function in PD).

Of the studies reporting medication profiles, a mean of two anti-parkinsonian drugs were taken (Grosset et al., 2005a, Grosset et al., 2009, Valldeoriola et al., 2010) with a mean of five daily PD drug doses (Grosset et al., 2005a, Grosset et al., 2009). Combined with other medication use, an average of 6 (range 4-11) prescriptions were taken daily (Leopold et al., 2004, Grosset et al., 2005a, Grosset et al., 2009, Valldeoriola et al., 2010). The mean PD daily tablet intake was eight doses (Grosset et al., 2005a, Grosset et al., 2009). The mean complete medication intake was 9 doses (range 5-11) (Leopold et al., 2004, Grosset et al., 2005a, Grosset et al., 2009).

Four studies assessed cognitive impairment using the Mini-Mental State Examination (MMSE) (Leopold et al., 2004, Evans et al., 2005, Grosset et al.,

2005a, Grosset et al., 2009). The combined mean was 28/30. One study reported cognitive impairment in 22% of participants but did not report the method of assessment (Valldeoriola et al., 2010).

3.4.2 Risk of Bias (Threats to Internal Validity)

The reporting quality was reasonable throughout the seven included studies. One study was accepted for publication prior to version one of the STROBE statement becoming available (Leopold et al., 2004). None of the observational studies published after the release of STROBE acknowledged adhering to the reporting guidelines.

Each article was evaluated against five potential biases using nine sub-bias items, as determined by the novel quality appraisal tool that was specifically developed for this review. Table 3.4 shows each study's specific risk of bias. The nine quality markers considered are presented below:

- Selection Bias   -   1. Diagnostic Inaccuracy

                                2. Participant Representativeness

                                3. Sampling

- Random variation/chance -   4. Sampling Size

- Detection Bias   -   5. Validity of Adherence Assessment

                           -    6. Follow-up

                           -    7. Blinding

- Attrition Bias   -   8. Loss to Follow-up

- Reporting Bias   -   9. Appropriateness of Analysis

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Table 3. 4 - Study Specific Risk of Bias

Risk of Bias/Threats to Validity	Evans et al (2005)	Grosset et al (2005a)	Valldeoriola et al (2010)	Leopold et al (2004)	Banks & Lawrence (2006)	Grosset et al (2009)	Drey et al (2012)
1. Selection Bias (Diagnostic Inaccuracy)	✓	✓	?	?	?	✓	?
2. Selection Bias (Participant Representativeness)	✓	✗	✓	✓	?	✓	✓
3. Selection Bias (Sampling)	✓	✓	?	?	?	✗	✓
4. Random Variation/Chance (Sample Size)	✓	✗	✓	✗	n/a	✗	n/a
5. Detection bias (Validity of Adherence Assessment)	✓	✓	✓	✓	n/a	✓	?
6. Detection Bias (Follow-up)	n/a	✓	n/a	✓	n/a	✓	n/a
7. Detection Bias (Blinding)	?	?	?	?	n/a	?	n/a
8. Attrition Bias (Loss to Follow-up)	n/a	✓	n/a	✓	n/a	✓	n/a
9. Reporting Bias (Appropriate Analysis)	✓	✓	✓	✓	✓	✓	✓

In the next part of this chapter I outline the performance of each included study in respect to the nine risk of bias items described.

Selection Bias (Diagnostic Inaccuracy):

All authors stated recruiting patients with PD. However, the diagnostic criteria used were only reported in three studies (Evans et al., 2005, Grosset et al., 2005a, Grosset et al., 2009). The accuracy of the PD diagnosis was uncertain in four of the reviewed studies (Leopold et al., 2004, Banks and Lawrence, 2006, Valldeoriola et al., 2010, Drey et al., 2012). As the purpose of the review was to identify factors associated with medication non-adherence in idiopathic PD, I felt the accuracy of PD diagnosis to be imperative. A lack of diagnostic accuracy could have resulted in patients with others forms of parkinsonism being included. These types of patients can have different medication profiles to people with idiopathic PD and may also have different reasons for not adhering to treatment. It is important to note, however, that the uncertainty of PD diagnosis in these four studies was a consequence of poor reporting.

Selection Bias (Participant Representativeness):

Five studies showed no evidence of biased participant representation (Leopold et al., 2004, Evans et al., 2005, Grosset et al., 2009, Valldeoriola et al., 2010, Drey et al., 2012). Grosset et al (2005a) excluded PD patients prescribed selegiline or amantadine. I regarded this as selection bias as no justification was given for this exclusion criterion. Banks and Lawrence (2006) provided no information concerning the representativeness of their sample.

Selection Bias (Sampling):

Only three studies provided sufficient information of sampling methods to discount selection bias (Evans et al., 2005, Grosset et al., 2005a, Drey et al., 2012). Two studies provided no information concerning participant selection and therefore an assessment of bias was not possible due to poor reporting (Leopold et al., 2004, Valldeoriola et al., 2010). Valldeoriola and colleagues (2010) described physicians enrolling three consecutive out-patients. The authors claimed selection bias was avoided in that patients were previously unselected and had to have been attending clinic the same day. I felt this description lacked clarity concerning how selection bias was actually avoided.

Banks and Lawrence (2006) were vague concerning their sampling method. Participants were identified by PD nurses, a PD partners and relatives database and eight participants contacted the research team directly. No further details were provided from which an adequate assessment of risk of bias could be made. I therefore was unable to discount selection bias in this study. Grosset et al (2009) reported selecting participants non-sequentially at the investigator's discretion. I believed this to represent substantial selection bias as investigators may possess prior knowledge of the patients' medication taking behaviour.

Chance/random Variation (Sample Size):

Of the seven studies included only Valldeoriola et al (2010) described a sample size calculation, reporting standard values for significance (0.05) and the statistical power (0.8) (the probability of finding an effect if one exists). The accuracy of the dependent variable (medication adherence) was reported as ± 4.6%. No clear

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explanation or justification was given for this value; however, the authors state that no previous data was available to facilitate a more informed sample size calculation.

Evans et al (2005) compared 25 patients with Dopamine Dysregulation Syndrome (DDS) (where patients develop a harmful pattern of compulsive drug use) to 100 PD patients without DDS. Although a sample of 25 is low for observational studies, it must be acknowledged that the prevalence of DDS in the PD population is small. Therefore, high numbers likely yielded from a sample size calculation would likely be problematic from a recruitment perspective. Despite the small sample, a statistically significant association between patient characteristics and non-adherence was identified. As associations were identified, even with a small sample, I felt this substantiated the reliability of the findings.

In support of this, Grimes & Schulz (2005) state that where the prevalence of cases is low compared to controls, increasing the number of controls up to a ratio of four to one is acceptable. As the ratio of patients in the study by Evans et al (2005) was four controls to one DDS case, I felt this sample ratio was acceptable. The lack of an appropriate sample size calculation however predisposes the findings to type 1 error (i.e. rejecting the null hypothesis when it should be accepted). I felt caution should therefore be exercised when interpreting the identified associations in this study.

The postal survey with interviews conducted by Banks and Lawrence (2006) provided no numerical data to warrant a sample size calculation. The same was the

case for the exploratory study by Drey et al (2012). As both were qualitative studies, sample size calculations do not apply. The remaining three studies were cross-sectional designs of which no research group calculated a sample size (Leopold et al., 2004, Grosset et al., 2005a, Grosset et al., 2009). As stated earlier, this predisposes to type 1 error and therefore I was cautious when interpreting the identified associations. As statistical significance was established, despite no sample size calculation, type 2 error which relates to statistical power (accepting the null hypothesis when it should be rejected) was not relevant.

Detection Bias (Validity of Adherence Assessment):

Three studies assessed adherence using MEMS devices, the reported gold standard method (Leopold et al., 2004, Grosset et al., 2005a, Grosset et al., 2009). Evans et al (2005) used the criteria for DDS as a marker for non-adherence (Evans et al., 2005). As this is clinically diagnosed I felt confident that participants in this study were over-medicating. Valldeoriola et al (2010) assessed adherence with the Morisky Medication Adherence Scale (MMAS-4). Although the interpretation of self-report measures requires caution, the MMAS-4 has been investigated and shown to be moderately comparable to pill counts in PD (Elm et al., 2007).

One study did not report any method for determining non-adherence as this was not the aim (Banks and Lawrence, 2006). Drey et al (2012) used an experienced healthcare interviewer with limited knowledge of PD to question patients on their medication taking behaviours. As non-adherence is often not self-confessed, under or overuse of drugs may not have been identified in many people. In contrast, this method may have encouraged more patients to provide greater insight into their

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medication taking practices without the worry of disappointing clinical staff. However, due to this uncertainty I was unable to discount bias.

Detection Bias (Follow-up):

Three studies had a follow-up assessment phase: two were one month post baseline (Leopold et al., 2004, Grosset et al., 2009) and one was 3 months post baseline (Grosset et al., 2005a). Although the studies were cross-sectional in design, follow-up assessments were required due to the use of MEMS (i.e. an adequate time interval is required to assess pill bottle opening). The remaining studies did not require a follow-up period.

Detection Bias (Blinding):

Four studies did not report whether patients or researchers were blinded (Grosset et al., 2009, Grosset et al., 2005a, Evans et al., 2005, Valldeoriola et al., 2010). As the studies were cross-sectional, I did not feel this represented a suitable risk of bias. Leopold et al (2004) withheld the study aim from participants so that medication adherence could be accurately determined.

Attrition Bias (Loss to Follow-up):

Three studies reported numbers lost to follow-up (Grosset et al., 2005a, Grosset et al., 2009, Leopold et al., 2004). In one study, 8 withdrew, 2 lost the MEMS device, 1 died, 1 had a prolonged hospital admission and 3 patients misused MEMS (Grosset et al., 2005a). Grosset et al (2009) enrolled 124 PD participants of which 1 patient died and 10 used MEMS inconsistently. These were therefore withdrawn leaving data for 112 participants. Leopold et al (2004) excluded 1 participant due to

symptoms of depression. The remaining three studies had no follow-up assessment phase (Evans et al., 2005, Banks and Lawrence, 2006, Valldeoriola et al., 2010). No researcher group described a method for imputing missing data.

Reporting Bias (Analytical Methods):

All seven research groups appropriately analysed their data. Authors used logistic regression analysis (Grosset et al., 2005a), multivariate linear regression (Grosset et al., 2009, Valldeoriola et al., 2010) or Pearson's correlation coefficients (Leopold et al., 2004) to identify associations between non-adherence and other variables. Interview transcripts were analysed with thematic analysis (Drey et al., 2012) and content analysis (Banks and Lawrence, 2006) techniques, however, in one study no method was reported (Banks and Lawrence, 2006).

3.4.3 Factors Associated with Medication Non-adherence

Various factors, both clinical and demographic, were found to be associated with medication non-adherence in PD. To transform the findings from a list of factors into something clinically useful, I ranked each factor independently according to the strength of association with medication non-adherence. My main justification for this approach was to aid healthcare professionals in identifying patients at risk of medication non-adherence by informing them of the most salient factors correlated with non-adherence in PD.

3.4.3.1 Assessing Study Risk of Bias

For each included article I provided an assessment of overall study quality; that is, high, moderate or low. For example, where the risk of bias in a study appeared to be low, the study was defined as high quality.

The risk of bias in each study was used to determine overall quality. From the risk of bias table presented earlier I divided the number of 'ticks' awarded by the total number of risk of bias items to produce a percentile for individual study quality. Studies scoring ≥70% were deemed high quality, 40-69% moderate, and <40% low quality. Table 3.5 shows how each score was determined for the seven individual studies. From this I was then able to rank the factors in order of clinical importance, as portrayed in Table 3.6, so that clinicians could see which factors appear to be most strongly associated with medication non-adherence. The importance of each factor was decided by the reported level of significance and by the number of participants associated with each factor.

Table 3. 5 - Calculating Risk of Bias

Study	N° of relevant threats to validity items according to research method	N° (√) given	N° (X) given	N° (?) given	Overall % given N° √ ÷ (√ + X + ?) x 100	Assessment of Bias
Leopold et al. (2004)	9	5	1	3	(5 ÷ 9) x 100 = 55	Moderate
Evans et al. (2005)	7	6	0	1	(6 ÷ 7) x 100 = 85	High
Grosset et al. (2005a)	9	6	2	1	(6 ÷ 9) x 100 = 67	Moderate
Banks and Lawrence (2006)	4	1	0	3	(1 ÷ 4) x 100 = 25	Low
Grosset et al. (2009)	9	6	2	1	(6 ÷ 9) x 100 = 67	Moderate
Valldeoriola et al. (2010)	7	4	0	3	(4 ÷ 7) x 100 = 57	Moderate
Drey et al. (2012)	5	3	0	2	(3 ÷ 5) x 100 = 60	Moderate

Risk of Bias:

≥ 70 %	High
40-69 %	Moderate
<40 %	Low

Table 3. 6 - Factors Associated with Medication Non-adherence

Rank	Factor for Poor Adherence	Authors	Non-adherence		Study Design	Study n =	Total n =	Correlation Coefficients	Level of Significance	Quality
1	Mood Disorders (i.e. depression)	Grosset et al (2005a)	n=11	(20%)	Cross-sectional	54		Not reported	P = 0.02	Moderate
		Evans et al (2005)	n=25	(20%)	Case-control	25	497	Not reported	P < 0.01	High
		Valldeoriola et al (2010)	n=163	(40%)	Cross-sectional	418		Not reported	P < 0.001	Moderate
2	Poor symptom control/poor reported QoL	Grosset et al (2005a)	n=11	(20%)	Cross-sectional	54		Not reported	P = 0.002 (PDQ-39)	Moderate
		Grosset et al (2009)	n=14	(13%)	Cross-sectional	112	599	$R^2 = 0.13$	P < 0.001 (PDQ-39 & UPDRS)	Moderate
		Valldeoriola et al (2010)	n=163	(40%)	Cross-sectional	418		Not reported	P < 0.001	Moderate
		Drey et al (2012)	n=15	(100%)	Qualitative study	15		n/a	n/a	Moderate
3	Regimen complexity/polypharmacy	Grosset et al (2005a)	n=11	(20%)	Cross-sectional	54	166	Not reported	P = 0.007, P = 0.01	Moderate
		Grosset et al (2009)	n=14	(13%)	Cross-sectional	112		Not reported	P = 0.0001	Moderate
4	Younger age/longer disease duration	Grosset et al (2005a)	n=11	(20%)	Cross-sectional	54		Not reported	P = 0.007	Moderate
		Grosset et al (2009)	n=14	(13%)	Cross-sectional	112	206	Not reported	NS	Moderate
		Evans et al (2005)	n=25	(20%)	Case-control	25		Not reported	P = 0.016	High
		Drey et al (2012)	n=15	(100%)	Qualitative study	15		n/a	n/a	Moderate
5	Impaired cognition	Valldeoriola et al (2010)	n=163	(40%)	Cross-sectional	418	432	Not reported	CI 95%: 1.24 – 3.61	Moderate
		Drey et al (2012)	n=15	(100%)	Qualitative study	15		n/a	n/a	Moderate
6	Poor knowledge of PD/	Valldeoriola et al (2010)	n=163	(40%)	Cross-sectional	418		Not reported	P = 0.04	Moderate
		Drey et al (2012)	n=15	(100%)	Qualitative study	15	472	n/a	n/a	Moderate
	More years in education (>16 yrs)	Leopold et al (2004)	n=35	(90%)	Cross-sectional	39		Not reported	P = 0.04	Moderate
7	Risk behaviours (alcohol, novelty seeking)	Evans et al (2005)	n=25	(20%)	Case-control	25	25	Not reported Not reported	P < 0.001 (novelty seeking) P = 0.006 (alcohol intake)	High
8	Not living with a spouse/life partner	Valldeoriola et al (2010)	n=163	(40%)	Cross-sectional	418	418	Not reported	P = 0.037	Moderate
9	Lower income	Valldeoriola et al (2010)	n=163	(40%)	Cross-sectional	418	418	Not reported	P = 0.05	Moderate
10	Gender	Leopold et al (2004)	n=35	(90%)	Cross-sectional	39	39	Not reported	P < 0.05	Moderate
11	Maintaining employment	Banks & Lawrence (2006)	n/a		Survey/interviews	24	39	n/a	25% self-reported	Low
		Drey et al (2012)	n=15	(100%)	Qualitative study	15		n/a	n/a	Moderate

3.4.3.2 Clinical Factors

Mood Disorders

Grosset et al (2005a) showed adherence was inversely associated with more severe depression. Evans et al (2005) reported individuals with DDS showed more depressive symptoms than PD patients without DDS. Valldeoriola et al (2010) reported a highly negative correlation between adherence to medication and depressive symptoms.

Cognition

Valldeoriola & colleagues (2010) identified a strong negative correlation between adherence to therapy and the presence of psychiatric symptoms. Such patients were almost twice as likely to take medication incorrectly. Specifically, the presence of hallucinations and psychosis were both negatively correlated with medication adherence. Patients with cognitive deterioration were also twice as likely to be non-adherent to prescribed regimens as non-cognitively impaired PD patients.

Drey et al (2012) found all of their respondents inadvertently non-adhered to medication doses, admitting to occasionally forgetting or becoming confused about which medications were due. Despite no objective measure being used to quantify cognitive capacity, the authors reported considerable variation in mental capacity. For example, 3 participants were heavily dependent on carers to manage their medications due to cognitive impairment.

Poor Symptom Control & Poor QoL

Due to the relationship between motor/non-motor symptom control and reported QoL in PD, I felt it necessary to combine these two factors. Banks & Lawrence (2006) found patients had difficulty maintaining a balance between medication taking and QoL, drawing particular attention to the burden of side effects which often outweighed symptom control. Grosset et al (2005a) showed poor QoL correlated with medication non-adherence, with the strongest association for low social support. Valldeoriola et al (2010) reported greater adherence in patients with good clinical control. Similarly, Grosset et al (2009) showed non-adherence was associated with a poorer clinical state. Drey et al (2012) found a perceived lack of efficacy of prescribed medication to control symptoms was associated with deliberate non-adherence:

"It's very obvious now (the tremors). I'm concerned that the medication is not doing what it's supposed to be doing so I don't bother with it sometimes."

(Respondent 7, Drey et al (2012))

Alternatively, some respondents reported taking extra doses to accommodate what they anticipated to be demanding activities, especially those which involved outings or work commitments:

"I always carry extra tablets when I go out to cover the sudden return of my symptoms. I panic if I realise I have forgotten to take extra with me, just in case I need them."

(Respondent 15, Drey et al (2012))

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Deliberate over-use of medication was also reported in relation to dose timing. One respondent moved all doses forward by 30 minutes to create a large enough time gap later in the day for an additional dose to be added. Across many respondents medication was manipulated to mask the symptoms of PD from other people:

"I often take my first dose very early so that my long walk coincides with the time when I feel the medication is most effective. This helps me to look normal should I strike up a conversation with somebody whilst out walking."

(Respondent 3, Drey et al (2012))

Most respondents believed that manipulating dose timing or taking extra doses reflected good symptom control and this approach was often adopted by many. One respondent reported taking the day's entire quota of tablets at once in order that he would be able to dance at a party. For others, such amendments had become more routine:

"I'm an early person. I kick off at six in the morning. They say it should be taken before or after eating but I don't eat then. I don't eat at six in the morning but I'm in need of them (tablets). So I take two at six, two more at ten and then two at two in the afternoon. That sorts me out. It often is around those times depending on what I'm doing that morning you see. Sometimes on a bad day I might take an extra two at some point."

(Respondent 14, Drey et al (2012))

Age/disease Duration

Whilst older age is not always associated with the later stages of PD, I felt it was reasonable to combine both age and disease duration when reporting them in the context of medication non-adherence. Evans et al (2005) reported patients with DDS were significantly younger at PD symptom onset (median 43 years, range 17-57) than people without DDS (median 56 years, range 21-76). Younger age of PD onset was also an independent predictor for developing DDS. Whilst non-DDS patients were older at PD onset, it is important to note that due to the small DDS sample (n=25) caution is required when interpreting the reliability of age of onset as a prognostic factor for developing DDS.

Grosset et al (2005a) showed older age was associated with better overall adherence (total dose taken, expressed as a percentage of the total dose prescribed), better daily adherence (percentage of days when correct number of doses were taken) and better timing adherence (percentage of doses taken at the correct time interval).

Grosset et al (2009) reported that poor timing adherence was associated with longer disease duration and younger age. However, only small differences in age and disease duration were reported (mean age for adherers 65, versus 63 for suboptimal adherers and mean PD duration for adherers 7 years versus 10 years for suboptimal adherers) of which the differences were non-significant. I therefore decided that insufficient explanation was provided to substantiate this claim. Similarly, Drey et al (2012) showed deliberate non-adherence was more prevalent in PD patients with longer disease duration.

Regimen Complexity & Polypharmacy

Grosset et al (2009) reported 12.5% of participants were medication underusers, defined as taking <80% of prescribed drugs. The prescribed dosage of levodopa in patients non-adhering to treatment was significantly higher than the dosage in those who adhered satisfactorily. Adherent individuals took a median of 8mg per day (Inter Quartile Range (IQR) 0-33) less than their prescribed dose of levodopa (a non-significant difference), whilst non-adherent patients took a median of 481 mg per day (IQR 205-670) less than the prescribed dose (P = 0.0006). Overall adherence and timing-adherence were all significantly higher for once-daily medications than drugs prescribed more frequently. This was true for once-daily versus three times daily dopamine agonists.

Grosset & colleagues (2009) showed 21% (n=23) of participants omitted one or more anti-parkinsonian drugs on at least one day during the month of monitoring. Longer periods of omission were also apparent: 12% (n=13) had 2-days with missed doses and 5% (n=6) had 3-days with missed doses. Most only reduced the number of doses taken, while some omitted all drugs. Exact numbers of missed doses were not provided. One patient overused anti-parkinsonian medication, reporting a personal total adherence of 134%.

Grosset et al (2005a) found that patients taking more medication on a daily basis adhered poorly to drugs. This was true for both PD and non-PD prescribed medications. Median overall adherence was 98% in adherent individuals compared to only 65% in the non-adherers. Median daily adherence was 84% in adherent individuals compared to only 27% in the under users. This suggests that those

taking less than 80% of their medications (under users) had many more days of sub-optimal dosing. Median timing adherence was 25% for satisfactory adherers compared to 11% in the underusers. As both are very low this may signify that even those categorised as satisfactorily adhering to treatment (i.e. taking > 80% of drugs prescribed), many PD patients can still struggle to take doses on time. This suggests that erratic drug-taking is likely to be common in PD.

Evans et al (2005) showed patients with DDS (n=25) had significantly higher Levodopa Equivalent Daily Doses (LEDD) (median 2000mg, range 700-3200mg) compared to PD controls (n=100) without DDS (median 700mg, range 0-1600mg). Valldeoriola et al (2010) found levodopa plus dopa-decarboxylase inhibitor benserazide (Madopar) was the only treatment showing a difference in the level of drug adherence. However, the authors did not specify what other treatments this was compared to or whether Madopar was associated with better or worse adherence.

Risk Taking Behaviours

Evans et al (2005) reported that patients with DDS had higher alcohol intake compared to PD controls. However, no level of statistical significance was provided. DDS patients showed greater past experimental drug use compared to non-DDS patients. Furthermore, patients with DDS had higher novelty seeking scores, characterised by increased impulsivity, addiction, an inability to delay gratification, recklessness and aggressive behaviour (Djamshidian et al., 2011). Higher current alcohol intake was also an independent predictor for developing

DDS. As stated above, these claims should be carefully considered due to the small sample of DDS patients in this study.

3.4.3.3 Demographic Factors

Education and Knowledge

Leopold et al (2004) showed participants with more than 16 years of education over reported their number of timing errors compared to MEMS data. This finding is inconsistent with the idea of greater education predicting better adherence behaviour. Although the actual number of participants with more than 16 years of education was not reported, the small study sample (n=39) led me to question the reliability of this finding.

Furthermore, this finding only suggests that individuals with more education may over estimate their errors. Therefore, the true prevalence of incorrectly timed doses may in fact be insignificant when the more objective MEMS data is used. As MEMS adherence rates for people with more than 16 years of education was not reported, I felt there was little evidence to substantiate this claim.

Contrary to Leopold et al (2004), Valldeoriola et al (2010) showed medication adherence was significantly worse in patients with limited knowledge of PD. In spite of this finding only just reaching significance (P=0.04), I felt the larger sample (n=418) to be more representative of PD patients to support the findings. However, it should be recognised that poor knowledge of PD is not the same as

years in education, which may partly explain the inconsistency between the two studies.

Drey et al (2012) found some respondents regarded afternoon sleep to be an effective method for symptom control. Whilst this strategy may provide some benefit for patients suffering with fatigue, this behaviour frequently resulted in missed doses. Despite this, respondents felt afternoon sleeping was a positive approach for managing PD fluctuations and often failed to understand or acknowledge the consequences of missing medication on their overall symptom management. This suggests that poor knowledge of anti-parkinsonian pharmacodynamics and insufficient understanding of the need for consistent medication dosing may be common in PD.

Spouse/life Partner

Valldeoriola et al (2010) reported marriage to be positively correlated with greater adherence behaviours compared to other relationship status. However, this association was non-significant following multivariate logistic regression modelling.

Income & Maintaining Employment

Valldeoriola et al (2010) reported low income was positively correlated with non-adherence in PD. However, as with the spouse/life partner association, this was also non-significant following multivariate logistic regression modelling.

Banks & Lawrence (2006) showed 25% (n=6) of participants (mean age, 51 years) reported that decisions relating to drug treatment had been influenced by how they thought it would affect their ability to work. One patient stated:

"My drug treatment is specifically geared to enable me to continue to work."

Findings showed that drug regimens were modified to facilitate work commitments. Participants reported taking higher doses than they would if not working, and/or adjusting medication timing in attempt to maximise the treatment effect during working hours. One participant said:

"I probably am taking more than I would want to take if I wasn't working. I need them to get through the working day more than when I am home."

Findings further revealed that more PD patients diagnosed in their 30's (50%) modified their treatment regimens to facilitate working commitments compared to people diagnosed in their 40's (42%) and 50's (36%). However, this trend was not statistically significant. Many respondents reported delaying the start of medication. Others were unwilling to dose escalate due to fear of potential side effects and a perceived lack of long-term efficacy, as exemplified by one participant:

"I was not prepared to medicate heavily and sooner than necessary in order to continue to work in view of the prospect of side effects from long-term drug use."

Drey et al (2012) further revealed how respondents concealed their diagnosis of PD from their employers through a regular strategy of extra dosing and rescheduled medication timings, especially in manual jobs where people feared loss of employment on the grounds of health and safety at work:

"I drive to work before the tablets kick in, so that hopefully they will be optimally effective ready for when my shift starts." If they start to run out, or I feel it's been some time since the last dose, I'll have another to try and prevent symptoms returning whilst I'm there."

Gender

Leopold et al (2004) showed females were more likely than males to accurately estimate the frequency of missed doses; however, males were more likely to report miss-timed doses. Despite significance, I felt the sample size (21 males, 18 females) was insufficient to provide firm evidence of this association.

3.5 Discussion

In this chapter I systematically reviewed the evidence to identify factors associated with medication non-adherence in PD. I assessed each included paper for their respective risk of bias and gave each study an arbitrary score for overall quality based on the nine risk of bias items described. The findings of the review were separated into demographic and clinical factors. Clinical factors included mood disorders (depression) impaired cognition, poor symptom control/QoL, younger age/longer disease duration, regimen complexity/polypharmacy and risk taking behaviours. Demographic factors included higher education and poor knowledge of PD, lack of spouse/partner, low income, gender and desire to maintain employment.

Medication non-adherence in chronic conditions is high (WHO, 2003), with reviews identifying non-adherence in 93% of people with diabetes and 60% of people with affective disorders respectively (Lingam and Scott, 2002, Cramer, 2004). Despite medication providing a degree of symptom relief for many people with PD, findings from studies described earlier in this thesis show non-adherence is prevalent. Due to the relationship between adherence and symptom control in PD, motivation to adhere is often assumed by clinicians (Setter, 2008, Bainbridge and Ruscin, 2009, Grosset, 2010). However, in many cases non-adherence is not accidental. Medication taking is a complex phenomenon which is affected by various factors and patient beliefs.

Despite proposed explanations for non-adherence in PD, few studies have reported data to substantiate such claims. Therefore, by undertaking this systematic review it was my intention to collate the evidence for factors associated with medication non-adherence in PD. Through this approach I envisaged the findings being directly applicable to healthcare professionals managing PD patients in both primary and secondary care environments.

Depression

Depression was associated with medication non-adherence in three studies. This replicates findings from other chronic conditions such as ischaemic heart disease, cancer, renal disease and rheumatoid arthritis (DiMatteo et al., 2000, Katon and Ciechanowski, 2002). As depressed patients are three times more likely to non-adhere to prescribed medication than their non-depressed counterparts (DiMatteo et al., 2000), this finding in a PD population was not unexpected.

Depression caused by the burden of living with a chronic condition may result in medication non-adherence. Patients can struggle to adapt to the limitations imposed upon them by their illness and many perceive treatments to lack worthwhile future benefit due to the progressive nature of their condition (DiMatteo et al., 2000, Katon and Ciechanowski, 2002). Specifically in PD, however, medication non-adherence may actually lead to the development of depressive symptoms. For instance, sub-optimal pill taking in PD can lead to reduced motor/non-motor function. Subsequently, this may result in poor QoL which could then lead to symptoms of depression.

Alternatively, Shiba and colleagues (2000) proposed that the pathogenesis of depression in PD may result, at least in part, from the degeneration of neurotransmitter systems. Supporting this theory are the findings of preliminary studies indicating that optimising dopaminergic therapy may provide anti-depressant properties (Poewe and Seppi, 2001, Rektorová et al., 2003, Antonini et al., 2010, Barone et al., 2010).

Whilst the association between depression and non-adherence is recognised, it is important to note that the overall relationship between PD severity and the incidence of depression remains poor (Schrag, 2006). This may suggest that disease severity may not be sufficient to explain depressive symptoms alone. Other factors are therefore likely to contribute to the development and severity of depression in PD, either due to extrastriatal pathology or psychological and environmental factors which may lead to reactive depression (Schrag, 2006).

As depression affects up to 40% in PD, often presenting early in the disease course (Shiba et al., 2000), one useful approach for clinicians is to be mindful of the potential emergence of depressive symptoms and consider the use of targeted anti-depressant interventions early, which may prevent non-adherence from developing. Regular surveillance of psychological wellbeing is therefore required throughout the entirety of the disease process. It is important to note however that the findings from this review provide no indication that management of depression would improve medication adherence. This subsequently requires specific investigation.

Quality of Life

Poor QoL/symptom control was associated with non-adherence in four studies. As with any association, causation cannot be inferred. However, it is more likely that non-adherence to anti-parkinsonian medications in PD causes poor QoL/symptom control, especially when considering that bradykinesia and rigidity respond well to therapy.

Alternative scenarios however must not be disregarded. Poor QoL may be associated with medication non-adherence in PD because of underlying symptoms of depression which may impact negatively on QoL. Furthermore, poor QoL and symptoms of depression may have a combined negative impact on medication adherence in PD; it is known that the presence and severity of depression in PD is strongly correlated with poor QoL and both have been reported to be associated with medication non-adherence (Grosset et al., 2005a, Bainbridge and Ruscin, 2009, Valldeoriola et al., 2010). Therefore, where PD patients report experiencing poor QoL in clinical settings, underlying symptoms of depression should be investigated and the overall impact on medication adherence should be considered.

There is an additional explanation for why poor QoL and poor symptom control are associated with non-adherence. In advanced PD patients will have been taking levodopa preparations for a considerable time. It is known that long-term levodopa use can result in dyskinesia & motor fluctuations in some patients and that these consequences of long-term treatment may be more negatively impactful on QoL than the symptoms of PD itself; the risk of motor fluctuations and dyskinesia is about 40% after 4-6 years of treatment (Ahlskog and Muenter, 2001) and

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dyskinesia is reported to develop in 100% of young onset PD patients (diagnosed before 40 years) after six years of levodopa use (Clarke, 2002). Therefore, some patients may attempt to off-set or minimise these debilitating consequences of dopaminergic therapy by intentionally non-adhering to prescribed regimens.

From the articles included in this review, one study reported dyskinesia in 26% of patients (Grosset et al., 2005a), whilst two studies reported motor complications in 76% and 71%, respectively (Grosset et al., 2009, Valldeoriola et al., 2010). Two thirds or more were taking levodopa and had had PD for 5 years or more. Although it may be more likely that poor QoL/symptom control results from medication non-adherence, the prevalence of motor complications within the reviewed studies and the known impact of these complications on QoL may provide an alternative explanation for non-adherent behaviours. This is particularly the case in advanced PD where such complications of treatment may be more prevalent.

Dose Manipulation

The findings of this review also suggest that people with PD manipulate drug doses for many other reasons. For example, symptom severity, treatment efficacy, perceived need for medication and the understanding of the indication for treatment have all been proposed as being contributory to non-adherence in PD (Setter, 2008, Bainbridge and Ruscin, 2009, Grosset, 2010, Drey et al., 2012). The following paragraph provides evidence for these factors.

Drey & colleagues (2012) showed that in addition to minor inadvertent non-adherence (occasionally forgetting medication), patients reported episodes of over-

medicating to accommodate situations anticipated to be especially demanding (deliberate non-adherence). Others described scenarios in which dose timings were purposely adjusted to facilitate participation in recreational activities, whilst some reported their desire/financial necessity to remain in employment resulted in them continuously altering doses in attempt to remain 'on' whilst at work. Moreover, dosing times were manipulated to mask the symptoms of PD from other people in the workforce, suggesting an underlying social stigma may be perceived by some with PD.

Whilst some appreciated that sporadic taking of medication satisfies criteria for non-adherence, many believed that taking additional doses or adjusting dose timings to accommodate planned events reflected good symptom management (Drey et al., 2012). This provides evidence of the disparity between patients and healthcare professionals views regarding the correct use of anti-parkinsonian drugs.

Alternatively, manipulating doses may be indicative of inadequate symptom management due to being under-medicated. Drey et al (2012) found patients carried extra medication to cover sudden exacerbations or re-emergence of symptoms. Grosset and colleagues (2009) reported that one PD patient had a personal total adherence of 134% of the prescribed dose. Whilst demographical information was not reported for this patient, the overuse of anti-parkinsonian agents in these studies may be indicative of sub-optimal symptom management.

Non-adherence also has consequences for the prescriber. Management decisions are based on the premise that patients are correctly taking their medication. Dose

escalation, adjunctive therapy use and in some scenarios diagnostic reconsideration may all result from seeing a patient in clinic who apparently has had a poor response to treatment (Grosset, 2010). These findings suggest that more regular reviews of PD medication may be required for ensuring patients are medicated optimally and to their individual need. Optimised adherence may also help clinicians monitor disease progression more reliably.

Furthermore, collaboration between patients and healthcare professionals is imperative for facilitating adherence (Grosset, 2010). Findings show that where patients and healthcare professionals make treatment choices together, adherence will be enhanced (Gray et al., 2006, Gray, 2011). It is likely to be beneficial therefore for clinicians to discuss treatment strategies with patients. Additionally, it may be useful to specifically train PD nurse specialists to help patients incorporate medication into their daily routines.

The consequences of non-adherence in PD must also be considered in the short-term. Adverse events associated with intermittent or sub-optimal medication use can be life-threatening. Sudden withdrawal of dopaminergic agents can cause suppression of central dopamine transmission and thus trigger the neuroleptic malignant syndrome, which may lead to fatality (Mizuno et al., 2003). Typically symptoms develop between 18 hours and 7 days following anti-parkinsonian treatment cessation (Newman et al., 2009). Patients develop pyrexia, increased muscle rigidity, reduced conscious levels (potentially leading to a coma), autonomic instability and a raised creatine kinase (Newman et al., 2009). Although the neuroleptic malignant syndrome is relatively rare, the potential for fatality

following acute withdrawal of dopaminergic treatments in PD makes the identification of medication non-adherence essential.

Age & Risk Behaviours

Grosset et al (2005a) showed younger age was associated with medication non-adherence. During early PD levodopa typically confers a long-duration response. Patients may miss doses while experiencing no functional decline and this may partly explain medication underuse in younger, more asymptomatic patients. However, the long duration response is not age dependent but is more likely related to disease severity. Therefore, in younger but more severely affected patients, the long duration response may not apply. In early PD healthcare professionals should monitor medication taking as non-adherence may not be recognised in asymptomatic/mild individuals. In younger, symptomatic patients medication adherence should be thoroughly investigated prior to consideration of dose escalation.

Evans et al (2005) reported medication overuse in patients with DDS. Whilst this represents an exceptional PD group, I felt it was essential to include this study as medication overuse is recognised as a modified drug adherence behaviour in DDS. Although DDS occurs more in younger PD patients, it is unlikely that age independently explains overuse in these individuals and therefore non-adherence should be considered in a wider context.

While Evans et al (2005) made no reference to Impulse Control Disorder (ICD), defined as a failure to resist temptation, urge or impulse that may result in harm

(Ceravolo et al., 2009), associations between non-adherence and increased alcohol intake, past experimental drug use and novelty seeking tendencies were identified. Epidemiological studies reveal substance addiction and impulsive sensation seeking primarily develop in young adulthood (Chambers et al., 2003). As DDS patients are younger but also experience novelty and impulsive sensation seeking, characteristic of ICD (Ceravolo et al., 2009), it seems more likely that over-medicating in patients with DDS results from a combination of behavioural/personality traits, with younger age related but not independently casually linked.

Although ICD characteristics were not directly reported by the authors in the reviewed studies, these traits may contribute to the non-adherence observed in patients with DDS. In a clinical context when treating a PD patient diagnosed at a young age, professionals should acknowledge personality phenotypes and consider screening for novelty seeking/compulsive behaviours which may help to prevent medication overuse. Moreover, treating susceptible individuals with dopamine agonists should be cautiously considered in light of their widely reported propensity to induce compulsive behaviours in some PD patients (Evans et al., 2005).

In contrast to findings reporting non-adherence in younger PD patients, Drey et al (2012) identified deliberate non-adherence was prevalent amongst patients with longer disease duration. This led the authors to propose that the expert patient concept (often associated with people who have managed a chronic illness for many years) may not be helpful in the management of PD. However, it is more

likely that other factors associated with older age are responsible for the non-adherence observed in this sample, especially considering that the notion of the expert patient is reported to benefit medication adherence (Badcott, 2005).

These findings may also propose the importance of patient-centred education in PD. Drey and colleagues (2012) showed that whilst patients appeared familiar with treatment goals, patients understanding of PD medication was not sophisticated enough to sufficiently manage their condition. In particular, patients did not appreciate that to achieve symptom control strict timing of doses can be imperative, especially in later stages of disease. A possible strategy may be therefore to develop an intervention that promotes patient awareness of the relationship between adherence and symptom control.

Regimen Complexity, Polypharmacy & Cognitive Impairment

Regimen complexity/polypharmacy was associated with non-adherence in PD (Grosset et al., 2005a, Grosset et al., 2009). This replicates findings in the elderly and other chronic disease areas where non-adherence is prevalent in patients taking a considerable number of daily doses (Cramer, 2004, Saini et al., 2009). A review by Saini & colleagues (2009) of medication use and polypharmacy in chronic conditions showed patients were as much as 44% more adherent to prescribed drugs taken once-daily compared to drugs requiring multiple daily doses. Furthermore, findings showed that once daily treatment regimens resulted in up to twice as many adherent days than in patients where more frequent dosing scheduled were prescribed.

