PREVALENCE AND DIAGNOSIS OF PARKINSON'S DISEASE: A COMMUNITY STUDY

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August 2008

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ABSTRACT

Clinicopathological and community studies have demonstrated misdiagnosis in Parkinson's disease (PD). Clinical trials of antiparkinson medication have also shown a subset of patients labelled as having PD have normal functional brain dopaminergic imaging. Conditions commonly misdiagnosed as PD include Essential tremor (ET), vascular Parkinsonism (VP) and dystonic tremor (DT).

This thesis examines the accuracy of clinical diagnosis of PD in a community setting by identifying misdiagnosed cases and supervising antiparkinson medication withdrawal. Prescription database searches and GP case record review were carried out in 92 West Scotland GP practices within a population of 511,927. 610 patients on antiparkinson medication for a PD diagnosis were identified and age-adjusted prevalence was 129.5 per 100,000. Patients were invited for assessment if there was (a) no increase in dopaminergic drug dose or (b) no recorded progression of disease over time, suggestive of possible misdiagnosis. 64 patients were assessed and this was supplemented with FP-CIT SPECT scanning in 25 uncertain cases. Patients considered unlikely to have PD were advised to reduce and discontinue antiparkinson drugs, with repeat PD motor scoring over 6 months. 33 of 64 patients (51.6%) successfully completed antiparkinson medication withdrawal. An age, sex and disease duration matched control group was also assessed.

The selection criteria allowed identification of a high proportion of misdiagnosed cases and FP-CIT SPECT was a useful diagnostic tool for assessing patients (previously diagnosed as PD) in whom there was diagnostic doubt.

DEDICATION

This thesis is dedicated to my parents, whose unfaltering love, encouragement and support over many years has always been a great inspiration.

ACKNOWLEDGEMENTS

DECLARATION OF AUTHORSHIP

This thesis is the work of the author unless specifically stated otherwise.

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University of Glasgow, August 2008

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Grosset, D. G., & **Newman, E. J**. 2007, " Diagnosis and disease monitoring in Parkinson's disease", in *Managing advanced Parkinson's disease: the role of continuous dopaminergic stimulation*, Aquilonius, S-M., Lees, A. J., Eds., ScopeMedical Ltd, Kent, pp.18-28

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LIST OF ABBREVIATIONS

AD   Alzheimer's disease

ADTC   Area Drug and Therapeutics Committee

ANOVA   Analysis of variance

CT   Computerised tomography

CBD   Corticobasal degeneration

CHP   Community Health Partnership

CK   Creatine kinase

COMT   Catechol O-methyltransferase

CSF   Cerebrospinal fluid

DAT   Dopamine transporter

DIC   Disseminated intravascular coagulation

DIP   Drug-induced Parkinsonism

DLB   Dementia with Lewy bodies

DRD   Dopa-responsive dystonia

DT   Dystonic tremor

ET   Essential tremor

FP-CIT   [^{123}I]*N*-w-fluoropropyl-2-carbomethoxy-3-(4-iodophenyl)nortropane

GP   General Practice / Practitioner

HVA   Homovanillic acid

ICD   International Statistical Classification of Diseases and Related Health Problems

IT	Indeterminate tremor
ITT	Intention to treat
LDR	Long-duration response
LE	Levodopa equivalents
LRRK 2	Leucine-rich repeat kinase 2
MAO-B	Monoamine oxidase B inhibitor
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
MPP+	1-methyl-4-phenylpyridium
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NHNN	National Hospital for Neurology and Neurosurgery
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NMS	Neuroleptic malignant syndrome
NPV	Negative predictive value
PET	Positron emission tomography
PINK 1	PTEN induced kinase 1
PD	Parkinson's disease
PDS	Parkinson's disease Society
PHS	Parkinsonism-hyperpyrexia syndrome
PP	Per protocol
PPV	Positive predictive value

PSP	Progressive supranuclear palsy
ROI	Region of interest
SD	Standard deviation
SDR	Short duration response
SEDAP	Subjects erroneously diagnosed as Parkinson's disease
SIGN	Scottish Intercollegiate Guideline Network
SMC	Scottish Medicines Consortium
SPECT	Single photon emission computed tomography
SWEDD	Subject with scan without evidence of dopaminergic deficiency
UPDRS	Unified Parkinson's disease rating scale
UPS	Ubiquitin proteasome system
UCH-L1	Ubiquitin carboxy-terminal hydrolase
UPS	Ubiquitin proteasome system
VP	Vascular Parkinsonism
WHO	World Health Organisation
^{18}F-dopa	18-fluorodopa
β-CIT	[^{123}I] 2-carboxymethoxy-3-(4-iodophenyl) tropane

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SUMMARY

The diagnosis of Parkinson's disease (PD) is clinical. The most widely used criteria are the UK Parkinson's disease society Brain Bank criteria. Fulfilment of Brain Bank criteria requires 3 steps:

1. diagnosis of a parkinsonian syndrome;
2. exclusion of other causes of parkinsonian syndromes; and
3. supportive features of a PD diagnosis (eg. persistent asymmetry of signs, excellent clinical response to Levodopa and a history of disease progression).

Often the diagnosis of PD is straightforward. However, clinicopathological studies have shown that patients, diagnosed with PD in life, have an alternate underlying diagnosis in up to 25% of cases. Greatest diagnostic accuracy is achieved when patients are assessed within a specialist movement disorder service and followed up over time. Community studies have suggested that up to 26% of PD patients do not have clinical evidence of Parkinsonism. Patients misdiagnosed with PD are often commenced on antiparkinson therapy and may be given inappropriate prognostic information. The most common conditions misdiagnosed as PD in the community are essential tremor (ET) and vascular Parkinsonism (VP).

Diagnosis of PD may be especially difficult in early disease and other causes of tremor (eg. ET, dystonic tremor) must be considered. Recently functional brain imaging using [^{123}I]*N*-w-fluoropropyl-2-carbomethoxy-3-(4-iodophenyl)nortropane (FP-CIT) to determine presynaptic dopaminergic function in striatum (reduced in PD) using single photon emission computed tomography (SPECT) has been shown to accurately differentiate degenerative Parkinsonism from non-degenerative tremor disorders. FP-CIT SPECT imaging is normal in ET, drug-induced and psychogenic Parkinsonism and has proved an extremely valuable tool in the diagnosis of patients with clinically uncertain syndromes. A subset of patients labelled as having PD who have been entered into clinical trials of antiparkinson drugs have normal dopaminergic imaging and have been referred to as SWEDDs (subjects with scans without evidence of dopaminergic deficiency) and the underlying diagnoses in this group of patients has been debated.

The aim of this thesis was to identify patients misdiagnosed with PD from searches within primary care and to supervise gradual withdrawal of antiparkinson medication in this group. The methodology used also allowed examination of prevalence of parkinsonian syndromes and analysis of antiparkinson drug prescription.

Searches of prescription databases and GP case records were performed in 92 West Scotland GP practices across 5 community health partnerships: South East Glasgow, South West Glasgow, South Lanarkshire, East Dunbartonshire and West Dunbartonshire. All patients prescribed antiparkinson medication (Levodopa, dopamine agonists, monoamine oxidase B inhibitors, catechol O-methyl transferase inhibitors, anticholinergic drugs and Amantadine) were identified. The indication for antiparkinson drug prescription was derived from patient case records.

In the areas studied 959 of 511,927 patients were prescribed antiparkinson medication for a non-parkinsonian syndrome (eg. anticholinergics co-prescribed with antipsychotic medication, dopamine agonists for pituitary tumour and restless legs syndrome, Amantadine for multiple sclerosis and Levodopa for dopa-responsive dystonia). 610 of 511,927 patients were prescribed antiparkinson medication for a PD diagnosis giving a crude PD prevalence of 119.2 per 100,000 and age-adjusted prevalence of 129.5 per 100,000.

Patients on antiparkinson medication for a PD diagnosis were invited for clinical assessment if there was no progression of movement disorder symptoms documented in the case records or if there was no increase in antiparkinson drugs in the 3 years preceding the search date. 64 of 89 patients (71.9%) meeting selection criteria were assessed by 2 movement disorder specialists. Following clinical assessment and FP-CIT SPECT (in 25 selected cases of diagnostic uncertainty) 36 of 64 patients (56.3%) were considered to be suitable for antiparkinson therapy withdrawal. 35 of 36 patients consented to supervised antiparkinson therapy withdrawal and were followed up for a mean period of 8.2 months. At serial out-patient clinics patients underwent repeat scoring on validated PD motor scales by a blinded PD nurse specialist. 2 of 35 patients (5.7%) had worsening of movement disorder

symptoms at 3 months following medication withdrawal. FP-CIT SPECT was then performed and was found to be abnormal in both cases. Both cases were considered to have PD and clinically improved following prompt re-introduction of antiparkinson therapy. 33 of 35 patients (94.3%) successfully completed therapy withdrawal without deterioration in movement disorder symptoms.

A control group of 64 patients (matched for age, sex and disease duration) was also assessed. Following clinical assessment and FP-CIT SPECT scanning (in 4 cases of diagnostic uncertainty) 3 of 64 control patients (4.7%) were considered to have a non-PD diagnosis and successfully completed therapy withdrawal. The final diagnostic break-down for patients considered to have a non-PD diagnosis in both groups was: ET = 17 cases; VP = 12 cases; drug-induced Parkinsonism = 3 cases; dystonic tremor = 3 cases; indeterminate tremor = 5 cases and gait ignition apraxia = 1 case.

We can conclude:

- There remains significant misdiagnosis of PD in the community;

- The selection criteria described in this study allow identification of a high proportion misdiagnosed cases;

- FP-CIT SPECT is a useful diagnostic tool in the assessment of patients labelled as having PD in whom there is diagnostic doubt; and

- Supervised antiparkinson medication withdrawal is safe in selected patients.

CHAPTER 1

INTRODUCTION: THE PATHOLOGY AND DIAGNOSIS OF PARKINSON'S DISEASE

The pathology of Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative condition, affecting 1-2% of the over-65 population, causing dopamine deficiency within the nigrostriatal system. Pathologically there is loss of neurones within the subtantia nigra pars compacta and other subcortical nuclei associated with the widespread occurrence of Lewy bodies. PD manifests clinically after the pathology has reached an advanced stage, with loss of approximately 50% of dopaminergic neurones (Jellinger 1987).

Lewy bodies are regarded as the morphological markers of PD (Forno 1986;Spillantini et al. 1997). They are found within surviving neurones within the substantia nigra and other subcortical and cortical locations (Jellinger 2002). Lewy bodies are spherical cytoplasmic inclusions (8-30μm in diameter) with a hyaline eosinophilic core. The major component of Lewy bodies is the pre-synaptic protein alpha-synuclein.

In 2003 a pathological staging system, based on the topographical extent of the lesions, was proposed (Braak et al. 2003). Lesions initially occur in the dorsal efferent motor nucleus of the glossopharyngeal and vagal nerves and the anterior olfactory nucleus. From the lower brainstem the disease processes ascends with involvement of more rostral brainstem areas. Cortical involvement usually follows, beginning with the anteromedial temporal mesocortex.

PD is a heterogenous disorder and is likely to result from a combination of genetic and environmental factors. Environmental toxins have previously been implicated in the development of Parkinsonism. In 1983 young intravenous drug abusers in California inadvertently synthesized and injected 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and developed an unremitting parkinsonian syndrome (Langston et al. 1983). In experimental models, the MPTP metabolite 1-methyl-4-phenylpyridium (MPP+) was shown to be taken up specifically in monaminergic neurones via the dopamine and serotonin transporters and to inhibit the multi-enzyme complex 1 of the mitochondrial electron-transport-chain (Betarbet et al. 2000;Fornai et al. 2005). The degenerative changes caused by MPP+ are most prominent in the dopaminergic neurones, suggesting

that these cells are especially vulnerable to inhibition of the mitochondrial respiratory chain.

Whilst the vast majority of PD is sporadic the identification of genes implicated in the development of familial PD has aided in the understanding of the pathogenesis of the sporadic form. However, the combination of all monogenic forms of PD accounts for only 5-10% of the total PD population (Gandhi & Wood 2005).

In common with other neurodegenerative conditions, it is thought that the pathogenesis of PD results from:

- The abnormal aggregation and processing of mutant or damaged protein
- The cellular response to that protein

Genetic causes of Parkinson's disease

Linkage studies of families with an apparent Mendelian pattern of inheritance have helped to identify the following genes implicated in monogenic forms of PD:

PARKIN (PARK 2) – This gene was first described in Japanese families with autosomal recessive juvenile Parkinsonism (Kitada et al. 1998). The gene is located on chromosme 6q and more than 100 mutations, including point mutations, exon deletions and multiplications, have been identified in many different ethnic groups (Mata et al. 2004).. In a European study of 73 affected families this gene caused 49% of familial early-onset PD and 18 % of sporadic early-onset disease (Lucking et al. 2000). Parkin is expressed in pre- and post-synaptic processes and functions as an E3-type ubiquitin-protein ligase that participates, in the selective transfer of ubiquitin molecules to protein substrates leading to their proteasomal degradation by the ubiquitin proteasome system (UPS) (Shimura et al. 2000;Zhang et al. 2000). Most parkin mutations are thought to cause loss of function resulting in the accumulation of parkin-specific toxic substrates (Gosal et al. 2006).