Schnitzler et al. (2010) reported that patients with PD showed 98% adherence to the daily applied rotigotine patch. Similarly, the once-daily tablet rasagiline has been associated with greater adherence rates than PD medications requiring multiple daily doses (Tarrants et al., 2010). Furthermore, Fargel et al (2007) revealed that patients with PD found a high tablet load difficult to manage. These combined findings therefore emphasise the importance of prescribing simpler treatment regimens in PD (Fargel et al., 2007). Valldeoriola and colleagues (2010) found Madopar was the only drug associated with non-adherence. The reasons for this are unclear but may result from Madopar preparations being mostly dispensed in capsules which can be more difficult to swallow than pills, particularly in patients with dysphagia.

This review identified cognitive impairment as being associated with medication non-adherence in PD. As deficits in cognition are estimated to affect 20-40% of PD patients (Aarsland and Kurz, 2010), this finding was not surprising. Dysfunctional planning, attention/mental flexibility and working memory, cognitive domains commonly affected in PD, have also been associated with medication non-adherence in other chronic conditions such as diabetes, cancer and hypertension (Stilley et al., 2010). Non-adherence in elderly patients with cognitive decline is also widely acknowledged (Arlt et al., 2008).

As cognitive impairment can be substantial in PD, and as studies show simpler drug regimens reduce non-adherence in many chronic conditions, it is sensible to focus on the early detection of cognitive dysfunction and where indicated prescribe simpler drug regimens to reduce pill intake. This may include prescribing longer

acting agents where possible or favouring, where tolerated, combined preparations which eradicate the need for further tablets. Additionally, assisting cognitively challenged individuals with problem solving strategies might help patients to find ways to adhere to prescribed drugs, particularly if treatment is placed within their own personal context.

Drey & colleagues (2012) found patients regularly missed doses due to episodes of sleeping during the afternoon or insomnia at night. This is often reported in patients suffering with fatigue or PD related sleep disruption such as restless legs syndrome or being *'off'* during the night (Ferreira et al., 2006). Despite recognising that missing doses would go against the prescriber's intentions, some patients appeared unable to instigate plans to prevent such episodes from recurring. This may suggest that daytime somnolence, combined with an inability to problem solve, could account for some of the non-adherent behaviours observed.

What's more, the capacity to anticipate the onset of fluctuating symptoms did not necessarily increase patients' ability to time medication successfully in order to try and prevent fluctuations from occurring. This may suggest that for some individuals with PD planning and problem solving may be problematic, resulting in sub-optimal medication taking. Alternatively, these findings may suggest that patients may not appreciate the importance of specific dose timing in PD.

Education & Knowledge of PD

Greater knowledge of PD was associated with better adherence. This is consistent with findings reporting improved timing adherence in PD patients after receiving

educational material (Grosset and Grosset, 2007). Drey & colleagues (2012) found that for some people with PD a lack of understanding concerning the necessity for timed medication resulted in frequently missed or miss timed-doses. This suggests that a greater emphasis on education may be beneficial for improving medication adherence in PD. Furthermore, educational material that is personally relevant may be more likely to have a positive impact on adherence behaviours.

Alternatively, however, higher levels of general education may in some cases hinder medication adherence. Leopold et al (2004) showed higher educational attainment was associated with sub-optimal adherence. This association was surprising and may be a result of more educated and better informed individuals having greater capacity to challenge medical opinion.

Gender and Spouse/carers

Males were less accurate at estimating the frequency of miss-timed doses. However, I believed that the small sample involved in this association reduced the reliability of this claim. Living with a spouse/life partner was associated with greater adherence. This is not surprising; in chronic illness caregivers are critical in helping to manage the disease. Specifically in PD, cognitive impairment can leave caregivers inheriting the responsibility of medication management. Therefore, it is paramount that spouse/caregivers are involved and supported throughout the entirety of the disease process, and that they themselves possess the appropriate knowledge of the importance of accurate dose timing.

Maintaining Employment

The desire to maintain employment was associated with non-adherence. Drey and colleagues (2012) found that some PD patients escalated doses to maximise working capacity whilst others withheld treatment fearing future motor complications which may inhibit working performance. Many patients also failed to accept that doses must be timed evenly to maintain consistent plasma dopamine levels.

Traditionally, deviation from prescribed medication regimens satisfies healthcare professionals' criteria for non-adherence. However, whilst dose timings are important in PD, professionals should recognise that the ultimate goal of treatment is to maintain Health Related QoL (HRQoL). For many the workplace affords self-fulfilment, helping to optimise QoL. Although findings seem to suggest that patients require greater knowledge of the effect of manipulating doses, it is evident that patients require their regimens to be specific to their need. Prescribers should acknowledge that medication may be focused around functioning optimally at work and therefore working collaboratively with patients through shared decision-making may help to maximise adherence in PD. It is worth noting however that although physical and cognitive demands may be considerably less in the elderly, their dysfunctions may be no less impactful on QoL and so this must also be considered.

3.5.1 Strengths and Limitations

When interpreting this review, some limitations require consideration. Statistical synthesis was not undertaken due to the heterogeneity of the seven included studies. As most studies were observational, causation between factors and non-adherence cannot be inferred. However, it is more likely that many of the identified factors cause non-adherence as opposed to being a product of non-adherent behaviour. The definitions and assessment methods for adherence also require consideration as these vary widely across studies. Nevertheless, irrespective of the definition, it is important to emphasise that adherence is a moving target which is likely to become increasingly more difficult to achieve with advancing disease.

Although the findings of the review did not identify financial or healthcare system constraints as factors for non-adherence, it is important to note that once daily drugs such as dopamine agonists which help reduce regimen complexity may not be readily available on prescription in some countries, such as the US. There are also financial barriers to prescribing expensive drugs for the sole purpose of reducing the number of daily doses.

The summation of the nine risk of bias items to produce an overall risk of bias score in this review should also be acknowledged. Although the described method allowed for ease of presentation and is advocated by organisations such as the Cochrane Collaboration, it is important to note that not all risk of bias items should be given the same weighting. For example, in a RCT the method of randomisation and concealment of allocation are risk of bias items that should be given the most importance.

Although I acknowledged that some risk of bias items for different studies were more important and thus should be given more weighting, this was not reflected in the overall risk of bias score. This may be deemed a limitation of the review. Furthermore, the cut-off scores for low, moderate and high risk of bias were arbitrary.

The major strength of this review is the critical appraisal of the literature against a novel risk of bias tool which I developed following a thorough systematic search of existing quality instruments. This risk of bias assessment tool was purposely designed for generic use and therefore is applicable to other disease areas and non-interventional studies. Another strength of this review is that identified factors were ranked by weight of supporting evidence. This novel approach allows clinicians to understand the most salient factors likely to be associated with medication non-adherence in PD. With such knowledge, healthcare professionals should be able to identify who is more likely to be non-adherent to anti-parkinsonian drugs.

It must be emphasised however that this ranking was based on the quality of each study, the number of patients associated with each factor, and the level of significance for each factor. As a result, factors such as the desire to maintain employment were ranked lower down in the list. Whilst this may not be as common as others ranked much higher (due to most people with PD being retired for example), it must be recognised that to individuals for whom this is relevant, such a factor may be no less impactful on their medication taking behaviour than some of the more highly ranked factors.

3.5.2 Summary

The symptoms of PD can be extremely debilitating and often result in poor QoL. Medication can be an effective treatment for controlling some of the reported symptoms in people with PD. However, findings show that many people with PD do not adequately adhere to treatment. Non-adherence is associated with a variety of both clinical and demographic factors, as described in this chapter. Moreover, contrary to existing belief, much of the non-adherent behaviours identified are not accidental. Healthcare professionals should acknowledge these factors when consulting patients which could prove beneficial for identifying patients at risk of medication non-adherence.

In light of the identified factors, targeted, patient-centred interventions that acknowledge factors associated with non-adherence should be investigated in an attempt to improve medication adherence in PD. Therefore, with a greater knowledge of adherence issues in PD, I decided to investigate what interventions have been used in PD for improving medication adherence. This work is presented in Chapter 4.

CHAPTER 4

Interventions to Improve Medication Adherence in Parkinson's disease

Background
Methods
Results
Discussion

4.1 Background

The investigation of the effectiveness of strategies aimed at improving medication adherence in PD has received little attention. This is in contrast to other chronic conditions where evidence from numerous systematic reviews has shown a number of interventions have been investigated in attempt to enhance adherence behaviour (Kripalani et al., 2007, Haynes et al., 2008, Nunes et al., 2009).

The aim of adherence interventions is to increase acceptance of, and persistence with, prescribed treatments (WHO, 2003, Nunes et al., 2009). Once factors associated with poor adherence have been identified and their mechanisms of action are understood, interventions aimed at enhancing adherence behaviours can be developed and investigated.

The National Institute for Health and Care Excellence in the UK recommend focusing on exploring patient beliefs and attitudes towards disease and drug treatments (NICE, 2009). Whilst some findings are equivocal, evidence mainly suggests that such an approach is beneficial for enhancing medication adherence in people with chronic illness (Horne and Weinman, 1999, Maneesakorn et al., 2007, Haynes et al., 2008, Alhalaiqa et al., 2011).

A recent review of medication adherence in the US showed a variety of interventions (e.g. educational and behavioural approaches) were beneficial for improving adherence rates in several chronic conditions (Viswanathan et al., 2012). However, despite various research groups reporting the efficacy of such interventions (Peterson et al., 2003, Kripalani et al., 2007, Haynes et al., 2008, Viswanathan et al., 2012), there is a paucity of evidence specifically investigating the effectiveness of adherence promoting interventions in a PD population.

Therefore, it is reasonable to suggest that an intervention aimed specifically at improving medication adherence, and that recognises factors associated with non-adherence, could be beneficial for improving adherence behaviours in PD. However, before a novel treatment can be developed I decided to investigate which interventions have been evaluated previously in PD. To answer this research question I conducted a Cochrane systematic review. Cochrane reviews mostly evaluate evidence relating to the efficacy of healthcare interventions. As I aimed to investigate adherence enhancing interventions in PD, I believed a Cochrane systematic review methodology was most appropriate.

4.2 Methods

The methods described in the next section of this chapter outline the process used when searching for and evaluating the relevant literature. The protocol, including the search strings used for each online database, was approved by expert systematic review and meta-analysis methodologists from the Movement Disorder Group at the Cochrane Collaboration. Appendix 3 shows the search strings used in this systematic review.

4.2.1 Criteria for Considering Studies for this Review (Inclusion Criteria)

4.2.1.1 Types of Studies:

- Published Randomised Controlled Trials aiming to increase adherence to anti-parkinsonian medications.

4.2.1.2 Types of Participants:

- Adults with a clinical diagnosis of idiopathic PD (as defined by the authors of the included studies) in a primary care, outpatient or community setting.

4.2.1.3 Types of Interventions:

For the purpose of this review I grouped studies by intervention type and proposed mechanism of action. The interventions were categorised into one of the following groups:

1. Simplification of Dose Regimen

These studies enhance adherence by amending dosage schedules in order to simplify the regimen. This can be by reducing the number of pills taken daily and/or the number of doses required daily for adequate symptom control to be achieved. Through this approach the burden associated with pill taking is reduced.

2. Patient Education

Studies designed primarily to educate patients through prescriptive/didactic means (i.e. educational material). This method is based on the premise that patients who possess greater knowledge of their illness and its respective treatment will be more informed and therefore more likely to adhere to prescribed therapies.

3. Behavioural Interventions

Studies using interventions designed to influence adherence behaviours. Such interventions are likely to have two proposed mechanisms of actions:

(i) Positive adherence behaviours are assumed; that is, it is expected that the patient wishes to adhere to drug regimens. By enhancing/maximising motivation the patient's ability to take medication as intended will be optimised. This may then benefit clinical outcomes (Haynes et al., 2008).

Interventions to facilitate this largely consist of problem solving, reminders (diaries), regular follow up appointments, social/community and professional support such as involvement of allied health professionals (e.g. nurse specialists, pharmacists).

(ii) Positive adherence behaviours are not assumed; that is, the patient may not wish to adhere to prescribed medication regimens. This type of intervention aims to modify beliefs/attitudes, which subsequently changes adherence behaviours leading to improved clinical outcomes (Nunes et al., 2009).

4. Combined or Complex Interventions

These interventions include two or more of the preceding categories and may have multiple phases for introducing the different types of interventions.

Control/treatment as usual groups either received no intervention or received usual care, as defined by the study authors.

4.2.1.4 Exclusion Criteria

1. Interventions that did not aim to enhance adherence to anti-parkinsonian medication,

2. Interventions that were not directed at patients with PD (e.g. education of healthcare professionals about the importance of adherence),

3. Studies that did not report the results in full (e.g. conference abstracts) and where further information (sufficient to make a fair appraisal of the methodological quality of the study) was not available from the authors,

4. Studies that did not report a measure of adherence.

4.2.1.5 Types of Outcome Measures:

As I was interested in interventions aimed specifically at improving medication adherence in PD, I felt that adherence should be the primary outcome.

Primary Outcome:

1. Adherence to medication (including any definition of adherence and noting how this was defined and measured in each study).

Secondary Outcomes:

1. Change in global clinical scale e.g. Unified PD Rating Scale,

2. Change in other clinical indicators e.g. off-time and dyskinesia,

3. Change in attitudes and beliefs towards medication,

4. Reporting of major clinical events associated with the consequences of poor medication adherence (e.g. increased dyskinesia, motor fluctuations, worsening of PD symptoms and on rare occasions psychosis),

5. Cost analysis of the intervention,

6. Potential adverse events of the intervention,

7. Acceptability of the provided intervention,

8. Carer load e.g. carer strain index.

In the next section of this chapter I outline the procedure used for identifying articles for consideration in this review. Furthermore, I discuss the process used for assessing risk of bias and I outline the method for conducting a meta-analysis if that was possible. Finally, I end this chapter by reporting and discussing the main findings.

4.2.2 Electronic Search Methods for Identification of Studies

I used a comprehensive sampling strategy to retrieve all relevant RCTs relating to medication adherence in PD. The following sources were searched:

- The Cochrane Central Register of Controlled Trials (CENTRAL)

- The Movement Disorder Society Specialised Register

- MEDLINE (Ovid, 1946 to February 2013)

- EMBASE (Ovid, 1974 to February 2013)

- AMED (Ovid 1985 to February 2013)

- PsycINFO (Ovid 1806 to February 2013)

- CINAHL (EbscoH, 1981 to February 2013)

I also searched the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal, Current Controlled Trials, the International Standard Randomised Controlled Trial Number (ISRCTN) register and the UK National Research Register (NRR) archive (all to February 2013) for on-going and recently completed trials. There was no restriction on language or publication status.

Appendix 3 shows the search strings used when searching the five online databases. When conducting the search I mapped key terms to database specific subject headings (MeSH terms) and exploded each to include all sub-categories. Truncations (*after search term) and Boolean operators (AND, OR, NOT) were also used to broaden the search window. Finally, I screened reference lists of all retrieved articles to identify additional records. Where necessary, I contacted the

authors of relevant studies to acquire additional information relating to an identified study/abstract.

4.2.3 Selection of Studies

All studies and abstracts were evaluated according to the methods highlighted in the Cochrane Handbook (Higgins and Green, 2009). Specifically, full paper copies of potentially relevant citations were sought and two reviewers (I and KHOD, one of my supervisors) independently assessed each full text against the review inclusion criteria. Disagreements were resolved by formal discussion.

4.2.4 Data Extraction and Management

The standardised data extraction form provided in the Cochrane Collaboration Handbook was used for data extraction (Higgins and Green, 2009). This acted as a template for data entry.

4.2.5 Assessment of Risk of Bias

Two reviewers (I and KHOD) independently assessed studies for risk of bias using the Cochrane Collaboration quality assessment tool (Higgins and Green, 2009). The assessment of overall risk of bias was based on the following bias items: (1) random sequence generation, (2) allocation concealment, (3) blinding, (4) selective reporting and (5) the potential effect of incomplete outcome data.

Other risk of bias items that I decided were appropriate for this review included idiopathic PD diagnostic accuracy (e.g. UK Brain Bank Criteria or other appropriately defined criteria) and the reliability/validity of reported outcome measures; that is, whether adherence assessment methods were standardised/valid and whether clinical outcomes used were standardised measures.

4.2.6 Dealing with Missing Data

Where data was insufficient or missing, additional information was sought from study authors. If there was no response, I planned to analyse the data that was available.

4.2.7 Measurement of Treatment Effect

I planned to perform all statistical analyses using the RevMan software provided by the Cochrane Collaboration. Before conducting the search I recognised that sufficient heterogeneity may exist between identified studies which could prohibit a meta-analysis of the results. Under such circumstances I planned to perform a descriptive 'narrative' review.

4.2.8 Data Synthesis

If a meta-analysis was possible I planned to use standardised statistical techniques to calculate and report the results as odds ratios (and 95% confidence intervals) for dichotomous outcomes and mean differences (MD) for continuous outcomes. The

significance of any differences between the odds ratios or MD would then be calculated using a standard method (Altman and Matthews, 1996).

As I anticipated that the true effect size of the intervention would vary considerably between studies, I planned to adopt a random-effects model where data synthesis was possible. Possible factors that I believed may vary substantially included: age of the participants, level of education, baseline level of adherence, disease severity and the intensity/type of the adherence intervention.

4.3 Results

The five databases searched yielded a total of 3615 records as shown in Table 4.1.

Table 4. 1 - Records Identified by Database

Database	Number of Records
MEDLINE (Ovid)	105
EMBASE (Ovid)	3332
AMED (Ovid)	0
PsychINFO (Ovid)	69
CINAHL (EbscoH)	109
Total:	3615

A further three records were identified from the Cochrane Central Register of Controlled Trials (CENTRAL). After combining the search results into one library and then removing duplicated records (n=230), a total of 3388 records remained. Figure 4.1 shows the PRISMA diagram depicting the stages of study identification.

After reviewing titles and abstracts of all 3388 identified records, 38 articles were suitable for full text retrieval. Five of these records were in fact conference abstracts (Bhidayasiri et al., 2009, Aguiar et al., 2010, Aljanati et al., 2010, Guo et al., 2010, Al-Din et al., 2012). All the authors' for each abstract were contacted to ensure that the study had not been published. Of the three authors who responded, all confirmed that the results had only been presented at a conference. These five abstracts were thus excluded as insufficient data was provided in the abstract from which an adequate assessment of risk of bias could be made.

Three records were not published in English language (German n=2, Dutch n=1). Email correspondence with the author of the Dutch study (Aerts et al., 2011) confirmed the paper had not been published in English in another journal. Also, as the paper was a literature review of adherence in PD it was not relevant. The two articles published in German language (Unknown, 1994, Ameri, 2009) were reviewed by a German speaking colleague who confirmed that they were commentary reports. These were therefore also not relevant to the systematic review.

I excluded a further five records as they were review papers (Antonini et al., 2010, Agyapong et al., 2011, Farlow and Somogyi, 2011, Hametner et al., 2011, Allen et al., 2012). An additional five records were excluded as they were not concerned with medication adherence (Hutton et al., 1996, Allain et al., 2000, Clarke et al., 2009, Pretzer-Aboff et al., 2011, Manning et al., 2012).

Fifteen studies were not RCTs and thus I excluded them on this basis (Al-Zakwani et al., 2003, Nausieda et al., 2005, Myllyla et al., 2006, Arbouw et al., 2009, Sethi et al., 2009, Davis et al., 2010, Delea et al., 2010, Schnitzler et al., 2010, Tarrants et al., 2010, Wood et al., 2010, Delea et al., 2011, Hamlen and MacGregor, 2011, Schlesinger and Rabinowitz, 2011, Sesar et al., 2011, Santos-Garcia et al., 2012).

Two studies were further excluded because they did not provide an assessment of medication adherence (Hinson et al., 2009, Pickering et al., 2013). An additional study by Stocchi and colleagues (2008) was excluded because the intervention

described did not constitute a reduction in the number of daily pills, as was portrayed in the abstract.

One final study by Montgomery and colleagues (1994) was excluded because the described adherence assessment did not constitute a valid method; drug usage was tabulated per patient per day but the actual doses prescribed and the timing of the doses was not documented.

Therefore, the evaluation of the 38 full texts yielded only 1 study by Grosset and Grosset (2007) that met the inclusion criteria for the Cochrane systematic review. The characteristics of this study are presented in Table 4.2.

In the final part of this chapter I provide a summary of the results and include an outline of the risk of bias assessment used. Following this I discuss the findings within the context of adherence enhancing interventions used in other chronic conditions.
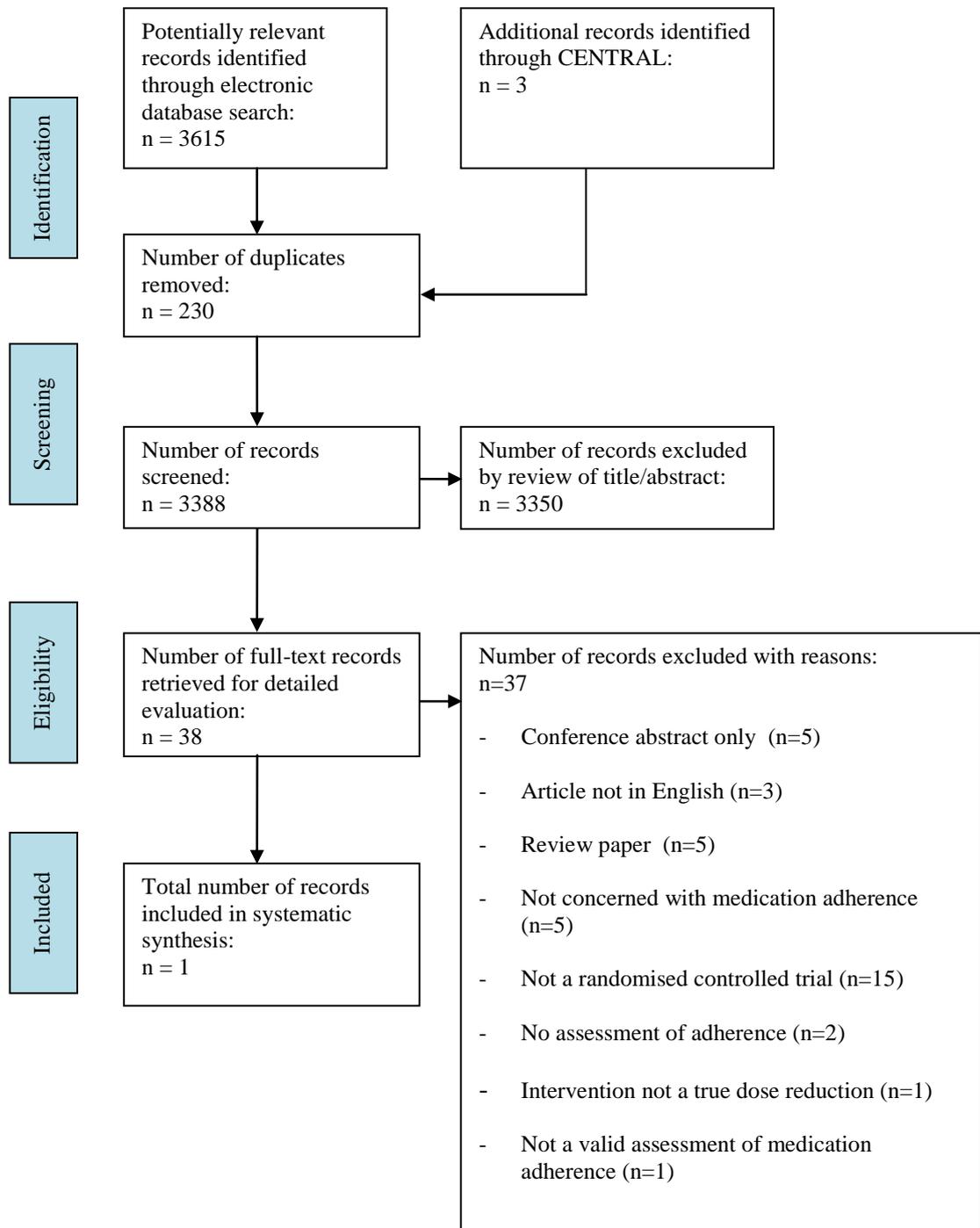
Figure 4. 1 - PRISMA Flow Diagram of Study Identification

Table 4. 2 - Characteristics of Included Study

Grosset & Grosset (2007)		Description
Methods	-	Parallel RCT, 3 month follow-up. Analysis employed intention to treat. A sample size calculation was carried out.
	-	Adherence determined using MEMS. Monitored drug intake during two 3 month periods (before and after the intervention).
Recruitment	-	Recruited from a regional movement disorder clinic. All were prescribed at least one anti-parkinsonian medication.
Participants	-	89 patients with PD (diagnosed by UK Brain Bank criteria) were asked to participate. 6 (7%) declined.
	-	43 were randomised to the active group and 40 to the control group using computer generated opaque envelopes. Randomisation preceded baseline assessment.
	-	14 dropped out during the first 3-month monitoring, 10 from the active group. Baseline adherence data were therefore available for 69 patients (33 active group and 36 control group).
	-	In the post intervention period, 17 patients dropped out (10 active group). Post intervention adherence data were evaluable for 52 patients (23 active group).
Intervention	-	After the first 3 months of monitoring using MEMS, patients in the active group were given verbal and written information about the dopaminergic theory and tailored written guidance on optimal medicine timing for their regimen.
	-	Control patients received standard care, but also had medication intake monitored using MEMS.
Outcomes	-	Unified Parkinson's Disease Rating Scale (UPDRS),
	-	Hoehn & Yahr assessment of disease severity,
	-	Schwab and England Scale (ADL assessment)
	-	Mini-Mental State Examination (MMSE),
	-	Geriatric Depression Score,
	-	Parkinson's disease Quality of Life Questionnaire (PDQ-39).
	-	All were assessed at baseline. The PDQ-39 was also repeated at the final visit. All clinical recordings were blind to patient group.

4.3.1 Assessment of Risk of Bias

The reporting quality of the included study was sufficient to adequately assess the potential risk of bias. Two reviewers (I and KHOD) independently assessed the included article for various aspects of bias using the risk of bias assessment tool from within the Cochrane Handbook (Higgins and Green, 2009). Specifically, we independently assessed the overall risk of bias based on the classification scheme for types of bias outlined in Table 4.3.

Table 4. 3 - Classification Scheme for Bias

Type of Bias	Description	Relevant domain in Cochrane's 'Risk of Bias' tool
Selection bias	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel.
Detection Bias	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment.
Attrition Bias	Systematic differences between groups in withdrawal from the study.	• Incomplete outcome data.
Reporting Bias	Systematic differences between reported and unreported findings	• Selective outcome reporting.

(Source: Higgins and Green (2009))

4.3.2 Judging Risk of Bias in Included Studies

When reviewing the included study, judgements regarding the risk of bias were categorised as: 'Low risk of bias', 'High risk of bias' or 'Unclear risk of bias' (Higgins and Green, 2009). Appendix 4 shows the specific criteria used when making a judgement of risk of bias. Table 4.4 shows the judgement for each risk of bias item in the included study.

Table 4. 4 - Risk of Bias

Grosset & Grosset (2007)

Bias Item	Judgement	Comment &/or support for judgement
Random sequence generation	Low risk	Computer generated
Allocation concealment	Low risk	Placed in opaque envelopes
Blinding - participants	High risk	Unavoidable with this intervention
Blinding - clinicians	High risk	Unavoidable with this intervention
Blinding - analyst	Unclear	No mention of statistician.
Blinding - outcome assessor	Low risk	Clinical recordings blinded to group allocation
Incomplete/missing data	Low risk	Intention to treat using last observation carried forward
Selective reporting	Unclear	Study protocol reported (NCT00361205). Although medication timing compliance and motor scores are mentioned, PDQ-39 and adverse events are not.
Diagnostic accuracy	Low risk	UK Brain Bank criteria used
Adherence assessment	Low risk	MEMS caps used.

4.3.3 Description of Adherence Intervention

As only one study met the inclusion criteria for this systematic review, it was not possible to pool the results and conduct a meta-analysis.

Of the different types of intervention described earlier in this chapter for improving medication adherence, Grosset and Grosset (2007) satisfied the criteria for patient education. Patients in the treatment group were given verbal and written information relating to the continuous dopaminergic theory 3 months after starting to use MEMS bottles. After receiving the intervention, MEMS monitoring continued for a further 3 months. Participants in the control group used MEMS for the entirety of the trial duration.

4.3.4 Baseline Measurements and Observations

At baseline, timing adherence was a median of 17% (IQ 9-51) in the active group versus 21% (IQ 10-59) in the control group. This difference was not significant. All other outcome measures did not differ significantly between the active and control groups. These measurements included: UPDRS, Hoehn & Yahr (measure of disease severity), Schwab and England scale (assesses activity of daily living) and the Mini-Mental State Examination (a non-disease specific assessment of cognitive impairment).

Timing adherence was significantly better at baseline for once daily drugs (median 82%, IQ 70-93) than drugs prescribed twice daily (33%, IQ 4-47) or more frequently ($p < 0.0001$).

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4.3.5 Efficacy of the Intervention

4.3.5.1 Primary Outcomes

Adherence

After receiving the educational intervention, timing adherence significantly improved in the active treatment group (n=23) (median 39%, Inter Quartile Range (IQR) 22–58) compared to the control group (n=29) (median 20%, IQR 10–47, p = 0.007). The intervention effect (difference in timing adherence pre to post intervention between the groups) was 13.4% (95% Confidence Interval (CI): 5.1, 21.7; p = 0.002). After excluding drugs taken once daily from the analysis, the intervention effect was 23.1% (95% CI: 11.7, 34.5, p = 0.0001).

4.3.5.2 Secondary Outcomes Reported

Change in Global Clinical Scales

The Parkinson's Disease Questionniare-39 total score increased by a mean of 6.0 (95% CI: 2.3, 9.7) in the active treatment group, versus a mean increase of 3.5 (95% CI: -1.6, 8.6) in the control group (p = 0.4). The mean change in UPDRS motor scores was 0.1 (95% CI: -3.4, 3.7) in the active treatment group versus 4.5 (95% CI: 1.6, 7.1) in the control group (p = 0.06). Both outcomes showed no statistically significant difference between the groups.

Potential Adverse Events of the Intervention

Grosset and Grosset (2007) reported there were no significant differences in frequency or type of adverse events between the two groups (active treatment

group 1.5 adverse events per patient, versus 1.1 in the control group). The authors report that the most common adverse effects (i.e. insomnia, sleepiness, dyskinesia and nausea) were in declining frequency. No further information was provided and so it was unclear whether this was anticipated to result from a changed pattern of medication taking.

4.3.5.3 Secondary Outcomes Not Reported

Change in Global Clinical Scale

The difference in the remaining measurements taken (i.e. Schwab and England, Hoehn and Yahr and the Mini-Mental State Examination) from baseline to follow-up between the two groups was not reported. Although these scales were completed at baseline and follow-up, Grosset and Grosset (2007) did not report that they were secondary outcomes.

Change in Other Clinical Indicators (e.g. off-time and dyskinesia)

Grosset and Grosset (2007) did not report off-time in study participants both before and after the intervention. Dyskinesia was acknowledged to be in declining frequency as described above. However, no data was provided to substantiate this claim.

Other Secondary Outcomes Not Reported

A change in attitudes and beliefs towards medication, carer load/burden, acceptability of the intervention provided and cost analysis of the intervention were not reported by Grosset and Grosset (2007).

4.4 Discussion

In this chapter I outlined the methods and results of a Cochrane systematic review. My aim was to identify randomised controlled trials that investigated the efficacy of interventions for improving medication adherence in PD. The search was performed using five online databases and a list of clinical registers to identify all possible trials of adherence interventions in PD. Furthermore, I endeavoured to identify unpublished RCTs through correspondence with all authors named within identified abstracts. Search strings for each of the five databases were extensive and were peer-reviewed by Cochrane methodology specialists. Despite the methodological rigour used to search for relevant RCTs, only one study was identified that met the inclusion criteria. This indicates the paucity of high quality research in this area.

4.4.1 Summary of Main Results

The intervention investigated in the included study consisted of didactic educational material relating to the continuous dopaminergic theory. Of the 83 participants randomised (n=43, active treatment group), only 52 completed the trial (n=23, active treatment group). Grosset and Grosset (2007) showed a statistically significant difference in timing adherence between the two groups, favouring the intervention group. However, clinical outcomes worsened in both groups over the trial period and showed no statistically significant difference between the groups.

4.4.2 Quality of Evidence

The overall risk of bias in the included study was low. The methods for both random sequence generation and allocation concealment were adequately reported and appropriate. The diagnosis of PD was determined using the UK Brain Bank Criteria and MEMS bottles were used to assess medication adherence. Both are reported gold standard methods and therefore the risk of bias regarding these items was low. Only blinding of participants and clinicians to group allocation resulted in a high risk of bias. However, as the intervention was in the form of educational material, blinding of participants and the clinicians providing the intervention was not possible. Therefore, I was not concerned by this risk of bias. Moreover, all clinical assessments at baseline and follow-up were completed by raters masked to group allocation, resulting in a low risk of bias. Therefore, using the method described earlier in table 3.5, this study had a moderate overall risk of bias.

4.4.3 Discussion of Findings

The evidence from this review suggests that providing simple, didactic information relating to the continuous dopaminergic theory is an effective strategy for improving timing adherence in patients with PD. In Chapter 2 I outlined the consequences of medication non-adherence in PD. Good timing adherence is encouraged to promote continuous drug delivery, which may theoretically help to prevent fluctuating motor symptoms and the development of sudden 'off' episodes (Grosset et al., 2005b). However, despite reporting improvements in medication adherence, Grosset and Grosset (2007) were not able to show improvements in either motor symptoms or QoL. Several factors may offer explanation for this.

Firstly, in PD it may be that there is a minimum adherence threshold that must be exceeded before clinical benefit is detected. This has been proposed by researchers investigating adherence in patients with hypertension to explain findings showing improvement in medication adherence but with an absence of clinical improvement (Alhalaiqa et al., 2013b). As the level at which sub-optimal adherence becomes clinically relevant in PD is not known, this may explain, at least in part, why improved medication adherence did not lead to improved symptoms in the study by Grosset and Grosset (2007). For example, at baseline timing adherence was 17% for the active treatment group. This increased to 39% post intervention. Despite the significant improvement observed, this percentage of correct timing of doses may not be sufficient to impact in a clinical context.

Secondly, the findings by Grosset and Grosset (2007) only refer to the effects of improved timing adherence. Although it is more likely that improving timing adherence in PD leads to optimal symptom control, whether improving total daily adherence leads to a greater benefit remains unknown.

Furthermore, unlike many chronic conditions that may require a sustained period of adherence prior to detecting clinical improvement, symptoms of PD can respond quickly to treatment. Therefore, it is surprising that improved timing adherence did not result in improved clinical outcomes. Once again, this may suggest that timing adherence is not as important as overall daily adherence for managing symptoms in PD. This particularly may be the case in less severely affected patients where the specificity for timely pill taking may not always be essential. This may also be relevant in patients who are prescribed a long acting dopamine receptor agonist.

A counter argument could however also be made as the short half-life of levodopa requires regularity in dosing to maintain steady plasma dopamine concentrations. Only in early stages of disease where neuronal degeneration is less severe can doses be missed without significant consequence to symptom control. As the patients in the active treatment group had been diagnosed with PD for over seven years and had moderate disease severity, it is probable that missed dose timings would result in a degree of poor symptom control in some of these patients.

The variability in PD symptoms may also explain the lack of clinical benefit observed by Grosset and Grosset (2007). Even when medication is optimised, patients with PD can experience episodes of poor symptom control. Whilst symptoms may have improved from baseline to 3 month follow-up, the known variability in symptom control in some patients may mask any overall improvements.

This, however, does not explain lower reported QoL, which can improve in PD even when motor symptoms do not change. This is because various non-motor symptoms such as mood are reported to have a greater impact on QoL than motor problems (Martinez-Martin et al., 2011) and have been shown to improve following the use of dopaminergic therapies (Kulisevsky et al., 2000, Poewe and Seppi, 2001, Antonini et al., 2009, Barone et al., 2010).

Another alternative explanation for the lack of clinical improvement shown by Grosset and Grosset (2007) may relate to the adherence assessment employed. Although MEMS caps are the reported gold-standard, there is no guarantee that

patients were taking all of their prescribed medication. It is known that PD patients may omit or increase/decrease drug doses based on perceived illness severity, treatment efficacy and the understanding of the indication for treatment, either accurate or fallacious (Bainbridge and Ruscin, 2009, Grosset, 2010, Drey et al., 2012). Therefore, it is possible that patients could have taken out the pills from the bottle (thus activating the MEMS cap) but then not ingested the medications.

It should be remembered that all participants were aware of the MEMS cap monitoring system, and so such deceitful behaviours may have been induced if participants wished to please the investigators but did not wish to take their medications. This could explain apparent improved adherence rates (according to MEMS readings) but lack of symptom benefit.

A further methodological limitation that may explain the non-significant findings for improvement in symptoms/QoL relates to the small sample. Whilst Grosset and Grosset (2007) conducted a sample size calculation, only 52 participants from the 83 participants randomised completed the trial. This can lead to analyses being underpowered to detect an effect on clinical outcomes (UPDRS & PDQ-39), even if an effect exists. Thus, being underpowered in this manner can result in a type 2 systematic error (i.e. the null hypothesis is accepted when it should be rejected).

4.4.4 Type of Intervention

The intervention investigated by Grosset and Grosset (2007) for improving adherence to medication in PD came under the category of patient education. The

findings reported replicate those from other chronic disease areas. A review by Dunbar-Jacob et al. (1991) reported the benefits of education based interventions for improving medication adherence in patients with hypertension. More recently, however, a large scale Cochrane review in patients with hypertension found that medication adherence did not improve overall after providing educational material relating to correct medication use, hypertensive disease and the potential effects of not medicating (Alhalaiqa et al., 2013b). This finding is consistent with Haynes et al. (2008) who found that even when assuming the largest magnitude of effect of education based interventions in a range of chronic conditions, this did not lead to significant improvements in adherence behaviour.

Despite the positive findings relating to adherence reported by Grosset and Grosset (2007), the large scale systematic reviews in other chronic disease areas propose that education may not be an effective intervention for improving adherence behaviours. However, as information regarding the importance of correct dose timing might be more relevant to patients with PD because of the greater potential for symptom fluctuation, it may be that education is perceived as being more important than in other chronic conditions. This could explain the inconsistency between the review findings and those identified by Grosset and Grosset (2007). Therefore, although the wider evidence suggests that patient education may lack therapeutic effectiveness in chronic conditions, interventions aimed specifically at PD may however be enhanced by the inclusion of educational material.

4.4.5 Alternative Strategies for Enhancing Adherence

Due to the lack of trials identified in the current Cochrane systematic review, it is not possible to determine whether other adherence enhancing interventions would show benefit in PD equal to, or above, the effect detected by Grosset and Grosset (2007) using educational material. Evidence from a review investigating adherence interventions in hypertension showed that behaviourally targeted treatments provide the greatest magnitude of effect for improving adherence behaviour (Alhalaiqa et al., 2013b). Moreover, reviews by Haynes et al. (2008) and Kripalani et al. (2007) showed that complex/combined interventions that explored patient beliefs about treatment were effective for increasing adherence rates across a variety of chronic disease areas.

Simplification of dose regimens is an alternate approach to improving medication adherence that has been shown to be effective in a range of chronic conditions. Connor et al. (2004) showed a positive trend towards enhanced medication adherence and improved clinical outcomes in hypertension, diabetes and medication management in the elderly when fixed-dose and single unit packaging were used. Bangalore et al. (2007) in a meta-analysis revealed that fixed dose combinations decreased the risk of medication non-adherence in patients with either diabetes, HIV, tuberculosis or hypertension.

Furthermore, Dezii et al. (2002) showed that initiation of once-daily medication resulted in better adherence and persistence to treatment compared with twice-daily regimens in patients with diabetes. When considering this evidence and the fact that Grosset and Grosset (2007) found baseline timing adherence to be significantly

better for once-daily drugs than more frequent regimens, it may be that interventions aimed at simplifying dose regimens are also effective in PD. However, as this review did not identify any interventions other than patient education, this remains unknown and thus is worthy of investigation.

The wide variety of factors associated with medication non-adherence in PD presented in Chapter 3 suggests that for some patients education may not be effective as a standalone intervention. Symptoms of depression, complex treatment regimens and poor cognition were factors most highly ranked as being associated with non-adherence in PD. Although educational material was shown to be effective by Grosset and Grosset (2007), it is unlikely that this type of intervention alone will impact positively on adherence in PD patients who have poor problem solving abilities or negative attitudes and beliefs surrounding medication use. It may be, as shown by reviews in other chronic disease areas, that patient centred interventions that explore beliefs and concerns about treatment and that assist in problem solving strategies are also effective in PD patients, especially if supplemented by educational material.

4.4.6 Implications for Research

The paucity of trials identified in this review suggests that studies investigating interventions for improving medication adherence in PD are in need of investigation. Although Grosset and Grosset (2007) showed a significant improvement in adherence after providing simple didactic material, it seems reasonable to suggest that future studies should adopt a tailored approach that

targets individual needs. NICE (2009) and WHO (2003) advocate in their respective guidelines that interventions for improving adherence in chronic conditions should adopt a patient centred, shared decision-making consultation style. These recommendations, coupled with the lack of trials identified in this review, emphasise the need for further RCTs in a PD population.

Furthermore, many of the secondary outcome measures stated earlier in this chapter (i.e. beliefs and attitudes towards medication, carer burden, patient acceptability of interventions and cost analysis) were not investigated by Grosset and Grosset (2007). Although patient education was found to be effective in PD, suggesting that poor knowledge of treatment may be an important factor for non-adherence, negative attitudes and beliefs towards treatment may also be an important reason for non-adherent behaviour. Therefore, it is essential that attitudes and beliefs towards medication are investigated when determining the effectiveness of adherence enhancing interventions in future RCTs.

The findings presented in Chapter 3 showed that living with a spouse/life partner was associated with greater adherence behaviour. As spouse/caregivers can inherit the responsibility of managing a loved one's medication, it is crucial that they are involved when designing interventions aimed at improving medication adherence in PD.

Despite the variety of interventions investigated for improving adherence in other chronic conditions, few researchers have evaluated their interventions. This is important for two reasons. Firstly, it is useful to establish the acceptability of the

treatment from the perspective of the patient. Secondly, by exploring patients'
experiences of the treatment, it may be possible to determine the interventions
mechanism of action. Identifying which components of a treatment are effective,
especially in complex therapies, would represent a valuable insight into both the
reasons for non-adherence and how such interventions can address these issues.

Finally, as with all interventions in healthcare, it is paramount that cost
effectiveness is considered. This is especially important when developing novel
interventions. Although the educational material provided by Grosset and Grosset
(2007) is likely to be of minimal cost to healthcare services, it is important that the
anticipated cost of more complex and time intensive interventions are also
explored.

Part 2

CHAPTER 5

Behaviour Change & Adherence Therapy

5.1 Introduction

In Chapter 3 I presented the findings of a systematic review showing there are a number of demographic and clinical factors associated with medication non-adherence in PD. The results I presented in Chapter 4 revealed that despite non-adherence being prevalent in PD, there are few published studies investigating the efficacy of adherence enhancing interventions. With a greater understanding of factors associated with non-adherence, it therefore seemed essential to develop and test the effectiveness of a novel intervention for improving adherence specifically in a PD population.

In this chapter I discuss the development of Adherence Therapy (AT). First I provide an overview of, and briefly discuss the evidence for, a range of widely reported behaviour change theories applicable to long-term medication adherence. Following this I briefly discuss evidence for the disciplines of Motivational Interviewing (MI) and Cognitive Behavioural Therapy (CBT). Finally, I show how these two disciplines and the described theories of behaviour change led to the development of the PD specific AT intervention.

5.2 Behaviour Change

Adhering to medication in order to manage a chronic condition can represent a considerable behaviour change for many people (Konkle-Parker, 2001). An individual may suddenly be required to take several pills a day for a newly diagnosed condition. Patients who previously took medication infrequently may have to adopt a stricter, more regular pattern of usage as a condition progresses. This is the reality for people with PD. What may have been a simple, relatively burden free course of treatment in early disease stages can develop into a more substantial medication load.

However, despite many people becoming dependent on their medication to remain functional and ambulatory, changing behaviour in order to incorporate medication into daily life is a complex phenomenon that represents a considerable challenge to health initiatives (Prochaska et al., 1993, Haynes et al., 2002b, Munro et al., 2007).

A fundamental principle of learning a new behaviour is that behaviour is determined by the perceived value of the outcome (Bandura, 1977). Therefore, understanding a patient's readiness to change, appreciating barriers to change and helping patients anticipate relapse are likely to be key to facilitating sound medication adherence.

For this reason, repeatedly educating the patient is not always successful (Willey et al., 2000). Promising patients improved health outcomes, particularly in conditions known to be progressive, also does not guarantee motivation for long-term change (Zimmerman et al., 2000). This is even more apparent when the improved outcome (e.g. reduction in dyskinesia) is not considered a priority by the patient.

Relapse during any treatment programme requiring a change in behaviour is essential to acknowledge. However, relapse is sometimes viewed by clinicians as a failure on the part of the patient. Classifying a patient in this manner does not promote self-efficacy and ignores the complexity of the behaviour change process (Zimmerman et al., 2000). Such an approach is therefore not likely to lead to improved rates of adherence.

5.3 Theories of Behaviour Change

Many interventions have been developed to improve medication adherence in chronic conditions. However, the underlying process of many treatment strategies is often not proposed. Currently more than 30 psychological theories of behaviour

change exist, making it difficult to select the most suitable approach when designing interventions for enhancing adherence behaviours (Michie et al., 2005).

Leventhal and Cameron (1987) identified five main theoretical perspectives related to adherence: biomedical, behavioural, communication, cognitive and self-regulatory. However, more recently a stage perspective of adherence has emerged with the Transtheoretical model of behaviour change being most widely reported (Brawley and Culos-Reed, 2000, Redding et al., 2000).

I will now briefly describe the main characteristics of the common theories of behaviour change and provide evidence for their use in interventions to promote long-term medication adherence.

5.3.1 The Biomedical Perspective

In the biomedical theory patients are assumed to be passive recipients of treatment. It is suggested therefore that non-adherence is a result of patient characteristics such as gender and age (Blackwell, 1992). Psycho-social influences and a patient's perspective of their illness or treatment are known to be contributory to poor adherence in chronic conditions (Blackwell, 1992, WHO, 2003). As the biomedical model ignores such factors, for this reason it is infrequently used as a theoretical basis when designing interventions for improving medication adherence.

The review presented in Chapter 3 showed there are a range of factors associated with non-adherence in PD, not just patient demographics. Therefore, due to the

passive assumptions of the biomedical model, it is unlikely to be of use when considering adherence issues in PD.

5.3.2 Behavioural (learning) Theory

This perspective focuses on the environment and the teaching of skills (strategies) to manage adherence (WHO, 2003). The theory is characterised by the use of internal and external antecedents (thoughts and environmental cues) and the consequences of their influence on adherence behaviour (punishment or reward). Figure 5.1 outlines the behavioural perspective diagrammatically.
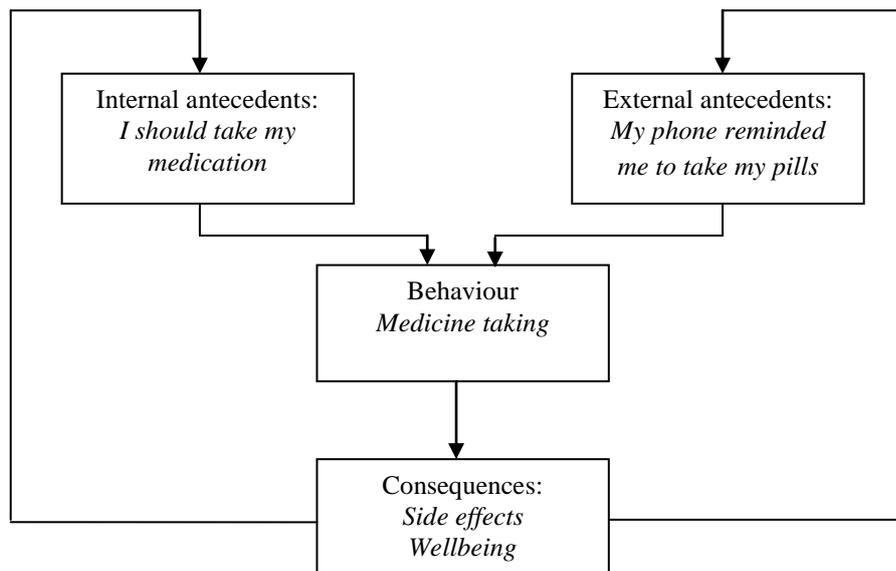
(Source: Munro et al. (2007))

Figure 5. 1 - Behavioural Learning Theory

Interventions incorporating elements of this theory have been shown to be effective for improving medication adherence in chronic conditions (Haynes et al., 2002a). In contrast, however, a meta-analysis by Simoni et al. (2006) found that many approaches derived from the behavioural learning theory, such as dose cueing, were no more effective than interventions not based on this theoretical perspective.

As the findings appear to be inconsistent between studies, it is reasonable to suggest that this model should not be recommended for use as a standalone theory when developing an adherence enhancing intervention. Furthermore, the theories emphasis on immediate reward and its lack of an individualised approach means it is unlikely to be beneficial if used as a foundation for an intervention to promote adherence in PD. This is because PD patients can have unique reasons for non-adhering to treatment which may require a patient centred approach to promoting adherence behaviour.

5.3.3 Communication Perspective

This perspective suggests that improved patient-professional communication will enhance medication adherence and implies that this can be achieved through patient education (WHO, 2003). Interventions aiming to improve patient-professional interaction are often grounded by this perspective.

A number of Cochrane reviews have examined the effects of interventions that include communication focused elements (Lewin et al., 2001, Murray et al., 2005, McKinstry et al., 2006). However, few studies have examined the effects of

communication styles on health behaviours. Reviews that have focused on patient-professional interaction have shown that such interventions can improve both communication in consultations and patient satisfaction (Lewin et al., 2001, McKinstry et al., 2006). However, these reviews also show limited and mixed evidence for the effects of communication based interventions on health behaviours, such as adherence. Furthermore, communication based interventions are unlikely to improve adherence to medication when used in isolation because of the impact of other possible factors such as attitudes towards treatment (Munro et al., 2007).

5.3.4 Cognitive Perspective

The cognitive perspective includes theories such as the health belief model (HBM), social-cognitive theory (SCT), the theories of reasoned action (TRA) and planned behaviour (TPB) and the protection motivation theory (PMT). These theories focus on cognitive variables as part of behaviour change and share the assumption that attitudes and beliefs (Stroebe, 2011) as well as expectations of future outcomes (Gebhardt and Maes, 2001) are major determinants of health behaviours such as adherence. Collectively, these theories suggest that patients will choose the action that will most likely lead to positive outcomes.

These theories have however been criticised because non-voluntary factors such as forgetfulness are not acknowledged to impact on adherence behaviour (Gebhardt and Maes, 2001). Also, researchers have suggested that these theories give little

attention to the origin of negative beliefs and how such beliefs influence health behaviours (Blackwell, 1992).

5.3.4.1 Health Belief Model

The HBM (Figure 5.2) views behaviour change as being based on a balance between the barriers to, and benefits of, a given action (Blackwell, 1992). In this model, perceived benefits and barriers of a given health behaviour (e.g. adherence) influence a patients perception of the effectiveness of the behaviour change.

Perceived susceptibility: *No disease in my family*		

| Perceived severity: *PD is a fatal disease* | Belief in a personal health threat: *I'll get over it* | |

| | | Health Behaviour (adherence): *If it gets worse I will take the medication* |

| Perceived benefit: *The medication will make me better* | | |

| Perceived barrier: *I may experience side effects* | Belief in the effectiveness of health behaviour: *I'm not sure if it will work* | |
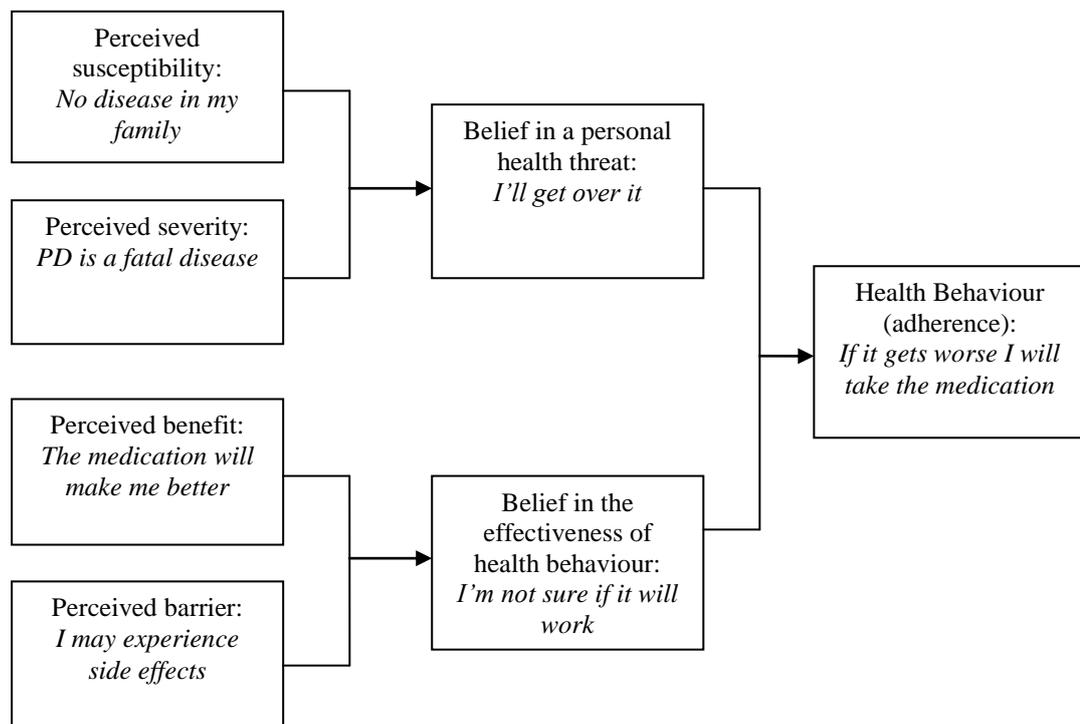
(Source: adapted from Stroebe and De Wit (1996))

Figure 5. 2 - The Health Belief Model

Generally, all of the model's components are seen as independent predictors of health behaviour (Armitage and Conner, 2000). Bandura (1997), however, suggests

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that perceived threats, especially perceived severity, have a weak correlation with health action. Recently self-efficacy was added into the theory. This incorporates the need to feel competent to engage in health behaviours for long-term change to be successful (Strecher and Rosenstock, 1997).

As with the previously described models, the HBM also has received criticism. Firstly, it is assumed that the variables do not moderate each other to produce an added effect. For example, if perceived seriousness is high but susceptibility is low, it is assumed that the likelihood of engaging in a particular health behaviour remains high. However, if both are high, it is unclear how this would affect the uptake of a new health behaviour (Stroebe and De Wit, 1996). In addition, some behaviour is based on habit rather than an active decision which this model fails to account for.

When applying this model to adherence interventions, it is suggested that the influence of social-psychological factors are considered. For example, beliefs and stigma regarding disease or its associated treatment may reduce an adherence intervention's effectiveness if psychological factors are not acknowledged (Harrison et al., 1992).

5.3.4.2 The Protection-Motivation Theory

According to the PMT theory, behaviour change may be achieved by focusing on an individual's fears. The magnitude of harm, the probability of the perceived harm occurring and the efficacy of the protective mechanism (e.g. medication) against

harm are all factors inherent in this model (Figure 5.3) (Rogers, 1975). These three factors are proposed to combine to determine the motivation to engage in preventative behaviour (e.g. medication adherence).
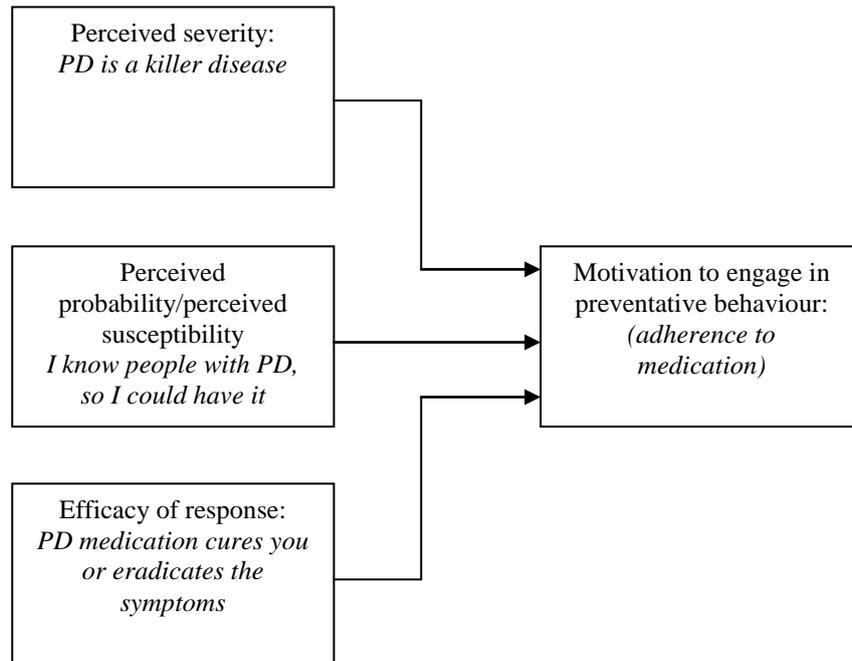
(Source: adapted from Rogers (1975))

Figure 5. 3 - Protection Motivation Theory

A meta-analysis examining interventions based on this theory found only moderate effects on behaviour (Floyd et al., 2000). This may relate to the fact that this model does not recognise environmental and cognitive factors as impacting significantly on adherence behaviour. Despite this, the model may be appropriate for adherence enhancing interventions in some patients with PD. For example, it is unlikely that patients routinely and consciously evaluate their medication taking practices (Munro et al., 2007). Therefore, acknowledging that improved adherence may lead

to improved symptoms could result in greater motivation to engage in optimal adherence behaviours.

5.3.4.3 Social-Cognitive Theory

This theory evolved from social learning theory and has been suggested to be the most comprehensive theory of behavioural change (Figure 5.4) (Redding et al., 2000). The theory proposes a causal relationship between motivation, action and wellbeing and provides possible predictors of adherence and guidelines for adherence promotion (Bandura, 1997, Bandura, 1998).

(Source: adapted from Munro et al. (2007))

Figure 5. 4 - Social-Cognitive Theory

Social-cognitive theory suggests that while knowledge of health risks and benefits are a requirement for change, additional self-influences are also necessary for change to occur (Bandura, 1998). Self-efficacy is one such influence.

Keller and colleagues (1999) reported that improved self-efficacy could explain between 4% and 26% of the variance in health behaviour. However, this was limited to studies of exercise behaviour and did not consider adherence to medication. Despite this, due to the models focus on self-efficacy, acknowledgement of the barriers and facilitators to change and knowledge of the benefits to change, it is possible that elements of this model will be effective as part of an adherence enhancing treatment.