The clinical phenotype is variable and has most commonly resembles sporadic disease (Gosal, Ross, & Toft 2006). However, features that have been reported include: early onset (often before 40 years), an excellent and sustained response to Levodopa, a symmetrical presentation, early development of dystonia, hyperreflexia, early development of Levodopa-induced dyskinesias, early postural instability and gait abnormalities (Kitada et al. 1998;Lucking et al. 2000;Lohmann et al. 2003). Interestingly, it has been reported that olfaction is preserved in parkin-related cases, unlike in sporadic disease (Khan et al. 2004).

The few neuropathological studies of parkin-positive early-onset patients with homozygous exonic deletions have shown selective nigrostriatal cell loss without the presence of Lewy bodies (Takahashi et al. 1994;Mori et al. 1998). However, Lewy body pathology has been described in heterozygous parkin-positive patients with later-onset disease (Farrer et al. 2001;van de Warrenburg et al. 2001;West et al. 2002).

LRRK 2 (PARK 8) – Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene can cause an autosomal dominant pattern of PD. These mutations are the most common identified in familial or sporadic disease (Elbaz 2008). This gene, located on chromosome 12, was initially mapped in a large Japanese family, known as the Sagamihara kindred (Funayama et al. 2002). LRRK2 encodes a large protein – dardarin. The functions of dardarin are not clear, although it is thought to have a role in vesicle dynamics and secondary messenger signalling (Cookson et al. 2005). To date 7 mutations of this gene have been recognised in patients of different ethnic origin, the most common being the G2019S mutation with lifetime penetrance of up to 74% (Schapira 2006;Healy et al. 2008a). Recent studies have demonstrated high proportions of PD patients carrying LRRK2 mutations in certain ethnic groups, namely North African Arabs (39% of sporadic cases, 36% of hereditary cases) and 10% in Ashkenazi Jews (10% of sporadic cases, 28% of hereditary cases) (Abou-Sleiman et al. 2006;Hulihan et al. 2008;Healy et al. 2008a).

Typically it presents clinically in patients over 50 years and phenotypically resembles sporadic disease with asymmetrical tremor, rigidity, bradykinesia, a good response to Levodopa and dyskinesia (Kachergus et al. 2005). The neuropathological findings of LRRK2-positive patients have been pleomorphic (Yang et al. 2009). Although there is striatonigral neuronal cell loss in all cases, some demonstrate widespread Lewy body pathology, whilst others have evidence of neurofibrillary tangles and tauopathy (Wszolek et al. 2004;Zimprich et al. 2004).

Recently there has been debate whether genetic testing for the G2019S LRKK2 mutation should be offered. Given that this mutation is only found in 2% of sporadic in white populations blanket testing of all cases is not appropriate (Healy et al. 2008c). However, testing of patients with an affected first degree relative or from high-risk populations (North African Arab or Ashkenazi Jew) has been recommended by some; although the absence of available neuroprotective therapies makes this controversial.

ALPHA SYNUCLEIN (PARK1) – The A53T mutation in the alpha-synuclein gene, located on chromosome 4q, was first identified in 1997 within a large Greek-Italian family known as the Contursi kindred and in 3 unrelated families of Greek origin (Polymeropoulos et al. 1996;Polymeropoulos et al. 1997). Alpha-synuclein is particularly abundant at pre-synaptic terminals but its normal function is largely unknown.

There are 3 known point mutations which are thought to act via a toxic gain in function (Schapira 2006). This is probably mediated by intracellular accumulation of abnormal alpha-synuclein inhibiting proteasomal function, leading to Lewy body formation and dopaminergic cell loss. The abnormal alpha-synuclein protein has an increased propensity to aggregate, a crucial step in the development of Lewy bodies (Gosal, Ross, & Toft 2006). It is unclear why dopaminergic neurones are selectively vulnerable to the toxic effects of alpha-synuclein. Elevated levels of wild-type alpha-synuclein may also cause PD, as suggested by the discovery of patients with duplication

and triplication of the alpha-synuclein gene, in the absence of any mutation (Singleton et al. 2003;Farrer et al. 2004).

The clinical phenotype is fairly typical for idiopathic Parkinson's disease with tremor, rigidity, bradykinesia, postural instability and a good response to Levodopa therapy (Golbe et al. 1996). However, age at onset is typically under 45 years and there is often rapid disease progression.

Neuropathological examination of alpha-synuclein positive patients has shown neuronal cell loss in the substantia nigra and locus coeruleus with Lewy bodies in the brainstem, cortex and glial cell inclusions (Gosal, Ross, & Toft 2006). Lewy body pathology appears to be more widespread when these cases are compared with sporadic disease.

PINK 1 (PARK 6) – Homozygous mutations in PTEN induced kinase 1 (PINK 1) cause autosomal recessive early-onset disease. This gene is located on the short arm of chromosome 1 and was identified following studies of 3 consanguineous Italian / Spanish families (Valente et al. 2004a). Further mutations have been identified in Asian and North American families (Hatano et al. 2004). The gene encodes a mitochondrial kinase and may protect cells against stress conditions that affect the mitochondrial membrane potential (Valente et al. 2004b). Mutations in this gene are thought to cause loss of function (Cookson, Xiromerisiou, & Singleton 2005).

The clinical phenotype includes onset in 20s and 30s, asymmetric onset, slow progression of disease, early onset of Levodopa-induced dyskinesia, sustained response to dopaminergic stimulation and rarely atypical features (Valente et al. 2004b). Affected patients have homozygous mutations. However, studies of early-onset sporadic cases have identified a higher proportion of patients with heterozygous mutations when compared with controls (Rogaeva et al. 2004;Healy et al. 2004;Valente et al. 2004b;Gosal, Ross, & Toft 2006). Heterozygous mutations therefore may confer an increased risk.

There are no neuropathological correlates in the literature. However, an ^{18}F-dopa PET study has shown a different pattern of dopaminergic dysfunction to sporadic disease, perhaps suggestive of different neuropathological features (Khan et al. 2002).

DJ-1 (PARK 7) – This gene, located close to the locus for PINK-1 on chromosome 1p, was identified in 2003 in 2 families in Holland and Italy with early-onset autosomal recessive disease (Bonifati et al. 2003). These loss-of-function mutations in DJ-1 are rare and are thought to account for around 1% of early-onset cases (Abou-Sleiman et al. 2003). ^{18}F-dopa studies of clinically unaffected heterozygote carriers are normal, suggesting that heterozygosity is not a risk factor for developing PD (Dekker et al. 2004).

The function of DJ-1 is not fully known. It is expressed in the mitochondrial membranes of astrocytes and is thought to be a sensor of oxidative stress. It has been shown that oxidative stress, using mitochondrial complex 1 inhibitors, wild-type DJ-1 translocates from the nucleus and cytoplasm to the outer mitochondrial membrane, suggesting a neuroprotective action (although it is not known how this protective action is conferred) (Canet-Aviles et al. 2004).

The clinical phenotype includes early-onset (20-40 years), asymmetrical onset, slow progression of disease, psychiatric disturbance, dystonia and sustained response to Levodopa therapy. In addition, psychiatric symptoms and focal dystonia are common (Abou-Sleiman et al. 2003). There are no neuropathological correlates in the literature.

UCH-L1 (PARK 5) – A single missense mutation in the Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) gene located on chromosome 4p was identified and felt to be the cause of an autosomal form of PD in 2 German siblings (Leroy et al. 1998). The protein UCH-L1 is a component of the UPS, involved in recycling of polyubiquitin chains back to monomeric ubiquitin and targeting proteins for UPS degradation. Dysfunction of this enzyme may lead to loss of recycling of ubiquitin monomers and subsequent dysfunction of the proteasomal-proteolytic pathway.

The clinical phenotype is fairly typical for PD: disease onset at 50 years and good response to Levodopa. There are no reported neuropathological correlates. This mutation has not been reported in any other families and its significance is not yet clear.

The clinical value of genetic testing in PD is not yet clear and no formal diagnostic testing guidelines exist. Testing is now available for mutations in parkin and PINK 1 genes. However, these tests are expensive, only done in certain centres and the results are often inconclusive.

Clinicopathological studies of Parkinson's disease

There is no known biological marker for PD. The clinician is required to differentiate idiopathic PD from other parkinsonian syndromes. Clinical diagnostic accuracy in PD is important for therapeutic and prognostic reasons. It is also fundamental for accuracy in epidemiological studies and clinical trials. Pathological examination remains the gold standard for diagnosis of PD. Unfortunately, there are no widely accepted pathological criteria defined for this diagnosis.

The usefulness of any diagnostic test can be assessed using sensitivity, specificity and positive and negative predictive values. The sensitivity of diagnostic criteria for PD is the proportion of patients with the disease who fulfil the criteria. The specificity of the criteria is the proportion of patients who do not have PD who do not fulfil the criteria. Given that sensitivity is conditional on the disease being present and specificity on the disease being absent, they should be unaffected by disease prevalence. The positive predictive value of the criteria is the probability that the patient has PD given that they meet diagnostic criteria. The negative predictive value of the criteria is the probability that the patient does not have PD, given that they do not meet diagnostic criteria. Positive and negative predictive values are dependent on the underlying prevalence of PD within the population being studied.

Traditionally the diagnosis of PD required the presence of 2 out of the 3 motor cardinal features of: bradykinesia, rigidity and resting tremor. Several attempts at clinical

diagnostic criteria have been proposed, but few have been applied consistently or assessed for reliability (Gibb & Lees 1988;Ward & Gibb 1990;Calne et al. 1992;Larsen et al. 1994;Gelb et al. 1999;Litvan et al. 2003). The most widely accepted clinical diagnostic criteria are the UK Parkinson's disease society Brain Bank (UKPDSBB) criteria (Gibb & Lees 1989). Diagnosis of PD using the Brain Bank criteria requires three steps (see Appendix 1). The first step simply confirms Parkinsonism, defined as bradykinesia (slowness in the initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive movements) plus one of the following: postural instability, muscular rigidity or a 4–6 Hz resting tremor. The second step of the criteria is exclusion of other causes of a parkinsonian syndrome, such as vascular, drug-induced, post-encephalitic, post-traumatic Parkinsonism, and the Parkinson-plus disorders. Finally, the third step prospectively supports PD and includes unilateral onset, prominent rest tremor, good Levodopa response and dyskinesia. Central to the development of these criteria were the findings from a series of clinicopathological studies (Gibb & Lees 1988;Gibb & Lees 1989;Hughes et al. 1992a;Hughes et al. 1992b;Litvan et al. 1998;Hughes et al. 2001b;Hughes et al. 2002;Rajput et al. 2004).

A prospective clinicopathological described the post-mortem findings in 59 patients who were diagnosed as having PD in life (Rajput et al. 1991a). All cases had been assessed by a single neurologist. The clinical diagnostic criteria employed in these cases required at least 2 of 3 cardinal features in the absence of any identifiable cause for Parkinsonism. All neuropathological examination was carried out by one neuropathologist who was blinded to the clinical observations. The pathological criteria used required substantia nigra neuronal loss greater than 50% and the presence of Lewy bodies. The patients were followed up for a median period of 11.7 years.

The initial diagnosis was idiopathic PD in 43 of 59 patients. Pathological examination confirmed the diagnosis in 28 of 43 (65%) cases. The final clinical diagnosis was idiopathic PD in 41 patients. This was pathologically confirmed in 31 of 41 cases (76%). The 10 false positive cases comprised 4 cases of striatonigral degeneration, 2 cases of striatonigral degeneration without Lewy bodies, 1 case of Alzheimer's disease

(AD), 1 case of drug-induced Parkinsonism and 2 cases where there was neurofibrillary tangle pathology in the substantia nigra and in the locus ceruleus. This was the first prospective clinicopathological study and suggested that 1 in 4 patients diagnosed with PD by a neurologist had an alternative diagnosis. It also demonstrated that clinical diagnostic accuracy improved when patients were followed up and re-evaluated over time.

Similar findings were reported in a clinicopatholigical study from the Brain Bank (Hughes et al. 1992b). This study described the post-mortem findings of 100 consecutive patients, all diagnosed as having PD in life, collected between 1987 and 1990. These cases were from all over the UK and the diagnostic criteria employed were poorly defined. Neurologists associated with the Brain Bank had prospectively assessed 70 patients, whilst other neurologists and geriatricians had assessed the remaining patients. 76 of 100 cases (76%) were pathologically confirmed as PD. The remaining 24 false positive cases comprised 6 cases of progressive supranuclear palsy (PSP), 5 cases of multiple-system atrophy (MSA), 3 cases of AD, 6 cases of Alzheimer's –type pathology with striatal involvement, 2 cases of nigral atrophy without Lewy bodies, 1 case of post-encephalitic Parkinsonism and one case that was pathologically normal. When the Brain Bank criteria were retrospectively applied to this patient group, using patient case notes, the diagnostic accuracy improved to 82% (73/89). The authors acknowledged that retrospective application of the clinical criteria was limited by how well the clinical findings had been documented.