5.3.4.4 Theory of Reasoned Action and Planned Behaviour

The TRA suggests behaviour change relates predominantly to intentions (Figure 5.5). In this theory intention to act is reported to be the single best predictor of performing a particular health behaviour (Sutton, 1997). Advocates further propose that intention to change behaviour is influenced significantly by attitudes towards the action. This includes beliefs about the value of the health outcome (e.g. improved adherence). Performing the health behaviour is also allegedly influenced by the perceived expectations of significant others (e.g. family members) (Fishbein and Ajzen, 1975).

```
┌─────────────────────────┐
│ Beliefs about the outcome of │
│ the behaviour:          │
│ If I take the medication I will be │
│ healthy                 │
└─────────────────────────┘

┌─────────────────────────┐
│ Evaluation of expected   │
│ outcomes:               │
│ Feeling better is good  │
└─────────────────────────┘

┌─────────────────────────┐
│ Normative beliefs:       │
│ Family and friends want me to │
│ take the pills          │
└─────────────────────────┘

┌─────────────────────────┐
│ Motivation to comply:    │
│ I want to do what they want me │
│ to do                   │
└─────────────────────────┘

┌─────────────────────────┐
│ Control beliefs:         │
│ Remembering the medication │
│ will be difficult       │
└─────────────────────────┘
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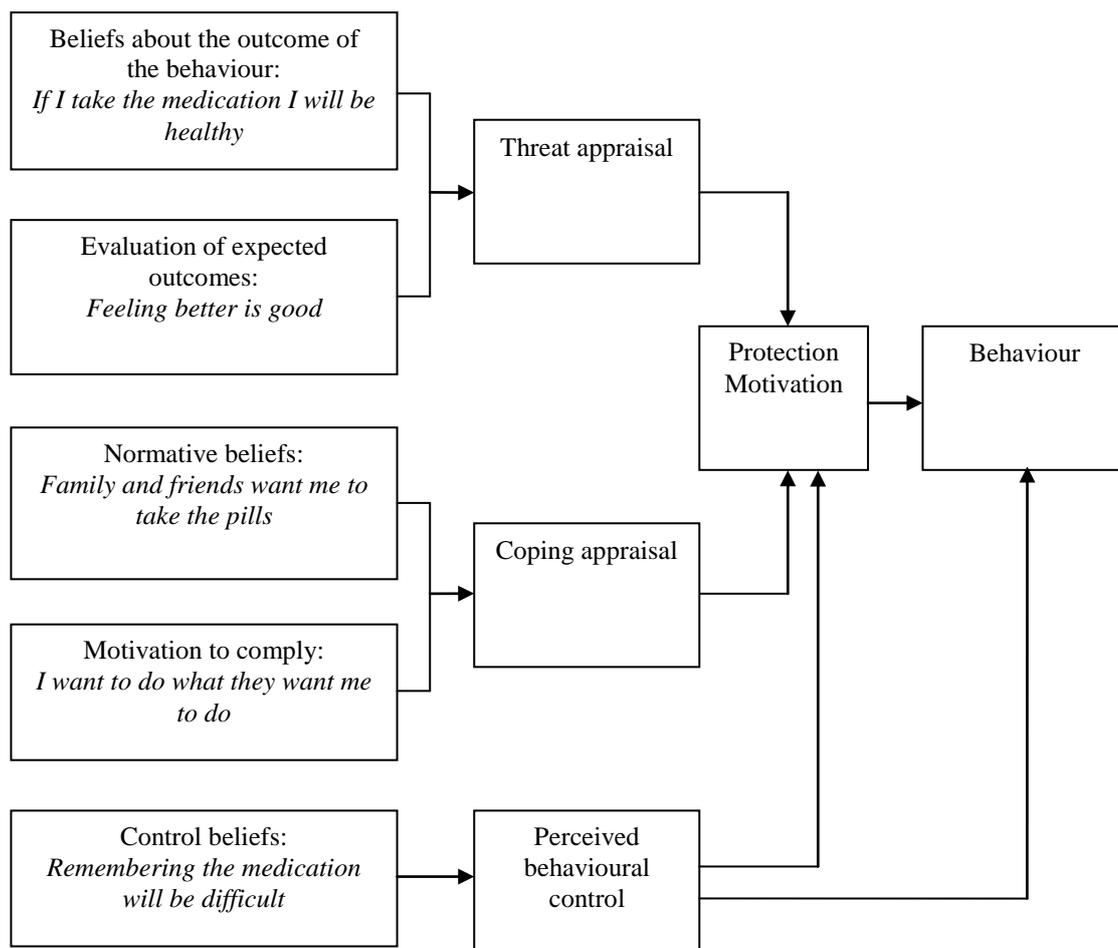
(Source: adapted from Stroebe and De Wit (1996))

Figure 5. 5 - Theory of Reasoned Action

A limitation of the TRA was that it failed to acknowledge behaviour as being unintentional. The authors therefore extended the model to include behavioural control (shown in Figure 5.5), and re-named the model as the theory of planned behaviour (TPB). According to the authors, behavioural control represents the perceived ease or difficulty of performing the health behaviour, and that this behavioural decision relates to beliefs (Sutton, 1997). Conceptually, this theory is similar to self-efficacy.

Meta-analyses examining the efficacy of various components of the theory have found inconsistent results (Godin and Kok, 1996, Armitage and Conner, 2001, Hardeman et al., 2002). Although not conclusive, the results of the separate analyses do show some positive effects on adherence behaviours. This suggests that the theory may be of benefit when designing interventions to improve adherence to medication. However, a limitation of this perspective is that it is based largely on rational processes and does not allow for alternative factors such as emotions/mood (Mullen et al., 1987). As mood disorders are known to be associated with non-adherence in chronic illness, particularly in PD as reported in Chapter 3, it is likely that this model requires some flexibility if adherence promoting treatments are to be successful.

5.3.4.5 Information-Motivation-Behavioural Skills (IMB) Theory

The IMB theory focuses on three components that result in behaviour change: information, motivation and behaviour skills. Information relates to basic knowledge about an illness and is an essential prerequisite for behaviour change in this theory (Fisher and Fisher, 1992). An intervention based on this approach would therefore target a patient's gap in knowledge. The second component, motivation, results from personal attitude towards adherence. Finally, behavioural skills include factors such as ensuring patients have the strategies and tools necessary to perform the health behaviour (Fisher and Fisher, 1992). As with previously described models, self-efficacy is also a key component of this theory (Figure 5.6).
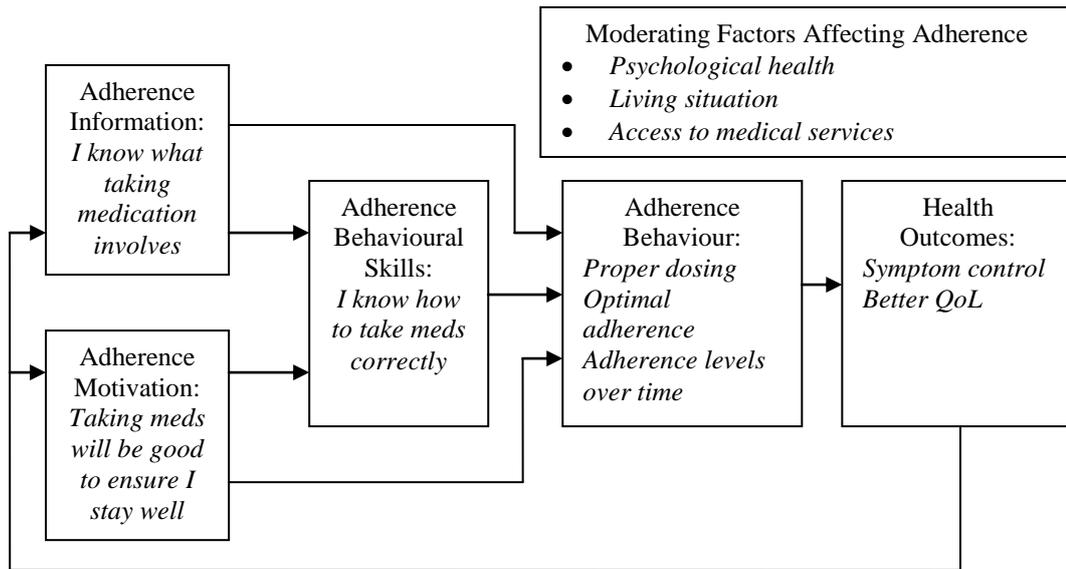
(Source: adapted from Fisher et al. (2006))

Figure 5. 6 - Information-Motivation-Behavioural Skills Model

In this model, information and motivation are thought to activate behavioural skills, which in turn result in behavioural change (Fisher et al., 2006). Although this theory has not been evaluated as part of a meta-analysis, researchers have shown the model to be effective in promoting behaviour change in chronic illness (Amico et al., 2005). As this simple, generalisable model has been shown to be effective in changing adherence behaviour, it may also be effective if used in an intervention aimed at non-adherent patients with PD.

5.3.5 The Transtheoretical Model (TTM)

This theory, established by Prochaska and DiClemente (1992), is the most prominent amongst the stage perspectives of health change (Figure 5.7). The authors propose a number of discrete stages of change and reasons that people move through these stages, typically relapsing before achieving success (Prochaska and DiClemente, 1992, Prochaska et al., 1993).
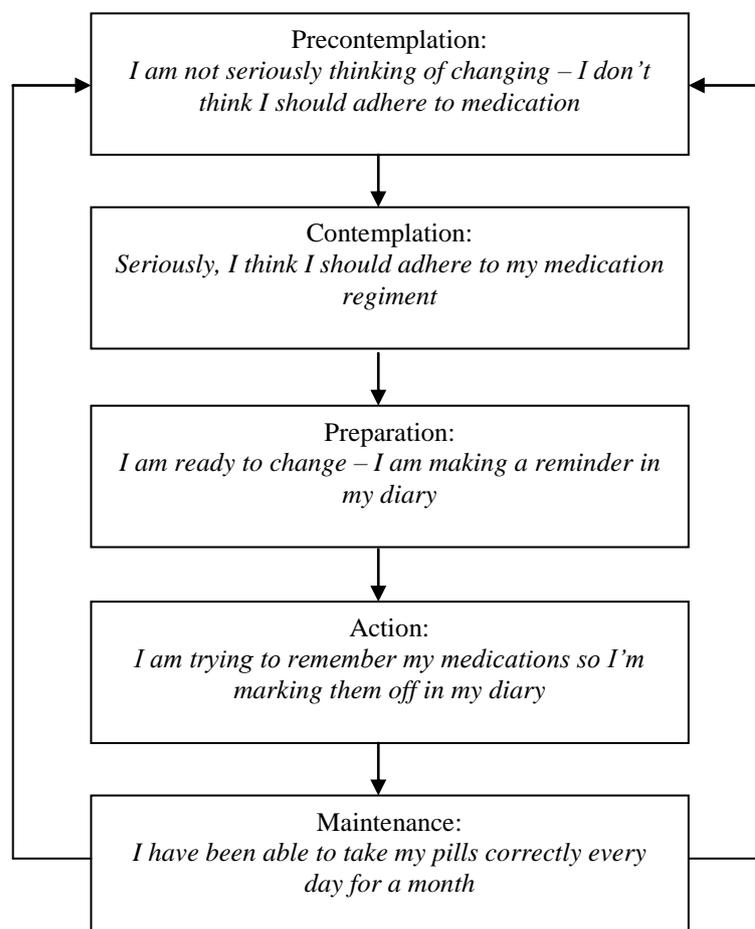
(Source: adapted from Munro et al. (2007))

Figure 5. 7 - The Transtheoretical Model (Stages of Change)

Crucially, healthcare professionals may be able to encourage change by identifying where a patient is in relation to the model (Zimmerman et al., 2000). With such knowledge, specifically targeted, stage dependent interventions may be useful for facilitating progression through the various stages of change.

Criticisms of the TTM include the stages postulated and their coverage and definitions. Specifically, Bandura (1998) argues that behaviour change is too multifaceted to fit into discrete stages and that to do so would constrain adherence promoting treatments. Additionally, the TTM provides little information concerning the mechanism of change or why some individuals relapse (Armitage and Conner, 2000).

A meta-analysis did not show support for this theory (Marshall and Biddle, 2001). However, this was used to promote adherence to exercise and not medication specifically. Whilst little evidence exists to support this theory for promoting medication adherence specifically, the model does allow interventions to be tailored to individual needs by identifying which stage of change a patient is in.

5.3.5.1 Related Constructs to the TTM

Decision-making and self-efficacy are constructs closely related to the TTM. Both have been proposed to be central to the process of behaviour change (Bandura, 1977, Rosenstock et al., 1988, Buchmann, 1997). Decision-making involves consideration of the potential benefits and losses before arriving at and maintaining a decision.

Theoretically, as people progress through the stages, the gap between perceived pros and cons reduces. Therefore, by identifying the positives and negatives to taking medication, therapists may be able to assist in decision-making which may lead to improved adherence (Konkle-Parker, 2001).

A second concept closely related to the TTM is that of self-efficacy. Once a patient decides to take medication, doubt about their ability to adhere may represent an underlying barrier to change (Willey et al., 2000). Therefore, enhancing self-efficacy may facilitate transition through the stages of behaviour change. Prochaska and DiClemente (1992) showed self-efficacy to be a positive predictor of successful progression into the action and maintenance stage in patients with affective disorders. As self-efficacy was not found to be a predictor of progression in early TTM stages, this may suggest that decision-making is more important in patients identified in these stages.

5.4 Summary of Behaviour Change Theories

Although there are many theories that can be used when developing interventions to improve medication adherence, there is limited evidence that facilitates a direct comparison of the perspectives. Researchers developing interventions may therefore be overwhelmed by the multiplicity of theories for which there is often limited evidence. There are also questions regarding the applicability of the theories outside of the context from which they were developed.

For example, health behaviour change theories have tended to encompass a wide range of health behaviours. Reviews have included papers ranging from smoking cessation to dietary adherence. It may therefore be the case that certain theories are more applicable to specific health behaviours. Furthermore, few studies have examined health behaviour theories in relation to long-term medication adherence. Therefore, it is unclear whether such theories may actually be useful when developing treatments aimed specifically at medication adherence in chronic conditions.

The application of theories to the design of adherence promoting interventions remains a challenge. Moreover, there is considerable debate regarding whether such theories are likely to be effective in informing intervention development (Eccles et al., 2005, Oxman et al., 2005). Despite the various theories, there is no clear evidence in favour of either perspective within the field of medication adherence. However, this does not mean that behaviour change theories are not useful. It may be possible to acknowledge the benefits of a variety of theories and incorporate them into a more flexible, pragmatic intervention.

In the next part of this chapter I focus on interventions as opposed to basic psychological theory. Specifically, I briefly outline the characteristics and evidence for the Motivational Interviewing (MI) approach and the discipline of Cognitive Behavioural Therapy (CBT) in relation to treatment adherence.

5.5 The Motivational Interviewing Technique

Motivational interviewing is tool for facilitating behaviour change. The approach places power in the hands of the patient by encouraging a patient focused consultation style. The technique aims to assist in resolving ambivalence by changing beliefs about medication (Miller and Rollnick, 1991). Since medication adherence is a complex behaviour, this patient-centred approach may be useful for facilitating improved medication adherence (Konkle-Parker, 2001). Five basic principles central to the therapist-patient interaction in MI are outlined in Table 5.1.

Table 5. 1 - Key Principles in Motivational Interviewing

Fundamental Principle	Description
1. Expressing empathy	Demonstrating an understanding of ambivalence towards medication adherence. It must be made apparent that ambivalence is entirely justified.
2. Developing discrepancy	Eliciting the patient's goals for medication use and encouraging the individual to recognise that non-adherence is not contributing towards meeting the goals.
3. Avoiding argument	The therapist must not be confrontational or the individual will be in a position to defend their non-adherence, which can strengthen the behaviour.
4. Rolling with resistance	Allow patients to take personal responsibility for change and help patients develop a number of alternative change options in order to allow them to begin solving their own problems.
5. Supporting self-efficacy	Supporting patients in the successes that they have experienced, no matter how small, and providing encouragement for further success. This assists individuals in believing that they can successfully perform the behaviour in question.

Practitioners of MI attempt to motivate patients rather than attempting to persuade them that change is necessary. One important differentiating factor is maintaining the focus of the interview on the individual and their expressed needs, not on the health problems or the clinical symptoms that most trouble the professional (Rollnick et al., 1992, Konkle-Parker, 2001).

Firstly, the therapist accepts and explores a patient's ambivalence to adhering to treatment, understanding that acknowledgement of the diagnosis or the debilitating symptoms associated with the condition are not sufficient for some individuals to be motivated to change.

The therapist and the patient then work collaboratively to arrive at a shared goal and work to resolve barriers that may inhibit progression. For this to occur, open-ended questions and reflective listening are critical. This allows a patient to see the benefits of change while avoiding commanding dialogue.

A strength of the approach is that it can be used alongside behaviour change theories. For example, for patients in the precontemplation stage of the TTM a decision balance sheet may be an effective strategy by listing the 'good things' and the 'not so good things' to taking medication (Armer and Miller, 2000).

For contemplators within the TTM who are ambivalent to change, identifying discrepancies between the patient's goals and the non-adherent behaviour may be an effective strategy for promoting adherence. For example, if a PD patient's goal is to remain ambulatory throughout a child's infancy, medication non-adherence

may not facilitate this goal. Problem solving strategies may also be crucial when discussing ways in which the patient can adhere to their treatment regimen.

5.5.1 Evidence for Motivational Interviewing

Unlike the psychological theories described earlier in this chapter, MI has been shown to be effective for achieving behaviour change (Dunn et al., 2001). A systematic review by Knight et al. (2006) showed MI improved psychological, physiological and life-style change outcomes in patients with diabetes, asthma, hypertension and heart disease. A meta-analysis by Rubak et al. (2005) showed a significant effect of MI in 75% of studies targeting treatment for patients with alcohol abuse, psychiatric problems and substance addiction. Furthermore, a positive effect in 72% of studies using MI to target weight loss, hyperlipidaemia, physical activity and smoking cessation was also observed. These findings provide evidence of the effectiveness of MI for achieving successful change in a wide variety of behaviours.

Despite the positive effects of MI in the general adherence literature, limited published information is available evaluating the use of MI for improving adherence to medication. A RCT in patients with asthma found those who received MI were significantly more likely to show an increased level of readiness to adhere to medication over time (Schmaling et al., 2001). Furthermore, in patients with psychiatric illness, MI significantly improved adherence to outpatient appointments (Swanson et al., 1999).

A small RCT of 21 patients with schizophrenia found that patients who received MI improved more in their attitudes towards medication than a control group (Hayward, 1995). Moreover, Ogedegbe et al. (2008) showed that the use of MI in patients with hypertension resulted in the maintenance of medication adherence over time compared to a significant decline in adherence for people in a control group. This difference in adherence was reported to have led to a modest, but non-significant, reduction of blood pressure in favour of the active treatment group.

Although many of the psychological theories do not show consistent effects on behaviour change, MI does have supporting evidence for improving adherence behaviour. Furthermore, although there is limited evidence, studies do show that MI may be beneficial if used as the basis for interventions to improve adherence to medication.

I will now briefly outline the fundamental characteristics of cognitive-behavioural therapy and provide evidence for its use in promoting adherence to medication.

5.6 Cognitive-Behavioural Therapy

Cognitive Behavioural Therapy (CBT) is a psychotherapeutic approach that aims to address dysfunctional emotions and cognitive processes. This technique acknowledges that there may be behaviours that cannot be controlled through rational thought. CBT therefore is problem focused (undertaken for specific

problems) and action oriented (a therapist tries to assist the patient in selecting specific strategies to help address those problems) (Schacter et al., 2010).

The cognitive model that CBT therapists use describes how perceptions of, or spontaneous thoughts about, situations influence emotional and behavioural reactions (Hayes et al., 2011). Individuals' perceptions are often distorted when subjected to distress. CBT therapists therefore attempt to identify and evaluate a patient's dysfunctional thinking so that it more closely resembles reality. Theoretically, when successful, distress decreases and individuals are able to function optimally (Hofmann, 2011).

The goal of CBT is to help individuals achieve a remission of their disorder and to prevent relapse. Much of the work in sessions involves aiding individuals to solve their own problems by teaching them to modify their distorted thinking and dysfunctional behaviour (Driessen and Hollon, 2010).

5.6.1 Evidence for Cognitive Behavioural Therapy

Cognitive behavioural therapy has demonstrated efficacy in the treatment of a wide variety of psychiatric disorders such as mood, anxiety, personality, eating, substance abuse and psychotic disorders. Furthermore, CBT has also been shown to be effective as an adjunctive treatment to medication in many conditions such as irritable bowel syndrome, hypertension, fibromyalgia, cancer, diabetes, migraine and other chronic pain disorders.

In spite of its proven effectiveness, little attention has focused on the use of CBT specifically for improving adherence to medication. Parsons et al. (2005) evaluated the combined effect of CBT and MI in patients' non-adherent to antiretroviral medication. Findings showed there was a significant reduction in substance use from pre-treatment to post-treatment with the combined therapy. However, despite positive trends, no statistically significant differences were found for changes in medication adherence.

Safren et al. (2009) showed that patients with Human Immunodeficiency Virus (HIV) who received CBT significantly improved in medication adherence and depression compared to a control group. Furthermore, those originally in the control group who chose to cross over to CBT showed similar improvements in both depression and adherence outcomes.

Due to the paucity of research investigating the efficacy of CBT for improving adherence to medication, it is difficult to appropriately evaluate the intervention. Despite the lack of evidence however, it is reasonable to suggest that CBT techniques may be effective for improving medication adherence in a PD sample.

The findings reported in Chapter 3 showed that both cognitive impairment and treatment regimen complexity are associated with poor medication adherence in PD. Problem solving is a cognitive domain that is known to be affected in many patients with PD (Cronin-Golomb et al., 1994). As CBT has been shown to be effective for assisting patients to problem solve, applying the approach to problem solving medication use in PD may be an effective strategy.

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5.7 A Need for Adherence Therapy

The World Health Organization (2003) and the National Institute for Health and Care Excellence (2009) in their respective guidelines on adherence encourage the use of an individualised consultation style that recognises patient involvement in treatment decisions as an integral process for facilitating improved adherence. A focus on exploring beliefs about illness and disease management, in addition to the transference of specific information from professional to patient, are also strongly advocated.

As outlined earlier in this chapter, many authors propose that the efficacy of adherence enhancing interventions may be optimised by using theory from behaviour change models (Lyons, 1997). However, as the evidence suggests, no single approach has been able to show consistent improvements in adherence behaviour. Many theories also have not been tested specifically in relation to medication non-adherence. However, as self-efficacy is a component of many behavioural change theories, this may suggest it is fundamental to improving adherence behaviour.

Motivational interviewing and CBT have been shown to provide benefit for improving adherence to medication. It is therefore likely that an intervention that conforms to the principles of these disciplines may be beneficial for improving adherence to medication in PD.

Factors associated with medication non-adherence in PD can be extensive and patient specific, as identified in Chapter 3. Therefore, administering an adherence promoting intervention that fails to acknowledge the factors associated with suboptimal adherence is unlikely to be effective. By recognising the factors that may lead to poor adherence, it is possible to target appropriate interventions to help enhance adherence behaviour in PD.

In summary, a therapy that uses MI and CBT techniques as a framework, recognises the importance of self-efficacy and acknowledges disease specific factors for non-adherence may likely lead to improvement in medication adherence. Adherence Therapy (AT) is one such intervention. I therefore used the core concepts of AT to develop a novel, patient-centred therapy specifically tailored to addressing medication non-adherence in people with PD.

In the remaining part of this chapter I will outline the characteristics of AT and report the findings of various RCTs evaluating the intervention in other disease areas.

5.8 Adherence Therapy

Adherence Therapy is a brief, person centred cognitive–behavioural approach aimed at facilitating a process of shared decision making where both therapist and patient work towards agreed goals (Gray, 2011). The fundamental principle is that when patients make shared choices with a professional they are more likely to continue with those choices because they are personally owned and meaningful (Gray et al., 2010).

5.8.1 Cornerstones of Adherence Therapy

Adherence Therapy utilises four key foundation skills that therapists employ throughout the patient-therapist encounter:

1. Engagement - focusing on the personally relevant benefit to treatment
The aim is to keep the patient engaged in talking about medication use. Focusing on the personally relevant benefit to medication and using a Socratic questioning style are essential for engagement in order to encourage patient reflection and an open dialogue.

2. Dealing with Resistance
Patients will not consider different perspectives or change their behaviour if there is tension in the relationship between the therapist and the patient. The aim therefore is to keep resistance low by working alongside the patient.

3. Exchanging Information

Exchanging information by using an elicit–provide–elicit model affords the provision of individually tailored information; that is, what does the patient want to know - provide the factual information the patient seeks - ask how the information has affected the patient's thought process.

4. Developing Discrepancies

The aim is to gently draw the patient's attention to inconsistencies (discrepancies) in their beliefs and attitudes about medication and illness. For example, asking the patient to consider and reflect on how they justify their position on medication use can facilitate this process without being challenging and confrontational to their perspective.

5.8.2 Adherence Assessment

The aim of the adherence assessment is to understand illness and treatment from the patient's perspective. Vital to the assessment is the exploration of the patient's perceived 'importance' of taking, 'confidence' in sticking to, and overall 'satisfaction' with their medication. Each of these domains is rated on a 1–10 (low–high) scale.

The ratings on these scores guide the rest of the therapy process. For example, if a patient thinks that medication is very important and is willing to take it, but is not confident because of forgetfulness, then AT exercises such as problem solving are likely to be indicated. Alternatively, if a patient has confidence in taking

medication, but does not think it is important, therapy can be directed at exercises that might increase perceived importance (such as exploring ambivalence). Re-rating these three items (allowing patients to recognise small but meaningful improvements) occurs throughout the therapy process as a tool to encourage Socratic dialogue and promote self-efficacy.

5.8.3 Key Adherence Therapy Exercises

The intervention is delivered using a combination of five key exercises that form the core of the therapy:

1. Structured Medication Problem Solving

The aim is to develop the patient's ability to sort out practical problems with medication for themselves by following a structured template. Problems may include strategies to cope with medication side-effects or approaches to facilitate improved memory regarding pill taking.

2. Looking Back

This helps the patient to review past experiences of illness and treatment and reflect on the effects of medication (both good and not so good). The aim is to help the patient learn from the past to plan for the future.

3. Exploring Ambivalence

By considering the 'good and not so good' aspects of not taking and the 'good and not so good' aspects of taking medication, the aim of this exercise is to help

patients explore, reflect and consider their natural ambivalence (uncertainty) toward taking medication.

4. Talking About Beliefs and Concerns

The aim is to 'test out' commonly held beliefs about medication (e.g. 'I can fight this without medication' and 'it is unnatural to take medicines'). One at a time, beliefs are rated on a conviction scale (0–100%). The evidence for and against the belief is then considered and discussed. The belief is then re-rated using the conviction scale.

5. Looking Forward

This exercise seeks to help the patient consider their future goals (short or long-term) and the role that medication might play in facilitating such goals.

This phased and layered package of foundation skills and key interventions, developed on the underlying principles of MI and CBT, form the AT intervention under investigation in this thesis. The therapy can be represented diagrammatically, as shown in Figure 5.8. The adaptability of the approach has resulted in a comprehensive programme capable of being tailored according to individual need, in conjunction with NICE guidelines (2009). The Adherence Therapy manual from which the intervention was developed can be requested from Professor Richard Gray (Richard.gray@uwe.ac.uk).
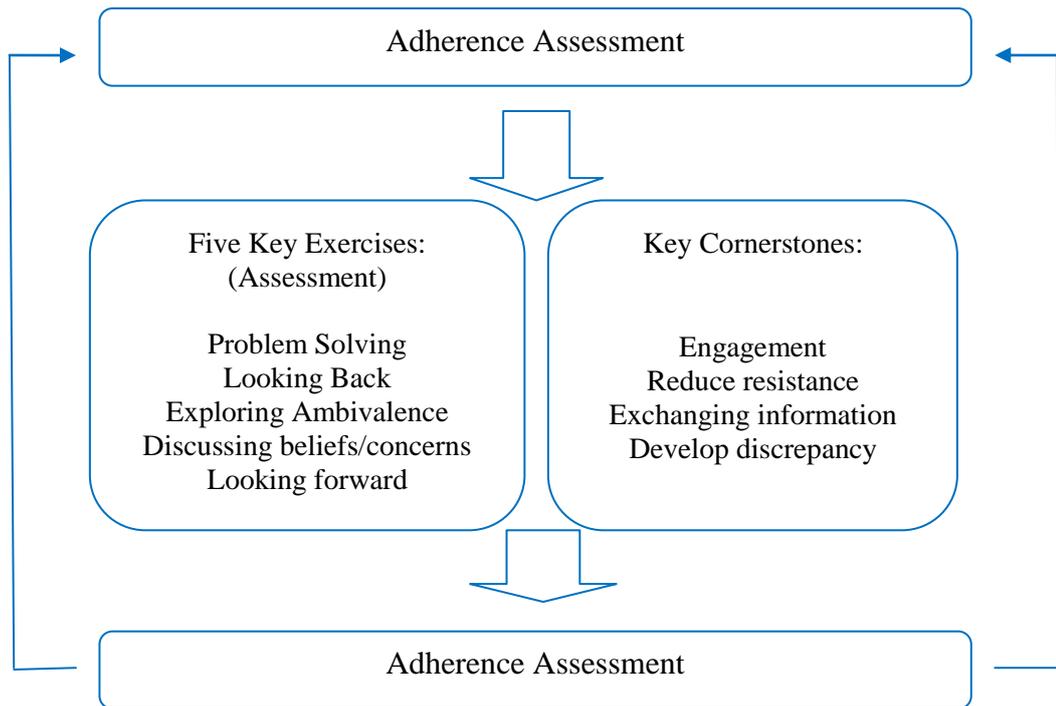
Figure 5. 8 - Adherence Therapy Model

5.9 Evidence for Adherence Therapy

To date, a number of RCTs have been conducted to evaluate the efficacy of AT for improving medication adherence and illness specific symptoms (Table 5.2). Of these trials, eight demonstrated that AT approaches were effective for improving medication adherence (Kemp et al., 1996, Kemp et al., 1998, Gray et al., 2004, Wong et al., 2005, Maneesakorn et al., 2007, Staring et al., 2010, Alhalaiqa et al., 2011, Cavezza et al., 2013). Despite the statistically significant improvements in medication adherence reported in these trials, five studies were unable to replicate the positive findings (O'Donnell et al., 2003, Byerly et al., 2005, Gray et al., 2006, Anderson et al., 2010, Schulz et al., 2013).

Table 5. 2 - Adherence Therapy Trials

Author	n	Patient population	Treatments		Primary Outcome	Follow-up (months)	Statistically Significant effect on adherence	Effect Size or mean difference reported
Kemp et al. (1996)	47	Psychosis	NSC	CT	Compliance	6	Yes	OR = 5.2
Kemp et al. (1998)	74	Psychotic disorders	NSC	CT	Compliance	18	Yes	19%*
Cavezza et al. (2013)	48	Psychotic illness	HE	AT	Psychopathology & adherence	End of therapy	Yes	not reported
Gray et al. (2004)	72	Schizophrenia	TAU	MM	Psychotic symptoms	6	Yes	17.79*
O'Donnell et al. (2003)	56	Schizophrenia	NSC	CT	Compliance	12	No	-
Byerly et al. (2005)	30	Schizophrenia	NR	CT	Compliance	6	No	-
Gray et al. (2006)	409	Schizophrenia	HE	AT	Quality of life	12	No	-
Maneesakorn et al. (2007)	32	Schizophrenia	TAU	AT	Psychotic symptoms	2	Yes	14.00, RR 2.29
Anderson et al. (2010)	26	Schizophrenia	TAU	AT	Psychotic symptoms	End of therapy	No	-
Staring et al. (2010)	109	Schizophrenia	TAU	AT	Service engagement & adherence	12	Yes	0.43†
Schulz et al. (2013)	137	Schizophrenia	TAU	AT	Adherence	3	No	-
Wong et al. (2005)	78	Diabetes	TAU	AT	Blood monitoring adherence	6	Yes	1.8*
Alhalaiqa et al. (2011)	136	Hypertension	TAU	AT	Systolic blood pressure	3	Yes	21.6*

RCT: Randomised Controlled Trial; AT: Adherence Therapy; CT: Compliance Therapy; TAU: Treatment as Usual; MM: Medication Management Training; HE: Health Education; NSC: Non-specific Counselling; NR: Not Reported

*= mean between group difference post intervention; RR= risk ratio; †= Cohen's effect size

Although some trials have not been successful in improving medication adherence after providing a form of AT, the positive findings do outweigh the negatives. This suggests that adherence enhancing interventions of this type may be beneficial for improving medication adherence in a range of chronic conditions.

Of the 13 RCTs evaluating the efficacy of AT interventions, 11 investigated its use in patients with psychiatric conditions. Most of these trials were based specifically in patients with schizophrenia. Interestingly, all five studies that failed to improve adherence to medication had evaluated the effectiveness of AT in patients with schizophrenia. In both trials where study participants were not diagnosed with a psychiatric illness (i.e. patients with diabetes or hypertension), adherence to medication improved significantly.

Although some studies report improvements in medication adherence following AT in patients with schizophrenia (Maneesakorn et al., 2007, Staring et al., 2010), the negative findings of most RCTs in this population suggests that brief interventions like AT may not be beneficial for such patients. This is not surprising considering that the characteristic symptoms of schizophrenia (e.g. paranoia) are known to be associated with poor medication adherence (Fenton et al., 1997).

Gray et al. (2006) conducted the largest trial of AT in which 409 patients with schizophrenia were randomised. As this trial recruited the most patients of all AT studies but did not identify significant improvements in medication adherence, this may suggest that AT lacks efficacy in patients with schizophrenia. However, an alternative explanation may explain the non-significant results. In this study non-

adherence to medication was not assessed prior to patients being recruited and subsequently randomised. Therefore, the inclusion of potentially medication adherent patients would act to dilute the therapeutic effect of the AT intervention. Had non-adherence to medication been part of the inclusion criteria in this large scale RCT, the true effect of AT may have resulted in a significant improvement in medication adherence.

Despite the inconclusive findings in patients with schizophrenia, it is encouraging that medication adherence improved significantly in patients with diabetes and hypertension. It is likely that the reasons for non-adherence in these populations differ greatly from patients with psychiatric conditions and this may explain the positive findings identified in these studies.

The findings presented in Chapter 3 showed the main factors that are associated with non-adherence in PD. With this knowledge, and considering that AT has been shown to be effective in chronic conditions, it is possible that the intervention may also be beneficial in PD.

To establish the efficacy of AT for improving medication adherence in PD, a well-designed RCT is required. In the next chapter of this thesis I outline the design and methods of a RCT to test whether PD patients who receive a programme of AT significantly improve in medication adherence and QoL compared to PD patients who receive only usual care.

CHAPTER 6

Methodology

6.1 Introduction

In Chapter 5 I outlined the development of, and evidence for, the AT intervention. In this chapter I describe the methods used for evaluating the effectiveness of AT in PD. Specifically, I outline the study design adopted; that is, a randomised controlled trial and provide justification for using this methodological approach. I then provide a detailed description of the study methods and analytical processes. Finally, ethical considerations are discussed in relation to the clinical trial.

6.2 The Randomised Controlled Trial

Randomised controlled trials (RCTs) are a quantitative methodology in which study participants are randomly assigned to one of two or more clinical interventions (Borenstein et al., 2009). The RCT is the most scientifically rigorous method of hypothesis testing available and is regarded as the gold standard design for evaluating treatment effectiveness (Akobeng, 2005). The basic structure of a RCT is presented in Figure 6.1.
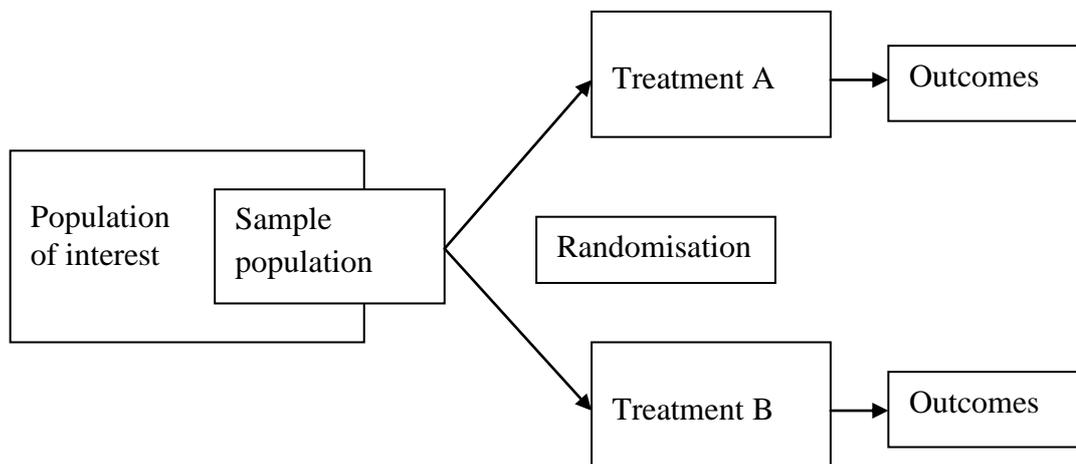
Figure 6. 1 - The Basic Structure of a RCT

A representative sample of the target population is randomly assigned to the active treatment/experimental group (participants receiving the intervention of interest) or a control group (participants receiving usual best practice care). Apart from one group receiving the experimental treatment, the two groups are treated and observed in an identical manner. All participants' complete measurements or observations at the start of the trial (baseline) before being randomised. At the end

of the study (a pre-defined time point), the measurements of interest are completed again by each group and are analysed. In most RCTs the analysis compares outcomes between groups from baseline to follow-up to establish whether a statistically significant difference exists. All outcomes and analytical methods are also pre-defined at the study outset (Akobeng, 2005).

6.2.1 Advantages of the Randomised Controlled Trial

There are many advantages to the RCT research design. The main benefit that randomisation provides is to prevent selection bias and the effect of confounding. These are prevented by evenly distributing the characteristics of patients at baseline that may influence the study outcome. By this means, any difference in the outcomes at study follow-up should be a consequence of the intervention only (Borenstein et al., 2009). Randomisation therefore makes it more likely that there will be an even balance of characteristics between groups with regards to both known and unknown factors (e.g. age, disease severity and duration, medication load).

6.2.2 Randomisation

Randomisation refers to the practice of assigning participants to experimental or control groups at random, such that each participant has an equal chance of being placed in either condition (Evans, 2003, Akobeng, 2005). As previously stated, the main purpose to randomisation is to eliminate selection bias and balance both the known and unknown confounding factors.

6.2.3 Block Randomisation

Block randomisation is often used to ensure a balance in the numbers of participants assigned to each group in a RCT (Chia, 2000). For example, participants may be considered in blocks of four at a time. Using this block size for two treatment groups (A and B) leads to six possible arrangements of two A's and two B's (blocks):

AABB, BBAA, ABAB, BABA, BAAB, ABBA

A random allocation sequence is then used to select a particular block out of the six available, which determines the allocation order for the first four participants who are randomised. The treatment group is then allocated in the order specified by another of the six blocks for the next four participants who enter the trial.

Despite this process, it may still be possible for researchers to anticipate what group a participant will be allocated to. As each block contains two A's and two B's, theoretically, researchers could track the block allocations in order to identify the next group allocation. For example, if two A's and one B have come up, the researcher would know the next allocation is going to be group B. Therefore, to ensure assignment is unknown, I will use block randomisation of four and six as detailed later in the procedure. This makes it impossible to determine the next allocation as researchers do not know whether a block of four or six is being used.

6.2.4 Allocation Concealment

Allocation concealment is the technique of ensuring that implementation of the random allocation sequence occurs without knowledge of which patient will receive which treatment. This is essential in RCTs because prior knowledge of the next group assignment could influence whether a patient is included or excluded based on an investigator's understanding of the patient's likelihood of success (Dettori, 2010).

6.2.5 Stratification

While randomisation may help remove selection bias and the influence of confounding, it may not always ensure that groups will be similar with regards to important patient characteristics or predictor variables (Chia, 2000). One way of ensuring groups are balanced is to generate separate block randomisation lists for combinations of factors that are known, or believed, to exert an effect on the outcome of interest. Randomising in this manner is known as stratification, with each possible category representing a specific stratum.

For example, it is known that the presence of a carer (often a spouse or family member) is associated with better medication adherence in people living with a chronic condition. Supporting this are the findings presented in Chapter 3 which identified that the lack of a spouse/carer is associated with medication non-adherence in people with PD. Therefore, with this knowledge, I felt it was essential to identify whether the presence of a spouse/carer had a significant impact on the effectiveness of AT in this study.

As the presence of a spouse/carer may be associated with better medication adherence in people with PD, to determine this I stratified study participants into two strata: spouse/carer present or no spouse/carer present. This meant that where a PD patient's spouse/carer was also randomised with the patient, they too received the experimental treatment as outlined later in the study procedure. Stratifying in this manner gave four possible categories as shown in table 6.1.

Table 6. 1 - Randomisation by Strata

Strata	Randomisation group	Numbers randomised
Treatment alone	Control	14
Treatment alone	Intervention	13
Treatment with a carer	Control	24
Treatment with a carer	Intervention	25

This method of stratification therefore allowed me at the analysis stage to test for a possible interaction (effect modification) between the presence of a spouse/carer and the outcome of interest (i.e. does having a carer present during AT result in a greater therapeutic effect than receiving AT without a carer present). It is worth noting however that despite this planned analysis, all sub-group analyses are subject to low statistical power which can result in a type 2 systematic error (i.e. accepting the null hypothesis when it should be rejected). Therefore, although a statistically significant interaction may exist between the treatment effect of AT and the presence of a spouse/carer, this planned sub-group analysis may not be sufficiently powered to detect it.

6.2.6 Other Advantages of the RCT

A further advantage of RCTs is that they are able to maintain external validity (generalisability). This is often dependent on how representative the sample is of the target population. Many trials, particularly studies investigating drug efficacy, can have very specific inclusion criteria which can fail to encompass a significant proportion of the population of interest. This often becomes problematic in PD where many patients may suffer from age related comorbidities and cognitive impairment, excluding them from participating in research studies.

Acknowledging this issue I endeavoured to select a set of inclusion criteria (described later) that best represents the PD population. With a representative sample, RCTs are able to provide a realistic compromise between observational studies (which often have high external validity) and more traditional experimental approaches (which often have good internal validity but can lack applicability to everyday life) (Chia, 2000).

The findings from RCTs are also essential in healthcare in that the effect sizes generated for an intervention can be pooled together (i.e. findings are taken from independent studies testing the same treatment in the same way) within a systematic review or meta-analysis. This allows researchers to establish whether cumulatively the evidence suggests a particular intervention is effective for a given outcome (Borenstein et al., 2009).

6.3 Hypothesis and Study Aims

When using a test of significance to compare two groups it is often appropriate to start with the null hypothesis that there is no difference between the sample populations. If this hypothesis is not true the alternative hypothesis must be true; that is, there is a difference. Since the null hypothesis specifies no direction for the difference, nor does the alternative hypothesis and so a two-sided test is appropriate. In a one-sided test the alternative hypothesis does specify a direction (i.e. an active treatment is better than a placebo) (Bland and Bland, 1994). Therefore, as the direction of a change cannot be specified in RCTs, a one-sided test (i.e. AT leads to improved adherence) was not appropriate in this trial.

6.3.1 Alternate Hypotheses (H_1) – Two-sided:

There will be a statistically significant difference in medication adherence and QoL in people with PD who undergo a seven week programme of Adherence Therapy (AT) in addition to Treatment as Usual (TAU) compared to those receiving TAU only.

6.3.2 Null Hypothesis (N_0)

There will be no statistically significant difference in medication adherence or QoL in people with PD who undergo a seven week programme of AT in addition to TAU compared to those receiving TAU only.

6.3.3 Primary Aims

To investigate if a seven week programme of AT is effective for improving medication adherence and QoL in non-adherent people with PD immediately post intervention and at twelve weeks post randomisation. The decision to use two primary outcomes is discussed later in this chapter.

6.3.4 Secondary Aims

To investigate whether the AT and TAU groups differ immediately post intervention and at twelve weeks post randomisation in terms of:

Person with Parkinson's disease:

- Overall disease state

- Activities of daily living

- Beliefs about medication

- Health related quality of life

Spouse/carer of Person with Parkinson's disease:

- Beliefs about medication

- Caregiving distress

Additional Secondary Aims:

- To investigate associations between baseline cognitive impairment and the efficacy of AT. I planned to explore this because the findings presented in Chapter 3 identified that cognitive impairment may be associated with medication non-adherence in PD.

- To investigate associations between baseline anxiety and depression and the efficacy of AT. Once again, I planned to examine this based on the findings presented in Chapter 3 which identified that mood disorders may be associated with medication non-adherence in PD.

- To investigate the acceptability/satisfaction of AT from the perspective of the trial participants who receive it.

- To investigate whether a change in adherence from baseline to follow-up is associated with a change in 'importance' 'confidence' and 'satisfaction' with medication (part of the AT assessment).

- To investigate whether the overall score and the individual domain scores on the Montreal Cognitive Assessment Scale correlate with poor adherence at baseline.

6.4 Selecting the Outcome Measures

When developing the protocol for the RCT there were several issues to consider when selecting a suitable primary outcome measure. Firstly, I had to decide whether it was more appropriate to measure adherence to medication or a PD specific clinical marker. As AT was aimed primarily at enhancing adherence behaviours, I felt that medication adherence should represent the primary outcome of interest. However, the aim of improving adherence to medication in any long-term condition is to impact positively in a clinical context. I therefore decided it was necessary to review the various methods of assessing both medication adherence and clinical markers in PD before an appropriate primary outcome could be selected.

6.4.1 Direct Methods for Measuring Adherence

Direct measures of assessing adherence to medication include mainly the evaluation of drug metabolite levels in blood plasma, urine or saliva samples. However the cost, relative discomfort/inconvenience to the patient and the ability to only determine adherence to doses consumed a short time prior to the samples being taken made this method impractical for the clinical trial (Nyholm, 2005).

Furthermore, the stage of disease was another important consideration when discounting this assessment method. As stated in Chapter 2, patients in early stages of PD can experience a long duration of therapeutic effectiveness; dopaminergic tone in the nigrostriatal pathway can be maintained in some cases even if patients

omit doses (Lopez et al., 2001). As a result, non-adherence in these individuals may not be identified from the assessment of a patient's plasma metabolite levels. I therefore decided against the direct methods of assessment.

6.4.2 Indirect Methods of Measuring Adherence

Indirect methods include pharmacy refill data, self-reports, simple pill counts and MEMS devices. In PD only a few studies have specifically investigated and compared methods of assessing adherence to medication (Grosset et al., 2006, Elm et al., 2007). Although it is widely reported in the adherence literature that MEMS devices are the 'gold standard' assessment technique, I decided not to use this method. MEMS devices are costly, especially when considering that at least one device would have been required for each participant. As I did not plan to exclude patients with severe PD, I envisaged that many patients would likely be taking more than one anti-parkinsonian medication and so a MEMS device would have been required for each prescription. This would have added significant cost to the study which made this approach unfeasible.

More importantly, I decided that the use of MEMS in a PD population was impractical, potential unethical, and would go against the purpose of the intervention; that is, to encourage adherence behaviours. This was for the reasons outlined below.

Firstly, many people with PD are elderly and the high prevalence of arthritis in this group may mean that the use of MEMS devices becomes problematic (Bainbridge

and Ruscin, 2009). This potentially could have resulted in patients being unable to access their medication, especially in those individuals with tremor dominant PD where the fine dexterity required to manipulate bottle tops may be burdensome. As a consequence, this could also have led to high participant attrition.

Secondly, the main purpose of AT is to maximise adherence behaviour within the patient's own context. Almost all PD patients do not have medication prescribed that comes in a bottle. It therefore seemed counterintuitive to insist on the use of MEMS bottles for the duration of the trial when it is not consistent with usual medication taking practices.

Thirdly, I anticipated that problem solving strategies surrounding the use of medication would be the focus in some PD patients. Asking the patient to change their usual routine for the purpose of the trial I felt was unethical and would not promote engagement in problem solving exercises. For these reasons I decided against the use of the MEMS devices.

Pill counts were shown by Elm and colleagues (2007) to offer a fair to moderate correlation with the Morisky Medication Assessment Scale (MMAS-4) self-report. Whilst the pill count approach would eradicate any concerns regarding the accuracy of self-report scales (patients can intentionally or unintentionally over/under report adherence), I decided that pill counts would be unfeasible from a pragmatic perspective.