In a follow-up to this study the authors reviewed the clinical features of these 100 cases (Hughes et al. 2001a). The proportion of cases with a specific clinical feature was then compared with the pathological findings. When certain features were present (asymmetrical onset, no atypical features and no possible aetiology for another parkinsonian syndrome) the diagnostic accuracy was increased to 93%. However, this was at the expense of decreasing the sensitivity of the clinical diagnosis (32% of pathologically confirmed cases of PD that were then rejected using these criteria). This

study found that a 'tremor dominant' pattern of disease was the single best clinical criterion for diagnosing PD.

A further Brain Bank study reported the pathological findings of 100 consecutive cases (Hughes, Daniel, & Lees 2001b). All patients were diagnosed as having PD during life. 90 of 100 cases (90%) were pathologically confirmed as PD. The 10 false positives consisted of 6 cases of MSA, 2 cases of PSP, 1 case of post-encephalitic Parkinsonism and 1 case of vascular Parkinsonism.

A further study reported the pathological results of 143 patients who had been assessed by neurologists associated with the movement disorder team at the National Hospital for Neurology and Neurosurgery (NHNN) in London (Hughes et al. 2002). 73 patients were clinically diagnosed with PD, and the remaining 70 patients were clinically diagnosed with atypical Parkinsonism. 72 of 73 patients (98.6%) diagnosed as PD were pathologically confirmed as PD. The single false positive case was pathologically confirmed as PSP. 7 of 70 (10%) patients diagnosed with atypical Parkinsonism were also pathologically confirmed as PD, giving rise to a sensitivity of 91.1%. This study reported greater diagnostic accuracy than previously found, perhaps suggesting that the clinical diagnosis of movement disorder specialists was more accurate than other clinicians.

These clinicopathological studies should be interpreted with caution. There are no set of agreed pathological criteria for the diagnosis of PD. Many of these studies are retrospective and contain small numbers. In addition donor tissue is more likely to be received from patients who have died in hospital and in patients in whom there has been greater diagnostic uncertainty (Gibb & Lees 1988). The clinical criteria employed in these studies are often vague and in some not mentioned at all. However, these studies do suggest that a significant proportion of patients diagnosed with PD have an alternative diagnosis, and that diagnostic accuracy is greatest when patients are assessed by movement disorder specialists and followed over a long period.

Community Studies of Parkinson's disease

Over the past 10 years several community studies of patients diagnosed as PD have been carried out. A North Wales study reported diagnostic accuracy for Parkinsonism and PD in a community based sample of patients (Meara et al. 1999). Patients on therapy for PD were identified using prescribing databases within 74 General Practices. Once identified patients were clinically assessed at a specialist movement disorder clinic, or seen at home.

502 patients were identified as taking antiparkinson medication for a PD diagnosis. The diagnosis of Parkinsonism had been made by a General Practitioner in 296 of 502 cases (59%). In total, 402 of 502 patients (80%) were examined. Parkinsonism was clinically detected in 299 of 402 cases (74%), with only 213 of 402 cases (53%) meeting Brain Bank criteria. There was no clinical evidence of Parkinsonism in 103 of 402 patients (26%). 50 of 103 patients (48%) were diagnosed with essential tremor (ET), 37 (36%) with gait apraxia and 16 (16%) with Lewy body dementia.

A further community study described searches of the computerised patient case records within 15 Greater London General Practices (Schrag et al. 2002). Those identified included all patients with a current or previous diagnosis of PD or Parkinsonism, all patients who had been prescribed antiparkinson therapy and all patients over 50 years in whom a tremor had been noted. Patients were excluded if they had been prescribed antiparkinson therapy for a separate diagnosis (eg. pituitary tumour, restless legs syndrome), if there was another known cause for tremor (eg. hyperthyroidism), if the patient had been prescribed dopamine depleting medications in the preceding 6 months, or if the patient had developed dementia prior to the onset of parkinsonian symptoms. Patients were assessed either at home, at their General Practice or in a specialist movement disorder clinic and PD was diagnosed using Brain Bank criteria.

Searches identified 241 patients and 202 of 241 (84%) patients agreed to be examined. Of the 202 patients examined, 134 (66%) had previously been diagnosed with Parkinsonism (131 with PD, 2 with vascular Parkinsonism and one with atypical

Parkinsonism). An additional 10 patients (5%) had been started on antiparkinson therapy without a specific diagnosis being applied. The diagnosis of PD was confirmed in 109 of 131 patients (83%). An additional 2 patients (1.5%) were found to have possible PD and the diagnosis was rejected in 20 patients (15%). Of these 20 patients, there were 4 cases of non-parkinsonian tremor, 6 cases of vascular Parkinsonism, 4 cases of PSP, 3 cases of MSA, 2 cases of idiopathic torsion dystonia and one case of dementia without Parkinsonism.

13 of 68 patients (19%) not previously diagnosed with PD, fulfilled Brain Bank criteria and a further 2 patients (3%) were classified as possible PD. Estimates of sensitivity, specificity and positive and negative predictive values for previous PD diagnoses were compared with diagnosis using Brain Bank criteria. Sensitivity was estimated at 88.1% and specificity 73.0%. Positive and negative predictive values were 84.7% and 78.3%. These values were also estimated according to whether patients had originally been diagnosed by specialists or non-specialists. Neurologists and geriatricians had a sensitivity and specificity of 93.5% and 64.5%, compared to 73.5% and 79.1% for non-specialists. Positive predictive values were also greater for specialists (88.7%) than for non-specialists (73.5%).

Although these two studies differ in their methodology, they agree that there is a significant proportion of patients in the community diagnosed as having PD and commenced antiparkinson medication that do not fulfil clinical diagnostic criteria. Common alternative diagnoses for these patients include benign tremor disorders, vascular Parkinsonism and dementia. The community and clinicopathological studies suggests that diagnostic accuracy in PD is greatest when patients are assessed within specialist movement disorder clinics, diagnosed using established diagnostic criteria and followed up clinically over time.

CHAPTER 2

PREVALENCE OF PARKINSON'S DISEASE IN THE WEST OF SCOTLAND

Introduction

Epidemiological studies in Parkinson's disease (PD) provide insights into suspected risk and protective factors for developing PD. They also allow the estimation of social and economic burdens that result from the condition, facilitating healthcare planning (von Campenhausen et al. 2005). Many studies have attempted to measure the prevalence of PD with varying results . There are two main sources of the variation observed: differences in case ascertainment methodology, and differences in the way the diagnosis is defined. However, studies have invariably found that both the incidence and the prevalence of PD increase sharply after 60 years of age. Therefore as the population ages, incidence and prevalence are also expected to increase.

In broad terms there are 2 types of prevalence study. In a door-to-door prevalence study all subjects within the sample are assessed for the relevant disorder. The second method relies on searches of hospital, general practice or pharmacy records, sometimes in combination. Published door-to-door studies have tended to overestimate the prevalence of PD as strict diagnostic criteria were not applied. However, case finding methods underestimate the prevalence as they exclude patients who have not yet come to medical attention. In a recent review, 39 European prevalence studies of PD were identified with crude prevalence rates varying from 65.6 per 100,000 in Sardinia to 12,500 per 100,000 for nursing home patients in Germany (Rosati et al. 1980;von Campenhausen et al. 2005).

UK prevalence and incidence studies

Several UK-based prevalence studies have been published (Brewis et al. 1966;Sutcliffe et al. 1985;Mutch et al. 1986;Sutcliffe & Meara 1995;Schrag et al. 2000;MacDonald et al. 2000;Porter et al. 2006). The crude prevalence rate for PD varies from 108 to 164 per 100,000. The crude prevalence rate relates to the observed population as a whole, without subdivision based on age, sex or other factors which influence the figures. These studies vary in their case finding methodology and the clinical diagnostic criteria for PD. No door-to-door prevalence studies have been undertaken in the UK.

A longitudinal study of a neighbourhood in Carlisle was published in 1966 (Brewis et al. 1966). Hospital, GP, private practice, death certificate and Medical Officer of Health records were all screened. Clinical criteria used for the definition of PD were not stated, and the study predates the UK Brain Bank criteria and other similar algorithms. The prevalence rate was estimated at 112.5 per 100,000 and incidence at 12.1 per 100,000, giving an approximate 9-fold difference between incidence and prevalence, which can be used to estimate average disease duration of around 9 years. Some hint of overdiagnosis may be implied by this survival rate, which is higher than might be expected for this era – predating the use of Levodopa, at a time when the only available drug treatment for Parkinson's disease was anticholinergic therapy.

In 1982 a cross-sectional study was carried out in Northampton (Sutcliffe et al. 1985). Data was gathered from GP and hospital records. Patients identified in the study were then interviewed and examined by a neurologist. The diagnosis of idiopathic PD was made if there was an akinetic-rigid syndrome, with or without tremor (this study also pre-dated the UK Brain Bank criteria). Idiopathic PD cases were considered, whilst other causes of parkinsonism were excluded. The crude prevalence was reported as 108.4 per 100,000. The same authors performed a further epidemiological study in Northampton in 1992 (Sutcliffe & Meara 1995). Again patients were identified from GP practice and hospital records. Diagnosis of PD was made using UK Brain Bank criteria. The crude prevalence was higher at 121 per 100,000 cases and incidence was estimated at 12 per 100,000. In the latter study the authors found a greater proportion of patients with disease of lesser severity and they therefore attributed the apparent increase in prevalence over the 10-year period to diagnosis of PD at an earlier stage.

A prospective incidence study of 148,600 patients in Aberdeen over an 18-month period reported a crude incidence of probable PD as 22.4 per 100,000 (Taylor et al. 2006b). Patients were identified from referrals from GPs, hospital doctors, searching of all out-patient referrals to neurology and medicine for the elderly, electronic searching of GP practice coding and questionnaire screening of the over-65 population. Probable PD was defined as 2 or more of tremor, bradykinesia, rigidity or postural instability. The

authors felt that this higher rate of crude incidence resulted from diagnostic inaccuracy and improved case ascertainment. Whilst screening of the over 65 population may improve the case ascertainment, the incidence may be artificially increased by bringing forward the diagnosis of some patients who would otherwise have been diagnosed later.

In 1986 the results from a cross-sectional study in Aberdeen were published (Mutch et al. 1986). In this study physicians were asked to refer all known PD cases. In addition records within nursing homes and psychiatric hospitals were checked. Patients were then assessed clinically by the authors. The crude prevalence rate from this study was 164.2 per 100,000.

In a longitudinal study of 13 London GP practices 100,230 patients were followed for 18 months for incidence of a variety of neurological disorders including PD (MacDonald et al. 2000) . A further 27,658 patients were followed for lifetime neurological disease prevalence. Patients were identified by medical students and diagnosis was confirmed by neurologists. The age-adjusted incidence for PD was 19 per 100,000 and the lifetime prevalence rate was 200 per 100,000.

In 2000 a cross-sectional study of 15 GP practices in London was published (Schrag, Ben Shlomo, & Quinn 2000). Records were screened for a diagnosis of PD or Parkinsonism, antiparkinson drug usage and tremor occurring under the age of 50 years. The crude PD prevalence (probable and possible) was 128 per 100,000.

Pharmacy records as a source of prevalence and incidence data

Pharmacy records are a reliable source of drug exposure (Lau et al. 1997). The use of pharmacy records for identification of PD patients in epidemiological studies is well established (Menniti-Ippolito et al. 1995;Chio et al. 1998;Martinez-Suarez & Blazquez-Menes 2000;van de Vijver et al. 2001;Lai et al. 2003;Porter et al. 2006;Brandt-Christensen et al. 2006).

Pharmacy records were compared with the results of a community-based prospective cohort study among persons aged over 55 years who were screened for PD in Rotterdam (van de Vijver et al. 2001). 86% of patients who were prescribed Amantadine, 94% who were prescribed Levodopa, 92% who were prescribed Bromocriptine and all patients prescribed either Selegiline or at least 2 antiparkinson medications had a diagnosis of PD. The authors therefore concluded that prescription of antiparkinson medication was a reliable surrogate for a diagnosis of PD. Only 46% of those patients prescribed anticholinergic medications had a diagnosis of PD.

In the British Columbia province of Canada (population 4 million) a regional pharmacy database (PharmaNet) which holds accurate information on prescriptions of approximately 97% of inhabitants was searched for antiparkinson medications (Lai et al. 2003). However, this database does not hold information regarding the clinical indication for drug prescription. The prevalence of PD was estimated using the prescription of one or more of Levodopa, Bromocriptine, Pergolide and Selegiline as a marker. Other antiparkinson medications, such as anticholinergics and Amantadine were not included in the searches. The authors considered the following factors and made adjustments in their calculations accordingly:

1. The proportion of undiagnosed patients with PD
2. The proportion of patients misdiagnosed as PD
3. The proportion of patients with PD not yet commenced on antiparkinson therapy
4. The proportion of patients prescribed Levodopa and Bromocriptine for reasons other than PD

The estimated prevalence of PD was 126 – 144 per 100,000 between 1996 and 1998. While this study reports on a large population, a more accurate assessment would require validation of the correction factors used.

A national prescription database (The Danish medicinal product statistics) was searched for patients using antiparkinson medications over a 7-year period (Brandt-Christensen et al. 2006). This database holds accurate information regarding all

prescriptions issued in Denmark, but does not have any clinical information or diagnostic data. Crude PD prevalence and incidence were 219.8 and 55.9 per 100,000. When the population was age-standardised to the European standard population using the direct method these rates fell to 164 and 43.4 per 100,000, indicating that the Danish population was older than the European standard. The authors acknowledge that these figures were significantly higher than previously estimated, both for incidence and prevalence. They attributed this to the prescription of antiparkinson medication for conditions other than PD (eg. restless legs syndrome, dopa-responsive dystonia, pituitary tumour) and they also suggested that there was a high rate of misdiagnosis of PD. They did not estimate the proportion of patients prescribed antiparkinson drugs for alternative diagnoses.

A further prevalence study of a population of 108,597 within North East England (Porter et al. 2006) was based on GP, consultant neurologist and geriatrician reporting of all patients with possible PD. GP and hospital pharmacy records were also checked to identify all patients on regular antiparkinson medications. All eligible patients were then invited for assessment at home, and diagnosis was based on UK Brain Bank criteria. The crude prevalence was estimated at 148 per 100,000.

Pharmacy and diagnostic review in West Scotland

In undertaking the programme of research central to this thesis, in which the main aim was to identify patients with an incorrect diagnosis of PD, the review of prescription databases within primary care allowed the calculation of incidence and prevalence, using methods similar to previous studies (Menniti-Ippolito et al. 1995;Chio, Magnani, & Schiffer 1998;Martinez-Suarez & Blazquez-Menes 2000;van de Vijver et al. 2001;Lai et al. 2003;Porter et al. 2006;Brandt-Christensen et al. 2006). Accordingly, a comparison with other UK studies could be undertaken. Moreover, because of the additional availability of diagnostic information from full case record review in all cases, the proportion of cases prescribed antiparkinson drugs for alternative diagnoses added precision to the calculated rates.

Methods

Multi-centre ethics committee approval was given by the West Glasgow Ethics Committee. All GP practices within the following 5 West of Scotland Community Health Partnerships were contacted: South-East Glasgow, South-West Glasgow, South Lanarkshire, East Dunbartonshire and West Dunbartonshire.

Individual GP practices were written to and invited to participate. In participating practices we recorded the total number of male and female patients and the proportion of patients within that practice over 65 and under 16 years of age. Searches were then completed of the prescription databases. Both acute and repeat prescriptions for all patients registered in each practice are contained within this database. Antiparkinson drugs (Levodopa, dopamine agonists, monoamine oxidase B inhibitors, catechol O-methyl transferase inhibitors and anticholinergic drugs, as listed in Table 2.1) were searched for using their generic and trade names at all available doses.

The GP case records of all patients prescribed one or more antiparkinson drugs were then reviewed. These case records contain all correspondence from consultations, ward admissions, and tests and results from attendance at secondary care, as well as on-site recordings from consultations with the GP and associated staff, and prior records for the patient in cases of change of address and/or general practitioner. The underlying diagnosis was obtained from this review of the full case record for each patient. It was noted whether the prescription of 'antiparkinson' medication (Levodopa or dopamine agonist) was for other dopa-responsive conditions (eg. restless legs syndrome, pituitary tumour); whether anticholinergics were prescribed for alternative diagnoses (eg. Huntington's chorea, drug-induced tremor); and whether Amantadine was prescribed for lethargy in multiple sclerosis or other similar disorders.

The date of diagnosis was also recorded from the case records. This date was taken as the first specific record of the making of the diagnosis, by the GP or the specialist, whichever came earlier. Patient age and the interval from diagnosis to the search date were also recorded.

Crude and age-adjusted prevalence were calculated using standard methods, based on the Scotland population in the 2000 census (General Register Office for Scotland 2008). Differences within geographical areas were tested with chi-squared, using k proportion testing and the Marascuilo procedure (XLSTAT version 2007.3, AddInsoft, New York). Factors potentially influencing PD prevalence were derived from the Scottish Health Survey 2003 (The Scottish Government 2008).

Results

Of 120 GP practices within the 5 Community Health Partnerships (CHPs), 92 (76.6%) agreed to participate in this study (no significant difference between CHPs). Searches were undertaken between December 2006 and August 2007 inclusive. The total patient population covered by these 92 practices was 511,927 (49.5% male, 50.5% female). South Glasgow and South Lanarkshire had larger populations than the remaining areas (See Table 2.2).There were 76,585 patients aged 65 and over, which represented 15.0% of the total catchment population, and 40.8% in this age bracket were male, and 59.2% female.

The number of patients prescribed antiparkinson medication was 1568 (0.3% of the catchment population) (See Figure 2.1). 916 of the 1568 (58.4%) were on antiparkinson therapy for reasons other than a parkinsonian syndrome. 688 of 916 (75.1%) patients were prescribed anticholinergic medication in relation to the use of traditional antipsychotics; 97 patients (10.6%) were prescribed dopamine agonists for pituitary tumour; 62 patients (6.8%) were prescribed dopamine agonists for restless legs syndrome; 53 patients (5.8%) were prescribed Amantadine for symptoms of multiple sclerosis; and 16 patients (1.7%) were prescribed Levodopa for dopa-responsive dystonia.

In total 653 patients were prescribed antiparkinson medication for a parkinsonian syndrome, of whom 610 (93.4%) had a diagnosis of PD. Of these 610 cases, 55.6% were male, and 44.4% female. Other parkinsonian syndromes were as follows (percentage figures are expressed out of the 653 cases):

a. Vascular Parkinsonism (VP): 23 (3.5%)

b. Dementia with Lewy bodies (DLB): 8 (1.2%)

c. Progressive supranuclear palsy (PSP): 6 (0.9%)

d. Multiple system atrophy (MSA): 3 (0.5%)

e. Drug-induced Parkinsonism: 2 (0.3%)

f. Post-encephalitic Parkinsonism: 1 (0.2%)

The crude prevalence of all parkinsonian syndromes was 127.6 per 100,000 (95% confidence interval: 118.8 – 136.4); and the prevalence for the population over 65 years was 728.6 per 100,000 (669.1 – 789.1).

The crude prevalence for PD was 119.2 per 100 000 (109.7 – 128.6), and the age-adjusted prevalence was 129.5 per 100 000 (119.6 – 139.4). The crude prevalence was significantly higher for males than females (133.1 per 100 000 (119.0-147.3) versus 105.3 per 100 000 (92.8-117.9), p=0.004); and this was also true for age-adjusted results (males 146.7 (131.8-161.6) versus females 113.3 (100.3-126.3), p=0.001) (See Table 2.3). There was a statistically significant difference across the geographical areas, for both males and females, considering age-adjusted prevalence (See Figure 2.2), and crude prevalence (data not shown). This was seen in both sexes, and in particular comparing South Glasgow males (98.3, CI 78.7-117.9) and females (83.9, CI 65.6-102.2) with South Lanarkshire males (202.7, CI 175.0-230.4) and females (151.1, CI 127.7-174.5), both p<0.001.

Crude prevalence in the over-65 population was 705.4 (645.1-765.8) which gave an age-adjusted prevalence of 723.4 (662.3-784.5) for this age group. There was an age-related increase in prevalence for both males and females (See Figure 2.3).

The overall proportion of patients attending a hospital clinic for PD management was 72.6%, but varied significantly across geographical areas: 62.2% in West Dunbartonshire, 64.1% in South Lanarkshire, 83.0% in South Glasgow, and 91.1% in East Dunbartonshire (p<0.0001).

Factors with potential influence on the prevalence of PD, according to geographical area, are in Table 2.4. The highest cigarette smoking rate and greatest educational deprivation was seen in South Glasgow. Also, population density was greatest for South Glasgow and least for South Lanarkshire. However, limitation of access to services (which includes healthcare) was least in South Glasgow.

Crude prevalence for other parkinsonian syndromes was as follows: VP 4.5 per 100,000 (over 65 years: 30.0); PSP 1.2 per 100,000 (over 65 years: 6.5); and MSA 0.6 per 100,000 (over 65 years: 3.9) (numbers too small to calculate confidence interval data).

Table 2.6 shows the number of new incident cases per year of parkinsonian syndromes between 1996 and 2006 (full year data for 2007 was not available hence this year is not shown). These figures are from searches of patients prescribed antiparkinson medication for PD at the time of the database search (2006-2007), and therefore exclude patients diagnosed with PD during this 10-year period who have died prior to the index date. The most accurate figures are therefore from 2005 and 2006 as fewer of the patients in this group will have died prior to the index date. The 2006 incidence of parkinsonian syndromes is 18.6 per 100,000 (95% CI 14.8 – 22.3); and the incidence in patients over 65 years was 124.0 per 100,000 (99.1 – 148.9). The incidence of PD was 15.4 per 100,000 (12.0 – 18.8); and the incidence in patients over 65 years was 107.1 per 100,000 (80.4 – 125.9). The incidence of VP was 2.2 per 100,000 (0.8 – 3.4); and the incidence of VP in patients over 65 years was 14.3 per 100,000 (5.87 – 22.8).

Discussion

This study covered more than 10% of Scotland's population and is the largest epidemiological study of PD in the UK. Review of patients' case records for diagnostic data greatly enhanced the understanding of the reasons for using antiparkinson medication, with an associated improvement in the accuracy of statistical interpretation. Most previous pharmacy-based epidemiological studies have not included case record review and the proportion of patients prescribed antiparkinson therapy for other

conditions was therefore only estimated (Martinez-Suarez & Blazquez-Menes 2000;Lai et al. 2003;Brandt-Christensen et al. 2006). The current study showed that antiparkinson medications are quite often prescribed for restless legs syndrome, pituitary adenoma and multiple sclerosis. However, the largest usage of 'antiparkinson' drugs for a diagnosis other than PD was of anticholinergic drugs in patients prescribed traditional anti-psychotic medications. Previous studies did not include anticholinergics within their drug searches (Lai et al. 2003;Brandt-Christensen et al. 2006), but may therefore slightly underestimate the number of PD cases; we found 2 cases with PD whose only treatment was an anticholinergic drug as monotherapy.

In virtually all cases it was possible to determine the reason for the antiparkinson medication prescription from the case record. In cases where it was not clear, the indication was discussed with the patient's GP, which allowed a specific conclusion to be reached for all cases. The prescription database did contain diagnostic information for each patient. However, this information was often incomplete, and therefore full review of the case record was essential to the full understanding of the clinical reason for drug prescription.

While the search strategy employed in our study was comprehensive, it will still miss patients within the population who are not registered with a GP, and those living in long-term institutions (such as psychiatric units and prisons). Migration into and out of the area also may affect the figures. Only immigrants who have registered with a GP within their Community Health Partnership will be identified, whilst some patients who have moved away from the region may still have case records within the GP practice.

The main unexpected finding was of significant variation in prevalence between geographical areas, in particular between a low rate in South Glasgow, and a high rate in South Lanarkshire. The size of the populations studied in these two areas was substantial and approximately equivalent. Our overall prevalence figures are comparable with previous UK studies (Sutcliffe et al. 1985;Schrag, Ben Shlomo, & Quinn 2000). There are several potential reasons for prevalence variations, of which case-finding and other

methodological differences have received greatest attention, but these are unlikely to influence the current findings. The study was conducted contemporaneously by the same investigator (EN) and employed the same search strategies, with similar acceptance rates by invited general practices. Other potential sources of variation, which could explain within-area differences, are now considered in turn.

High cigarette smoking rate and lower education levels are both associated with lower rates of PD (Frigerio et al. 2005;Ritz et al. 2007). Other environmental factors implicated in the development of PD include rural living and certain occupational exposures (de Lau & Breteler 2006). While the observed higher rate of cigarette smoking, combined with higher levels of education deprivation, and greater urban community could reduce the PD prevalence in South Glasgow relative to South Lanarkshire, the magnitude of such effects (an approximate two-fold difference between the two areas) is larger than indicated from relative risk studies (Frigerio et al. 2005;de Lau & Breteler 2006;Ritz et al. 2007), and suggests that other influences are likely to be present.

Age is the greatest risk factor for developing PD, with an exponential increase above age 65. While significantly more patients were over 65 in South Lanarkshire versus South Glasgow, an even higher proportion of elderly was present in East Dunbartonshire, and the within-area prevalence differences persisted after age-adjustment to the Scottish population. Migration is minimal in the areas studied (0.5% over 10 years) (General Register Office for Scotland 2008), but selective migration following a diagnosis of PD might affect prevalence, for example reducing them in urban areas.

Another potential reason for the difference in prevalence between areas studied to consider is genetics. Recent studies have demonstrated very high prevalence of the G2019S mutation in LRRK2 in North African Arabs and Ashkenazi Jews (Hulihan et al. 2008;Healy et al. 2008b). It is possible that there is cohort of patients within South Lanarkshire carrying pathogenic mutations which explain the high PD prevalence. However, the South Lanarkshire population is not genetically homogenous, and immigration and emigration to surrounding areas makes this extremely unlikely.

Several additional inter-related factors, which might potentially be influenced by availability and access to specialist clinics, deserve consideration.