For instance, without the use of a blinded rater this method would require me visiting the trial participants to count their pills. As patients would be aware that their tablets would be monitored in this way, they may have been more likely to take their medication rather than them doing so because of the effectiveness of the AT process. Assessing adherence in this way I believed would have represented a sizeable confounder when determining the efficacy of the AT intervention.

Additionally, this approach would also require actively taking a patient's drugs out of their packet (in many cases their dosette box) and dispensing them into the container from which they could be countered (to ensure standardisation throughout trial participants). This is not consistent with usual routine and therefore I decided against the method.

This left me with self-reports. As Elm and colleagues (2007) were able to show a fair to moderate correlation between pill counts and the MMAS-4, I decided the self-report scale was the most appropriate and feasible method of adherence assessment to use in this particular trial.

6.4.3 Clinical Outcome Measures

The Unified Parkinson's Disease Rating Scale (UPDRS) is the acknowledged gold standard assessment tool in PD. The UPDRS is reported to be the most frequently administered scale for both clinical and research purposes and is used widely in clinical trials investigating drug efficacy (Goetz et al., 2007). As stated, the purpose of improving adherence to medication is to impact positively on symptom control.

An assessment of symptom control would therefore represent a justifiable approach to evaluating the effectiveness of an adherence intervention, such as the one investigated in this clinical trial.

However, after considering the use of the scale I realised that a clinical assessment that focused on PD symptoms may be problematic. This was for a variety of reasons. Firstly, part three of the scale requires a rater to undertake an assessment of motor function. Despite completing the Movement Disorders Society's online assessment for becoming a trained rater of the UPDRS, and having sufficiently practiced administering the scale with patients during routine neurology clinic appointments, I felt that rating a patient's motor function with the knowledge of their group allocation (i.e. active treatment or TAU) would lead to considerable bias. An alternative trained rater could have been used. However, this would have added significant cost to the study as the rater would have been required to visit each trial participant three times in their own home.

Secondly, it is well established that both motor and non-motor function in PD can vary on a daily, or even hourly, basis. This is dependent on the severity of the disease, the response to therapy and whether the patient is in the '*On*' or '*Off*' phase at the time of assessment. Patients can experience regular motor fluctuations, dyskinesia, or simply just not feel as well controlled one day to the next (Ahlskog, 2009). I felt this could represent a considerable problem if I was to use the UPDRS as a primary outcome for establishing the efficacy of Adherence Therapy. Whilst a participant's adherence may have improved, even with a noticeable improvement to function in some cases, the potential for variation in UPDRS scores (particularly

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the motor score) could result in a false negative (i.e. no difference in symptoms being detected even though there may be a small improvement).

Finally, whilst symptom focused instruments such as the UPDRS are useful for clinical studies, they often do not provide a comprehensive overview of the impact of disease. Crucially, such forms of assessment often lack the capability to determine how PD effects QoL from the perspective of the patient (Peto et al., 1998).

Treatment of PD is often aimed at improving motor function. However, PD is often complicated by additional problems such as treatment related complications, falls, depression and dementia which may have far greater impact on QoL than the characteristic motor symptoms of PD (Schrag et al., 2000b). In acknowledging these limitations I reviewed widely used PD QoL scales that I believed could be of use in the trial as a primary outcome measure.

Many features to QoL have been identified and it is well established that QoL as a conceptual framework represents a combination of clinically relevant, patient focused dimensions that should be the focus of healthcare interventions. Various QoL assessment scales have been tested in patients with PD and generic scales like the 36-Item Short-Form Health Survey (SF-36) have been widely used across disease populations (Ebersbach et al., 2006). However, a limiting factor in generic scales is the lack of specificity and sensitivity to disease specific problems. Quality of life measures have therefore been developed for use specifically in PD patients. Notably, specific PD QoL scales allow for small, but clinically important, changes

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to be detected following intervention which generic scales may be unable to detect (Fitzpatrick et al., 1997).

The most widely used PD QoL scale is the Parkinson's Disease Questionnaire (PDQ-39). Many researchers have used the PDQ-39 in clinical trials and have found it to be sensitive to a variety of treatments including drugs delivery, deep brain surgery and therapeutic rehabilitation interventions (Fitzpatrick et al., 1997). Its disease specificity and the single summary index offer the opportunity to assess the overall impact of illness. Additionally, findings have shown that domains such as depression, cognition and mood might be more relevant to PD patients in-terms of QoL than impaired motor function (Schrag et al., 2000b). Therefore, an easy to interpret QoL measure may provide greater focus on the problems patients report as being most impactful on their daily life. This is opposed to simply assessing motor function which may not be principally concerning for many patients.

As the PDQ-39 is a well-established outcome measure, and considering that the scale is completed as a self-report, I decided that its use as a primary outcome would be more pragmatic and feasible in the trial than a predominantly symptom driven instrument (e.g. UPDRS) that may not show clinical improvement due to potential symptom variability.

6.4.4 Deciding Upon the Primary Outcome Measure

In view of the discussed measures for assessing adherence and clinical change (e.g. QoL), I had to decide which outcome was most appropriate to measure for the evaluation of the clinical trial. In making this decision I considered the individual scales of choice (i.e. the MMAS-4 and the PDQ-39) and the theoretical mechanism of AT in a non-adherent PD population.

As the MMAS consists of only four items (Appendix 5), I was mindful that the scale might not possess the required sensitivity to detect a subtle change in adherence, even though patients may in fact verbally report improved pill taking. For example, the first two items on the MMAS-4 relate to problems remembering to take medication. Whilst a patient may verbally report improved adherence in that they forget fewer doses than prior to participating in the therapy process, the wording of the first two items (i.e. do you 'ever' forget to take your Parkinson's disease medication / do you 'ever' have problems remembering to take your medication) may prevent patients from answering differently than at baseline.

Despite some patients potentially reporting improvement in remembering to take medication, patients may still feel obliged to answer 'yes', indicating no change. This may be because patients do occasionally forget doses or miss dose timings, even though they may be substantially better than prior to receiving AT. Despite feeling that the assessment of adherence should be a primary outcome in the clinical trial, I believed this potential insensitivity of the items to detect change represented a problem.

When considering the PDQ-39, although the scale has been extensively tested clinimetrically (Peto et al., 1998, Peto et al., 2001), like the MMAS-4 I feared the scale may not be sensitive to change in this particular trial. Whilst symptoms/motor function may theoretically improve as a consequence of greater adherence, such improvements may not result in a clinically significant impact on QoL. My reasoning for this assumption related to a hypothesised mechanism of action of AT in PD; that is, improved adherence to anti-parkinsonian medication leads to improved function as symptoms become better managed. This ability to function more optimally then translates into greater reported QoL.

However, as improved adherence and QoL are arguably at opposite ends of the theoretical model (i.e. patients may require a substantial improvement in symptoms/function prior to it impacting positively on QoL), I thought it may be ambitious to assume that the short adherence intervention in this trial could impact significantly on QoL.

Furthermore, this simplistic theoretical model assumes that increasing motor function will enhance QoL. As stated earlier, in PD many non-motor symptoms such as depression, cognition, sleep and autonomic dysfunction impact greatly on QoL, more so than motor symptoms in many individuals (Martinez-Martin et al., 2011). It may therefore be the case that improving the motor symptoms which are most sensitive to anti-parkinsonian medication (i.e. rigidity and bradykinesia), and thus are more likely to benefit from greater medication adherence, may in fact not impact significantly on QoL.

Contrary to this theory, however, I was mindful that improving adherence to medication may actually impact positively on the dimensions of QoL that are not motor symptom focused; recent findings suggest that non-motor symptoms can be responsive to targeted treatments, including dopaminergic agents (Honig et al., 2009, Zesiewicz et al., 2010).

Furthermore, it is suggested that control of non-motor symptoms can change depending on whether a patient is in the '*On*' or '*Off*' phase, similar to motor symptoms (Chaudhuri et al., 2010). Therefore, it is reasonable to suggest that if enhancing adherence to medication improves symptom control, it may well improve '*On*' time for people with PD. Therefore, as a consequence, greater adherence may also be beneficial for managing some non-motor symptoms and this may be identified by improved QoL scores (Honig et al., 2009, Nissen et al., 2010, Zesiewicz et al., 2010).

For the reasons discussed above I felt that assessing QoL was equally as important as measuring adherence to medication. I therefore made the decision to use both the MMAS-4 and PDQ-39 as primary outcome measures in the clinical trial investigating the efficacy of AT. Although the use of two primary outcome measures is unorthodox, I believed the decision was justified and could be accounted for when calculating the study sample size.

6.4.5 Primary Outcome Measures

Morisky Medication Adherence Scale:

The MMAS-4 is a self-report scale developed by Morisky and colleagues (1986) for identifying medication non-adherence that has been used previously in PD (Elm et al., 2007). The scale has four items which can be answered by 'yes' or 'no'. Three or four 'yes' responses signifies very poor adherence and four 'no' responses signifies high adherence. Participants scoring ≥ 1 were eligible for the trial as validated by the scale authors (Morisky et al., 1986) Originally a score of ≥ 2 was used but this criteria was subsequently changed by the Trial Steering Committee (TSC) members. This is discussed later in the chapter under protocol amendments.

Parkinson's Disease Questionnaire - 39:

The PDQ-39 (Appendix 6) is a PD-specific QoL questionnaire that uses 39 items to assess eight dimensions of health: mobility, ADL, emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort.

6.4.6 Secondary Outcome Measures

Movement Disorder Society - Unified Parkinson's Disease Rating Scale:

The MDS-UPDRS (Appendix 7) is the revised version of the widely used and cited UPDRS (Goetz et al., 2007, Goetz et al., 2008). The MDS-UPDRS comprises of sixty-five items in four parts; namely, I: Non-motor Experiences of Daily Living; II: Motor Experiences of Daily Living; III: Motor Examination; IV: Motor Complications. Clinimetrically the scale has been shown to have high internal consistency, reliability/validity and correlates well with the original UPDRS (Goetz

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et al., 2008). Part I, II and IV were completed at each data collection point in the trial. MDS-UPDRS Part III (the motor examination) was not assessed due to practical limitations. Specifically, as I would have been required to assess part III instead of a blinded rater, I believed this would result in a high risk of bias.

Beliefs about Medication Questionnaire:

The BMQ (Appendix 8) is comprised of two scales, one with eight items and one with eleven items. Together, these assess beliefs about the necessity of prescribed medication for controlling symptoms, concerns about taking medications and concerns about general medication overuse and harm (Horne et al., 1999). Respondents rate each item on a five point Likert scale ranging from one to five (one being strongly disagree and five being strongly agree) depending on their degree of agreement. Higher scores indicate more positive attitudes towards medication. Scores obtained from the eight and eleven item scales are summated.

The questionnaire has four sections which evaluate attitudes about:

1. Specific Concerns (S-C) i.e. concerns about the harmful effects of medicines prescribed for a specific condition (six questions).

2. Specific Necessity (S-N) i.e. beliefs about the necessity of medicines prescribed for a specific condition (five questions).

3. General Overuse (G-O) i.e. beliefs about the way in which medicines are used by doctors (four questions).

4. General Harm (G-H) i.e. beliefs about the intrinsic nature of medicines in general (four questions).

EuroQoL (EQ-5D):

The EQ-5D (Appendix 9) is an established, standardised generic health utility index instrument used extensively in clinical studies (Brooks, 1996). It comprises of five domains covering mobility, self-care, usual activity, pain/discomfort and anxiety/depression. A visual analogue scale represents one final characteristic of the instrument. The scale provides a simple descriptive profile and can be used to estimate a single index value for a respondent's health status and change in Quality Adjusted Life Years (QALYs).

Caregiving Distress Scale:

The CDS (Appendix 10) is a concise measure designed to assess and profile levels of distress in informal caregivers (Cousins et al., 2002). The scale was developed from various caregiving measures which included a wide range of items associated with distress for caregiving. The CDS comprises of five distinct dimensions which cover 17 separate items. Answers are provided on a Likert scale ranging from 0-4.

6.4.7 Additional Baseline Assessments

As the findings presented in Chapter 3 revealed that cognitive impairment and mood disorders (anxiety and depression) are associated with medication non-adherence in PD, I decided to screen all randomised participants at baseline for these symptoms. Cognition was assessed using the Montreal Cognitive Assessment Scale. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale.

Montreal Cognitive Assessment Scale (MoCA):

The MoCA (Appendix 11) is a 30-point scale covering a range of executive functions. Although a plethora of cognitive batteries exist, in a review on behalf of the PD study group the MoCA was recommended for use in clinical trials where screening of cognitive impairment was necessary (Chou et al., 2010). The scale has six orientation questions and a five word memory recall task. A clock drawing task and a cube copy test assess visuospatial function. Attention/concentration is assessed using serial 7's, target mapping and forwards and backwards digit span tasks. Confrontation naming and repetition tasks assess language. Executive functions are evaluated using a shortened version of the Trail Making B Test, phonemic fluency, and a verbal abstraction task.

Hospital Anxiety and Depression Scale (HADS):

The HADS (Appendix 12) is a self-screening questionnaire for anxiety and depression (Zigmond and Snaith, 1983). It consists of fourteen questions, seven for each anxiety and depression and has been widely used and validated (Bjelland et al., 2002).

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Where patients scored moderate/severe on the HADS (i.e. a score above ten on the depression scale) I recommended they contact their GP. I also provided the patient with an ethics approved information sheet (Appendix 13). Where only mild symptoms were identified (i.e. a score between eight and ten on the depression scale), I provided patients with information relating to self-help websites (Appendices 14). Patients scoring seven and below satisfied the criteria for no depressive symptoms. These participants were therefore not given any further information.

Where participants did show signs of depression as determined by the HADS, a letter was posted to the patient's General Practitioner informing them of their patient's HADS score and of what recommendations the research team had made to the patient (Appendix 15).

6.4.8 Patient Demographics and Clinical Characteristics

The following demographic and clinical data were collected at baseline using a standardised baseline participant demographics form (Appendix 16). These characteristics were recorded to determine the success of the randomisation process and in order to present the demographical distribution of the sample:

- Age
- Gender
- Ethnicity
- Duration of PD

- Disease severity (Hoehn and Yahr Scale, Appendix 17)

- Medication profile:

    - Prescriptions (PD and non-PD drugs)

    - Levodopa Equivalent Daily Dose

    - Dose and regimen

    - Whether medication was self-administered

- Co-morbidities

- Whether a spouse/carer was present in the home

- Occupation

- Socioeconomic status (estimated using the first half of a patient's postcode)

Each participant's Levodopa Equivalent Daily Dose (LEDD) was calculated using a standard method as described by Tomlinson et al (2010). For each anti-parkinsonian medication taken by trial participants, a conversion factor was used to calculate the equivalent Levodopa dose. For example, the conversion factor for the dopamine agonist Ropinirole is reported by Tomlinson and colleagues to be a factor of twenty. Therefore, the LEDD for a participant prescribed 30mg daily Ropinirole was 600mg (30mg x factor of 20).

6.5 Methods

6.5.1 Study Design

This study was a parallel group, RCT to compare AT with TAU for non-adherent people with PD and their spouse/carers. The study compared the two groups

immediately post intervention and at twelve weeks post randomisation (primary follow-up point). The RCT was conducted from September 2011 to March 2013 within the departments of Neurology and Medicine for the Elderly (MFE) at a University Hospital in the East of England.

The trial protocol was registered with the International Standard Randomised Controlled Trial Register (ISRCTN07830951) and published in the TRIALS Journal (Daley et al., 2011).

6.5.2 Study Participants

Study participants were people with idiopathic PD attending Medicine for the Elderly or Neurology outpatients for a routine appointment with their Neurologist or Consultant physician. Spouse/carers of PD patients wishing to participate were also invited into the study.

6.5.3 Inclusion Criteria

All patients meeting the following selection criteria who attended either of the outpatient clinics were invited to participate:

1. Adults diagnosed with Idiopathic PD - three out of four of the chief UK Brain Bank Criteria (Appendix 18) had to have been satisfied (Gibb, 1988). This information was determined by careful review of Consultant clinic letters. Where

there was doubt, for instance whether a patient had idiopathic PD or a Parkinsonism, the treating physician was consulted for verification.

2. Were prescribed one or more anti-parkinsonian medications by a Consultant Neurologist or Consultant physician with specialist knowledge of movement disorders.

3. Were English speaking and literate (participants were required to actively engage in the therapy process).

4. Were on a stable medication regime i.e. not altered within the previous month and not expected to change during the period of the RCT (twelve weeks).

5. Were not diagnosed with dementia or significantly cognitively impaired. Where there was reasonable doubt in the clinic letters the clinical team made a judgement as to whether the patient had the cognitive capacity required to participate fully in the trial; that is, be able to read patient information, complete self-report questionnaires and engage actively in the therapy process.

6. Showed poor adherence as determined by a MMAS-4 score ≥ 1.

As the review presented in Chapter 3 showed that both young and older age was associated with medication non-adherence, likely for different reasons as discussed, I did not feel it appropriate to have an age restriction. What's more, I was keen to

ensure the sample was as representative as possible. I therefore felt that exclusion because of older age was not justifiable for this clinical trial.

6.5.4 Exclusion Criteria

Patients were excluded if either of the below criteria were satisfied:

1. Patients did not have a diagnosis of PD (i.e. I was unable to attribute the movement disorder to Parkinson's disease). This included patients with a diagnosed Parkinsonism (e.g. Vascular Parkinsonism, Multiple Systems Atrophy, Progressive Supranuclear Palsy and Dementia with Lewy body disease).

2. Patients whose medication regimen had altered within the previous month.

3. Patients being treated with anti-parkinsonian medications for a mental health problem e.g. psychosis.

4. Were diagnosed with dementia.

5. Patients who had a life expectancy of < 6 months.

6.5.5 Recruitment Procedure

Patients fulfilling the screening criteria were informed of the study by post. A member of the clinical team (PD nurse specialist), acting in the capacity as a data

clerk, posted an information pack to PD patients meeting the screening criteria two/three weeks prior to their upcoming routine outpatient appointments with a Neurologist or movement disorder specialist.

Each information pack contained the MMAS-4, an invitation letter (Appendix 19), a patient information sheet (Appendix 20) and a consent form for the MMAS-4 (Appendix 21). Spouse/carer specific information was placed in a separate envelope within the patient pack. This contained an information sheet (Appendix 22) and an initial consent form indicating interest in the study (Appendix 23). Patients were asked to return the MMAS-4 and the consent form accompanying the scale prior to their upcoming routine outpatient appointment if they were initially interested in the study.

Upon receiving the MMAS-4, those showing poor adherence to medication as determined by a score ≥ 1 were deemed eligible for further participation. In this instance I contacted the patient by phone and informed them of their eligibility. In most instances I arranged a suitable time to visit the patient and their spouse/carer at home to discuss the study in greater detail before a decision to participate fully was made. This was often because I did not receive the MMAS-4 and the accompanying consent form prior to their clinic appointment.

Where I did receive the MMAS-4 and consent form before the arranged clinic visit, I made suitable provisions to see patients in a private room directly before or after their appointment with their Consultant. If still wishing to participate after discussing the study in greater detail and having had the opportunity to ask

questions, patients signed an informed consent form (Appendix 24) and completed all baseline outcomes measures. Consenting spouse/carers also signed an informed consent form (Appendix 25) and completed relevant outcome measures. Eligible patients not seen on their appointment day completed the consent forms and baseline measures during their home visit. Patients not scoring ≥1 were informed by phone of their ineligibility and thanked for their participation.

6.5.6 Randomisation and Allocation Concealment

All study participants were randomly assigned to either the AT or TAU group following the completion of baseline measures. This was to ensure that a patient's baseline response to the self-report questionnaires did not change as a result of being randomised into the TAU group.

Where patients were seen directly following their outpatient appointment, randomisation took place in a private room following signed informed consent and completion of baseline measures. Randomisation and allocation concealment were completed using computer generated random numbers accessed via a web-based randomisation system developed by the Clinical Research Trials Unit (CRTU) at the University of East Anglia (UEA). Participants were allocated a unique identifier number which was sent to CRTU where allocation was undertaken by permuted random blocks of four and six (explained earlier in this chapter).

Participants were stratified into 'spouse/carer present' or 'no spouse/carer present' strata at randomisation in order to investigate the potential effect modification

(interaction) of the spouse/carer on the treatment effect. This was also described earlier in this chapter.

All randomised participants were assigned a randomisation number by CRTU. Additionally, each participant who was initially invited into the study (regardless of whether they were non-adherent or subsequently randomised) was given a unique 'study' identification number. This number, in addition to CRTU's randomisation number, was placed on all participant documents for the remainder of the trial allowing me to track and record patient data anonymously without the need of patients' names. All Excel/SPSS spread sheets contained these personal identifiers to maintain anonymity.

6.5.7 Treatment Groups

Treatment as Usual Group (TAU):

To conduct a robust RCT there is a need to have a group that is matched with individuals in the active treatment group in all aspects except the intervention under investigation. This group is usually referred to as the control group. A control group is an essential part of the RCT design, functioning to ensure that any changes observed in an active treatment group are due only to the experimental intervention (Akobeng, 2005).

A limitation of the control group, however, is that it may lead to difficulties when interpreting the results. Specifically, the findings may only show whether a particular intervention offers benefit when it is compared to no intervention at all,

as implied by the control group. The findings will not however show if the intervention under investigation offers greater efficacy than existing treatments. For this reason many researchers now refer to TAU as an alternative where patients randomised into the TAU group receive current best practice. Whilst this removes full power from the researchers as it may not always be clear what information is given to patients in this group from various health professionals, this approach does show the efficacy of the intervention against current best practice treatment. Furthermore, the concept of TAU is ethically more acceptable as participants are not left untreated.

In this study patients in the TAU group received no additional information regarding medication adherence from members of the clinical team. Care continued as usual according to routine practice. This largely consisted of Consultant outpatient appointments and input from PD nurse specialists. I specifically did not provide any guidance to the clinical team as to the content of the TAU package. However, the clinical team were asked not to discuss treatment adherence and were to avoid any intervention relating to this topic, unless they deemed it necessary for the wellbeing of the patient. In this instance they were asked to record what information had been provided.

Active Treatment (AT) Group:

In addition to TAU, patients allocated to the active treatment group received seven 30-45 minute sessions at weekly intervals of AT delivered in their own home. Where a patient's carer consented to the trial, AT was also delivered to the carer at the same time (hence Carer Assisted AT, (CAAT-PARK)). Ten sessions of AT

over the course of the trial were audio recorded to determine treatment fidelity. Participants were made aware of this in the participant information sheet and were asked to consent for this at the particular visit.

6.5.8 Follow-up Outcome Assessment

Baseline outcome measures were repeated immediately post intervention (week seven or eight) and at twelve weeks post randomisation (primary follow-up point), as depicted in Figure 6.2. For the group receiving TAU, assessments were at week seven and week twelve. For the active treatment group, post intervention assessments were at week seven or eight and then at week twelve. This additional week at the immediate post intervention time point accommodated potential sickness or time spent away from home, providing flexibility to the process from a pragmatic perspective. Table 6.2 shows when each outcome was assessed throughout the trial duration and the average time for completion.

Post-intervention follow-up periods

Randomisation/ Baseline Ax   **Weeks   7   8**   **week 12 Ax**

T. group

TAU group
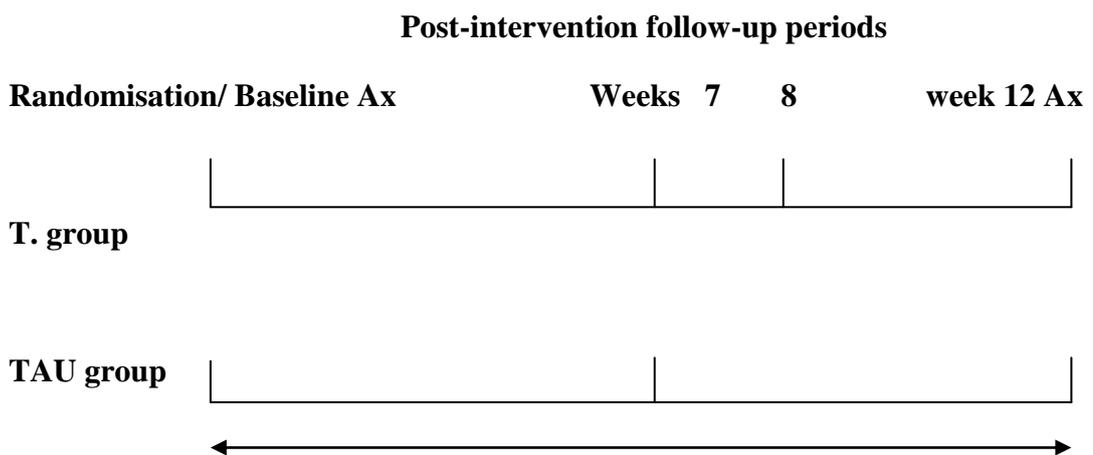
Figure 6. 2 - Outcome Measure Assessment Time Points

Table 6. 2 - Outcome Measure Assessment Points

Measures	Baseline / randomisation	Week seven	Week Twelve	Time for Outcomes (min)
Patients				
MMAS-4	x	x	x	2.0
PDQ-39	x	x	x	10.0
EQ-5D	x	x	x	2.0
BMQ	x	x	x	5.0
MDS-UPDRS (I-III)	x	x	x	15.0
MoCA	x			10.0
HADS	x			10.0
Total Time	54 min	34 min	34 min	
Spouse/Carers				
BMQ	x	x	x	5.0
CDS	x	x	x	5.0
Total Time	10 min	10 min	10 min	

6.5.9 Adverse Events Monitoring

Adverse events (AE) were recorded at each weekly visit and commenced from the point of randomisation up to week twelve follow-up. An AE checklist (Appendix 26) was developed following consensus views of the TSC and medical specialists. AEs were reported to the TSC members (Appendix 27) and the clinical team responsible for the management of a specific PD patient for appropriate action.

All AEs were addressed according to local Standard Operating Procedures (SOPs) for clinical trials of non-Investigational Medicinal Products (non-IMPs) developed in accordance with the Medicines for Human Use Regulations (2004) and the Department of Health's Research Governance Framework for Health and Social Care for identifying, recording, and reporting adverse events in clinical trials.

6.6 Determination of Sample Size

My aim was to recruit a total of ninety-two family units (patient/carer pairs or patients alone), forty-six per treatment group. This included an additional 15% (n = 6) in each group for potential participant attrition. Where possible I aimed to recruit patients with a spouse/carer. I did not exclude participants who did not have a spouse/carer but who were themselves wishing to participate.

Using the primary outcomes (MMAS-4 and PDQ-39) it was calculated that a sample size of forty participants per treatment group would provide 81% power, with an alpha of 0.05, to detect a difference of 25% improvement in medication adherence in the active treatment group against 0% in the TAU group. Improvement in the MMAS-4 was detected by a one point shift. This calculation also provided 80% power to detect a Cohen's effect size of 0.69 (typically considered large) in the PDQ-39 overall score, based on the published standard deviation of 8.89 in a PD patient group (Peto et al., 2001). This calculation allowed for a minimally important clinical difference in means of 6.13 (8.89 *S.D.* $\times$ 0.69 *E.S.*) in the PDQ-39 to be detected.

6.7 Analysis

6.7.1 Data Entry & Quality Control

Double Data Entry

To ensure the accuracy of data entry, all measurements for both primary outcomes (MMAS-4 and PDQ-39) taken at baseline, week-7 and week-12 were entered into

two separate Excel spread sheets (double data entry). Each participant had 9 cells containing PDQ-39 scores (8 sub-domains and 1 total score) and 1 cell for the MMAS-4 score. This provided a total of 760 cells (10 cells per participant multiplied by 76 participants) of data for each spread sheet at each of the three assessment time point. Each pair of spread sheets relating to baseline, week-7 and week-12 measurements were then overlapped to assess for differences in scores. Where scores differed, that participant's raw data set was re-assessed for the correct value.

Quality Assurance

To ensure the accuracy of outcome measurement calculations, a 10% random sample of primary outcome data was independently calculated by a second rater naive to the study aims. The rater was given instructions on how to calculate a score for the MMAS-4 and PDQ-39. There were no discrepancies in scores between the initial calculations of the primary outcomes and that of the secondary rater. The MMAS-4 and PDQ-39 contained no participant identifiable information and did not reveal group allocation to the second rater.

6.7.2 Baseline Comparisons

The SPSS statistical program version 18 for windows was used to analyse the quantitative data. In addition to my independent analysis, a blinded medical statistician also analysed all data for accuracy.

Baseline comparability of the groups by demographics was described using descriptive statistics. Where data appeared to be non-normally distributed according to the Shapiro-Wilks test, medians and inter-quartile ranges were used to describe the data. Where data was normally distributed, means and standard deviations were used.

The following discrete variables were recorded and tabulated: gender, occupation, numbers living with a spouse/carer, ethnicity and disease severity. All other recorded demographic data were continuous: age, duration of PD, number of comorbidities, number of PD drugs/non-PD drugs, number of daily PD/non-PD doses, number of PD tablets taken daily, LEDD, MoCA score and HADS score.

6.7.3 Efficacy Analyses

Determining the efficacy of AT was made by comparing baseline primary outcome measurement data to that of week-12 follow-up using inferential statistical analysis. Originally it was decided that the primary outcomes (MMAS-4 and PDQ-39) would be analysed using the parametric student-t test for comparing mean change between the two intervention groups. However, because the interaction between the subgroup factors (presence or absence of a spouse/carer, baseline HADS and baseline MoCA scores) and the treatment effect were to be investigated, responses for the MMAS-4 were used to form two outcome categories: 'no change or increase' and 'decrease'. This meant the student-t test for comparing means was not appropriate.

For example, a patient who scored two on the MMAS-4 at baseline and again at week-12 follow-up satisfied the criteria for the 'no change or increase' category. Likewise, if a patient's adherence worsened as indicated by a score of 1 at baseline and then ≥2 at week-12 follow-up, they also were categorised into the 'no change or increase' group. Alternatively, patients who improved in medication adherence (indicated by a lower MMAS-4 score from baseline to week-12 follow-up) were categorised into the 'decrease' group as their overall MMAS-4 score had reduced. Categorising the MMAS-4 score in this manner therefore produced a binary outcome: 'no change or increase' or 'decrease', regardless of the actual baseline and week-12 follow-up score.

This binary outcome was then compared between treatment groups using a logistic regression model, which adjusted for the stratifying factors (i.e. presence of spouse/carer). Linear regression analysis is a way of predicting a future outcome variable from a predictor variable or several predictor variables for continuous outcomes (Field, 2009). Logistic regression is an extension of linear regression models in that it is designed to predict the outcome of a categorical variable from either continuous or categorical predictor variables. Regarding the MMAS-4, as the binary outcome was either 'no change or increase' or 'decrease' in adherence score, a logistic regression model was appropriate.

As the logistic regression model was used in this study to predict a binary outcome (i.e. improvement in medication adherence or not) based on a categorical predictor variable (i.e. exposure to AT or not), I decided to present the findings statistically (P values) and using an effect size (ES). This was in order to provide greater

meaning to non-specialist audiences and to identify the magnitude of effect of AT which p-values are unable to confer.

The Odds Ratio (OR) (a measure of ES) is an index that compares the likelihood of an event or outcome occurring in one group (e.g. active treatment group) compared with another group (e.g. TAU) (Ellis, 2010). Therefore, using this measure of ES allowed me to state how likely a person was to report improved medication adherence if they received the programme of AT compared to people who do not receive the therapy.

Though this measure has several statistical advantages and is used extensively in both clinical research and epidemiology, the index may not be helpful in clinical decision making. In addition to presenting the findings for change in adherence as ORs, I wanted the results to be easily interpreted by clinicians who may wish to know how many patients need to be treated with AT before one patient's medication adherence improves. I therefore also decided to present as an alternative level of effect the Numbers Needed to Treat (NNT).

Numbers needed to treat is a method of summarising the effect of treatment in terms of the number of patients a clinician needs to treat with a particular intervention to expect to prevent one adverse event (Cook and Sackett, 1995). In RCTs the NNT is often a measure of treatment benefit where a binary outcome is used. As medication adherence in this trial was determined by a binary outcome, I used the logistic regression model to estimate the NNT for AT in order to show

how many patients would need to be treated before one extra person improved in medication adherence.

As all other outcomes were continuous (PDQ-39, UPDRS, BMQ, EQ-5D, CDS), a linear regression model was used to compare the two groups from baseline to week-12 follow-up. Stratifying factors (i.e. carer or no carer) were adjusted for as with the logistic regression model. The assumptions of normality for both the logistic and linear regression models were checked by comparing the results of these parametric tests to those using the non-parametric bootstrap (where any distribution is assumed). The model results were found to be robust to the model assumptions, indicating that parametric regression models were justified.

Intention to Treat (ITT) analyses were performed for all outcomes and comprised of all patients who had been randomised. For the active treatment group, this was irrespective of their compliance with AT. The principle of ITT was adopted as it provides a pragmatic estimate of the benefit of a change in treatment policy compared to the potential benefit in patients who receive treatment exactly as planned. As AT was planned for delivery over a seven week period, some participants may not have received all the planned sessions. As this is more likely to reflect usual practice, primary analyses of all outcomes were conducted according to the ITT principle.

Per Protocol (PP) analyses were planned for participants who had not deviated from the AT protocol in such a manner that the assessment of efficacy could be biased. This was defined as patients completing at least five out of the seven

planned AT sessions. However, as no patient deviated from the intervention as defined, PP analysis was not undertaken.

Imputation of missing/incomplete data was planned for using iteratively chained equations for all outcome measures. However, no primary outcome data was missing from the trial participant data sets and so multiple imputations were not required.

6.7.4 Subgroup Analysis

As the review presented in Chapter 3 suggested that mood disorders, impaired cognition and the lack of a spouse/carer may be associated with medication non-adherence in PD, subgroup analyses were undertaken testing for the impact of these factors on the primary outcomes. Subgroup effects were tested for with the presence or absence of a spouse/carer, HADS anxiety, HADS depression and MoCA scores with respect to both primary outcomes. Logistic regression was used to test the interaction between the subgroups and MMAS-4 scores. Linear regression was used to test for the interaction between the subgroups and PDQ-39 scores.

6.7.5 Correlation Analyses

As part of the AT assessment each patient provided a score for three separate scales: 'importance', 'confidence' and 'satisfaction'. These were answered in relation to how a patient felt about their prescribed anti-parkinsonian medication.

All three scales were scored from 0-10 and were completed formally at baseline, week-7 and week-12 follow-up. In order to determine whether a change in these three domains was associated with baseline MMAS-4 scores or a change in MMAS-4 scores from baseline to week-12 follow-up, a Spearman's rank correlation coefficient was calculated.

As a separate analysis, the Spearman's rank correlation coefficient was also used to determine whether the overall score on the MoCA and the seven individual sub-domains (visuospatial/executive function, attention, naming, language, abstraction, delayed recall and orientation) were associated with poor adherence at baseline as determined by the MMAS-4.

6.8 Ethical Considerations

6.8.1 Declaration of Helsinki

I ensured that this study was conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

6.8.2 International Conference of Harmonisation Good Clinical Practice

I ensured this study was conducted in full conformity with the relevant regulations and the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

6.8.3 Participant Confidentiality

All data was handled in accordance with the Data Protection Act (1998), which requires data to be anonymised as soon as it is practical to do so. Participants were identified only by participant ID numbers (CRTU and study ID). Each participant had their own Case Record File (CRF) containing consent forms, completed outcome measures, AE forms and demographic information as previously described. Only I, the direct study supervisors and the nurse specialists assisting in recruitment were able to access personal identifiable data.

The study participants were identified in their CRF and in electronic databases only by their unique 'study' identification number. Only I had access to an encrypted Excel spread sheet containing patients names and addresses (required initially for study invitation and then for home visits if later randomised). Databases and all documents were stored securely on a password protected computer or in a locked cabinet.

On an annual basis I completed Good Clinical Practice training. I also held a valid Honorary NHS Research Associates contract at all times throughout the duration of the clinical trial which facilitated access to clinical environments.

6.8.4 Research Ethics and Governance

Prior to commencing the study, a copy of the full trial protocol (Appendix 28) and all associated documents were submitted for ethical review by Cambridge Central NHS Research Ethics Committee. The study was awarded a favourable ethical on

June 7th 2011 (Appendix 29). Approval was also granted from Norfolk and Norwich University Hospital (NNUH) Research & Development (R&D) department.

6.9 Protocol Amendments

6.9.1 Amendment to Inclusion Criteria

In the initial protocol it was stated that patients scoring ≥ 2 on the MMAS-4 would be considered eligible for inclusion in the trial. However, the authors of the MMAS-4 suggest that a score of ≥ 1 (i.e. one 'yes' response out of four) is adequate to signify non-adherence. This scoring system was validated by the authors and has been used in this light in other research studies.

Originally I increased the cut-off from ≥ 1 'yes' response to ≥ 2 'yes' responses. However, increasing the cut-off in this way resulted in 11 patients who scored 1 'yes' response being deemed ineligible for the study. Therefore, in order ensure the recruitment target was achieved I sought ethical approval to lower the MMAS-4 score from ≥ 2 'yes' responses to ≥ 1 'yes' response. This request was reviewed by the ethics committee and was awarded a favourable ethical opinion on 29th November 2011 (Appendix 30). The 11 patients who were initially excluded were contacted again by post and asked to complete the MMAS-4 again if they still wished to participate in the clinical trial. Of the 6 who responded, all were subsequently randomised.

6.9.2 Protocol Breach

During the trial period a protocol breach occurred, resulting in a temporary halt to study recruitment. This protocol breach happened when I provided the names and contact details of some study participants to another PhD student at UEA who had almost identical inclusion criteria. The information below provides further detail.

Dr Katherine Deane (primary supervisor to another PhD student and secondary supervisor to myself) asked me to identify patients suitable for this student's project from my RCT study data. These were the patients who replied to my study invitation, indicated their interest and returned the screening questionnaire but were adherent to their medication and thus not suitable for the RCT.

Retrospective identifying of potential participants was permitted within the other student's study protocol where it was intended that clinical staff would identify potentially eligible patients (both retrospectively and prospectively) and send them an invitation pack by post from the clinic.

The error occurred when names and addresses of potentially eligible patients were transferred from me to the other PhD student by UEA email. This student received the names and addresses of 90 patients (with the implicit information that they had PD). The student then sent invitation packs to 44 of the patients inviting them to participate in their research. This activity breached both study protocols.

The other student and I were informed by Dr Katherine Deane beforehand that this process was acceptable. This was because I held a valid NHS Honorary Contract

and it was believed that I represented a member of the clinical team (which the clinical leads of Neurology and Medicine for the Elderly departments had approved). As the other PhD student's protocol specified a member of the clinical team could identify prospective study participants, I was therefore asked to do this which is where the error occurred. This unfortunate error was realised by the research teams within a few days of the letters being posted by the second PhD student. Both studies ceased recruitment on 10.02.12.

At this juncture my role as a member of the clinical team was also queried with the NHS ethics committee, despite having approval from the NNUH R&D department that this was acceptable.