A delay to reaching a diagnosis of PD (underdiagnosis) is a known influence on incidence and prevalence, and the proportion of these undiagnosed cases can be estimated from screening studies. The Europarkinson collaborative combined data from 5 community prevalence studies in France, Italy, Holland and Spain; 24% of 468 PD cases had not been previously diagnosed, within a 14 636 population aged 65 years and older (de Rijk et al. 1997). In Aberdeen, Scotland, community screening by postal questionnaire of 1556 patients over 65 years identified 2 new cases of PD (Taylor et al. 2006a), which is numerically consistent with the Europarkinson report. The number of undiagnosed cases in the community is therefore substantial, and gives a further opportunity for prevalence variation between different areas.

Overdiagnosis of PD as benign tremor disorders occurred in 10-26% of cases in UK community studies (Meara, Bhowmick, & Hobson 1999;Schrag, Ben Shlomo, & Quinn 2002), leading the National Institute for Clinical Excellence to recommend that PD patients are seen and their diagnosis reviewed frequently in a movement disorder service (2006). Specialist management of PD, or possible PD, is likely to differ from that in general practice. Both health service access and specialist clinic attendance rates were better for South Glasgow than South Lanarkshire. One explanation is that the South Lanarkshire cohort includes a higher proportion of misdiagnosed cases.

The timing of initiating antiparkinson therapy is also subject to known variations. By depending on prescription of antiparkinson therapy to find PD cases, we did not include diagnosed patients not yet commenced on therapy (mainly because they have mild early disease without significant functional disability). This proportion is estimated at 10-20% (Mutch et al. 1986;Tandberg et al. 1995), but may decrease in future if evidence strengthens about benefits of early treatment (Grosset & Schapira 2008). Variation in clinical practice between areas could again influence prevalence rates, within this subset of cases of PD.

The incidence and prevalence figures obtained in this study are comparable with previous UK studies (Brewis et al. 1966;Sutcliffe et al. 1985;Sutcliffe & Meara 1995;Schrag, Ben Shlomo, & Quinn 2000). A recent review estimated the incidence of PD between 16-19 per 100,000 (Twelves et al. 2003). Using the year 2006 figure as the most representative in our study, the incidence of PD in the West of Scotland is 15.4 per 100,000, close to the lower point of the range from these studies. We cannot determine whether the incidence of PD is increasing over time using our data; this would require an additional search on a further index date. Whilst the total population covered by the 92 GP practices will fluctuate with births, deaths, immigration and emigration, the West of Scotland population is fairly static, with only a 0.5% increase from 1996 to 2006 (General Register Office for Scotland 2008). Current migration from East Europe to the United Kingdom is much greater, however, and this might potentially influence the analysis of any repeated searches within our study population.

Some previous pharmacy-based epidemiological studies have not stated clearly if they included PD only or extended to all forms of Parkinsonism. In a recent US study the authors concluded that administrative patient data were limited in the ability to distinguish between PD and Parkinsonism using ICD-9 codes and pharmacy data (Swarztrauber et al. 2005). In our study we estimated the prevalence and incidence of several parkinsonian syndromes, VP, DLB, PSP and MSA, based on full case record review. However, the use of prescription databases in epidemiological studies of atypical Parkinsonism is not established and it is likely that it's incidence and prevalence is underestimated in the current study. This is primarily because we initially identified patients taking antiparkinson therapy, and many patients with atypical Parkinsonism are not prescribed such therapy. For example, patients presenting with MSA in which cerebellar or autonomic features are dominant will often not be appropriate for antiparkinson therapy, and some patients in the later stages of MSA and PSP, who may initially have shown some response to antiparkinson therapy, will have such drugs stopped when the response wanes and/or they develop therapy-associated side-effects such as postural hypotension. It is therefore to be expected that our prevalence rate of 0.6

per 100,000 for MSA is lower than published rates of 1.9 – 4.9 per 100,000 (Schrag et al. 1999;Vanacore 2005). The situation is similar for PSP, where we found a rate of 1.2 per 100,000 while the prevalence is reported at 6.4 per 100,000 (Schrag, Ben Shlomo, & Quinn 1999). In addition, the role of antiparkinson therapy in patients with vascular Parkinsonism and drug-induced Parkinsonism is not clearly established, and it is likely that the prevalence of such diagnoses is larger than implied by our observations.

Conclusion

Prescription database searches of antiparkinson medications followed by case record review provide epidemiological data on PD and other parkinsonian syndromes, with greater accuracy than simply analysing data from pharmacy databases which often do not have diagnostic information. Variation in PD prevalence between geographical areas occurs, which is not explained by methodological differences. While there are differences between areas for risk factors for the development of PD, the magnitude of prevalence variation is great, and justifies more detailed research into the relative importance of several potential causes.

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┌─────────────────────────────────────────────────────────────────────────┐
│           Patients prescribed anti-parkinson medications, n=1569          │
└─────────────────────────────────────────────────────────────────────────┘
                                    │
        ┌───────────────┐    ┌────┐      ┌──────────────────────────────────────────┐
        │ Diagnosis:    │───▶│ NO │─────▶│ Antipsychotic drug therapy n=688(43.8%)   │
        │ PARKINSONIAN  │    └────┘      │ Pituitary tumour n= 97 ( 6.2%)            │
        │ SYNDROME      │               │ Restless legs syndrome n= 62 ( 4.0%)      │
        └───────────────┘               │ Multiple sclerosis n= 53 ( 3.4%)          │
                │                       │ Dopa-responsive dystonia n= 16 ( 1.0%)    │
        ┌───────────────┐               │ TOTAL n=916(58.4%)                        │
        │ YES n=653     │               │ % out of 1569 cases on anti-parkinson     │
        │ (41.6% of 1569)│               │ medication                                │
        └───────────────┘               └──────────────────────────────────────────┘
                │
        ┌───────────────┐    ┌────┐      ┌──────────────────────────────────────────┐
        │ Diagnosis:    │───▶│ NO │─────▶│ Vascular parkinsonism n=23(3.5%)          │
        │ PARKINSON'S   │    └────┘      │ Dementia with Lewy bodies n= 8(1.2%)      │
        │ DISEASE       │               │ Progressive supranuclear palsy n= 6(0.9%) │
        └───────────────┘               │ Multiple system atrophy n= 3(0.5%)        │
                │                       │ Drug-induced parkinsonism n= 2(0.3%)      │
        ┌───────────────┐               │ Post-encephalitic parkinsonism n= 1(0.2%) │
        │ YES n=610     │               │ TOTAL n=43(6.6%)                          │
        │ (93.4% of 653)│               │ % out of 653 cases with parkinsonian       │
        └───────────────┘               │ syndrome                                  │
                                        └──────────────────────────────────────────┘
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Figure 2.1: Indication for antiparkinson therapy within a population of 511 927 patients. The most common reason for using antiparkinson therapy was anticholinergic use in patients prescribed antipsychotic drugs. Most patients with a parkinsonian syndrome had Parkinson's disease.
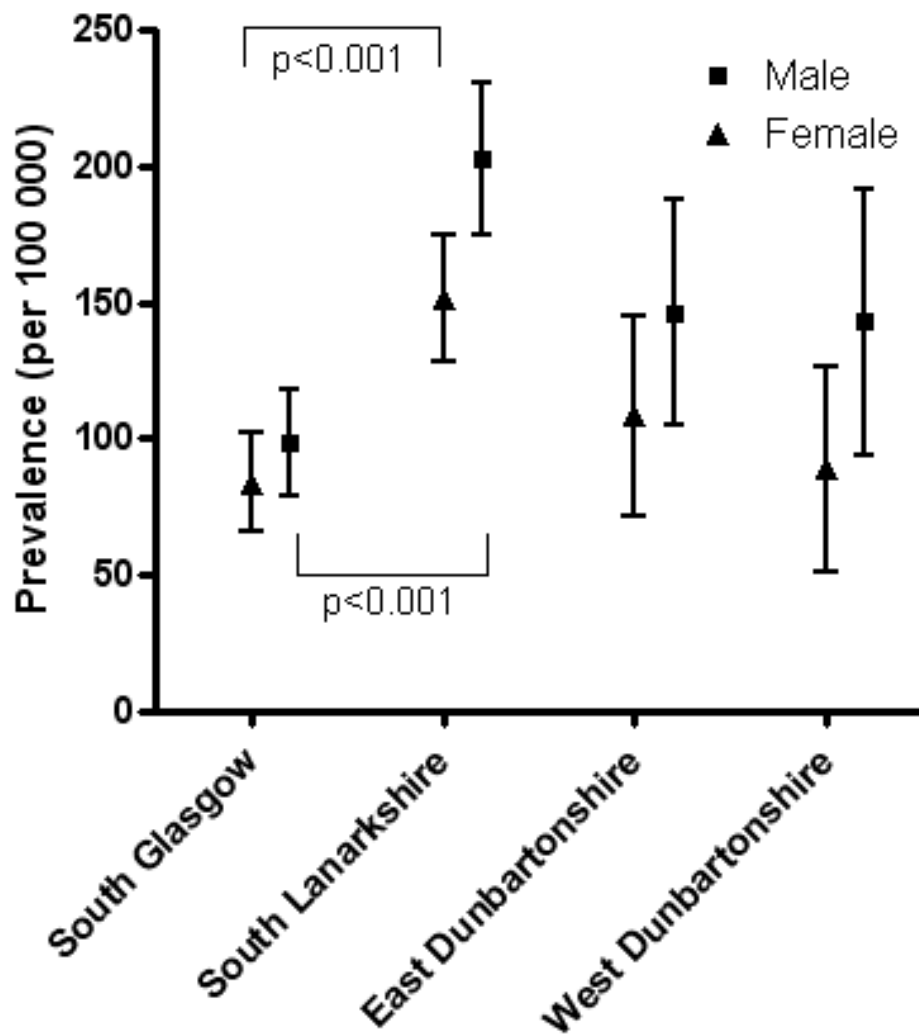
Figure 2.2: Prevalence of Parkinson's disease by area and sex. There was a significant variation in prevalence across geographical areas, for both males and females, in particular comparing South Glasgow with South Lanarkshire. Prevalence is age-adjusted to the Scotland population, and shown as mean (95% confidence interval).
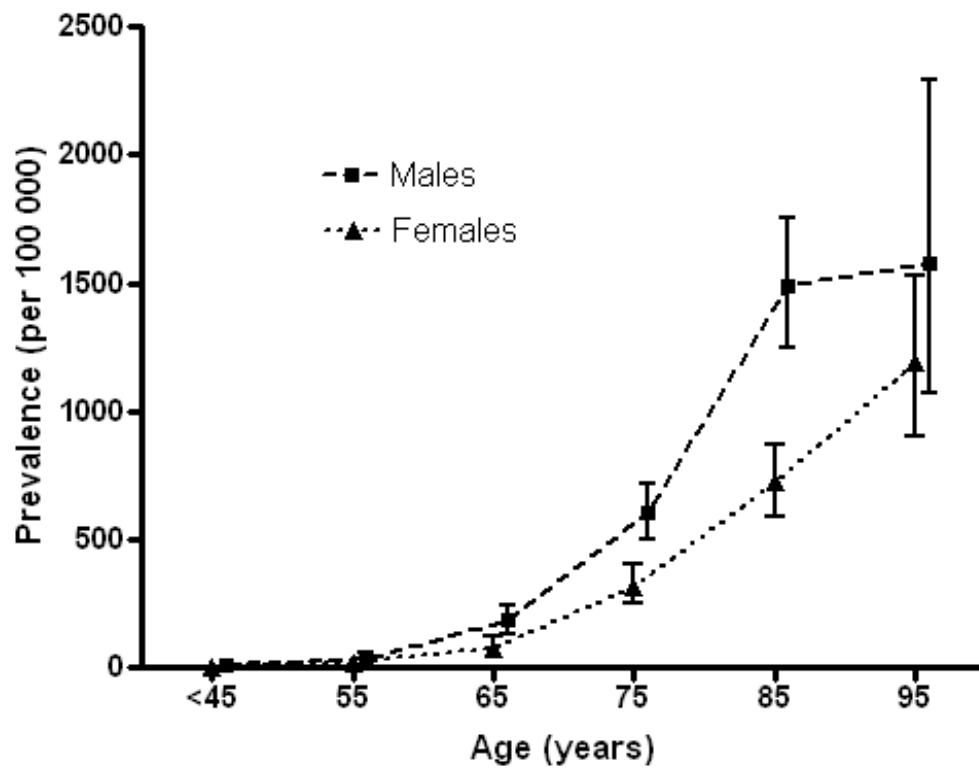
Figure 2.3: Prevalence of Parkinson's disease by age and sex. There was an age-related increase in prevalence for men and women. Prevalence is shown as mean (95% confidence interval).