6.9.2.1 Actions Taken to Rectify

Initially advice was sought from NNUH and UEA Data Protection Officers regarding whether the Information Commissioner's Office needed to be informed. The Caldicott Guardian was also informed via NNUH R&D in addition to UEA R&D and the sponsor (Sue Steel, Contracts Manager, UEA). The following actions took place:

The Research Governance offices of both UEA and NNUH (having taken advice from the Data Protection Officers for UEA and NNUH) wrote a joint letter to all 90 patients whose data had been inappropriately shared. None of the patients in receipt of this letter registered a complaint.

The NNUH Research Governance Committee met and recommended that those involved complete further training in ICH GCP and NHS Information Governance. All involved completed the appropriate training as requested.

The NHS REC decided that it was not appropriate for me to continue in my capacity as a clinical team member and that approval for this should not have been granted by the NNUH R&D department. It was suggested that a data clerk employed by NNUH take over initial screening for my clinical trial.

6.9.2.2 Conclusion to Protocol Breach

Cambridge Central REC issued a favourable opinion letter for the restart of participant recruitment (Appendix 31). The NNUH Research Governance Committee stated that they were content for recruitment to restart for both studies once training certificates had been received. A letter was subsequently issued on 27th April 2012 from NNUH R&D office stating that recruitment was able to recommence (Appendix 32).

6.10 Chapter Summary

This chapter commenced by introducing the RCT as a research design commonly employed in studies investigating the efficacy of interventions. The characteristics of the design that result in the high internal validity associated with RCTs was outlined and the use of stratification was highlighted. Having described the development of AT in Chapter 5, the hypothesis and aims for a RCT were presented. Justifications for the selection of the study outcomes were given and a detailed account of the trial methods and analytical techniques were reported. The chapter ended with a discussion of the main ethical considerations of the study. In the next chapter I present the findings of the clinical trial.

Part 3

CHAPTER 7

Trial Results

7.1 Introduction

This chapter reports the findings of a RCT investigating the efficacy of a novel intervention (Adherence Therapy) for improving medication adherence and QoL in medication non-adherent patients with PD. A diagram of participant flow through the trial is presented and the baseline demographic and clinical characteristics of the trial participants are reported. Results for week-12 (primary analysis) and immediately post intervention (week-7) are presented and the findings of all sub-group analyses are reported.

7.2 Participant Flow

During the recruitment period (September 2011 to January 2013) a total of 2508 patients were screened from Neurology and Medicine for the Elderly clinics. Of these, 1783 were excluded due to having no Parkinsonian condition. A further 298 did not meet the remaining inclusion criteria. A total of 427 patients were invited by post to participate in the study. Of the 249 who responded, 173 (69%) reported sound adherence (MMAS-4 = 0). The remaining eligible patients (n=76) were randomly assigned to either the active treatment group (n=38) or TAU (n=38).

Throughout the trial duration, no patients withdrew from either treatment group. Twenty-five (66%) of the patients in the active treatment group were randomised with a spouse/carer compared to 23 (61%) in the TAU group. One carer discontinued the trial from both groups due to not being able to attend many of the scheduled sessions.

No patient or spouse/carer who completed the trial received less than 5 of the 7 therapy sessions. Five patients (13%) completed 5 out of the 7 sessions and 8 (21%) completed 6 out the 7 therapy sessions. For the spouse/carers, 6 (25%) completed 5 of the 7 AT sessions and 8 (33%) completed 6 of the 7 sessions. The mean duration of an AT session was 40 minutes (range 30-60). Figure 7.1 displays the CONSORT diagram (Schulz et al., 2010) showing the flow of participants through the trial.
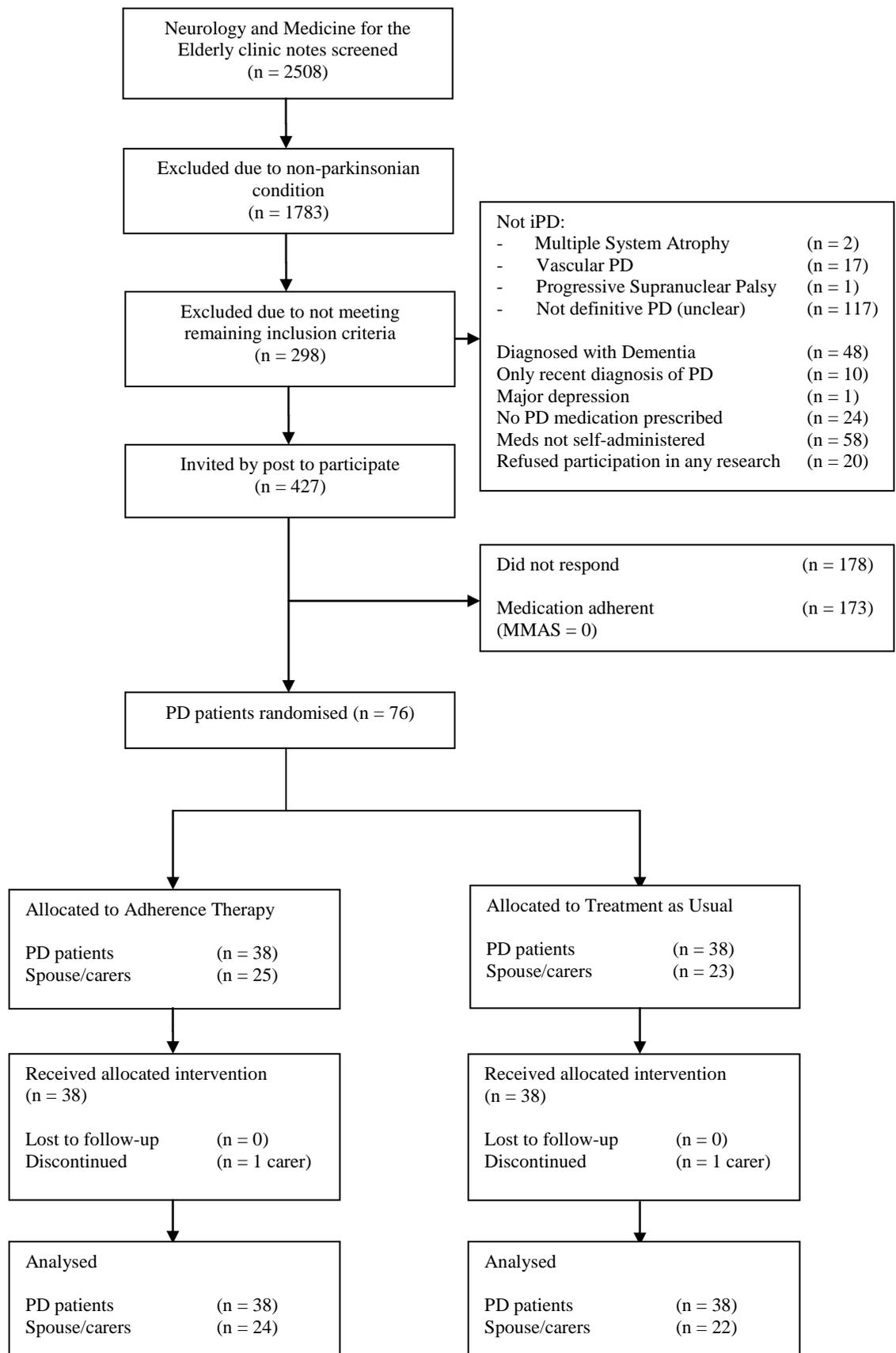
Figure 7. 1 - Trial CONSORT Participant Flow Diagram

7.3 Study Population

7.3.1 Baseline Demographic & Clinical Characteristics

Demographic and clinical characteristics of the study participants by treatment allocation at baseline are presented in Table 7.1. Baseline demographics and clinical characteristics were mostly balanced evenly between the two treatment groups, indicating randomisation had been successful. There was a difference in the numbers reporting dyskinesia at baseline. As this did not relate to either of the study primary outcomes, the TSC did not deem this to be problematic.

The mean age of the trial participants was 72 years. Almost all participants were Caucasian and British, typical of the geographical area from which they were recruited. Both treatment groups were similar in relation to MoCA and HADS scores at baseline. Medication profiles for both treatment groups were almost identical for Levodopa Equivalent Daily Doses and both groups shared a comparable number of daily PD tablets/doses. Slightly more of the active treatment group were retired and had slightly longer disease duration. However, for disease duration the between group difference was small compared to the within group standard deviations (variance). Hence, I did not consider that this would confound the effect of the intervention.

Table 7. 1 - Baseline Demographic & Clinical Characteristics

Characteristic	Active Treatment n=38		TAU n=38		P=
Age in years (mean & s.d.)	72.2	(9.5)	71.6	(8.3)	0.78
Male (%)	25	(65.8)	24	(63.2)	0.81
Hoehn & Yahr (mean & s.d.):	2.1	(1.1)	2.2	(1.1)	0.96
Duration of PD in years (mean & s.d.)	8.7	(6.4)	7.8	(4.2)	0.50
Reported dyskinesia (%)*	15	(39)	9	(24)	-
Reported motor fluctuations (%)*	18	(47)	18	(47)	-
Retired (%)	37	(97.4)	32	(84.2)	0.71
Living with spouse/carer (%)	25	(65.8)	23	(60.5)	0.81
White British (%)	38	(100)	36	(94.7)	0.49
MoCA	27.0	(3.0)	26.0	(4.0)	0.20
HADS – anxiety	4.0	(5.0)	3.5	(6.0)	0.77
HADS – depression	5.0	(3.0)	5.0	(6.0)	0.55
Number of comorbidities	2.0	(3.0)	1.0	(3.0)	0.39
LEDD (mg)	669.4	(629.8)	660.6	(634.4)	0.87
Number of PD drugs prescribed	2.0	(1.0)	2.0	(1.0)	0.57
Number of PD Tablets Taken Daily	6.0	(5.0)	6.5	(5.0)	0.92
Number of PD Daily Doses	4.0	(1.0)	4.0	(1.0)	0.94
Number of Non-PD Tablets Taken Daily	6.0	(7.0)	4.0	(7.0)	0.13
Number of Total Tablets Taken Daily	13.0	(9.0)	11.5	(8.0)	0.18

Median & IQR: Interquartile Range, unless stated otherwise; MoCA: Montreal Cognitive Assessment Scale; HADS: Hospital Anxiety & Depression Scale; LEDD: Levodopa Equivalent Daily Doses; *: Movement Disorders Society – Unified Parkinson's Disease Rating Scale part IV

7.3.2 Baseline Outcome Measures

Baseline outcome measure scores for each treatment group are presented in Table 7.2. All outcome scores were reasonably comparable between the groups with exception of the MMAS-4, where there was a slight imbalance in the number of patients scoring 3 or 4 with no participants in the TAU group scoring either at baseline.

Table 7. 2 - Baseline Outcome Measure Scores

Characteristics	Active Treatment n=38		TAU n=38		P=
MMAS-4 (%):	-	-	-	-	0.46
1	9	(23.7)	8	(21.1)	-
2	24	(63.2)	30	(78.9)	-
3	3	(7.9)	0	(0.0)	-
4	2	(5.3)	0	(0.0)	-
PDQ-39: (Total score)	33.9	(13.3)	31	(14.2)	0.35
PDQ-39: mobility	47.9	(25.9)	40.1	(28.1)	0.21
PDQ-39: Activities of daily living	42.6	(23.0)	37.6	(23.6)	0.36
PDQ-39: Emotional wellbeing	30.7	(19.8)	27.3	(20.0)	0.46
PDQ-39: Stigma	21.7	(23.0)	23.2	(22.1)	0.76
PDQ-39: Social support	14.3	(18.9)	13.1	(16.5)	0.76
PDQ-39: Cognition	41.7	(18.9)	41.6	(21.3)	0.98
PDQ-39: Communication	27.9	(19.7)	24.6	(20.7)	0.47
PDQ-39: Body discomfort	45.0	(24.8)	39.9	(24.8)	0.38
BMQ: Specific concerns	17.3	(4.2)	18.5	(3.7)	0.19
BMQ: Specific necessity	19.8	(3.2)	19.5	(2.6)	0.63
BMQ: General overuse	11.6	(2.4)	11.2	(2.4)	0.48
BMQ: General harm	9.9	(1.9)	9.7	(1.7)	0.53
MDS-UPDRS: part 1	3.9	(3.3)	3.9	(2.9)	0.97
MDS-UPDRS: part 2	29.9	(11.8)	26.5	(10.0)	0.17
MDS-UPDRS: part 4	3.8	(4.8)	2.8	(3.5)	0.34
EQ-5D (utility)	0.6	(0.3)	0.6	(0.2)	0.47
	n=25		**n=23**		
CDS (total)	22.5	(12.6)	21.1	(13.0)	0.90
BMQ Overuse (Carers)	12.1	(2.7)	12	(2.6)	0.89
BMQ Harm (Carers)	9.1	(2.1)	9.7	(2.6)	0.79

Means & s.d. unless stated otherwise; MMAS-4: Morisky Medication Adherence Scale; PDQ-39: Parkinson's disease Questionnaire-39; BMQ: Beliefs about Medication Questionnaire; MDS-UPDRS: Movement Disorders Society – Unified Parkinson's Disease Rating Scale

7.4 Efficacy Analyses

7.4.1 Primary Outcomes

Medication Adherence (MMAS-4):

Week-12 primary analysis showed that 60.5% of the active treatment group improved in medication adherence from baseline compared to only 15.8% in the TAU group, with those in the active treatment group having more than 8 times the odds of decreasing their MMAS-4 score than those in the TAU group (Odds Ratio [OR] 8.2; 95% confidence interval [CI] 2.8, 24.3; $p<0.001$). Week-12 analysis revealed the NNT was 2.2, indicating that for every 2.2 patients treated with AT 1 more would experience a decrease in their MMAS-4 score than if treated with TAU alone (95% CI: 1.6, 3.9) (Table 7.3a/b).

Separate analysis from baseline to week-7 (directly post intervention) showed that 64.8% of the active treatment group improved in medication adherence compared to 26.3% in the TAU group, with those in the active treatment group having more than 6 times the odds of decreasing their MMAS-4 score than those in the TAU group (OR 6.1; 95% CI: 2.2, 16.4; $p<0.001$). Week-7 analysis revealed the NNT was 2.4 (95% CI: 1.6, 4.6) (Table 7.4a/b).

Quality of Life (PDQ-39):

The PDQ-39 improved from 33.9 at baseline to 27.1 at week-12 follow-up (-6.8) in the active treatment group, but worsened from 31.0 to 33.3 (+2.3) in the TAU group. This between group difference was statistically significant (-9.0; 95% CI: -12.2, -5.8; $p<0.001$).

The PDQ-39 also improved from 33.9 to 30.1 at week-7 follow-up (-3.8) in the active treatment group, but worsened from 31.0 to 31.5 (+0.5) in the TAU group. This between group difference was also statistically significant (-4.2; 95% CI: -7.2, -1.3; p=0.004).

Separate analyses from baseline to week-12 follow-up for the eight domains of the PDQ-39 showed that participants in the active treatment group significantly improved in mobility (-10.9; 95% CI: -16.0, -5.9; p<0.001), activities of daily living (-13.2; 95% CI: -19.4, -7.0; p<0.001), emotional wellbeing (-5.4; 95% CI: -10.0, -0.9; p=0.020), cognition (-9.9; 95% CI: -16.1, -3.9; p=0.002), communication (-8.5; 95% CI: -14.4, -2.6; p=0.005) and body discomfort (-13.2; 95% CI: -22.1, -4.3; p=0.004) compared to participants in the TAU group.

7.4.2 Sensitivity Analysis

As stated above, the active treatment group had a slight imbalance towards higher MMAS-4 scores compared to the TAU group at baseline (5 active treatment group patients scored >2 compared to no controls). Due to the large magnitude of effect observed in the MMAS-4 between the two treatment groups, I did not believe that this small between group imbalance was sufficient to significantly confound the results. However, as this may have resulted in a greater potential for change in the active treatment group, I decided to conduct a sensitivity analysis by removing these five patients. The findings showed that whilst the odds ratios are slightly smaller for both week-7 (OR 5.6; 95% CI: 2.0, 15.6) and week-12 (OR 7.2; 95% CI: 2.4, 22.0) analyses, a highly significant effect (P<0.002) was still observed.

7.4.3 Secondary Outcomes

For secondary outcomes, the BMQ (general harm domain) improved from 9.9 at baseline to 9.1 (-0.8) at week-12 follow-up in the active treatment group, but worsened from 9.7 to 9.9 (+0.2) in the TAU group. This between group difference was statistically significant (-1.0; 95% CI: -1.9, -0.2; p=0.019). There was no statistically significant difference between the groups from baseline to week-12 follow-up for the BMQ general overuse, specific concern and specific necessity domains. Only the MDS-UPDRS part II (motor experiences of daily living) differed significantly between the groups from baseline to week-12 follow-up (-4.8; 95% CI: -8.1, -1.4; p=0.006), with the active treatment group improving from 29.9 to 28.3 (-1.6) compared to the TAU group who worsened from 26.5 to 29.7 (+3.2). There was no statistically significant difference between the groups from baseline to week-12 follow-up in the EQ-5D or either of the two spouse/carer outcomes (i.e. BMQ and CDS).

Table 7. 3a - Adjusted Outcomes (Baseline to Week-12 Follow-up)

Outcome Measure	Active Treatment n=38 (24 carers)		TAU n=38 (22 carers)		Adjusted for Carer				
	N	*(%)*	*N*	*(%)*	*Odds ratio*	*(95% CI)*	*P-value*	*NNT*	*95% NNT*
MMAS-4 no change or increase	15	(39.5)	32	(84.2)					
MMAS-4 decrease	23	(60.5)	6	(15.8)	8.2	(2.8 - 24.3)	<0.001	2.2	(1.6 - 3.9)
	mean	*(s.d.)*	*mean*	*(s.d.)*	*difference*	*(95% CI)*	*P-value*		
PDQ-39: (Total score)	-6.8	(6.4)	2.3	(7.4)	-9.0	(-12.2, -5.8)	<0.001		
PDQ-39: mobility	-8.4	(12.7)	2.5	(8.9)	-10.9	(-16.0, -5.9)	<0.001		
PDQ-39: Activities of daily living	-8.7	(11.5)	4.6	(15.1)	-13.2	(-19.4, -7.0)	<0.001		
PDQ-39: Emotional wellbeing	-5.3	(9.9)	0.2	(9.9)	-5.4	(-10.0, -0.9)	0.020		
PDQ-39: Stigma	-6.1	(13.3)	-0.6	(13.9)	-5.4	(-11.4, 0.7)	0.080		
PDQ-39: Social support	-4.7	(12.4)	-1.8	(9.2)	-2.8	(-7.8, 2.2)	0.267		
PDQ-39: Cognition	-4.1	(14.0)	5.9	(12.6)	-9.9	(-16.1, -3.9)	0.002		
PDQ-39: Communication	-5.3	(13.5)	3.3	(12.1)	-8.5	(-14.4, -2.6)	0.005		
PDQ-39: Body discomfort	-11.3	(19.9)	1.2	(19.0)	-13.2	(-22.1, -4.3)	0.004		
BMQ: Specific concerns	-1.0	(4.2)	0.03	(2.6)	-1.1	(-2.6, 0.5)	0.179		
BMQ: Specific necessity	0.4	(3.4)	0.3	(2.1)	0.2	(-1.1, 1.4)	0.779		
BMQ: General overuse	-0.6	(2.7)	0.4	(1.8)	-0.9	(-1.9, 0.1)	0.079		
BMQ: General harm	-0.8	(2.2)	0.2	(1.4)	-1.0	(-1.9, -0.2)	0.019		
MDS-UPDRS: part 1	-1.0	(2.7)	0.1	(2.2)	-1.1	(-2.2, 0.02)	0.054		
MDS-UPDRS: part 2	-1.6	(8.8)	3.2	(5.4)	-4.8	(-8.1, -1.4)	0.006		
MDS-UPDRS: part 4	-0.3	(3.6)	-0.1	(2.6)	-0.2	(-1.6, 1.2)	0.787		
EQ-5D (utility):	0.04	0.3	-0.03	0.3	0.07	(-0.1, 0.2)	0.055		
CDS (total): median (IQR)	-2.0	(4.5)	0.5	(5.0)			0.064		
BMQ Overuse: median (IQR)	-1.0	(2.0)	-0.5	(2.0)			0.250		
BMQ Harm: median (IQR)	-1.0	(1.0)	0.0	(0.0)			0.181		

Table 7. 4b - Unadjusted Outcomes (Baseline to Week-12 Follow-up)

Outcome Measure	Active Treatment n=38 (24 carers)		TAU n=38 (22 carers)		Unadjusted for Carer				
	N	*(%)*	*N*	*(%)*	*Odds ratio*	*(95% CI)*	*P-value*	*NNT*	*95% NNT*
MMAS-4 no change or increase	15	(39.5)	32	(84.2)					
MMAS-4 decrease	23	(60.5)	6	(15.8)	8.2	(2.8 - 24.3)	<0.001	2.2	(1.6 - 4.0)
	mean	*(s.d.)*	*mean*	*(s.d.)*	*difference*	*(95% CI)*	*P-value*		
PDQ-39: (Total score)	-6.8	(6.4)	2.3	(7.4)	-9.1	(-12.2, -5.9)	<0.001		
PDQ-39: mobility	-8.4	(12.7)	2.5	(8.9)	-10.9	(-16.0, -5.9)	<0.001		
PDQ-39: Activities of daily living	-8.7	(11.5)	4.6	(15.1)	-13.3	(-19.4, -7.1)	<0.001		
PDQ-39: Emotional wellbeing	-5.3	(9.9)	0.2	(9.9)	-5.5	(-10.0, -0.9)	0.020		
PDQ-39: Stigma	-6.1	(13.3)	-0.6	(13.9)	-5.6	(-11.8, 0.6)	0.080		
PDQ-39: Social support	-4.7	(12.4)	-1.8	(9.2)	-2.9	(-7.9, 2.2)	0.256		
PDQ-39: Cognition	-4.1	(14.0)	5.9	(12.6)	-10.0	(-16.1, -3.9)	0.002		
PDQ-39: Communication	-5.3	(13.5)	3.3	(12.1)	-8.6	(-14.4, -2.7)	0.005		
PDQ-39: Body discomfort	-11.3	(19.9)	1.2	(19.0)	-13.1	(-22.0, -4.2)	0.004		
BMQ: Specific concerns	-1.0	(4.2)	0.03	(2.6)	-1.03	(-2.6, 0.6)	0.202		
BMQ: Specific necessity	0.4	(3.4)	0.3	(2.1)	0.13	(-1.2, 1.4)	0.841		
BMQ: General overuse	-0.6	(2.7)	0.4	(1.8)	-0.9	(-2.0, 0.1)	0.081		
BMQ: General harm	-0.8	(2.2)	0.2	(1.4)	-1.03	(-1.9, -0.2)	0.018		
MDS-UPDRS: part 1	-1.0	(2.7)	0.1	(2.2)	-1.1	(-2.2, 0.007)	0.054		
MDS-UPDRS: part 2	-1.6	(8.8)	3.2	(5.4)	-4.8	(-8.1, -1.5)	0.005		
MDS-UPDRS: part 4	-0.3	(3.6)	-0.1	(2.6)	-0.2	(-1.6, 1.2)	0.005		
EQ-5D (utility):	0.04	0.3	-0.03	0.3	0.07	(-0.05, 0.2)	0.250		
CDS (total): median (IQR)	-2.0	(4.5)	0.5	(5.0)			0.064		
BMQ Overuse: median (IQR)	-1.0	(2.0)	-0.5	(2.0)			0.250		
BMQ Harm: median (IQR)	-1.0	(1.0)	0.0	(0.0)			0.181		

Table 7. 5a - Adjusted Outcomes (Baseline to Week-7 Follow-up)

Outcome Measure	Active Treatment n=38 (24 carers)		TAU n=38 (22 carers)		Adjusted for Carer				
	N	*(%)*	*N*	*(%)*	*Odds ratio*	*(95% CI)*	*P-value*	*NNT*	*95% NNT*
MMAS-4 no change or increase	12	(31.6)	28	(73.7)					
MMAS-4 decrease	26	(64.8)	10	(26.3)	6.1	(2.3 - 16.4)	<0.001	2.4	(1.6 - 4.6)
	mean	*(s.d.)*	*mean*	*(s.d.)*	*difference*	*(95% CI)*	*P-value*		
PDQ-39: (Total score)	-3.8	(7.3)	0.5	(5.7)	-4.3	(-7.2, -1.3)	0.004		
PDQ-39: mobility	-5.7	(10.8)	1.2	(9.4)	-6.8	(-11.5, -2.2)	0.005		
PDQ-39: Activities of daily living	-7.1	(14.0)	2.1	(14.6)	-9.1	(-15.7, -2.5)	0.007		
PDQ-39: Emotional wellbeing	-4.5	(9.9)	0.7	(8.5)	-5.	(-9.4, -0.9)	0.019		
PDQ-39: Stigma	-4.7	(13.4)	-1.3	(10.3)	-3.2	(-8.4, 2.1)	0.232		
PDQ-39: Social support	-0.6	(15.8)	-1.6	(7.7)	1.1	(-4.6, 6.8)	0.701		
PDQ-39: Cognition	-1.2	(15.8)	3.2	(10.1)	-4.4	(-10.5, 1.7)	0.159		
PDQ-39: Communication	-0.9	(12.4)	0.9	(13.5)	-1.8	(-7.8, 4.2)	0.548		
PDQ-39: Body discomfort	-5.9	(15.8)	-0.9	(19.2)	-5.2	(-13.3, 2.8)	0.199		
BMQ: Specific concerns	-0.3	(3.9)	4.9	(32.4)	-5.4	(-15.9, 5.2)	0.313		
BMQ: Specific necessity	0.2	(2.7)	0.4	(2.2)	-0.2	(-1.2, 0.9)	0.779		
BMQ: General overuse	-0.4	(2.2)	0.2	(1.9)	-0.5	(-1.5, 0.4)	0.276		
BMQ: General harm	-0.6	(2.3)	-0.2	(1.5)	-0.4	(-1.3, 0.5)	0.361		
MDS-UPDRS: part 1	-1.2	(2.9)	-0.3	(2.0)	-0.8	(-1.9, 0.3)	0.154		
MDS-UPDRS: part 2	-1.6	(5.9)	1.7	(5.5)	-3.4	(-5.9, - 0.7)	0.015		
MDS-UPDRS: part 4	-0.03	(3.3)	-0.2	(2.7)	0.2	(-1.2, 1.5)	0.828		
EQ-5D (utility):	0.01	0.3	0.01	0.2	0.003	(-0.1, 0.1)	0.962		
CDS (total): median (IQR)	-0.5	(6.5)	1.0	(7.0)			0.269		
BMQ Overuse: median (IQR)	0.0	(1.5)	0.0	(2.0)			0.354		
BMQ Harm: median (IQR)	-0.5	(2.5)	0.0	(1.0)			0.637		

Table 7. 6b - Unadjusted Outcomes (Baseline to Week-7 Follow-up)

Outcome Measure	Active Treatment n=38 (24 carers)		TAU n=38 (22 carers)		Unadjusted for Carer				
	N	*(%)*	*N*	*(%)*	*Odds ratio*	*(95% CI)*	*P-value*	*NNT*	*95% NNT*
MMAS-4 no change or increase	12	(31.6)	28	(73.7)					
MMAS-4 decrease	26	(64.8)	10	(26.3)	8.2	(2.8 - 24.2)	<0.001	2.4	(1.6 - 4.6)
	mean	*(s.d.)*	*mean*	*(s.d.)*	*difference*	*(95% CI)*	*P-value*		
PDQ-39: (Total score)	-3.8	(7.3)	0.5	(5.7)	-4.3	(-7.3, -1.3)	0.006		
PDQ-39: mobility	-5.7	(10.8)	1.2	(9.4)	-6.8	(-11.5, -2.2)	0.004		
PDQ-39: Activities of daily living	-7.1	(14.0)	2.1	(14.6)	-9.2	(-15.7, -2.6)	0.007		
PDQ-39: Emotional wellbeing	-4.5	(9.9)	0.7	(8.5)	-5.2	(-9.4, -0.9)	0.017		
PDQ-39: Stigma	-4.7	(13.4)	-1.3	(10.3)	-3.4	(-8.8, 2.1)	0.224		
PDQ-39: Social support	-0.6	(15.8)	-1.6	(7.7)	1.1	(-4.6, 6.8)	0.706		
PDQ-39: Cognition	-1.2	(15.8)	3.2	(10.1)	-4.4	(-10.4, 1.7)	0.155		
PDQ-39: Communication	-0.9	(12.4)	0.9	(13.5)	-1.8	(-7.7, 4.1)	0.543		
PDQ-39: Body discomfort	-5.9	(15.8)	-0.9	(19.2)	-5.1	(-13.1, 2.9)	0.209		
BMQ: Specific concerns	-0.3	(3.9)	4.9	(32.4)	-5.2	(-15.8, 5.3)	0.326		
BMQ: Specific necessity	0.2	(2.7)	0.4	(2.2)	-0.2	(-1.3, 0.9)	0.742		
BMQ: General overuse	-0.4	(2.2)	0.2	(1.9)	-0.5	(-1.5, 0.4)	0.281		
BMQ: General harm	-0.6	(2.3)	-0.2	(1.5)	-0.4	(-1.3, 0.5)	0.355		
MDS-UPDRS: part 1	-1.2	(2.9)	-0.3	(2.0)	-0.8	(-2.0, 0.3)	0.147		
MDS-UPDRS: part 2	-1.6	(5.9)	1.7	(5.5)	-3.3	(-5.9, - 0.7)	0.015		
MDS-UPDRS: part 4	-0.03	(3.3)	-0.2	(2.7)	0.2	(-1.2, 1.5)	0.818		
EQ-5D (utility):	0.01	0.3	0.01	0.2	0.003	(-0.1, 0.1)	0.953		
CDS (total): median (IQR)	-0.5	(6.5)	1.0	(7.0)			0.269		
BMQ Overuse: median (IQR)	0.0	(1.5)	0.0	(2.0)			0.354		
BMQ Harm: median (IQR)	-0.5	(2.5)	0.0	(1.0)			0.637		

7.5 Sub-group Analyses

For the analyses testing for an interaction between the subgroup factors (spouse/carer or no spouse/carer, baseline HADS and baseline MoCA scores) and the treatment effect of AT, only a score of <8 on the HADS anxiety domain (indicating no anxiety) compared to ≥8 (indicating symptoms of anxiety) predicted greater medication adherence. Those in the active treatment group had more than 21 times the odds of decreasing their MMAS-4 than participants in the TAU group (OR 21.1; 95% CI: 4.1, 107.6; p=0.05). There was no statistically significant interaction of either subgroup factor on PDQ-39 scores (Table 7.5).

Table 7. 7 - Sub-group Interactions with Primary Outcomes

Outcome Measure	Subgroup	Odds ratio	(95% CI)	Interaction p-value
MMAS-4 change	Carer	12.4	(2.9, 53.6)	0.35
	No carer	4.3	(0.8, 22.9)	
	HADSA (0 – 7)	21.1	(4.1, 107.6)	0.05
	HADSA (8 +)	1.4	(0.2, 9.8)	
	HADSD (0 – 7)	6.9	(1.9, 25.1)	0.36
	HADSD (8 +)	34.1	(2.0, 581.5)	
	MoCA (0 – 25)	7.6	(0.7, 79.5)	
	MoCA (26 +)	9.1	(2.3, 36.1)	0.92

PDQ-39 change	Subgroup	Mean difference	(95% CI)	Interaction p-value
	Carer	-10.4	(-15.0, -5.9)	0.24
	No carer	-6.5	(-10.15, -2.8)	
	HADSA (0 – 7)	-8.4	(-11.74, -5.0)	0.40
	HADSA (8 +)	-11.7	(-20.47, -2.9)	
	HADSD (0 – 7)	-9.5	(-12.4, -6.6)	0.92
	HADSD (8 +)	-9.0	(-20.13, 2.1)	
	MoCA (0 – 25)	-9.6	(-15.8, -3.4)	
	MoCA (26 +)	-9.2	(-12.82, -5.5)	0.89

7.6 Correlation Analyses

7.6.1 MMAS-4 & Importance, Confidence and Satisfaction

At baseline each patient participant in the active treatment group provided a score for three separate ordinal scales (i.e. importance of, confidence with, and satisfaction with medication). These scales were completed as part of the AT assessment and were answered based upon how participants perceived their anti-parkinsonian medication. All three scales were scored from 0-10 and were completed formally at baseline, week-7 and week-12 follow-up. Table 7.6 shows the mean values for each three domains for participants in the intervention group at each of the three assessment points (baseline, week-7 and week-12).

Table 7.6 - Importance, Confidence and Satisfaction Scores

Domain	n = 38		
	Baseline	Week-7	Week-12
	Mean	Mean	Mean
Importance	8.5	9.2	9.3
Confidence	6.5	8.2	8.2
Satisfaction	7.0	7.7	7.7

To determine whether a change in MMAS-4 score was associated with a change in score for either of the three domains from baseline to week-12 follow-up, a Spearman's rank correlation coefficient was calculated. Additionally, I used the Spearman's rank test to determine whether a change in MMAS-4 from baseline to week-12 follow-up was associated with baseline scores for importance, confidence and satisfaction. Table 7.7 shows the differences in MMAS-4 scores from baseline to week-12 follow-up. Negative scores imply a higher score at baseline. For

example, a change of -2 indicates a 2 point reduction in MMAS-4. This could be from 4 to 2, from 3 to 1, or from 2 to 0.

Table 7. 7 - Difference in MMAS-4 from Baseline to Week-12

Change in MMAS-4	Number of participants (total n=38)	Percentage of participants
-3	2	5.3
-2	6	15.8
-1	15	39.5
0	14	36.8
1	1	2.6

The analysis revealed that a change in MMAS-4 score from baseline to week-12 follow-up was not correlated with a change in importance (Spearman's: r= -0.14, p=0.39); change in confidence (r = 0.15, p=0.37) or change in satisfaction (r = -0.11, p=0.51) from baseline to week-12 follow-up. Similarly, there was no statistically significant association between the change in MMAS-4 scores from baseline to week-12 follow-up and baseline scores for importance (r = 0.01, p=0.95); confidence (r = -0.02, p=0.91) and satisfaction (r= -0.1, p=0.55).

7.6.2 MMAS-4 and MoCA Overall and Sub-domain Scores

Additionally, I used the Spearman's rank correlation coefficient to determine whether the overall score on the MoCA and the seven sub-domains (visuospatial/executive function, attention, naming, language, abstraction, delayed recall and orientation) were associated with poor adherence at baseline, as determined by the MMAS-4. Table 7.8 presents the Spearman's rank coefficients between MMAS-4 scores at baseline and the MoCA total score and the individual

sub-domains. The findings revealed there was no significant association between baseline MMAS-4 scores and the MoCA total score or either sub-domain score.

Table 7. 8 - Association between MMAS-4 and MoCA at Baseline

MoCA total and sub-domain	Correlation coefficient	p-value
Overall score	-0.03	0.82
Visuospatial/executive function	-0.10	0.38
Attention	-0.15	0.19
naming	-0.06	0.63
Language	0.19	0.10
Abstraction	0.12	0.29
Delayed Recall	0.07	0.52
Orientation	-0.08	0.51

7.7 Serious Adverse Events

Throughout the duration of the trial there was one serious adverse event. One participant from the active treatment group was admitted to hospital resulting from general deterioration. The admission was non-parkinsonian related and was not thought to be associated with participation in the clinical trial. The TSC was informed and NNUH's Standard Operating Procedures for reporting of AE's was adhered to. This participant had been allocated to the active treatment group and had completed all AT sessions prior to the hospital admission. The patient agreed to complete week-12 outcome measures as an inpatient.

7.8 Cost of Adherence Therapy in PD

The average time of each AT session was around 40 minutes (range 30–60). Based on an NHS mid-range band seven salary (£35,536/$54,121) (the typical salary of a PD nurse specialist), a 40 minute session of AT is anticipated to cost (£12.21/$18.60). Therefore, to deliver the seven sessions of AT this would cost around (£85/$129.46) per patient.

The average time to travel to the trial participants in this study was around 30 minutes in each direction. Using this average time this would cost around £128 ($194.9) to complete the seven visits. When added to the cost of time spent conducting the AT sessions, this totals £213 ($324.40) per patient.

The cost of fuel also needs to be acknowledged. Based on the average distance travelled for a return journey in this study (44 miles) and the typical claim of 45p per mile travelled, for seven patient visits this would cost around £139 ($211.70).

Therefore, the total cost of seven AT sessions when delivered in a patient's own home by a band 7 PD nurse specialist is estimated to be around £352 ($536.10) per patient.

7.9 Summary of Results

The trial results demonstrate that a seven week programme of AT plus TAU significantly improved medication adherence and QoL compared to TAU alone in medication non-adherent patients with PD.

Improvements were shown in the PDQ-39 overall score and in a range of sub-domains. The improvement in the PDQ-39 overall score was both statistically significant and clinically relevant; that is, the differences from baseline to week-12 follow-up were greater than the minimal clinically important difference reported in a PD sample (Peto et al., 2001).

CHAPTER 8

Discussion of Trial Results

Introduction
Discussion of Results
Correlation Analyses
Implications of Trial Findings
Strengths & Limitations
Adverse Events
Cost of CAAT-PARK
Conclusion

8.1 Introduction

In Chapter 7, I presented the findings of a parallel-group RCT investigating the efficacy of a novel intervention, Adherence Therapy, for improving medication adherence and QoL in people with PD. I hypothesised that there would be a statistically significant difference in medication adherence and QoL in people with PD who received a seven week programme of CAAT-PARK in addition to TAU, compared to those who received TAU only.

During the recruitment period (September 2011 to January 2013) a total of 76 PD patients were randomly assigned to the active treatment group (n=38) or TAU (n=38). No patients withdrew from the trial. Twenty-five of the PD patients in the

active treatment group were randomised with a spouse/carer compared to 23 in the TAU group. One spouse/carer from each group did not complete the study.

Study measurements were completed at baseline, directly post intervention (week-7) and at week-12, the primary analysis point. Primary outcomes were a change from baseline to week-12 follow-up in medication adherence (MMAS-4) and QoL (PDQ-39). Secondary outcomes were a change from baseline to week-12 follow-up in the MDS-UPDRS (parts I, II, IV), BMQ and the EQ-5D. Spouse/carer outcomes were a change in BMQ and CDS.

For primary outcomes, week-12 analysis showed that the active treatment group significantly improved in medication adherence compared to participants in the TAU group. Similarly, participants in the active treatment group showed a statistically significant improvement in QoL compared to those in the TAU group.

This chapter discusses the findings of the trial within the context of related literature. The study strengths and limitations are highlighted and the clinical and research implications of the findings are discussed.

8.2 Discussion of Results

8.2.1 Efficacy Analyses (Medication Adherence)

The findings of the RCT presented in Chapter 7 confirm the usefulness of AT for improving medication adherence and clinical outcomes. These findings replicate those shown in other chronic disease areas. An RCT of AT in patients with hypertension showed that better adherence post intervention significantly lowered blood pressure (Alhalaiqa et al., 2011). When AT was investigated in patients with schizophrenia, psychotic symptoms and attitudes towards medication significantly improved (Maneesakorn et al., 2007).

In both of these studies, shifting patients' beliefs about medication was suggested to result in the improved adherence behaviours observed. However, in the RCT presented in this thesis only a small improvement in beliefs was detected. This may suggest that beliefs and concerns about treatment play a less significant role as a factor contributing to medication non-adherence in people with PD.

Before this theory is dismissed however, the statistically significant difference between the groups in the BMQ general harm domain must not be ignored. This finding may suggest that beliefs about medication use in general are an important factor for enhancing adherence behaviours in PD. One of the BMQ general harm domain items relates to whether patients feel people should intermittently stop their treatment. It is possible therefore that the active treatment group participants scored more positively on this item as a result of improved understanding and acceptance of the need for treatment in PD (discussed later in this thesis). This may provide

some support for the importance of enhancing beliefs about medication in PD and may explain, at least in part, the improved rates of adherence identified in this trial.

It is important to note however, that considering many trial participants did not have negative beliefs at baseline regarding the necessity of PD specific medicines (BMQ specific necessity domain), it is unlikely that the statistically significant improvement in the general harm domain accounted for the improved rates of adherence in this trial. Alternative explanations may however explain such findings.

For example, most PD patients in the active treatment group missed or miss-timed doses due to forgetfulness and/or poor drug management. This was especially prevalent in patients where cognitive impairment and/or treatment regimen complexity was apparent. It is known that PD can affect a variety of cognitive processes such as attention, planning and problem-solving. Therefore, it is possible that such cognitive deficits may have led to difficulties in drug management in some individuals with PD in this study. This may then have resulted in poor adherence (Green et al., 2002).

Furthermore, in PD patients may be prescribed intricate drug regimens to manage symptoms and maximise '*On*' time. This can soon become a polypharmacy which can complicate treatment (Grosset et al., 2005a). Problem solving interventions are believed to work by assisting individuals in developing meaningful strategies to help themselves, such as findings methods to improve adherence behaviours (Gray, 2011). Therefore, using AT techniques to facilitate problem solving strategies

within a patient's own context may explain some of the observed improvements in adherence in PD.

Importantly however, unlike the problem solving strategies adopted in usual CBT approaches where self-generation of ideas is greatly emphasised, the known deficits in problem solving ability in PD patients may mean that self-generated ideas might not always be a realistic goal. It is worth noting that many patients in the active treatment group often required several prompts during the problem solving sessions to help facilitate the generation of useful strategies. Therefore, in PD problem solving is likely to be more effective and relevant if assisted by a therapist and/or spouse/carer, as was the case in the current study. This should therefore be acknowledged when addressing sub-optimal adherence in PD where poor problem solving abilities are thought to be contributory.

The AT assessment (a structured interview) showed ambivalence towards medication, symptoms of depression, denial concerning the indication for treatment and poor understanding of basic anti-parkinsonian pharmacodynamics were all reasons for non-adherence to medication in the active treatment group sample. As these factors are consistent with the systematic review findings presented in Chapter 3 and with proposed reasons for poor adherence described in the existing literature (Bainbridge and Ruscin, 2009, Grosset, 2010), I incorporated my greater understanding of these issues into the AT intervention.

In this trial many patients often miss-timed drug doses as they were unaware of the reasons for medicating according to prescribed time intervals. Facilitating a greater

appreciation of pharmacodynamics, by visual reference to the cumulative effect of erratic dosing (using a simple graphical representation of how fluctuating dopamine concentrations relates to symptom control), greatly enhanced adherence behaviours as patients could visualise how their pill taking practices may affect their unique symptom control.

8.2.2 Efficacy Analyses (QoL)

In addition to improving medication adherence, AT had a statistically significant effect on QoL including a range of PDQ-39 sub-domains. Due to the relatively small sample and the known variability in PD symptoms, this finding was not expected. Although I did not assess MDS-UPDRS motor function (part 3) as part of the clinical trial, the mobility sub-domain did improve on the PDQ-39. As rigidity and bradykinesia are sensitive to anti-parkinsonian medication (Schapira et al., 2009b), and therefore are arguably most likely to respond to optimal treatment, it is reasonable to suggest that the improved adherence observed may account for the identified improvement in mobility. This assumes a linear mechanism of action for AT; that is, improving medication adherence improves symptoms which then impacts positively on QoL. This may not however represent the only mechanism of action of AT, as I will discuss later in this thesis.

Surprisingly, cognition significantly improved according to the PDQ-39. This result was also surprising. Although major cognitive dysfunction is recognised as being refractory to dopamine replacement, bradyphrenia (slowed thinking) is however levodopa responsive with patients often reporting regaining their mental

edge when sufficiently medicated. Researchers have shown improvement in neuropsychological tests following optimisation of dopamine replacement therapy in patients with PD (Kulisevsky et al., 2000, Molloy et al., 2006). As the trial participants were not substantially cognitively impaired, it may be possible therefore that the identified improvements in cognition result from participants feeling mentally more alert due to improved medication adherence. This however is speculative and requires specific investigation.

8.2.3 Sub-group Analyses

The sub-group analyses testing for an interaction between the presence of a spouse/carer, baseline depression and baseline MoCA scores and the treatment effect of AT were all non-significant in this study. It is worth noting that these analyses, as with all sub-group analyses, used small samples. Such analyses are therefore likely to be underpowered to detect a statistically significant effect. For this reason these non-significant associations were expected. However, as the lack of a spouse/carer, symptoms of depression and the presence of cognitive impairment have been found to be associated with non-adherence by previous researchers (as shown in the findings of Chapter 3), greater statistical power may show an interaction between these factors and the treatment effect of AT. A larger RCT that is specifically powered for these sub-group analyses is required to determine whether a significant interaction exists.

Unlike symptoms of depression and poor cognition, a score of <8 on the HADS anxiety scale (no symptoms of anxiety) compared to ≥8 (indicating symptoms of

anxiety) predicted greater medication adherence, with those in the active treatment group found to have significantly greater odds of improving their MMAS-4 score. While symptoms of anxiety appear to be associated with poor adherence in PD (as shown in Chapter 3), due to the underpowered sample and considering that all other interaction analyses were non-significant, this finding was surprising.

Although depression is the most common neuropsychiatric disturbance in PD (Bainbridge and Ruscin, 2009), anxiety is also considerably prevalent; 25-40% of people with PD are reported to experience symptoms of anxiety (Simuni and Fernandez, 2013). Researchers have shown anxiety to be one of the most highly reported non-motor symptoms affecting QoL (Chaudhuri and Martinez-Martin, 2008, Barone et al., 2009, Martinez-Martin et al., 2011). Furthermore, anxiety has been associated with poor medication adherence in the general elderly population, in which PD is most prevalent (Coons et al., 1994). Considering that AT was aimed specifically at patients' unique reasons for non-adherence, it is reasonable to suggest that patients may have felt less anxious as a result of the individualised intervention. As anxiety is associated with QoL in PD, improving the symptoms may also partly explain the improvements in QoL observed in this trial.

It is important to note that the HADS was only completed at baseline in this study. Future investigations of AT in PD should therefore ensure that both symptoms of anxiety and depression are specifically assessed at follow-up as a formal study outcome.

8.3 Correlation Analyses

8.3.1 Correlation: MMAS-4 & Importance, Confidence and Satisfaction

Correlation analyses revealed that a change in MMAS-4 scores from baseline to week-12 follow-up was not statistically associated with a change in scores for either 'importance', 'confidence' or 'satisfaction' with medication. Additionally, analyses showed there was no statistically significant correlation between a change in MMAS-4 scores from baseline to week-12 follow-up and baseline scores for 'importance', 'confidence' or 'satisfaction' with medication. These findings were mostly not surprising and several factors may offer explanation for the non-significant associations.

Firstly, as reported in Chapter 7, beliefs and concerns about medication did not change substantially in this trial. Only beliefs about the use of medication in general and the degree to which they are perceived as fundamentally harmful (BMQ general harm domain) showed a statistically significant difference between the groups. Although the AT assessment identified that some participants held negative beliefs concerning the use of medication, mainly PD patients in this study had positive attitudes towards treatment. For this reason the 'importance of medication' scale was already scored highly by participants at baseline. Therefore, even where medication adherence did improve from baseline to follow-up, the inability of patients to score sufficiently higher on the 'importance of medication' scale may offer an explanation for the non-significant finding in this analysis.

The 'satisfaction with medication' scale was also scored highly by almost all active treatment group participants at baseline. Once again, the inability for a large degree of change and the small numbers involved in the analysis (n=38) suggest that it is not surprising the result was statistically insignificant.

Furthermore, although poor understanding of the indication for treatment may be a factor for non-adherence in PD, whether a relationship between non-adherence and low satisfaction with treatment exists is unknown. Whilst people with PD may be dissatisfied with medication perhaps because of a perceived lack of efficacy or due to the development of motor complications (resulting in them becoming non-adherent to medication), this was not supported in the current study. Therefore, when taking account of these factors, the lack of association between satisfaction with medication and a change in adherence was not unexpected.

Although it was not surprising that a change in MMAS-4 score was not associated with a change in importance of and satisfaction with medication, a significant association between a change in MMAS-4 and the 'confidence in taking medication' scale was expected. As stated above, many patients reported that forgetfulness and poor drug management led to them being non-adherent. Furthermore, issues with problem solving or feeling ambivalent towards medication were apparent in several trial participants. Considering that patients in the active treatment group described feeling more confident after receiving AT (discussed later in this thesis), it is surprising that this was not reflected in the association analysis. The small (n=38), underpowered sample may be a likely explanation for this.

An alternative explanation must also be acknowledged however. As there was a significant effect of AT on QoL, it may be that the enhanced feelings of confidence reported in the post intervention interviews (discussed later) relate specifically to an increased confidence in daily life, and not specifically to confidence in using medication. This may explain the discrepancy between participants verbally reporting increased confidence and the non-significant association between 'confidence in taking medication' and change in adherence.

This offers an important insight into a possible mechanism for the improved QoL observed in this trial. Specifically, this suggests that QoL may be improved in PD after receiving AT without the need for improvements in confidence using/taking medication. The linear mechanism of action of AT proposes that improving medication use/adherence is a pre-requisite to improving clinical outcomes. However, this theory suggests that an alternative mechanism of AT may exist; that is, improving confidence in general, and not specifically confidence using medication, may be an effective method for improving QoL. This will be discussed in greater detail later in this thesis.

The analysis investigating a possible association between a change in MMAS-4 scores from baseline to week-12 follow-up and baseline scores for 'importance', 'confidence' and satisfaction' was also not statistically significant. Again, due to the small sample (n=38), this was expected.

When planning this analysis there was no indication that low scores for either 'importance', 'confidence' or 'satisfaction' would in fact be associated with little

or no improvement in adherence. Likewise, there was no indication that higher scores for these three domains would be associated with greater improvements in medication adherence. Despite this, it may be possible that some patients with low scores are less likely to show improvement in adherence.

For example, it is acknowledged that depression is associated with poor medication adherence in PD (as discussed in Chapter 3). As a consequence, it is reasonable to argue that depressed patients may potentially have lower baseline scores for 'importance', 'confidence' and satisfaction' with medication than their non-depressed counterparts. Therefore, in such patients it is possible that low scores at baseline may result in patients being less likely to improve in adherence when receiving AT, due to underlying symptoms of depression. This theory however is largely theoretical, especially when considering that the interaction analysis discussed earlier between baseline HADS scores and the effectiveness of AT was non-significant for depression. A greater powered study with a depressed PD sample would be required to establish whether depression is associated with lower baseline scores for 'importance', 'confidence' and satisfaction' and whether this then correlated with little or no change in adherence behaviour.

8.3.2 MMAS-4 and MoCA Overall & Sub-domain Scores

Analyses revealed that neither the MoCA overall score nor any of the seven sub-domains were associated with poor medication adherence at baseline (as determined by the MMAS-4). It is known that people with PD can suffer from a variety of cognitive deficits and researchers have found the MoCA to be sensitive

to the detection of cognitive dysfunction in PD (Zadikoff et al., 2008, Nazem et al., 2009). However, to my knowledge the possible association between specific cognitive domains on the MoCA and medication non-adherence in PD has not been investigated previously.

Due to the small numbers involved in this analysis the insignificant findings were not unexpected. Additionally, considering that adherence was determined using only the four item MMAS, detecting a correlation between cognitive dysfunction and poor adherence was not likely. Despite the non-significant findings, it is possible that certain cognitive deficits may be more likely to result in sub-optimal pill taking than others. For example, it is reasonable to suggest that patients who have particular problems with attention may be more likely to miss and/or miss-time doses than a patient who performs less well on the naming and language domains. Therefore, a larger sample of cognitively impaired patients using a more sensitive adherence outcome could show that a poor score on certain domains on the MoCA may be prognostic of sub-optimal adherence. Such a finding may be clinical useful for identifying PD patients most likely to not adhere to treatment.

8.4 Implications of the Trial Findings

The beneficial effect of AT observed in this trial has an important clinical implication. Optimising adherence to anti-parkinsonian medication in PD is just as essential as optimising dosage. It is therefore critical to ensure that adherence is optimised before dose escalation is considered by clinicians. This highlights the

requirement to consider drug adherence when medications are reviewed in PD in both in-patient and out-patient settings. Furthermore, acknowledging the factors associated with medication non-adherence in PD may help clinicians to identify medication non-adherent patients in clinical settings.

Adherence Therapy is a brief intervention that can be delivered by professionals with just a short training period. Ideally healthcare professionals should be able to facilitate optimal medication taking by utilising the principles of AT from diagnosis. This is especially important when considering that early PD is a potential risk factor for non-adherence, as was discussed previously in this thesis.

Grosset and Grosset (2007) showed improvements in medication adherence after providing PD patients with didactic educational material. Whilst such approaches may be effective for some PD patients, as discussed earlier in Chapter 4, the diversity of factors associated with medication non-adherence means that people with PD may require a more patient focused intervention such as that described in this thesis. This is particularly likely to be necessary for those individuals where poor knowledge of PD and its treatment may not represent the main reason for their non-adherent behaviour.

8.5 Strengths and Limitations

This clinical trial had several strengths. Firstly, the sample recruited was largely representative of the PD population. Trials of drug efficacy in PD often exclude patients due to older age (>65), greater disease severity and impaired cognition (Wheatley et al., 2002). I purposely did not exclude such patients and therefore the findings are generalisable for older patients in whom PD is prevalent.

A further strength to this trial is that unlike many adherence interventions, AT was delivered in participants' own homes. As a consequence, severely affected patients were able to participate that could not have done so if required to attend clinic.

Furthermore, deficits in set-shifting (defined as the process of updating cognitive strategies for changing environments/tasks) are prevalent and are associated with poor problem solving abilities in PD (Cronin-Golomb et al., 1994). Therefore, it is possible that the delivery of AT in the familiar home environment, where set-shifting can be minimised by focusing on specific tasks in the correct home context, may have helped patients to problem solve more effectively. Delivering AT in this manner may therefore enable patients to develop meaningful strategies to facilitate improved adherence behaviours. This helps to emphasise the importance of administering adherence promoting interventions in the patient's own home, especially when poor problem solving ability is suspected.

The use of the self-report PDQ-39 as a primary outcome was a significant strength in this study. As described earlier in this thesis, this allowed clinical improvement to be quantified on a scale relevant to patients.

Finally, delivery of AT within the home environment resulted in patients being highly committed. This helps to emphasise the acceptability of and engagement with the AT intervention. This will be discussed in greater detail later in this thesis.

Despite the strengths of this study, there are also some limitations. Firstly, a longer follow-up period would have been desirable to evaluate whether improved adherence was sustained over time. Furthermore, if adherence did show signs of declining over time, a longer period of study would have showed how this correlated with clinical outcomes. This requires specific investigation in future research of AT in PD.

Secondly, the TAU group did not receive an intervention outside of usual care. This makes it difficult to determine whether improvement in outcomes in the active treatment group resulted from the efficacy of AT, or simply due to increased patient-professional interaction. Therefore, a TAU placebo intervention that offers increased professional contact (e.g. such as regular phone calls) would be ideal in larger scale investigations.

Thirdly, I noted that the active treatment group had a slight imbalance towards higher MMAS-4 scores compared to the TAU group at baseline (5 active group patients scored >2 compared to no TAU patients). This might have resulted in a

greater potential for change in the active treatment group. Due to the observed magnitude of effect, I believed it was unlikely that this small imbalance accounted for the significant between group differences in adherence observed at follow-up. However, despite this, I removed these five patients in a sensitivity analysis as described in the previous chapter. Whilst the odds ratios were slightly smaller (5.6 and 7.2 for week-7 and week-12, respectively), a highly significant effect of the intervention on adherence to medication was still observed.

A further limitation to the study is the potential effect of bias. As I was the only person who delivered the seven sessions of AT, bias may have been introduced. For example, as a highly committed PhD student patients may have responded to the AT process differently than if another trained therapist had delivered the intervention. Furthermore, despite all completed measures being self-reports, the lack of blinding of myself to group allocation may have resulted in participants in the active treatment group over-reporting adherence rates in order to please me. Collection of follow-up measures by an individual masked to group allocation would have been desirable and is recommended in future studies of AT.

A final limitation in this trial was the lack of MDS-UPDRS part III (an objective assessment of motor function). As this clinician rated assessment would have been completed by me, this would have led to a large risk of bias. Therefore, future investigations of AT in PD should ensure that the entire MDS-UPDRS is assessed by a rater who is masked to treatment allocation. Additionally, self-efficacy was not assessed as an outcome in this trial. As self-efficacy is linked closely with QoL in chronic conditions, and considering that the findings presented in the next part of

this thesis suggests that improving self-efficacy might be important for optimising adherence in PD, future studies should ensure that this is assessed as a key outcome measure.

8.6 Adverse Events

As stated in the previous chapter, only one adverse event occurred throughout the duration of the clinical trial. This event was not believed to be associated with the AT intervention. This suggests that AT delivered in patients own homes is likely to be an intervention associated with low patient risk.

During the planning of the clinical trial I anticipated that improving medication adherence in some PD patients may lead to the development of motor complications, and in rare situations the onset of psychosis. It is known that these responses to treatment can occur when patients over medicate with dopaminergic therapies. Grosset (2010) suggested that where non-adherence to medication in PD is undetected in clinical settings, this may result in clinicians over prescribing anti-parkinsonian agents in attempt to control symptoms. Acknowledging this, it was reasonable to believe that increased adherence to medication as a result of the AT intervention may lead to complications due to overdosing on anti-parkinsonian agents. Although this was not apparent in the current study, larger scale investigations of AT in PD should acknowledge this potentiality.

8.7 Cost of Adherence Therapy in PD

Although no formal health economic analyses were conducted, the cost for an NHS band seven PD nurse specialist to deliver seven sessions of AT to one patient is estimated to be around £352 ($521). When acknowledging the small NNT outlined in Chapter 7 and considering the potential future cost savings of increased adherence in PD, this suggests AT is likely to be a cost effective treatment. Kulkarni et al. (2008) showed that sub-optimal medication adherence in PD was associated with poor symptom control, increased unplanned hospital visits for PD related problems and a poorer overall prognosis compared to medication adherent PD patients. It is possible therefore that optimising symptom control through improvement in medication adherence may be financially beneficial to healthcare systems globally.

As reported in Chapter 7, the EQ-5D did not show a statistically significant difference between the intervention groups at week-12 follow-up. As with all the secondary outcomes, lack of statistical power may explain the non-significant result. However, an alternative explanation is also likely. Unlike the PDQ-39, the EQ-5D is not disease specific. Therefore, a large change in a patient's perception of their symptoms and their ability to perform ADL's is likely to be required for change to be detected in a PD sample using the EQ-5D. This may explain why the PDQ-39 showed a significant between group difference and the non-specific EQ-5D did not. As there was no change in the EQ-5D, I did not assess health utility.

It is important to note that the average length of an AT session in this clinical trial was greater than in studies of AT in other chronic conditions. Due to the older age of many trial participants and the known impairments in attention and set-shifting in PD, it is important that adequate time is provided for AT to be effectively delivered in this patient population. Although AT may be a cost effective intervention in PD, conducting a health economic analysis in larger scale studies where sufficient time is allocated to each session is required.

8.8 Conclusion

In summary I conclude that AT may be an effective therapy for improving medication adherence and QoL in people with PD. Health professionals could easily be trained to utilise the core principles of AT as part of their routine clinical practice. The small NNT observed and the anticipated low cost of the intervention suggests AT is likely to be a cost effective treatment, especially when considering the potential future cost savings of increased adherence.

A larger scale study is therefore required to examine the clinical and cost effectiveness of this intervention in routine clinical settings when delivered by multiple therapists using a placebo control group. Whether the efficacy of this short seven week intervention is sustained for longer periods of time also requires further evaluation.

CHAPTER 9

Investigating the Experience & Acceptability of Adherence Therapy

Introduction
Data Collection in Qualitative Research
Methods
The Analytical Process
Results

9.1 Introduction

The systematic review presented in Chapter 4 revealed only one RCT had been published that specifically aimed to improve medication adherence in people with PD (Grosset and Grosset, 2007). Despite this paucity of evidence in PD, interventions for improving medication adherence in other chronic conditions have been widely investigated (Peterson et al., 2003, Nunes et al., 2009). For example, researchers have evaluated a variety of intervention types, ranging from pharmacological approaches such as dose simplification to complex behavioural therapies. However, despite the array of strategies investigated in other chronic conditions, the effect on adherence and clinical outcomes are largely inconsistent between studies (Haynes et al., 2008).

The findings presented in Chapter 7 showed AT was effective for improving medication adherence and QoL in PD. As the improvement in QoL exceeded the minimally important difference reported in a PD population (Peto et al., 2001), the findings suggest the effect size of AT is likely to be clinically relevant.

Despite various adherence enhancing treatments being investigated, few researchers have evaluated their interventions. This is both in terms of the treatments underlying mechanism of action and the acceptability of the intervention from the perspective of patients. Consequentially, for many interventions the mechanism of action remains theoretical. This is the case in PD. Although the results presented in Chapter 7 suggest AT may be an effective treatment, the mechanism of action is unclear.

Alhalaiqa et al. (2013a) evaluated the experience of receiving AT in patients with hypertension. Findings showed that modifying attitudes and beliefs about medication was an important component of the therapy which may have led to the reported improvement in medication adherence. In PD, as prescribed medication and the factors associated with non-adherence are likely to be disease specific, it is probable that the mechanism of action of AT may differ from hypertension. For example, despite showing significant improvements in adherence and QoL in PD, patients' beliefs about medication did not change substantially. This is in contrast to patients with hypertension.

Therefore, the aim of this part of my thesis was to investigate the experience of people with PD receiving AT. In particular, I was interested in evaluating the

acceptability of AT and determining which elements of the therapy PD patients found most useful.

In the next part of this chapter I briefly outline two commonly used data collection methods in qualitative research and provide justification for deciding to conduct interviews in this study. I outline the interview procedure used and justify my choice of thematic analysis for analysing the interview transcripts. I also describe the analytical method used.

9.2 Data Collection in Qualitative Research

Researchers often use qualitative approaches to better understand effects that cannot easily be measured by quantity, frequency or intensity. Two methods most commonly employed in qualitative data collection are participant observation and interviewing (Glesne, 2006).

9.2.1 Participant Observation

Observation is a fundamental technique used in qualitative research for studying behaviour (LoBiondo-Wood and Haber, 2006). This method of collecting data is particularly useful in studies using ethnographic or grounded theory based methodological approaches (Macnee, 2004).

9.2.2 Interviews

Interviewing is widely used in healthcare research because it can be either structured or semi-structured, depending on the study purpose (Macnee, 2004). The flexibility provided by a semi-structured interview enables participants to express their unique perspective (LoBiondo-Wood and Haber, 2006). For this reason interviews are highly appropriate for exploring patients experiences in healthcare (Glesne, 2006).

9.3 Methods

9.3.1 Aim

The aim of this aspect of work was to understand PD patients experience of receiving a seven week programme of AT as part of the RCT reported earlier in this thesis. Specifically I was interested in patient satisfaction with, and acceptability of, the therapy process.

9.3.2 Design

The design of this study was a qualitative approach using semi-structured interviews. As semi-structured interviews are flexible and encourage participants to discuss openly (Boyatzis, 1998), I believed its use was appropriate for the study aim.

The purpose of the qualitative interviews was to evaluate the AT intervention described earlier in this thesis from the perspective of the RCT participants.

Although qualitative methodological theories; that is, phenomenology, grounded theory and ethnography can be useful for generating new insight, as stated by Avis (2003), it is not always necessary to adopt such approaches when undertaking qualitative investigations. Due to the specific study aims (i.e. determining the acceptability of AT), I therefore used a pragmatic approach. By focusing on these aims I intended to explain the quantitative findings presented in Chapter 7, without being required to adhere to the philosophies of a particular methodological theory.

9.3.3 Participants

The first ten PD patients that agreed to be interviewed after their course of AT had finished was taken as the study sample. Where the PD patient's spouse/carer participated in the AT sessions, they too were invited to take part in the interview.

9.3.4 Procedure

After completing the seven AT sessions, I informed participants about the qualitative study. Patients who expressed initial interest were given a participant information sheet specifically for the interview after the seventh AT session (Appendix 33). Participants were asked to read the information sheet relating to the interview. If a participating spouse/carer also showed interest in the interview, a separate spouse/carer information sheet was provided (Appendix 34). Participants

were contacted by phone one week after being provided with the interview specific information sheet. Those who were still interested in participating in the interview were visited again at home and informed consent was obtained using study specific informed consent forms for both patients and spouse/carers (Appendix 35 & 36).

9.3.5 Data Collection

All interviews were audio recorded and continued until saturation of data had been obtained. I subjectively determined this point when participants were providing no new information of relevance to the study aim. On average interviews were 30 minutes in duration. The informed consent form included consent to audio record the interview.

During each interview I made brief notes to accompany the audio data. Each interview was conducted in the participants' own homes where AT had taken place. Interviews were conducted on a one-to-one basis, unless a spouse/carer also participated. Lay person's language was used throughout the interview process. However, due to the variability in patients understanding of PD and treatment approaches, where possible I mirrored the patients' own choice of vocabulary as appropriate to encourage a relaxed, informal atmosphere.

All participants were informed that the nature of the interview was not to assess their own understanding or recollection of AT, but was to ascertain their opinion of the AT programme. At the time of completing the interviews both I and the participants were unaware of the RCT results.

The interview schedule explored the following broad topics:

- Components of the AT intervention

- Communication style and therapy environment

- Participant's perceptions of the therapy

- What participants had learnt

The prompt questions used in the semi-structured interviews are presented in Appendix 37.

9.3.6 Thematic Analysis

There are numerous methods for analysing interview transcripts, many of which depend on the philosophical qualitative approach adopted (Aronson, 1994). Thematic analysis is a method which focuses on identifying and reporting patterns (themes) within data sets (Braun and Clarke, 2006, Green and Brown, 2008). Data sets are not only organised by this analytical method, but additionally the processes inherent in thematic analysis facilitate the interpretation of data that may not be directly observable from initial transcripts (Boyatzis, 1998).

Thematic analysis is widely used by healthcare researchers because it provides an accessible form of analysis that can be used across a variety of qualitative research philosophies (Braun and Clarke, 2006). Furthermore, there is definitive instruction on how thematic analysis should be undertaken when analysing interview transcripts (Attride-Stirling, 2001).

As this piece of work was not based on a qualitative philosophical approach such as grounded theory or phenomenology, the use of thematic analysis was entirely appropriate (Attride-Stirling, 2001, Braun and Clarke, 2006). The next part of this chapter details the analytical process.

9.4 The Analytical Process

The stage by stage procedures used for analysing interview transcripts in this study are summarised in Table 9.1 below. Data analysis was not conducted in a linear process by moving from one phase to the next. Instead I used an iterative process, moving back and forth as the data required, as described by Braun and Clarke (2006).

Table 9. 1 - Phases of Thematic Analysis

Phase	Description of the phase
1. Familiarising oneself with the collected data	Transcribing data, reading and re-reading the data, noting down ideas.
2. Generating initial codes	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
3. Searching for themes	Collating codes into potential themes, gathering all data relevant to each potential theme.
4. Revising themes	Checking if the themes work in relation to the coded extracts (level 1) and the entire data set (level 2).
5. Defining and naming themes	On-going analysis to define the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.

(Source: Braun and Clarke (2006)

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9.4.1 Phase One: Familiarisation of the Data

To ensure full immersion in the data, each transcribed interview was read several times in an active manner; that is, searching for meaning and patterns in the data. This continued until I was familiar with the content of each interview. Braun and Clarke (2006) suggest that maintaining comprehensive notes is a fundamental procedure to adopt throughout the entire analysis process. Therefore, note keeping began in phase one with the documentation of ideas for potential coding schemes.

9.4.2 Phase Two: Initial Code Generation

The main topics of interest from within the data were used to generate initial codes. These codes formed the basis of repeated patterns (sub-themes) across the data set. The meaning of an interview extract, and an appropriate code to suit that meaning, was written in the margins of the interview transcripts. Codes were given a definition of its correct use and misuse (coding rules), which were referred to continuously. Often code definitions were tweaked or re-named to accommodate new, but similar, text segments. Once the entire data set had been coded, extracts with the same code were copied into a separate document. Inevitably, some extracts appeared to portray so much meaning during the coding process that they were placed under a variety of codes. This meant they appeared throughout the coded categories.

The coding framework described above was based mainly on the data itself, as opposed to preconceptions about the data. Appendix 38 shows an example of some of the common codes and their respective description. Appendix 39 shows a

segment of an interview transcript. Codes were written in the margins of the interview transcripts.

9.4.3 Phase Three: Searching for Themes

Phase three began once coded extracts had been assigned to code specific categories. This resulted in a glossary of codes accompanied by definitions for their use. The emphasis of this phase was to develop themes that encompass related codes. To facilitate this I arranged the codes into plausible sub-themes and then collated all data extracts relevant to each sub-theme. This was a similar process to that described in phase two. The end of this phase was marked by a collection of candidate sub-themes housing all codes and related data extracts.

9.4.4 Phase Four: Revising the Themes

This phase involved two levels of reviewing and refining sub-themes. In level one I reviewed the collated extracts from each sub-theme to ensure they followed a logical pattern. Level two involved a similar process, but in relation to the entire data set. Specifically, I re-read the entire data set to ensure that the generated themes were consistent with the original interview data.

9.4.5 Phase Five: Defining and Naming Themes

Once a working collection of sub-themes had been compiled, broader themes were generated and defined according to their overall meaning. When defining themes I

tried to emphasise what was interesting about the theme, as opposed to simply paraphrasing it. Names given to the working themes were short, but nevertheless portrayed enough information for any reader to have an understanding of the broad content of each theme. A clear identification of distinct themes marked the end of this phase.

9.4.6 Quality Assurance of the Analysis Process

When creating the codes and sub-themes I was mindful that my interpretation may be biased by preconceptions about the meaning of the data. Therefore, to ensure the analysis was free of such bias, a second analyst naive to PD and AT reviewed all the transcripts independently.

This individual, an experienced qualitative researcher, coded the interview transcripts according to the data set using the method described above. After I and the second rater had completed our independent analysis, we met to discuss the findings. Despite often generating different code names for the same interview extract, the meaning of the codes were consistent. Each code was discussed further and the most appropriate was selected for use.

In the next part of this chapter I outline the demographic and clinical characteristics of interviewed participants and I provide the results of the thematic analysis.

9.5 Results

9.5.1 Study Population

Baseline demographic and clinical characteristics of the patients who participated in the interviews are presented in Table 9.2. All interview participants were white Caucasian. All of the participants were retired from work besides participant 10 who did not work on the grounds of ill health (due to her PD). It is unknown how many retired prematurely due to their PD. The mean age of the interviewees was 69.1 (s.d 10.2) years. The mean time since PD diagnosis was 6.6 (s.d 4.5) years. All were taking at least one levodopa preparation. No patient refused to participate in the interviews. The spouse of participant 10 was not available to be interviewed due to work commitments.

9.5.2 Codes and Themes

From the ten interview transcripts a total of 175 codes were generated. These codes were used to produce 11 sub-themes. These sub-themes were then grouped under 3 main overarching themes:

1. Perceptions prior to Adherence Therapy
2. Positive effects of Adherence Therapy
3. Attributes of Adherence Therapy

Table 9.3 displays the themes and sub-themes generated by the codes.

Table 9. 2 - Baseline Characteristics of Interview Participants

Interview Participant	Age	Sex	H&Y	Duration of PD (yrs)	MoCA	HADS Anxiety	HADS Depression	LEDD	PD Drugs	Daily Doses
1	56	Male	3	7	25	6	11	640	1	4
2	69	Male	2	7	28	6	3	740	2	7
3	72	Female	1	2	18	10	6	1038	2	4
4	63	Male	3	4	27	5	2	1758	4	12
5	71	Female	3	14	26	4	5	2319	5	18
6	68	Female	1	6	30	4	3	247.5	2	4
7	72	Female	4	14	25	9	7	900	3	9
8	87	Female	0	2	24	3	1	187.5	1	3
9	80	Female	3	2	28	8	7	312.5	2	5
10	53	Female	1	8	27	13	10	480	3	13

H&Y: Hoehn & Yahr; MoCA: Montreal Cognitive Assessment Scale; HADS: Hospital Anxiety & Depression Scale; LEDD: Levodopa Equivalent Daily Doses

Table 9. 3 - Themes and Sub-themes

Theme	Sub-theme	N⁰ of patients
1. Perceptions prior to Adherence Therapy	1. Poor knowledge & understanding of PD and meds	9
	2. Low mood / confidence	5
	3. Decreased support / Isolation	5
2. Positive effects of Adherence Therapy	1. Increased acceptance	5
	2. Increased self-awareness	5
	3. Increased confidence	4
	4. Increased knowledge / understanding of PD / meds	10
	5. Increased control / self-discipline	6
	6. Improved relationships	4
3. Attributes of Adherence Therapy	1. Therapy Attributes	
	- Flexibility, continuity & timing	6
	- Involved spouse	3
	- Face to face / in home environment	10
	- Time to talk / openness	8
	2. Therapist Attributes	
	- Specialist knowledge	10
	- Understanding & interest	6
	- Equal relationship	7
	- Easy to understand	5

9.6 Perceptions Prior to Adherence Therapy

Most participants talked about their experiences and perceptions prior to therapy. Specifically, participants referred to their previous poor knowledge and understanding of PD and its treatment, how the disease impacted on their mood and confidence and how they felt isolated with little support.

9.6.1 Poor Knowledge & Understanding of PD and Medication

Almost all of the participants described having poor knowledge of their PD prior to receiving AT, attributing this to lack of previous explanation and opportunity to be informed in a way that was personally meaningful to them:

"Explaining the nature of the disease, and what it is. Nobody had ever explained that. I know the affect it has on me, but nobody had explained it".

(Participant 1, male, 56 yrs, depressed on HADS)

The lack of knowledge and understanding prior to AT was not specific to the disease. Similarly, participants described how poor previous knowledge specific to medication use was also problematic:

"Whereas before I would pop a pill and not understand the reason for it, now I understand the peaks and troughs and why it's essential to maintain a steady line,

concentration, to keep equilibrium of the system level for the chemical that I'm

missing".

(Participant 2, male, 69 yrs)

9.6.2 Low Mood / Confidence

Half the interviewees talked about their experiences of mood states prior to AT which they associated with their diagnosis of PD. Having low mood or feelings of depression before the start of the AT process also appeared to be related to their lack of acceptance of the disease, which impacted negatively on medication use in some participants:

"I was very low in mood when we met. Actually, I think I was depressed. When I filled my medication wallet up for the week I used to hate myself and hate my pills. I felt guilty for having it (PD), like I'd let my family down. Those feelings made me hate the situation so I'd say oh well stuff the pills. I felt resentful towards the pills"

(Participant 10, female, 53 yrs, depressed on HADS)

The spouse of one participant spoke of the devastating effect that PD had had on the patient's mood and confidence to remain engaged in general life:

"After he was diagnosed he just wanted to be left. With that he became depressed. He wanted me to take him to Switzerland to end it all. He became non-compliant and under confident in everything, not just medication."

(Spouse of participant 1)

9.6.3 Decreased Support / Isolation

Half the PD patients expressed that before AT they had felt isolated from people who may be able to help them better understand what they were going through. This feeling of isolation and perception of living alone with the disease had a detrimental impact on day to day life:

"Even though you go to see the doctor, you're still living it alone inside yourself. There is nobody that you can point to and say that's what's happening to me. Before this (AT) I felt isolated and lonely living with PD, even though Peter is here with me."

(Participant 5, female, 71 yrs)

In addition, people perceived having a lack of professional support and felt that they were left alone to face their disease:

"Before we felt isolated and neglected. We didn't know where to turn or anything about what was coming. We felt we were the only people facing this."

(Spouse of participant 1)

9.7 Positive Effects of Adherence Therapy

Of the three generated themes, positive effects of AT represented the largest. Participants spoke of having increased acceptance of PD and the need for medication. This increased acceptance appeared to be related to the impact of acquiring greater knowledge and understanding of PD and its treatment. Furthermore, many participants described how self-awareness, confidence in daily life, support, self-control, relationships with others, self-discipline and an ability to function and cope in daily life were all improved after experiencing the AT intervention.

9.7.1 Increased Acceptance

Several patients spoke of how they had come to develop an increased acceptance of, and relationship with, PD. This increased acceptance of living with PD appeared to be associated with a developed understanding and acceptance of the indication for medication to control PD related symptoms:

"Before I was very much in denial. I couldn't off-load anything. Fear was the biggest thing for me, being frightened of my future. I then tried to ignore it and that included the symptoms and the pills. Now though, I think my relationship with medication has changed and improved because of how we spoke about it. I'm no longer scared you see."

(Participant 10, female, 53 yrs, depressed on HADS)

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Participants described how the experience of talking about PD and its treatment as part of the AT interaction helped them to develop a new perspective of living with their disease:

"It made me look at the situation for the first time through fresh eyes. I've tried to keep it contained, the fact that I've got Parkinson's. Suddenly I see I've got to look at it. I certainly felt that week we spoke about it I wasn't in fear of anything".

(Participant 5, female, 71 yrs)

Some participants described how being involved in AT and developing a new perspective of life with PD helped them to re-evaluate their attitudes towards the use of medication to control their symptoms:

"I realise now I've got to take more control of the medication I'm taking. Had you not come I would still be in the same situation. I'd still be ambivalent to the medicines. The very point that we've talked about it has somehow changed me. Without talking about it to you I would not have changed how I felt inside."

(Participant 5, female, 71 yrs)

As part of developing an increased acceptance of the diagnosis of PD, a few patients talked about how after receiving AT they no longer felt the need to hide their condition from others:

"I am not afraid now to say I'm disabled can you help me please. Before, I

wouldn't even go outside. People do help you. I am much better at explaining what

I've got now."

(Participant 1, male, 56 yrs, depressed on HADS)

9.7.2 Increased Self-awareness

Some interviewees discussed feeling an enhanced sense of self-awareness following participation in the AT process. Specifically, a greater attentiveness of their own PD related symptoms was portrayed by some patients:

"Perhaps I should go to see the specialist because I do stagger quite a lot which

I've become more aware of since I've been thinking about Parkinson's."

(Participant 9, female, 80 yrs)

A few participants further described how prior to AT possible episodes of poor therapeutic control, such as *'going off'*, were perceived as not being related to sub-optimal medication use. However, an increased self-awareness on one's own symptom control seemed to result from the enhanced knowledge and understanding gained during the AT process:

"Before I had the onslaught of eating constantly when I felt tired, exhausted, to try

and get some energy. Now though I realise the sinking feeling is the Parkinson's. I

am going off. Having the medicines more strictly, I haven't felt it as much."

(Participant 3, female, 72 yrs, MoCA 18)

9.7.3 Increased Confidence

Some participants spoke of how their experience of receiving AT had improved their overall confidence in living with PD. Specifically, perceptions of improved symptom control, attributed by patients and carers to better medication adherence and acceptance of the diagnosis, enhanced feelings of confidence in one's ability to manage life with PD:

"Once I was taking my meds as we agreed, I did feel a huge difference. I didn't stop freezing but the length of freezing was much less. I felt more confident to go outside and not worry about getting back. I went for a coffee alone. It felt great to be honest. I haven't done that for three years. I just felt more confident to do it."

(Participant 1, male, 56 yrs, depressed on HADS)

Some patients also described how their increased confidence in daily life led to greater social participation and engagement with others:

"Even though it's not something we talked about, it's helped me personally and socially. I think it's increased my confidence, definitely. I suppose I feel that I've started to accept the condition. Before we met I wouldn't tell anyone. Now I don't mind talking to strangers about it."

(Participant 2, male, 69 yrs)

Additionally, the spouse/carers of a few patients spoke of how increased confidence to manage PD was used by patients to encourage optimal medication adherence in others who routinely take medication for other chronic conditions:

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"He is now promoting what you've said to other people, telling them how it's helping him. It's getting their brains ticking now. So when they say once the session is over you forget, I'm sorry but he has never forgotten. He now talks to others about it."

<div align="right">(Spouse of participant 2)</div>

9.7.4 Increased Knowledge & Understanding of PD Meds

All participants spoke of how they had come to develop an increased understanding of PD and its pharmacological treatment approaches. Patients described how after receiving AT they could appreciate the importance of medication for controlling their own symptoms. Specifically, all participants talked about how improved knowledge and understanding of basic anti-parkinsonian pharmacodynamics greatly enabled them to see the relevance of medication to their own lives:

"The way I view medication has definitely changed now. I didn't know much about it before and I didn't realise the effects it had on me. Now I know that it's because I'm putting the dopamine into the brain and I can see now how that makes a difference."

<div align="right">(Participant 8, female, 87 yrs)</div>

A few patients described how they greatly appreciated having a more scientific explanation of how their medication exerted its therapeutic effect:

"The most helpful was the information I gained about taking drugs, the effect that they have and how they specifically work. That was interesting to me. The scientific bits I wanted to know."

<div align="right">(Participant 6, female, 68 yrs)</div>

Although a few wanted scientific explanations for their own drugs mechanism of action, many preferred to better understand the importance of correct time interval dosing. Most patients described how gaining an improved understanding of the continuous dopaminergic theory greatly resonated with them, particularly when this was discussed in relation to their own symptom control (the diagram used for this explanation can be seen in Appendix 40):

"I have learnt about peaks and troughs regarding the medication and why it's important to take your medicine at certain times. In a way I've learnt that in some respects I am governed by the clock. I know that I need to be somewhere so that I can take the medication at the time required."

<div align="right">(Participant 2, male, 69 yrs)</div>

Some patients appeared to link their increased knowledge and understanding of PD medication to their improved self-awareness of symptoms:

"The peaks and troughs diagram you showed me was one of the most fascinating explanations I've ever come across. It was very powerful for me.

I can now feel it you see. I realise now that I am dipping, and I recognise what it is.

I can see me falling so it spurs me to take the medication correctly."

(Participant 1, male, 56, depressed on HADS)

Some spouse/carers also described how an improved understanding of basic antiparkinsonian pharmacodynamics led them to be more mindful of how the PD patient was medicating:

"I think learning about the peaks and troughs were important, the picture you showed us was helpful. It helped us realise. I understood he would deteriorate if he didn't take the medication altogether. But I didn't know that his medication if taken properly could keep him on an almost even keel, so to speak. Whereas if he takes it late or misses it he can drop too low."

(Spouse of participant 1)

Additionally, some spouses felt that the increased understanding of PD and its treatment gave them more confidence to discuss their relative's symptoms in a clinical setting:

"Now I have a much better understanding. I know what is happening when he misses his medication and how medication affects him. I feel I can have a conversation now and state my point, especially with the GP."

(Spouse of participant 1)

9.7.5 Increased Control / Self-discipline

Several participants discussed how their experience of receiving AT increased their perceived self-control and self-discipline with using anti-parkinsonian medication. This appeared to be linked with a greater recognition of the importance of medication to one's self. Specifically, participants spoke of how they felt they had become stricter with themselves regarding their medication use, describing a sense of increased power and ability to cope:

"The discussion we had made me strict with myself, because I know now that by doing that I know it's going to benefit me. I think it (AT) made me think about things, rather than you telling me things I must do."

(Participant 6, female, 68 yrs)

Others spoke about how they felt the AT process had helped them to fight back against the symptoms of PD, stating that this was due to their improved awareness of their symptoms and the need to use medication optimally:

"It's given me the strength to bounce back. It's shown me I can adapt and challenge PD, by being smart with medication and recognising my symptoms. It's not pleasant but it's not as dark as it was."

(Participant 1, male, 56 yrs depressed on HADS)

Furthermore, some patients described how specific problem-solving strategies, identified collaboratively through shared decision making, helped them to develop a sense of control over the use of their medication:

"I'm remembering now which I wasn't before. Actually, I often think about it before the alarm goes off. It's like in the morning when you wake up before your alarm wakes you. Now I sometimes remember the pills before the alarm gets chance to remind me. It's almost like sometimes, I don't feel I need the alarm to remind me anymore."

(Participant 8, female, 87 yrs)

9.7.6 Improved Relationships

Some participants talked about how receiving AT improved their relationships with family members. Patients put this down to an increased sense of symptom control, which was associated with feeling happier and more confident to do things:

"When I was non-compliant I could hardly move so I convinced myself I couldn't do anything. I used to sit there thinking I can't even decide what pots to use. But then I sat there thinking I can do this. Then, for the first time in years I cooked my own dinner and the wife's too. She cried when she got home from work and saw what I'd managed to do"

(Participant 1, male, 56 yrs, depressed on HADS)

A few participants also spoke of how formal community healthcare assistants and family members (including children) had noticed a difference in the patient's ability to be more active and participatory:

"My granddaughter would come round and whereas I'd say sit there, we were out going to the park. So I was doing more things and she noticed as well. I thought well this has only happened in the last few weeks."

<div align="right">(Participant 4, male, 63 yrs)</div>

This increased sense of control over symptoms and the heightened confidence in one's ability to be more active was described by some patients as having had a positive effect on their relationships when within a caring role. This helped to instil confidence in them from their direct relations:

"My daughter, she is now firmer with me and my medication. She saw the effect it sometimes had on how I was with the granddaughter. That helps her because she knows I'm getting the meds on time and then she doesn't have to worry, especially when I'm babysitting."

<div align="right">(Participant 4, male, 63 yrs)</div>

9.8 Attributes of Adherence Therapy

All participants talked about their experiences of going through the AT process. Participants spoke of the positive attributes of the AT intervention itself and of the individual therapist attributes that they believed to be key to the patient-professional interaction.

9.8.1 Therapy Attributes

Patients talked about how they believed their success from participating in the therapy resulted from the range and flexibility of the topics discussed. The method in which the topics were introduced was also believed to be fundamentally important. Patients felt that the inclusion of the spouse/carer was helpful for different reasons. Furthermore, all participants described how the collaborative, participatory and face-to-face nature of the AT interaction was essential for the successful uptake of the therapy. The honesty and openness encouraged during the patient-professional interaction was also described as being critical to the process.

9.8.1.1 Flexibility, Continuity & Timing

Participants talked about how the continuity of linking sessions together with the same therapist, the timing of the AT sessions and the flexible approach adopted were all important factors that they believed contributed positively to the AT experience.

Some patients described how the AT sessions could have been longer to facilitate greater in-depth discussion:

"They were too short. It hardly seemed to start and then it was gone. You were just getting the momentum and then it ended. It was interesting, but too short."

(Participant 2, male, 69 yrs)

Although a few talked about how having a more staggered approach would have been helpful, such as sessions every two or three weeks, most favoured the weekly delivery of AT:

"I helped having you come each week. It gave me time to think about what we'd discussed and try out a few things before you came back again."

(Participant 6, female, 68 yrs)

Spouse/carers also praised the flexibility and continuity of the AT process, stating that the ability to adapt the therapy to individual need was an important component of the therapy:

"It depends on the person, whether they think it's enough for them. Some people, like us, may want a few extra weeks. It's a case of getting the balance right."

(Spouse of participant 2)

Linking the AT sessions by going over what had been previously discussed was commented on by most patients as being important. This helped patients to remember what had been discussed and made the experience of AT feel less formal:

"I like the way you said we'll go over last week. It felt like we started from where we left which was helpful. It made a big difference and it also reinforced to me that you were listening."

(Participant 10, female, 53 yrs, depressed on HADS)

9.8.1.2 Involved Spouse

All three participants described how the presence of a spouse/carer in the AT sessions was helpful, especially when the spouse/carer took an active role in medication management. Specifically, spouse/carers described how being involved in the AT process was vital to acquiring an increased understanding of medication issues:

"There was a lot for me as the carer because you opened my eyes to many key points which at the time didn't seem as important as they are now."

(Spouse of participant 7)

9.8.1.3 Face to Face / In the Home Environment

Most participants talked about how the delivery of AT face to face in their own homes was important. All participants spoke of how they felt other forms of delivery such as phone calls would not be as effective as one to one dialogue:

"The way in which it (AT) was presented I've got to say made a hell of an impact on me. How can you judge someone and their reactions over the phone? You need to see the person."

<div align="right">(Participant 2, male, 69 yrs)</div>

A few patients suggested that AT would be helpful as part of routine care. Specifically, patients talked about how having AT sessions between consultant and PD nurse appointments would be very helpful:

"It (AT) could be incorporated in-between seeing the doctor and nurse. Somewhere this sort of thing needs to slot in so that when you go to the hospital on a one to one basis you are not afraid of opening up."

<div align="right">(Participant 2, male, 69 yrs)</div>

9.8.1.4 Time to Talk / Openness

Amongst the various aspects of AT that participants reported upon favourably, having time to speak in an open, unstructured manner was acknowledged by several participants as being particularly beneficial. This facilitated a relaxed atmosphere that enabled more in-depth discussion:

"Sometimes I wasn't sure if I was on the right track. But you welcomed me every time to say exactly what I thought. That helped me to be less anxious and so I could talk freely, so to speak."

<div align="right">(Participant 10, female, 53 yrs, depressed on HADS)</div>

Additionally, patients described how having the time to talk and feel that they were being listened to had a positive impact:

"It felt like I was given the time in my own home so I wasn't under pressure like in hospital appointments. With you, knowing you had more time to sit and listen made a big difference. Talking the way we did was the first time I felt able and ready to do that since getting it (PD) nine years ago."

(Participant 10, female, 53 yrs, depressed on HADS)

9.8.2 Therapist Attributes