Table 2.1: Antiparkinson medications included in database searches

Levodopa + carbidopa or benserazide
Co-beneldopa, Co-careldopa, Madopar, Sinemet

Levodopa + carbidopa + catechol O-methyltransferase inhibitor
Stalevo

Dopamine agonists
Apomorphine, Bromocriptine, Cabergoline, Lisuride, Pergolide,
Pramipexole, Ropinirole

Catechol O-methyltransferase inhibitors
Entacapone, Tolcapone

Monoamine oxidase-B inhibitor
Selegiline, Rasagiline

Anticholinergic drugs
Benzatropine, Orphenadrine, Procyclidine, Trihexphenidyl
hydrochloride

Other
Amantadine

Table 2.2: Populations studied by geographical area and sex

Area	Male	Female	Total (% over 65 years)
South Glasgow	97 832	96 086	193 918 (13.9%)
South Lanarkshire	101 468	106 209	207 677 (15.5%)
East Dunbartonshire	32 433	31 044	63 477 (16.5%)
West Dunbartonshire	22 904	23 951	46 855 (14.8%)
ALL	254 637	257 290	511 927 (15.0%)

Table 2.3: Prevalence of Parkinson's disease in different areas of west Scotland

Area	Males		Females	
	Crude	Age-adjusted	Crude	Age-adjusted
South Glasgow	88.9 (70.2-107.6)	98.3 (78.7-117.9)	81.2 (63.2-99.2)	83.9 (65.6-102.2)
South Lanarkshire	177.4 (151.5-203.3)	202.7 (175.0-230.4)	132.8 (110.9-154.7)	151.1 (127.7-174.5)
East Dunbartonshire	144.9 (103.5-186.3)	146.3 (104.7-187.9)	103.1 (67.4-138.8)	108.4 (71.8-145.0)
West Dunbartonshire	109.2 (66.4-151.9)	142.7 (93.8-191.6)	83.5 (46.9-120.1)	89.0 (51.2-126.8)
TOTAL	133.1 (119.0-147.3)	146.7 (131.8-161.6)	105.3 (92.8-117.9)	113.3 (100.3-126.3)

Prevalence expressed per 100 000; Data are mean (95% confidence intervals)

Table 2.4: Factors with potential influence on Parkinson's disease prevalence

Area	Cigarette smokers	Education deprivation	Health deprivation	Access to services deprivation	Persons per hectare
South Glasgow	34.0	43.9	49.0	0.1	28.9
South Lanarkshire	26.2	16.6	16.3	11.1	1.7
East Dunbartonshire	18.6	2.4	2.4	7.9	6.2
West Dunbartonshire	33.3	17.8	17.8	10.2	5.9

Data expressed as percentages (except persons per hectare)

Table 2.5: Prevalence and incidence of parkinsonian syndromes

Parkinsonian syndrome	Crude prevalence (per 100,000)	Prevalence in over 65's (per 100,000)	Incidence in 2006 (per 100,000)	Incidence for over 65's for 2006 (per 100,000)
All parkinsonian syndromes	127.6 (118.8 – 136.4)	728.6 (669.1 – 789.1)	18.6 (14.8 – 22.3)	124.0 (99.1 – 148.9)
Parkinson's disease	119.2 (110.4 – 128.0)	676.4 (619.1 – 734.7)	15.4 (12.0 – 18.8)	107.1 (80.4 – 125.9)
Vascular parkinsonism	4.5	30.0	2.2	13.1
Dementia with Lewy bodies	1.6	10.4	0.4	2.6
Progressive supranuclear palsy	1.2	6.5	0.2	1.3
Multiple system atrophy	0.6	3.9	0.4	2.6
Drug-induced parkinsonism	0.2	2.6	0	0
Post-encephalitic parkinsonism	0.4	1.3	0	0

95% confidence intervals are in brackets

Table 2.6: Number of incident cases of parkinsonian syndromes per year 1996 – 2006

Year	Total PS	PD	VP	DLB	PSP	MSA	DIP
1996	16	15	0	1	0	0	0
1997	22	22	0	0	0	0	0
1998	30	28	1	0	0	1	0
1999	38	36	2	0	0	0	0
2000	41	41	0	0	0	0	0
2001	44	40	1	1	2	0	0
2002	52	49	3	1	0	0	0
2003	82	77	4	0	0	0	0
2004	62	60	0	0	1	0	1
2005	75	70	1	1	2	0	1
2006	95	79	11	2	1	2	0
Total	**557**	**517**	**23**	**6**	**6**	**3**	**2**

Total PS = all patients with a parkinsonian syndrome, PD= Parkinson's disease, VP= vascular parkinsonism, DLB= dementia with Lewy bodies, PSP= progressive supranuclear palsy, MSA= Multiple system atrophy, DIP= drug-induced parkinsonism

CHAPTER 3

COST ANALYSIS OF ANTIPARKINSON THERAPY IN WEST SCOTLAND: A

COMMUNITY STUDY

<u>Introduction</u>

Parkinson's disease (PD) is treated pharmacologically with a combination of Levodopa, dopamine agonists, monoamine oxidase B inhibitors and catechol O-methyltransferase inhibitors. Drug therapy aims to improve PD symptoms, but does not alter the underlying pathological process. In early disease drug therapy can improve symptoms such as bradykinesia, rigidity, and to a lesser extent tremor. Not all patients are treated immediately on diagnosis. The traditional approach to drug management in PD has been to wait until there is significant functional impairment resulting from movement disorder symptoms before commencing antiparkinson drugs. There are also patients with early disease who remain undiagnosed. However, with progression of symptoms over months to years the large majority of PD patients will come to medical attention and be commenced on life-long drug therapy. In later disease, drugs are used increasingly in combination regimens, to try to control the motor fluctuations associated with long-term Levodopa.

With an ageing population, it is expected that the incidence and prevalence of PD will also increase (See Chapter 2). The cost of managing PD patients is significant and increases with disease severity (LePen et al. 1999;Findley et al. 2003). Patients require greater access to primary and secondary care services, including specialist PD out-patient clinics. Younger patients may suffer loss of earnings and older or more advanced patients may require nursing care (Whetten-Goldstein et al. 1997;Hagell et al. 2002). A UK-based study reported the mean cost of care for 432 PD patients at £5993 per year (Findley et al. 2003). This study assessed employment status, utilization of social services, private expenditure, and primary care and secondary care costs. Costs increased significantly with disease severity (as measured using Hoehn and Yahr staging), and the single biggest factor was whether or not the patient required nursing care. Antiparkinson medication accounted for 24% of the overall costs. Mean drug costs were lower with increasing age, being £3.87 per patient per day in the under 65 age-group, and £1.56 in the over 85 age-group. The cost of antiparkinson drugs did not change significantly with increasing disease severity, and the authors suggested this may result from simplification of drug regimens with increasing disability, especially cognitive impairment.

Many new drug preparations have become available over the past 10 years but there has been relatively little examination of the costs and influences of antiparkinson drug prescription. Typically within the UK patients are commenced on a single antiparkinson drug. With clinical disease progression, the dose of this drug is increased and other drugs are added.

A 2006 study compared the antiparkinson drug costs for a cohort of 286 German and 152 Norwegian PD patients attending a specialist PD clinic (Vossius et al. 2006). Both groups were comparable for age, disease duration and stage of disease. Mean daily drug costs were Euro 5.78 in the German group and Euro 3.92 in the Norwegian group, with higher drug expense with disease severity and duration. The difference in costs between the two groups was explained by two factors: that antiparkinson drugs are around 20% more expensive in Germany and that there was greater prescription of multiple drugs at an earlier disease stage within the German group (48% of the Norwegian group were on antiparkinson monotherapy compared to 28% of the German group).

A further study from Germany analysed antiparkinson medication from 6,500 PD patients who responded to a questionnaire addressing sudden onset of sleep from the deutsche Parkinson-Vereinigung (dPV), a national PD support group (Moller et al. 2005). 94.2% of patients were prescribed Levodopa, 71.7% dopamine agonists, 40.1% Amantadine, 27.6% Selegiline, 20.4% Entcapone, 11.8% anticholinergics whilst only 14 (0.21%) patients were prescribed subcutaneous Apomorphine. The mean daily drug cost per patient was Euro 13.10 and only 8.4% of patients were treated with monotherapy rather than a combination of antiparkinson drugs.

A French study reported the medical costs of 294 PD patients (LePen et al. 1999). 54 (18%) patients were managed by their GP and 240 (82%) attended a Neurology out-patient clinic. The mean daily drug cost was Euro 2.83 per patient. Costs were higher in older patients and those with greater disease severity, motor complications, and in those patients who attended a Neurology clinic. A retrospective analysis of 127 Swedish PD

patients attending a movement disorder clinic found a mean daily drug cost of Euro 3.90 (Hagell et al. 2002). A German clinic-based report of 409 PD patients reported a daily drug cost of Euro 5.50 (Dodel et al. 1998). This study found that drug costs were higher in those patients with motor complications and with the akinetic-rigid subtype of PD. Within the European studies there is therefore a wide variation in mean daily cost of antiparkinson therapies (Euro 2.83 - 9.10).

As part of the larger study described in Chapters 2 and 4, in which the main aim was antiparkinson therapy withdrawal in patients erroneously diagnosed as PD, detailed information was obtained about antiparkinson drug doses, from which cost calculations could be made. It was also possible to relate drug usage to demographic factors, such as duration of the diagnosis. The following were the main aims of the current work:

- To examine the pattern and cost of antiparkinson drug prescription within a primary care setting in the UK
- To identify factors that influence choice of antiparkinson drug therapy in this group

Methods

Prescription databases within 92 GP practices within 5 West Scotland Community Health Partnerships were searched for all patients prescribed antiparkinson medications (See Table 2.1) between December 2006 and August 2007. The case records for all patients prescribed antiparkinson drugs were reviewed and all those prescribed therapy for conditions other than PD were excluded from analysis.

Information recorded included age, sex, time since PD diagnosis, current antiparkinson drug prescription and specialist clinic attendance. Movement disorder clinics only were considered as specialist clinics; neurology and general medicine clinics were considered as non-specialist clinics; patients without attendance for their PD at any hospital clinic were defined as primary care cases.

The cost of antiparkinson medications was calculated according to basic National Health Service prices, as listed in the British National Formulary (British Medical Association 2006). Doses of dopaminergic medication were compared using Levodopa equivalents (LE) (Grosset et al. 2004) (eg. 100 mg Levodopa =1 mg Pergolide = 1.5 mg Pramipexole salt = 6 mg Ropinirole = 1.5 mg Cabergoline).

Statistical Analysis

Data for the cost of antiparkinson medications was not normally distributed and showed a positive skew and was therefore summarised as median and interquartile range. Drug costs between different groups were compared using unpaired t-tests and one-way ANOVA; proportions of patients prescribed different medications were compared using chi-squared contingency tables.

Results

Out of a total population of 511 927, 610 patients were prescribed medications for PD. The total daily cost of these antiparkinson drugs for all patients was £1665.58. The median daily cost per patient was £0.79 (interquartile range: £0.34 to £3.76). The maximum daily cost for an individual patient was £31.38. Levodopa was prescribed in 543 patients (89.0%) at a median daily cost of £0.44 (£0.26 to £0.97). Levodopa accounted for 32.0% of the total cost of antiparkinson medications. However, over 50% of the total cost of Levodopa resulted from the prescription of Stalevo (a combination of Levodopa and Entacapone) in 94 of 610 patients (15.4%).

175 of 610 patients (28.7%) were prescribed a dopamine agonist at a median daily cost of £5.83 (£3.70 to £7.74). The cumulative cost of all dopamine agonists accounted for 63.4% of the total cost of antiparkinson medications. The two dopamine agonists prescribed most commonly were Ropinirole and Pramipexole. 98 of 610 patients (16.1%) were prescribed Ropinirole at a median daily cost of £5.83 (£4.50 to £7.52) and 57 patients (9.3%) were prescribed Pramipexole at a median daily cost of £5.89 (£1.85 to £7.74).

380 of 610 patients (62.3%) were prescribed one antiparkinson drug (ie. monotherapy); 154 (25.2%) were on a combination of 2 drugs; 63 (10.3%) on 3 drugs; 12 (2.0%) on 3 drugs and 1 (0.2%) patient on 5 drugs.

The most expensive antiparkinson drugs used were Apomorphine and Cabergoline with respective median daily costs of £8.04 (£3.66 to £16.08) and £8.30 (£4.15 to £10.67) (see Table 3.1). Apomorphine was prescribed for 8 (1.3%) patients and Cabergoline for 12 (2.0%) patients. The cheapest drugs were Selegiline (£0.12/day, £0.12 to £0.15) and Amantadine (£0.60/day, £0.30 to £0.90). Only 21 patients (3.4%) were treated with anticholinergic drugs and only 5 patients (0.8%) were treated with the relatively new monoamine oxidase B inhibitor Rasagiline. None of the patients studied were prescribed Tolcapone.

355 of 610 patients (58.2%) had current attendance at a specialist clinic; 74 (12.1%) had current attendance at a non-specialist clinic (40 of 74 (54.1%) at neurology and 34 of 74 (45.9%) at general medical clinics); 161 (26.4%) did not currently attend a clinic; 45 (7.4%) had previously attended a clinic but had no on-going clinic attendance; 115 (18.9%) had never attended a clinic; and clinic attendance was unknown for 19 (3.3%) (See Table 3.2). Patients currently attending a clinic (either specialist or non-specialist) were significantly younger than those who had never attended a clinic (74.4 years (67.7 to 80.2) versus 80.1 years (74.3 to 85.5), $p<0.0001$). A greater proportion of patients with current attendance at a clinic were male compared with those who had never attended a clinic (252 of 429, 58.7% versus 55 of 115, 47.8%, $p<0.05$). Patients attending a clinic were prescribed a significantly higher dose of dopaminergic medications than those not attending a clinic (400 LE (300 to 658) versus 300 LE (150 to 400), $p<0.0001$).