In addition to the positive attributes of the intervention, all interviewees further described how they believed the characteristics of the therapist providing AT were also vitally important for inspiring confidence and building a rapport. Specialist knowledge of PD and its treatment by the therapist delivering AT was regarded as being of paramount importance. Participants reported how important it was to feel that the therapist understood their perspective and was not judgemental, even if they disagreed. The ability of the therapist to explain topics in a way that was easy to comprehend by patients was also considered to be an essential trait that helped facilitate the therapy process.

9.8.2.1 Specialist Knowledge

All participants spoke of how they believed people administering AT should possess specialist knowledge of PD, stating that this was essential for understanding patients' issues with medication:

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"Because you had an understanding of PD I was halfway there with you. There were so many issues I had within me that when one came out talking with you it often rolled into another one. I've not been able to do that with other people at the hospital."

(Participant 10, female, 53 yrs, depressed on HADS)

9.8.2.2 Understanding & Interested

Several participants talked about how they believed it was important that the therapist could understand a patient's perspective of what it is like living with PD:

"To have somebody that you can talk to that seems to understand where you're coming from was very helpful."

(Participant 5, female, 71 yrs)

Patients also felt that the ability of the therapist to understand their issues and show genuine interest was a key component to encouraging meaningful conversation about PD and treatment:

"You being interested in what having Parkinson's is like I think made you ask questions in such a way that made me want to give you an answer. It made me look at the situation differently for the first time."

(Participant 9, female, 80 yrs)

9.8.2.3 Equal Relationships

Several participants spoke of how honesty and a non-judgemental approach were key for encouraging open dialogue:

"It was welcoming not having to justify some of my actions. I felt I could say what was on my mind without you judging what I was saying."

(Participant 2, male, 69 yrs)

One spouse described how the rapport that was developed between the patient and therapist was essential and helped to instil a level of trust which helped to facilitate the AT interaction:

"I think you learnt to trust David didn't you? You know inviting strangers into your own house isn't easy and you've got to learn to converse with them. You've got to feel that you're equals."

(Spouse of participant 2)

Several participants also discussed how building a rapport with the therapist was paramount for gaining the trust that was required to facilitate open and honest discussion:

"I felt comfortable with you to tell you my fears that I'd held inside for so long. You think oh that sounds silly so you put things to the back of your mind. I didn't feel that with you. I was able to say the simplest things and you put me at ease."

(Participant 10, female, 53 yrs, depressed on HADS)

9.8.2.4 Easy to Understand

Many interviewees described how having a therapist who was easy to understand and was able to explain things clearly on a patient's level was an essential component of the patient-professional interaction within AT:

"You explained things clearly and functionally without a lot of big fancy words. You used everyday language, not like sitting behind a desk and quoting out long medical terms. That means nothing to me."

(Participant 2, male, 69 yrs)

9.9 Summary of Results

Of the 175 codes generated from the ten interview transcripts, 11 sub-themes were developed. These sub-themes were arranged to form 3 over-arching themes: perceptions prior to AT, positive effects of AT and attributes of AT.

In the next chapter of this thesis I will use these findings to propose a possible mechanism of action for AT specific to people with PD.

CHAPTER 10

Discussion of Interview Findings

Introduction
Perceptions Prior to Adherence Therapy
Positive Effects of Adherence Therapy
Attributes of Adherence Therapy
Strengths and Limitations
Summary

10.1 Introduction

In the previous chapter I reported the findings of a qualitative study. The aim of this aspect of work was to investigate the experience of receiving a seven week programme of AT in people with PD who participated in the clinical trial described earlier in this thesis. Determining the acceptability of AT was also an important objective of this evaluation.

In this chapter I will discuss the qualitative study findings within the context of related literature. Furthermore, I will discuss a potential mechanism of AT specific to PD that may be helpful in explaining the RCT findings presented previously in this thesis.

10.2 Perceptions Prior to Adherence Therapy

Although the intention of this study was to evaluate the experience and acceptability of receiving AT, most patients talked about their experiences and perceptions of life with PD prior to the therapy process. Specifically, participants referred to their previous poor knowledge and understanding of PD and its pharmacological treatment. Having low mood and confidence and feeling isolated with little support was also reported by several interviewees as being significant prior to the therapy.

In many chronic disease areas patients can become expert at managing their symptoms and recognising their reaction to medication (Badcott, 2005). As this developed expertise results from taking medication for a considerable time to manage symptoms, sound adherence to treatment is often assumed (Badcott, 2005). However, despite this assumption, the findings described in Chapter 3 suggest non-adherence in PD may be associated with longer disease duration. Although many factors can impact on adherence behaviours, the lack of knowledge about disease and treatment in patients who have had PD for several years may indicate that the expert patient concept should not always be presumed in PD.

Drey and colleagues (2012) showed that whilst patients were vaguely familiar with treatment goals, their understanding of PD medication was often not adequate enough to sufficiently manage their condition. In particular, patients did not appreciate that to achieve symptom control strict timing of doses may be imperative, especially in later stages of disease. As the interviewed patients from

the current study reported having poor knowledge of disease management prior to participating in the AT process, these findings appear to be consistent.

Whilst comprehensive knowledge of PD is not essential, the ability to recognise one's own response to treatment and have a sufficient understanding of basic anti-parkinsonian pharmacodynamics is important. Despite many patients having access to nurse specialists or being regular attenders at PD community groups/networks (where information is often provided), the findings presented in Chapter 9 suggest that this essential knowledge is lacking in many people with PD. Although only ten PD patients were interviewed from the clinical trial sample, considering that most described having poor prior knowledge suggests that lack of understanding may be common in the general PD population. Specific investigation is required however to confirm this.

In addition to having poor knowledge prior to AT, some interviewees talked about how they felt their low mood was associated with their diagnosis of PD and their dependence on treatment. Low mood or feelings of depression also seemed to be related to their lack of acceptance of the disease, which impacted negatively on medication adherence in some participants.

As described earlier in this thesis, the burden of living with a chronic condition can lead to the development of depressive symptoms. It is also well established that depression is associated with poor adherence to medication in chronic conditions (DiMatteo et al., 2000). Specifically, depression is a factor most strongly associated with non-adherence in PD, as was identified in Chapter 3. It was therefore not

surprising that low mood was reported by some participants, especially as research suggests that depression is prevalent in as many as 40% of people with PD (Shiba et al., 2000).

A general feeling of low confidence was apparent from the interview data. As low confidence and self-esteem are associated with low mood (Charmaz, 1991), this was once again not unexpected; it is known that low confidence in one's ability to cope and function optimally (low self-efficacy) is common in people living with a chronic condition (Charmaz, 1991).

Researchers have shown that interventions aimed at enhancing self-efficacy may be beneficial for improving self-management behaviours in chronic conditions (Farrell et al., 2004). Although not specifically investigated in PD, this may include adherence to treatment. Therefore, considering that low confidence and low mood are related and can impact negatively on adherence to medication and general participation/engagement in life, this may explain why patients reported this as being significant when participating in the post intervention interviews.

Additionally, patients expressed a strong feeling of isolation from other people. Feeling isolated and lacking general support was reported to have a detrimental impact on patients' day to day life. This may suggest that current service provision for people with PD, such as access to nurse specialists, may not be sufficient to adequately deal with the concerns of some people with PD. Considering that AT was a seven week intervention that encouraged participation in a way that

previously patients may not have experienced, this may explain why many interview participants felt it was important to discuss their experiences prior to AT.

Furthermore, by discussing experiences and feelings prior to receiving AT, it is possible that participants were comparing this with how they felt after the AT process. This suggests that poor knowledge of disease and treatment, low mood/confidence and feelings of isolation may have been improved by receiving the AT intervention.

In the next part of this chapter I will discuss such potential positive effects of AT, as reported by the interview participants. In so doing, this will lead me to propose a mechanism of action for AT which may be useful for explaining the beneficial effects in some PD patients in the clinical trial.

10.3 Positive Effects of Adherence Therapy

All participants talked about the positive effects of the AT intervention. Specifically, patients spoke of having an increased acceptance of PD and an enhanced understanding of the indication for treatment. Acquiring greater knowledge of the importance of PD medication was also reported as being beneficial by all interviewed participants. Interestingly, many participants described how self-awareness, confidence in daily life, self-control, relationships with others, self-discipline and an ability to function and cope (e.g. social participation/engagement) also improved after experiencing the AT process.

10.3.1 Improving Knowledge and Understanding

All participants described how receiving AT had enabled them to better understand PD and the need for treatment. Specifically, a greater understanding of the requirement for correct dose timings was acknowledged by many patients. Interestingly, rather than simply enhancing understanding of basic pharmacodynamics, patients described how this acquired knowledge had led them to develop an increased sense of self-awareness and self-discipline.

Considering that poor self-awareness of symptoms has been reported in PD (Vitale et al., 2001, Sitek et al., 2008), the fact that patients described having an increased sense of self-awareness may suggest that discussing medication use in relation to patients specific symptoms provides greater meaning because it is relevant at a personal level. This may account for the improved adherence behaviours in patients

who may not have been aware of the relevance of medication for managing their symptoms prior to AT.

An enhanced feeling of self-discipline to take medication correctly was also described by participants in the current study. This may propose that the process of AT not only helps to improve adherence to treatment, but additionally encourages and educates patients how to successfully self-manage their condition. Some participants described adapting their problem-solving strategy, while others described using their greater insight of pharmacodynamics to plan correct drug dosing. Therefore, this may propose that after receiving AT patients are confident and competent to self-manage; that is, patients might use their enhanced symptom awareness and knowledge of treatment to better manage PD, without the need for continuous input from a health professional.

Furthermore, as a lack of awareness is known to be a factor for poor self-management in patients with a chronic condition (Jerant et al., 2005), it is possible that AT helped the trial participants to better manage their condition by enhancing self-awareness of symptoms and the importance of medication use.

10.3.2 Improving Acceptance of PD and Confidence in Daily Life

The interview data revealed that a lack of acceptance of PD and denial concerning the indication for treatment was prevalent in some participants. When acknowledged alongside underlying symptoms of anxiety and depression, these factors appear to represent some of the main reasons for poor adherence to treatment in these individuals.

As previously described, low mood and anxiety are known to detrimentally impact on adherence behaviours. Additionally, the lack of acceptance of a condition and denial concerning the need for treatment is common in chronic conditions (Charmaz, 1991, Telford et al., 2006).

Although participants stated that improving their knowledge and assisting them with problem solving strategies was beneficial, several patients also talked about how improving their acceptance of PD and improving their confidence in daily life was essential. Although medication adherence and QoL significantly improved in participants who received AT, improving factors such as the acceptance of PD and confidence in daily life was not expected and nor was it the intention in the clinical trial.

As described earlier, the linear mechanism of action for AT proposes that improving attitudes and beliefs about treatment, exchanging information and assisting in problem solving strategies leads to improved adherence behaviours (Horne and Weinman, 1999, Gray, 2011). Better adherence leads to improved

clinical outcomes as a consequence. A diagram of this linear mechanism can be seen in Figure 10.1.
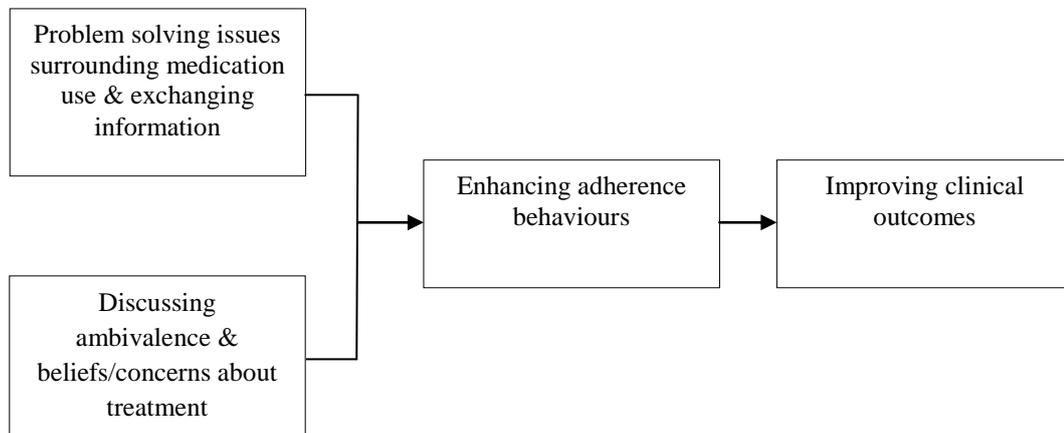
<div style="text-align: right">Gray (2011)</div>

Figure 10. 1 - Linear Mechanism of Action of Adherence Therapy

Considering that enhancing adherence to medication was the main objective of AT, it is unlikely that a greater acceptance of PD and greater confidence in daily life improved as a result of improved adherence behaviours. Furthermore, as acceptance of a condition and confidence in one's ability to cope (self-efficacy) are likely to be important for optimising QoL (Charmaz, 1991), this may suggest that some of the improvements in QoL observed in the clinical trial may result from other mechanistic pathways, and not just the linear pathway described above. Although the linear mechanism of action is important in PD, the improvements in acceptance and confidence reported by participants may suggest that QoL can be enhanced by delivering AT, but without the requirement for enhanced adherence to medication.

As with the linear model, these distinct mechanistic pathways are likely to commence with the identification of a patient's unique reasons for not adhering to treatment. This may include, for example, a lack of acceptance of PD and underlying symptoms of anxiety/depression. However, unlike the linear model where addressing such factors for non-adherence is suggested to lead directly to improved medication taking, addressing the lack of acceptance of PD and exploring symptoms of anxiety/depression may take an alternative route by first improving one's confidence to cope with PD (i.e. improving self-efficacy). It is worth noting that greater self-efficacy has been associated with better reported QoL in people with chronic obstructive pulmonary disease and chronic heart failure (Arnold et al., 2005). Thus, it is possible that an enhanced sense of control and perceived ability to cope may lead to improved medication adherence in PD.

Therefore, unlike the linear model of AT which is uni-directional (i.e. improving adherence leads to better clinical outcomes), acknowledging the importance of enhancing self-efficacy to improve QoL suggests that the mechanism of AT may in fact be bi-directional in PD.

This may propose that patients with PD have unique pathways to improved clinical outcomes such as QoL. Therefore, although adherence to medication was the principal target of AT in the clinical trial, the intervention's therapeutic effect could be more holistically beneficial. Figure 10.2 shows a diagram of this proposed bi-directional mechanistic pathway of AT in PD.
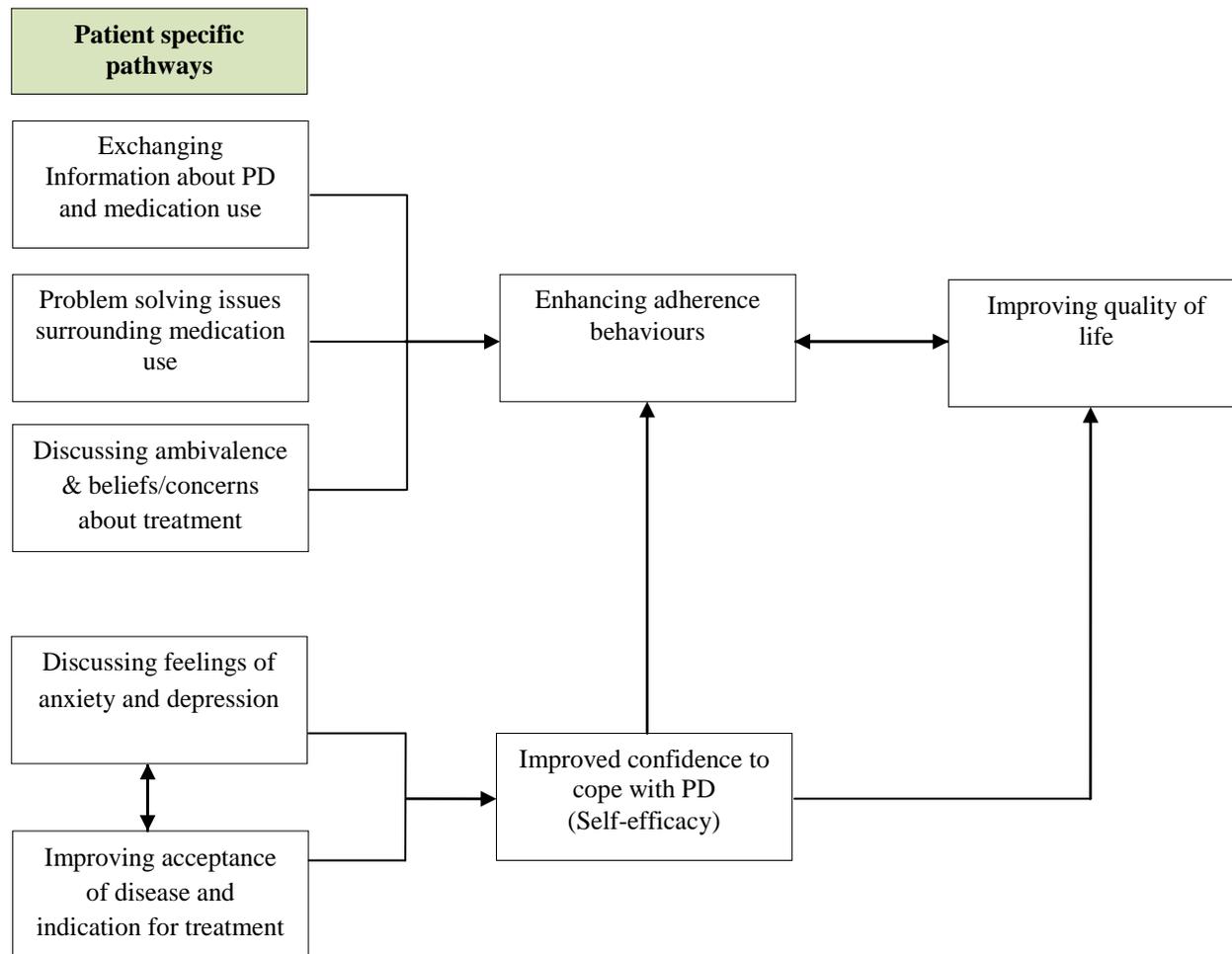
Figure 10. 2 - Bi-directional Model of AT Mechanism in PD

10.4 Attributes of Adherence Therapy

10.4.1 Therapy Attributes

Participants described how they felt the range of topics, flexibility in delivery, continuity and timing of the AT sessions were all key to the success of the therapy. This is consistent with findings reported by Alhalaiqa et al. (2013a) who showed that participants with hypertension who received AT also favoured this style of delivery. Although the qualitative interviews described in this thesis represent only the second evaluation of AT from the perspective of patients, the evidence seems to suggest that the intervention is well accepted.

Some patients specifically spoke about session continuity, stating that they felt it was vital for the same therapist to deliver the therapy. This proposes that AT is likely to provide the most benefit when delivered by a single therapist for a given patient. Furthermore, considering that many patients particularly liked how each AT session appeared to naturally follow on from the previous session, this would again propose that a single therapist is needed. Gray et al. (2004) showed that training community mental health nurses to deliver AT resulted in statistically significant improvements in medication adherence, attitudes towards medication and psychotic symptoms in patients with schizophrenia. Researchers should therefore investigate whether training multiple nurse specialists to provide AT as a service for people with PD leads to similar positive effects on outcomes as was shown in the current clinical trial (where only one therapist was used).

Most patients reported that the length of each AT session was sufficient. Some patients expressed that more sessions would have been helpful whereas others felt they required fewer sessions. Furthermore, some participants believed that AT would have greater benefit if delivered every few weeks, whereas others suggested that this type of intervention would be helpful if delivered in phases (i.e. as and when patients felt they needed it).

In the current clinical trial AT was administered once a week for seven consecutive weeks. This is similar to many trials of AT, as was outlined earlier in this thesis. However, when acknowledging the interview findings it may be that AT is likely to be better received by patients when delivered in a style more consistent with individual patient need. Such an approach is consistent with various guidelines for managing chronic conditions (WHO, 2003, DH, 2005, NICE, 2009) and with findings showing that medication adherence is enhanced when sufficient time is allocated for exploration of patient problems (Sookaneknun et al., 2004). It may be therefore that some patients require 'top-up' sessions whereas others only need a short duration of therapy to achieve the same therapeutic effect.

Thus, rather than being prescriptive in the number and time of each session, the findings of the qualitative interviews may infer that AT is more of a pragmatic, principles based intervention. Future research of AT should investigate whether the positive effects on adherence and QoL observed in the current clinical trial are maintained when the intervention is delivered in a flexible manner according to the need of individual patients (as judged by the treating therapist).

To my knowledge, the clinical trial described in this thesis was the first study of AT to incorporate a spouse/carer. Considering that carers can take on an active role in managing medication in people with PD, I believed their inclusion in the AT programme was important. Although the interaction between the presence of a spouse/carer and the treatment effect of AT was not statistically significant, patients believed that their inclusion in the therapy process was helpful. Similarly, the three spouse/carers interviewed reported how beneficial acquiring greater knowledge of anti-parkinsonian pharmacodynamics was to them in their capacity as a carer.

It is known that spouse/carers can be crucial for helping patients to manage their condition and that they themselves require support and education to facilitate them in their role (A'Campo et al., 2010a, A'Campo et al., 2010b). Furthermore, it is recognised that depression in caregivers of people with PD is prevalent and can impact detrimentally on their ability to cope (Caap-Ahlgren and Dehlin, 2002). As the inclusion of spouse/carers in the clinical trial appeared to be an important component of the process according to the interviewed participants, it is important that this is acknowledged when investigating AT in future research.

All participants described how they believed the face-to-face nature of the AT interaction, set within the home environment, was essential for the successful uptake of the therapy. Furthermore, having time to talk and feeling encouraged to discuss concerns openly was viewed by many as contributing to the success of the intervention.

Whilst patients favoured the flexibility in time and content of AT sessions, such findings may infer that delivery of AT outside of the home environment is not anticipated by patients to be as effective. As described earlier in this thesis, it is likely that helping patients to problem solve issues around medication use in their own home has a greater impact than if undertaken in a clinical setting.

Furthermore, the honesty and openness encouraged during the patient-professional interaction was also described as being critical to the process. Patients reported feeling more comfortable to discuss their problems than if asked to do so in a clinical setting. This is particularly in scenarios where they suspected the healthcare professional would not agree with their perspective.

It is likely therefore that delivering AT in patients' homes offers several benefits. Firstly, problem solving is likely to be more easily facilitated, particularly where cognitive impairment is evident. Secondly, patients may feel more at ease to discuss topics that would normally make them anxious when discussed in a clinical setting. Thirdly, unlike clinical environments where patient-professional interactions are often directed by professionals, the flexibility and patient focused nature of AT in the home may mean that patients perceive the power dynamic to shift. This may explain why many participants felt comfortable to discuss honestly and openly in a way that they might not have done so.

According to the interviewed participants, it therefore appears that AT delivered in the home is likely to have greater benefit than if delivered by a different method (i.e. over the phone or in a clinical setting). However, alternative to this theory,

Alhalaiqa et al. (2013a) showed a statistically significant improvement in medication adherence and blood pressure in patients with hypertension who received AT in either the home environment or an outpatient department. Treatment evaluation through one-to-one interviews showed that patients were comfortable receiving AT in both environments. This may suggest that AT delivered in clinical settings is just as effective as when delivered in patients' homes. Therefore, considering the potential cost of travel to patient's homes, AT delivered in clinic is likely to be more cost effective and thus more attractive to policy makers and service commissioners.

Nevertheless, it is important to acknowledge that considering the multiplicity of reasons for non-adherence in PD, it is unknown whether AT delivered in a clinical context will be as effective as in patients' homes. It may be beneficial therefore for researchers to investigate the efficacy of AT in PD when delivered via alternative means (e.g. over the phone or in a clinical setting). However, since the interviewees in the current clinical trial felt that delivery of AT in the home environment was a significant strength of the intervention, it is unlikely that the therapeutic effect observed will be maintained if delivered outside of the home environment in people with PD.

10.4.2 Therapist Attributes

Participants stated that certain characteristics of the individual providing AT were extremely important to the therapy process. Specifically, specialist knowledge of PD was regarded as being paramount. Considering that some causes of non-

adherence to medication may be specific to PD (e.g. poor problem solving ability resulting from cognitive impairment), it is probable that AT can only be delivered by a professional with sufficient knowledge of the disease. Furthermore, this may suggest that AT is likely to be more effective and better received by patients when delivered by PD nurse specialists or individuals with significant experience dealing with PD patients.

Participants further reported how it was essential to feel that the therapist understood their perspective and was non-judgemental. The motivation of the therapist and ability to explain topics in a motivational way that was easy to understand was also considered to be an essential trait that helped facilitate the therapy process. Once again, this suggests that specialist knowledge of PD is vital for successful delivery of AT.

Légaré et al. (2008) showed in a systematic review of barriers and facilitators to implementing shared decision-making that a motivational communication style was important to encouraging patient participation and an equal patient-professional relationship. Furthermore, Alhalaiqa et al. (2013a) found that hypertensive patients who received AT greatly appreciated the communication style and motivational approach of the therapist. It is therefore important that professionals delivering AT are able to engage patients sufficiently in the therapy process. As patient engagement is an essential element of AT, this may partly explain why PD patients were comfortable with the communication style and felt confident openly discussing their issues and concerns.

10.5 Strengths and Limitations

This evaluation of AT in PD using a qualitative methodology has several strengths. Firstly, all participants were interviewed within one week of completing the AT process and so their memory of the sessions content would have been maximised. Secondly, selection bias was minimised as participants were the first ten to complete the seven AT sessions who subsequently consented to be interviewed. Thirdly, although there is a large body of literature relating to the experience of caring for a person with PD, the work presented in this thesis is the first to investigate spouse/carer experiences of receiving an adherence promoting intervention. The final strength of this study rests in the quality assurance procedure used as part of the analysis process. As I was the person who delivered AT and then completed the interviews, my opinion of the meaning of the data was likely to be biased. Thus, the secondary analysis by an expert qualitative researcher naive to AT and PD ensured that the findings were a true reflection of the data and not a result of my own preconceived ideas.

There are also some limitations to this evaluation of AT. Firstly, only 10 participants were interviewed. Although this sample size is not considered small in qualitative research, it is possible that the views of the other trial participants may differ. I did not use the saturation of data as a point to determine the sample size. Rather, a prior sample size of 10 was determined. However, considering that the demographics of the interviewed patients appeared to reflect the overall RCT sample, it is possible that the views of other participants would not be substantially different. Secondly, although the interview transcripts were robustly analysed by

more than one researcher, the study themes and sub-themes were not verified for accuracy by the interviewed participants.

Symptoms of anxiety and depression were assessed in the RCT but as a baseline measure only. Self-efficacy, however, was not assessed at all in the study. As the interview findings suggest that enhancing self-efficacy and exploring symptoms of anxiety and depression may be beneficial for improving confidence to cope with PD, it is important that these are assessed at baseline and follow-up in future investigations of AT in PD.

Finally, considering that I delivered AT and conducted the post intervention interviews, it is possible that participants may have been reluctant to raise negative views of the therapy. Therefore, the interview content may be subject to positive reporting bias. An independent interviewer would be desirable in future evaluations of AT.

10.6 Summary

This study explored the experiences of people with PD and their spouse/carers who received a seven week programme of AT as part of the previously described clinical trial. The aim was to determine the acceptability of the intervention and to identify what patients found most beneficial. Analysis of the interview transcripts generated three main themes and eleven sub-themes. Evaluation of the patient experience and the identification of the three themes greatly enhanced the

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understanding of what patients found most helpful. The data allowed a new mechanism of action of AT in PD to be proposed which future research should seek to confirm. The next chapter provides a summary of this thesis and discusses the implications for both future research and clinical practice.

CHAPTER 11

Implications and Conclusions

Summary of This Thesis
The Cochrane Systematic Review Including CAAT-PARK
CAAT-PARK within the Wider Adherence Literature
Implications of This Work
Dissemination of This Work
Conclusions

11.1 Summary of This Thesis

In Chapter 3 of this thesis I conducted a systematic review of factors associated with medication non-adherence. Seven studies were identified that met the inclusion criteria. The risk of bias for each study was assessed using a novel quality appraisal tool that I specifically developed. Eleven factors were identified that were associated with medication adherence behaviours in people with PD, six clinical and five demographic: mood disorders, cognition, poor symptom control/ QoL, younger age/longer disease duration, regimen complexity/polypharmacy, risk taking behaviours, poor knowledge of PD/education, lack of spouse/partner, low income, desire to maintain employment and gender. These factors were ranked by weight of their overall evidence.

In Chapter 4 I conducted a Cochrane systematic review of interventions used to enhance adherence to medication specifically in people with PD. Following the evaluation of 38 full texts, only 1 study met the inclusion criteria indicating the paucity of high quality research in this area. The included study showed that simple, didactic patient education relating to the continuous dopaminergic theory significantly improved adherence to medication in people with PD.

In Chapter 5 I outlined a variety of behaviour change theories. The disciplines of motivational interviewing and cognitive behavioural therapy were also outlined. Adherence therapy was introduced and a brief overview of the supporting evidence to date was provided. I used my greater understanding of adherence issues in PD and the core principles of motivational interviewing and cognitive behavioural therapy to develop a novel, PD focused version of AT. In Chapter 6 I provided the justification for, and research design of, a RCT to test the efficacy of this novel intervention for improving medication adherence and QoL in a PD sample (CAAT-PARK).

In Chapter 7 I reported the findings of the CAAT-PARK clinical trial. A statistically significant improvement in medication adherence and QoL was observed in the active treatment group compared to the TAU group. In Chapter 8 I provided a discussion of the results.

In Chapter 9 I reported the findings of a qualitative study that aimed to explore the experience and overall acceptability of AT in ten PD patients and 3 spouse/carers who participated in the RCT. Eleven sub-themes were identified which generated

three main themes: perceptions prior to AT, positive effects of AT and attributes of AT. These findings were discussed in Chapter 10 where I proposed a mechanism of action for AT in PD.

In this final chapter I will discuss how the findings of the Cochrane systematic review change when the results of the clinical trial are acknowledged. I will then outline how this work relates to the wider adherence literature. Finally, I discuss the overall implications of this work for future research and clinical practice.

11.2 The Cochrane Systematic Review Including CAAT-PARK

To my knowledge, CAAT-PARK is only the second clinical trial to test the effectiveness of an intervention for enhancing adherence to medication in PD. Grosset and Grosset (2007) showed that providing didactic information relating to the continuous dopaminergic theory significantly improved timing adherence in patients with PD. In the Cochrane systematic review this intervention type satisfied the criteria for patient education. The RCT described in this thesis is therefore the first study to use a complex, behaviourally targeted intervention to improve adherence in patients with PD.

Both the study by Grosset and Grosset (2007) and CAAT-PARK were able to show a statistically significant improvement in adherence to medication. CAAT-PARK, however, also significantly improved QoL. As described in Chapters 8 and 10, there were several reasons why participants in my RCT did not adhere to

prescribed treatment regimens. For example, many patients reported having poor knowledge of the importance of correct dose timing. As exchanging information was an important element of AT, this may partly explain why the RCT findings presented earlier were consistent with Grosset and Grosset (2007). Therefore, although only two RCTs have aimed to enhance medication adherence in PD, the evidence from these studies suggests that improving knowledge and understanding is likely to be beneficial.

However, considering that participants in my RCT presented with a variety of reasons for not adhering to treatment (e.g. ambivalence to medication, lack of acceptance of PD and impaired ability to problem solve), it is possible that behaviourally targeted interventions such as that described in this thesis may result in greater improvements in adherence to medication than when providing simple educational material as a standalone intervention. This is because not all patients non-adhere to treatment because of poor knowledge. For example, patients may hold negative beliefs about treatment which didactic educational material may not be capable of addressing.

It is also important to note however, that due to the different methods used for assessing adherence to medication between Grosset and Grosset (2007) (where MEMS were used) and CAAT-PARK (where MMAS-4 was used), it is not known whether CAAT-PARK enhanced adherence behaviours in individual patients more than in the study by Grosset and Grosset (2007). Furthermore, it is not clear whether AT delivered as part of the CAAT-PARK trial had a positive impact on more individuals than in the RCT conducted by Grosset and Grosset (2007).

Therefore, whilst it is reasonable to argue that behaviourally targeted interventions such as AT may be more effective for enhancing adherence behaviours than simply providing educational material, from the current evidence this is speculative.

Based on the findings of the two existing RCTs, behavioural interventions may be more likely to impact positively on clinical outcomes (shown in CAAT-PARK) than simple educational material. One reason for this may be because improving confidence and acceptance of the indication for treatment (which may be the focus of a behavioural intervention for some patients) could improve self-efficacy. In turn this could lead to improvements in QoL, as was described in Chapter 10.

Therefore, whilst improving knowledge was shown by Grosset and Grosset (2007) to enhance adherence to treatment, as clinical markers did not improve in this study it is unknown whether providing educational material as a standalone intervention could lead to improvements in clinical outcomes. However, the current work presented in this thesis suggests that both adherence and clinical outcomes may improve when more patient focused, behaviourally targeted treatment approaches are utilised in PD.

11.3 CAAT-PARK within the Wider Adherence Literature

As discussed in Chapter 4, despite Grosset and Grosset (2007) reporting the benefit of a patient education intervention in PD, findings from large scale systematic reviews suggest that patient education is mostly ineffective for improving

adherence in chronic conditions in general (Haynes et al., 2008, Alhalaiqa et al., 2013b).

Unlike patient education approaches however, behaviourally targeted treatments have been shown to be beneficial in chronic conditions. Systematic reviews by Kripalani et al. (2007) and Haynes et al. (2008) both revealed that complex, behaviourally targeted interventions that explored patient beliefs and concerns about medication were more effective than simple treatments such as educational strategies for increasing adherence rates across a variety of chronic disease areas. Furthermore, a Cochrane systematic review by Alhalaiqa et al. (2013b) in patients with hypertension showed that behaviourally targeted interventions provide the greatest magnitude of effect for improving adherence behaviours. As the AT intervention evaluated in my RCT (CAAT-PARK) was a complex/behaviourally targeted treatment, the findings appear to be consistent with the various systematic review findings.

However, as previously stated, considering that only one RCT was identified that had investigated an adherence enhancing intervention in PD (i.e. didactic patient education), it is not known whether AT is more effective than simple education in PD for enhancing adherence behaviours. Nevertheless, when acknowledging the findings of previous systematic reviews in other chronic disease areas, it is reasonable to argue that behavioural interventions such as AT may be more effective for improving adherence to medication in PD than simple educational strategies.

The findings from the RCT presented in this thesis therefore add to the current body of evidence supporting the use of complex/behavioural interventions for improving adherence to medication in chronic conditions. However, unlike many complex/behavioural interventions reported by Kripalani et al. (2007) and Haynes et al. (2008) which did not show an improvement in clinical outcomes (despite enhancing adherence behaviours), CAAT-PARK did show a clinically relevant improvement in QoL. This may result from AT in CAAT-PARK being specifically targeted towards a patient's unique reasons for not adhering to treatment.

Furthermore, factors associated with poor medication adherence in PD were acknowledged when developing the AT intervention. This suggests that complex/behavioural interventions may be more effective when developed and targeted for a specific disease area. Furthermore, it is possible that complex/behavioural treatments will have optimal benefit if delivered by the same therapist in the home environment, as was the case in CAAT-PARK.

11.4 Implications of This Work

11.4.1 Implications for Clinical Practice

The RCT findings presented earlier suggest that a relatively short dose of AT may be effective for improving adherence and QoL in PD. Although the current paucity of evidence for adherence enhancing interventions in PD means that healthcare policy is unlikely to change as a result of the findings of CAAT-PARK, the core principles of AT could be adopted by clinicians. Many of the fundamental

characteristics of AT were developed from well-established motivational interviewing and cognitive behavioural therapy principles. Therefore, whilst a seven week programme of AT is unlikely to be delivered by clinicians in the near future, exercising the basic core skills of AT when undergoing routine patient consultations may be of benefit for maximising adherence to treatment. This is particularly relevant to healthcare professionals such as PD nurse specialists who are more likely to visit patients at home.

Furthermore, my systematic review highlighted that a variety of factors are associated with non-adherence to treatment in PD. Considering the ramifications of poor adherence to medication, routinely assessing for non-adherence in clinical settings by acknowledging the factors described in Chapter 3 is likely to help clinicians identify non-adherent patients. As a lack of acceptance of PD and the indication for treatment was identified as being a reason for non-adherence in some of the interviewed CAAT-PARK participants, this should also be acknowledged when treating patients with PD.

11.4.2 Implications for Future Research

As identified in Chapter 8, there were some limitations to the CAAT-PARK trial that future investigations of AT in PD should attempt to address. Firstly, all CAAT-PARK sessions were delivered by one trained therapist. It is therefore unknown whether AT delivered on a larger scale by clinical team members knowledgeable about PD and its pharmacological treatment (i.e. PD nurse specialists) will be as effective as was demonstrated in the RCT presented in this

thesis. As AT does not require a large amount of training time, future studies should incorporate multiple therapists (such as PD nurse specialists) from a variety of movement disorder centres to establish the efficacy of AT when delivered as part of a wider NHS service. It is important to note, however, that patients should only receive AT from one trained individual, as was suggested by the qualitative study findings presented earlier in Chapter 9.

Secondly, due to time limitations, CAAT-PARK had a short follow-up period. Future studies should therefore incorporate a longer follow-up period to evaluate whether improved adherence is sustained over time. The impact of sustained adherence on clinical outcomes should also be investigated. Specifically, future studies need to investigate the duration of AT sessions required in PD and how long sessions should continue for in order to sustain the therapeutic effect. It may be possible that 'top-up' sessions delivered intermittently are able to maintain the treatment effect of AT over time. This however requires specific investigation as part of a longitudinal study.

Thirdly, the TAU group in the CAAT-PARK RCT did not receive an intervention outside of usual care. As previously described, this limitation makes it difficult to determine whether the improved outcomes resulted from the efficacy of AT or simply due to increased patient-professional interaction. A TAU placebo intervention that offers increased professional contact (e.g. such as regular phone calls) would therefore be ideal in future investigations of AT in PD.

Furthermore, despite estimating the cost to deliver AT, larger scale studies of AT in PD should undertake a formal health economic analysis to accurately determine the cost effectiveness of the intervention.

Finally, the qualitative findings suggested that the mechanism of AT in PD may be bi-directional, as was discussed in Chapter 10. Future studies in PD should therefore seek to confirm this model by evaluating the effect of AT on self-efficacy as part of a RCT. Additionally, observational studies may reveal whether low self-efficacy is associated with non-adherence to anti-parkinsonian medication.

11.5 Dissemination of This Work

11.5.1 Conference Presentations

I was invited to speak at the 2012 East Anglia Movement Disorder Group Conference where I presented the protocol for the CAAT-PARK RCT. I also presented a poster of the systematic review outlined in Chapter 3 at the 2012 Parkinson's UK Research Conference.

11.5.2 Published Papers

1. The protocol for the RCT was published in the open access journal *TRIALS*. The reference for this publication is as follows:

Daley DJ, Deane KH, Gray RJ, Worth PF, Clark AB, Sabanathan K, Pfeil M, Myint PK. The use of carer assisted adherence therapy for people with Parkinson's disease and their carers (CAAT-PARK): study protocol for a randomised controlled trial. Trials 2011;12:251.

This can be accessed at: http://www.trialsjournal.com/content/12/1/251

2. The systematic review of factors associated with medication non-adherence in people with PD was published in *Parkinsonism & Related Disorders*: The reference for this publication is as follows:

Daley DJ, Myint PK, Gray RJ, Deane KHO. Systematic review on factors associated with medication non-adherence in Parkinson's disease. Parkinsonism and Related Disorders 2012;18(10):1053-1061.

This can be accessed at:

http://www.sciencedirect.com/science/article/pii/S1353802012003458

Both of these published papers can be seen in Appendix 41.

11.5.3 Manuscripts Submitted

The RCT findings have been submitted to *Parkinsonism & Related Disorders*. The manuscript is currently under review.

11.5.4 Manuscripts in Preparation

The qualitative study paper and the Cochrane systematic review are both under preparation.

11.6 Conclusion

For many people the symptoms of PD are controllable, particularly in earlier stages of the disease. Thus, appropriately titrated anti-parkinsonian medication can help to optimise QoL. This can allow some individuals to remain active and ambulatory for many years. However, in spite of this, poor adherence to treatment is prevalent in PD.

The work presented in this thesis identified which factors are associated with medication non-adherence in PD. These factors were acknowledged when developing a novel therapy for improving adherence in PD (i.e. AT). This PD specific intervention was tested in a RCT (CAAT-PARK). Findings showed that medication adherence and QoL significantly improved in participants who received AT. A qualitative study was conducted to determine the acceptability of AT in people with PD. Findings showed that AT was highly acceptable and a mechanism of action for AT in PD was proposed. Researchers should seek to both confirm this proposed mechanism and establish the effectiveness of AT when delivered on a larger scale by clinical team members (i.e. PD nurse specialists) as part of a wider NHS service.

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