The median daily cost of antiparkinson medication was greatest for patients who had previously attended a clinic but had no on-going clinic attendance (£2.77, £0.65 to £5.15) and lowest for those who had never attended a clinic (£0.48, £0.26 to £2.90).

Daily medication cost was significantly lower for patients who had never attended a clinic compared with those who had current attendance (£0.89 (£0.34 to £3.85), p<0.05).

Significantly more patients who had never attended a hospital clinic for PD management were prescribed antiparkinson monotherapy (either Levodopa, or a dopamine agonist, or a monoamine oxidase-B inhibitor, or an anticholinergic) compared with those who had attended a clinic (either currently or previously) (84 of 115, 73.0% versus 283 of 475, 59.6%, p<0.01). The percentage of patients prescribed monotherapy according to the duration of diagnosis is shown in Figure 3.1. The proportion on monotherapy was higher in patients who had never attended a hospital clinic throughout the first 10 years following the PD diagnosis, but slightly lower at more than 10 years following diagnosis. All patients prescribed Apomorphine, Bromocriptine, Pergolide or Rasagiline had current attendance at a specialist clinic.

The median daily cost of antiparkinson medications was £0.74 (£0.34 to £3.82) for males and £0.85 (£0.34 to £3.70) for females, but this difference was not significant (p=0.77). The proportion of patients treated with monotherapy, Levodopa or dopamine agonists did not differ significantly between males and females.

Median drug cost per day varied with duration of PD diagnosis (See Figure 3.2). 164 of 610 (26.9%) patients had been diagnosed with PD within the past 2 years. The median daily cost of antiparkinson medication for patients 0-2 years since diagnosis was £0.67 (£0.34 to £5.04). The median daily cost peaked at £1.41 (£0.37 to £3.84) for patients 4 - 6 years since diagnosis and expenditure decreased thereafter. This change in costs over time was not significant (p= 0.46).

The proportion of patients prescribed either Levodopa or a dopamine agonist is shown against disease duration in Figure 3.3. Since dopamine agonists are significantly more expensive than Levodopa, and the proportion of patients prescribed Levodopa gradually increases with disease duration, while the proportion of patients prescribed dopamine agonists is highest in earlier disease, the total daily cost of antiparkinson

medication did not increase with disease duration. 82 of 88 (93.2%) patients more than 10 years since diagnosis were prescribed Levodopa, while the prescription of dopamine agonists peaked at 38% in patients 2-4 years since diagnosis and declined to 22% in patients with PD for more than 10 years.

The median daily cost of antiparkinson drugs was greater for patients aged under 70 years compared with those aged 70 years and over, but this difference was not statistically different (£1.36 (£0.35 to £5.18) versus £0.67 (£0.34 to £3.49), p=0.07). However, there were significantly more patients under 70 years prescribed dopamine agonists (54 of 157, 34.4%) when compared with patients 70 years or over (122 of 453, 26.9%) (p<0.05).

Discussion

The greatest factor affecting antiparkinson drug prescription was whether patients were managed in hospital out-patient clinics or primary care. The daily cost of antiparkinson medication was significantly higher for patients who attended any clinic (either currently or previously) compared with patients who had never attended a clinic. The highest proportion of patients prescribed Levodopa monotherapy was in those who had never attended a specialist clinic. This is important as current best clinical practice is to limit doses of Levodopa in order to delay motor complications (eg. dyskinesia) and instead to support Levodopa with adjunct drugs. 27% of patients who had never been assessed in a hospital clinic for PD were treated with more than one antiparkinson medication compared with 41% of patients with current attendance at a specialist clinic. Although patients attending specialist clinics were prescribed significantly higher overall daily doses of dopaminergic medications (by 150mg Levodopa equivalents) this was largely through Levodopa sparing strategies. Whether patients not seen in clinics are treated optimally cannot be concluded from the current study, since the clinical status of the patient influences the referral decision, ie. patients were not randomised to clinic attendance, and baseline clinical factors are not balanced between clinical attenders and non-attenders. An additional potential confounding factor is a higher misdiagnosis rate

within primary care (see Chapter 4), which will be a further influence on choice of treatment and dose escalation rates.

The highest daily cost of antiparkinson medication and the greatest proportion of patients prescribed more than one dopaminergic drug was found in patients who had previously attended a clinic but were currently managed in primary care. Disease duration was also longest for this group. It seems most likely that this subset of patients is discharged back to their GP in an advanced state after therapy has been maximised, and it is considered that additional drug treatments will not provide added benefit.

Some factors that influenced whether patients were managed in a hospital clinic or in primary care were identified. Significantly more male patients had current hospital clinic attendance than female patients although this overall gender difference was not apparent when considering specialist clinic attendance. This observation was not explained by a greater proportion of male patients with other concurrent diagnoses. Patients never seen in a clinic were significantly older (by around 6 years) than patients who had been seen in a clinic (either currently or previously). In addition, almost 20% more patients under 70 years had current clinic attendance compared with those 70 years and older.

Increased overall costs with more advanced disease (eg. measured with the Hoehn and Yahr scale) are well documented (Rubenstein et al. 1997;Dodel et al. 1997;LePen et al. 1999). We found an increased daily antiparkinson drug cost in the first 6 years following diagnosis, but that costs were thereafter lower. The only other study to observe lower costs in more advanced disease was also UK-based (Findley et al. 2003). In the current study we found that fewer patients with longer disease duration were prescribed dopamine agonists and this was the major reason for the lower cost. This study did not examine the reasons for this difference in prescription, but this may result from dopamine agonists being withdrawn in some cases because of poor tolerance of higher doses, co-morbid disease or the simplification of drug regimens with increased cognitive

impairment. Alternatively, drug choices may be changing over time such that more recently diagnosed patients are more likely to receive dopamine agonist therapy.

None of the patients studied were prescribed Tolcapone, an inhibitor of catechol O-methyltransferase (COMT). COMT inhibitors increase 'on' time and reduce 'off' time in patients with motor complications (Lees 2008). Tolcapone was approved for treatment of PD in 1997, but was later withdrawn following 3 cases of fatal hepatotoxicity and 1 case of reversible severe liver injury that were attributed to the drug (Olanow & Watkins 2007). After the safety data were reviewed the drug was re-introduced with regular monitoring of liver function tests: every 2 weeks for the first year, every 4 weeks for the next 6 months and every 8 weeks thereafter. It is possible that these regular blood tests were felt to be an inconvenience for the patient and their doctor, especially when such monitoring was not necessary with Entacapone, another COMT inhibitor. However, there is some evidence that Tolcapone has greater efficacy than Entacapone with a meta-analysis of 14 studies demonstrating that the mean difference in increased 'on' time state for Tolcapone-treated patients was twice that in Entacapone-treated patients (Deane et al. 2004).

There are surprisingly little UK data on medication costs in PD, but other European studies report varied costs. These studies all used the mean daily cost of antiparkinson medication per patient to summarise drug costs. In the current study, the antiparkinson medication costs were significantly positively skewed, resulting in wide interquartile ranges, and the mean drug cost was over 3 times higher (£2.73) than the median drug cost (£0.79). Fluctuations in currency exchange rate make cost comparisons difficult, but using the current rate (£1.00 = Euro 1.22, 20/06/2008) this is equivalent to a mean cost of Euro 3.33 per day. This approximates to the reported costs from a Norwegian study and is less than 2 German groups (Moller et al. 2005;Vossius et al. 2006). In the current study 62% of patients were treated with antiparkinson monotherapy, which compares with 48% of patients in Norway and between 8% and 28% across the 2 German studies. This is in keeping with known policies in some other European countries to combine lower doses of different antiparkinson drugs from a much earlier disease

stage (Vossius et al. 2006). However, there may have been some selection bias in these European studies with all patients in one of the German studies and the Norwegian study attending specialist clinics, and all the patients responding to a national PD support group questionnaire in the other German study, while our study is inclusive of all patients within participating general practices.

We found that 29% of patients were prescribed dopamine agonists. These findings are very similar to the 30% from Norway and 31% from Sweden (Hagell et al. 2002;Vossius et al. 2006). In contrast, in the two German cohorts 55 and 61% received dopamine agonists, of which a higher proportions were prescribed older ergot-derived dopamine agents such as Bromocriptine, Cabergoline, Lisuride and Pergolide (Dodel et al. 1998). The German costs are high despite greater use of ergot-derived agonists such as Bromocriptine and Pergolide, both of which are off-patent and therefore less expensive. Further, the additional drug safety monitoring for these agents would increase associated costs.

Newer therapies such as subcutaneous apomorphine and intra-jejunal Levodopa (Duodopa) aim to provide continuous dopaminergic stimulation and are proving effective in managing the motor complications of advanced disease. These therapies are costly and likely to make managing advanced disease more expensive in the future. Duodopa has only recently been licensed and it was not surprising that it had not been prescribed in any of the patients studied. There are no studies to date reporting the proportion of patients for whom it may become appropriate. In our study 8 patients (1.3% of 610) were were prescribed subcutaneous Apomorphine, which was significantly greater than the 14 of 6500 (0.21%) reported in a German group (p<0.001) (Moller et al. 2005).

Conclusion

The most influential factor affecting antiparkinson medication prescription is whether the patients attended a hospital clinic or were managed within primary care. Patients attending hospital clinics were younger and a greater proportion were male, but were not different in other respects. This may reflect a biased delivery of, or variable

access to, specialist services across the areas studied and deserves to be examined further across a wider population with greater attention to individual reasons for medication prescription (initiation and discontinuation). Patients attending hospital clinics for Parkinson's disease are more likely to be prescribed more than 1 antiparkinson medication, at higher doses and at greater cost than patients managed in primary care.

Table 3.1: Cost of antiparkinson medication in 610 patients

	No. of patients	% of patients	Median cost per patient per day on drug (£)	% of total costs
Levodopa-based				
All levodopa-based drugs	543	89.0	0.35	32.0
Stalevo	94	15.4	2.90	16.5
Dopamine agonist				
Apomorphine	8	1.3	8.04	5.2
Bromocriptine	2	0.3	1.45	0.2
Cabergoline	12	2.0	8.30	5.9
Ropinirole	98	16.1	5.83	34.9
Pergolide	1	0.2	1.66	0.1
Pramipexole	57	9.3	5.89	17.3
All dopamine agonists	176	28.9	5.83	63.4
COMT inhibitors				
Entacapone	24	3.9	0.60	0.9
Monoamine oxidase inhibitors				
Selegiline	45	7.4	0.12	0.9
Rasagiline	5	0.8	2.53	0.8
Anticholinergics				
All anticholinergics	21	3.4	0.75	1.3
Other				
Amantadine	20	3.3	0.60	0.6
Total	**610**	**100**	**0.79**	**100**

Note – some patients were prescribed a combination of Madopar, Sinemet and Stalevo; and 2 patients were prescribed an oral dopamine agonist in addition to Apomorphine.

Table 3.2: Demographic and disease characteristics of 610 patients on antiparkinson therapy, according to clinic attendance.

	Current clinic attendance (specialist and non-specialist)	*Current specialist clinic attendance*	*Current non-specialist clinic attendance*	Previous clinic attendance	Never attended a clinic	Unknown clinic attendance	**All patients**
Number of patients	428	*354*	*74*	47	116	19	**610**
Age in years	74.4 (67.7 to 80.2)	*74.5 (67.9 to 80.2)*	*73.6 (65.4 to 79.9)*	77.7 (70.9 to 82.3)	80.1 (74.3 to 85.5)	77.1 (70.7 to 82.4)	**76.0 (69.7 to 81.6)**
Male	58.7%	*57.7%*	*63.5%*	51.1%	47.8%	45.0%	**55.6%**
Disease duration in years	4.1 (1.7 to 7.8)	*4.3 (2.0 to 8.1)*	*2.8 (0.9 to 4.7)*	6.0 (3.5 to 12.6)	4.6 (2.0 to 7.3)	2.0 (0.75 to 5.9)	**4.1 (1.7 to 7.9)**
Anti-PD drug intake in LE/day	400 (300 to 658)	*450 (300 to 697)*	*328 (285 to 520)*	400 (280 to 420)	300 (150 to 400)	320 (200 to 505)	**400 (260 to 568)**
Prescribed monotherapy	60.6%	*59.2%*	*67.6%*	48.9%	73.0%	65.0%	**62.3%**
Daily cost of anti-PD drugs (£)	0.89 (0.34 to 3.85)	*0.96 (0.34 to 3.86)*	*0.63 (0.34 to 3.80)*	2.77 (0.65 to 5.15)	0.48 (0.26 to 2.90)	0.35 (0.24 to 3.74)	**0.79 (0.34 to 3.77)**

Data are expressed as median (interquartile range) or percentage

PD = Parkinson's disease, LE = Levodopa equivalents
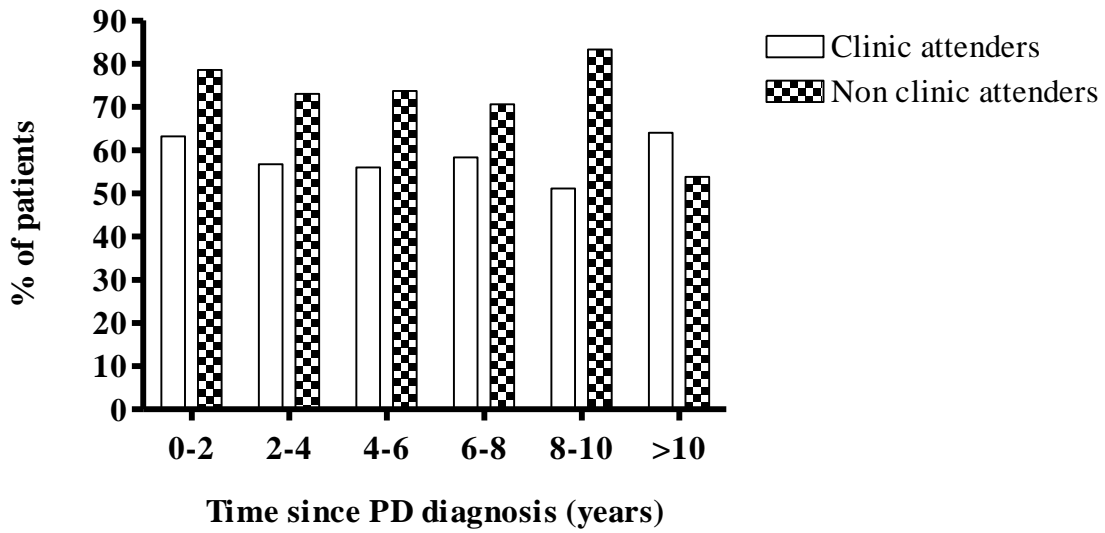
Figure 3.1: Proportion of patients prescribed antiparkinson monotherapy according to clinic attendance. A higher proportion of non-clinic attenders were prescribed monotherapy, compared to clinic attenders (either current or previous), for all disease durations except over 10 years.
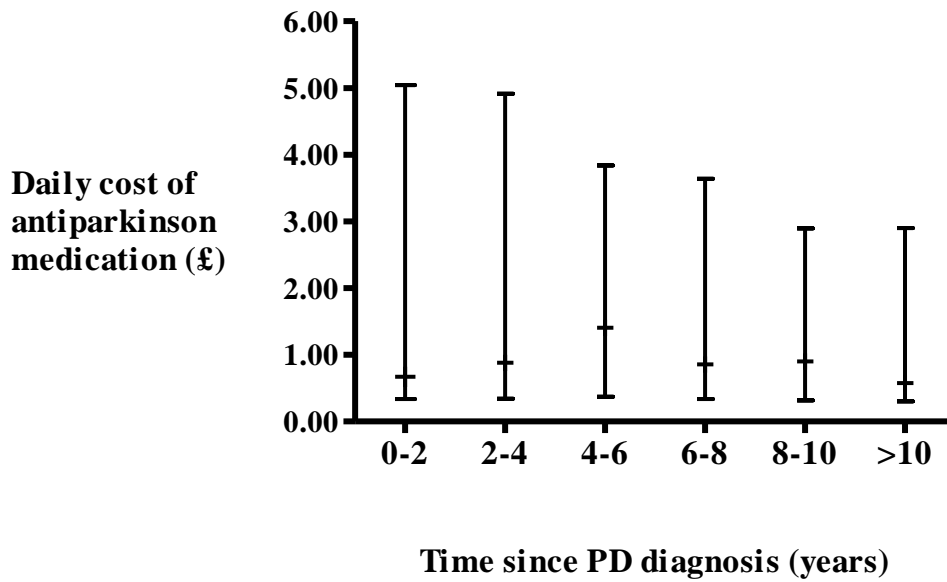
Figure 3.2: Daily cost of antiparkinson medication according to disease duration. The median cost for patients 0-2 years since diagnosis was £0.67 (£0.34 to £5.04), peaked at £1.41 (£0.37 to £3.84) for patients 4-6 years since diagnosis, and decreased thereafter. Summary data are median and interquartile range.
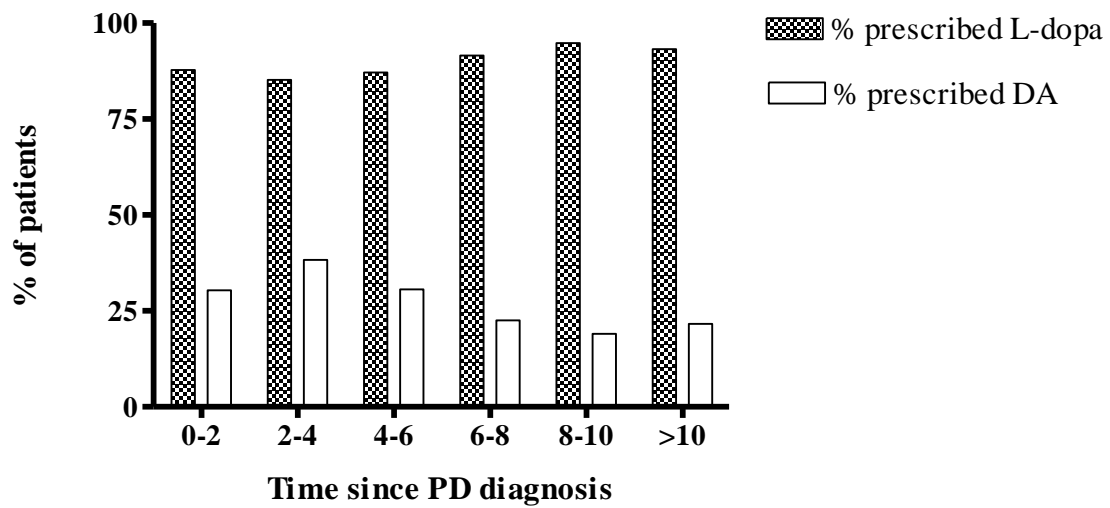
PD = Parkinson's disease; L-dopa = Levodopa; DA = Dopamine agonist

Figure 3.3: Proportion of patients prescribed Levodopa and dopamine agonists against disease duration. The percentage of patients prescribed Levodopa increased from 88% <2 years since diagnosis and peaked at 95% 8-10 years following diagnosis. The percentage of patients prescribed dopamine agonist drugs is 30% <2 years since diagnosis, peaked at 38% at 2-4 years and decreased to 22% at 8-10 years.

CHAPTER 4

MEDICATION WITHDRAWAL IN PATIENTS WHO DO NOT BENEFIT FROM

ANTIPARKINSON MEDICATION

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition and is traditionally characterised by bradykinesia, resting tremor, muscular rigidity and postural instability. Accurate diagnosis of parkinsonian syndromes is fundamental for prognostic and therapeutic reasons and is also essential in epidemiological studies and clinical trials. In many cases the clinical diagnosis of PD is straightforward. However, a series of clinicopathological studies suggested that the positive predictive value of a clinical diagnosis of PD was 76 – 91% (Rajput, Rozdilsky, & Rajput 1991a;Hughes et al. 1992a;Hughes et al. 1992b;Hughes et al. 2002) and accuracy was greatest with diagnostic re-evaluation over time, the use of strict criteria, and assessment within a specialist movement disorder service. The most widely accepted clinical diagnostic criteria for PD are the UK Brain Bank criteria (Gibb & Lees 1989) and these are based on the correlation of clinical symptoms and neuropathology (Hughes, Daniel, & Lees 2001b) (See Appendix 4.1). There are 3 steps: (1) diagnosis of Parkinsonism, (2) exclusion of other parkinsonian syndromes, and (3) identification of supportive clinical features.

NICE guidelines for the management of PD within primary and secondary care recognise diagnostic difficulties, recommending that patients with suspected PD should be referred quickly for a specialist opinion and that the diagnosis should be reviewed at 6-12 month intervals (2006).

Recent advances in functional imaging have improved diagnosis of parkinsonian syndromes. Dopamine transporter (DAT) imaging using single photon emission computerised tomography (SPECT) allows an indirect measure of dopaminergic neuronal degeneration. DAT-SPECT demonstrates reduced striatal uptake of the radioligand (eg. FP-CIT, β-CIT, TRODAT) in patients with degenerative Parkinsonism, such as PD, progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal degeneration. DAT-SPECT is abnormal even in early PD and striatal uptake correlates with disease duration and motor severity (Benamer et al. 2000b). DAT imaging is normal in patients with essential tremor (Asenbaum et al. 1998;Benamer et al. 2000a), and drug-

induced (Booij et al. 2001) as well as psychogenic Parkinsonism (Tolosa et al. 2003;Marshall & Grosset 2003a).

Misdiagnosis of PD is also recognised in randomised clinical trials. Between 1.4 and 15% of patients in 3 large studies had normal DAT imaging (The Parkinson Study Group 2002;Whone et al. 2003;Seibyl et al. 2004;Fahn et al. 2004). There is also evidence of significant diagnostic re-evaluation within 2 UK-based community studies. Meara and colleagues identified 502 patients on antiparkinson therapy for PD within 74 GP practices in North Wales (Meara, Bhowmick, & Hobson 1999), and clinically assessed 402. There was evidence of Parkinsonism in 299 patients (74%), with only 213 (53%) fulfilling Brain Bank criteria. Revised diagnoses were essential tremor (48%), vascular Parkinsonism (36%) and Alzheimer's disease (16%).

A study of 15 GP practices within central London assessed 131 patients with a PD diagnosis (Schrag, Ben Shlomo, & Quinn 2002). 109 of 131 patients (83%) met Brain Bank criteria, 2 patients (1.5%) were diagnosed as possible PD and the diagnosis was rejected in 20 patients (15%). Revised diagnoses in this group comprised 4 patients with non-parkinsonian tremor (essential tremor or dystonic tremor), 6 patients with vascular Parkinsonism, 4 patients with progressive supranuclear palsy (PSP), 3 patients with multiple system atrophy (MSA), 1 patient with idiopathic torsion dystonia and 1 patient with dementia without Parkinsonism.

We know that diagnostic accuracy in PD is improved when the patient is followed clinically over time. Excellent and prolonged clinical response to Levodopa and a history of disease progression over time are key features of PD (step 3 of Brain bank criteria for PD). With disease and symptom progression the dose of Levodopa (and other antiparkinson medication) is likely to increase over time. Therefore if there is either no recorded progression of symptoms over years within clinical records, a record of a poor clinical response to antiparkinson medication, poor compliance with medications (which may indicate a lack of clinical response), or no increase in the dose of medication over time, the diagnosis of PD may be incorrect.

Studies that re-evaluated the clinical diagnosis of PD show that misdiagnosis is a significant problem across primary and secondary care. Patients with a non-parkinsonian diagnosis are unlikely to derive benefit from antiparkinson medications. However, few studies report therapy withdrawal in this patient group; in one single study of 11 selected patients in a specialist clinic, antiparkinson medication withdrawal was successful in 11 patients, all of whom had normal FP-CIT SPECT imaging (Marshall et al. 2006). These patients had clinical features of Parkinsonism, carried a diagnosis of PD and have been termed "subjects with scans without evidence of dopaminergic deficit" or SWEDDs. Patients had a median follow-up period of 3 years and no clinical deterioration was noted following medication withdrawal.

The present study was undertaken to examine these issues in greater detail, with larger patient numbers and on a community basis, in order to quantify the problem of diagnostic error and inappropriate antiparkinson drug treatment in clinical practice. The study objectives and endpoints were defined at baseline, and were as follows:

Primary and secondary objectives

Primary objective: To identify patients within the community who do not benefit from antiparkinson medications and to supervise and clinically monitor the withdrawal of therapy in this patient group.

Secondary objective: To develop objective criteria for identification of patients taking antiparkinson medication in whom therapy can be withdrawn without clinical deterioration.

Primary and secondary endpoints

Primary endpoint: The proportion of patients successfully withdrawn from antiparkinson therapy expressed as a percentage of patients taking such therapy for PD.

Secondary endpoint: The difference in the proportion of patients in whom antiparkinson therapy is successfully withdrawn comparing those identified using specified criteria with matched controls of patients taking antiparkinson therapy who do not meet criteria.

<u>Ethical considerations</u>

This study was given multi-region ethical approval by the West Glasgow Ethics Committee in September 2006. Local ethics approval was then obtained from Primary Care for Greater Glasgow and Clyde and Lanarkshire.

<u>Methods</u>

All GP practices within the individual following Community Health Partnerships (CHP) were invited to participate in this study: South West Glasgow, South East Glasgow, South Lanarkshire, East Dunbartonshire and West Dunbartonshire.

Step 1: Practice-based prescription database search and case note review

Within participating GP practices searches of prescription databases were performed to identify all patients prescribed antiparkinson medications. A search for each drug was made using generic and trade names (See Table 2.1) at all available doses in both new and repeat prescriptions. Case record review was then undertaken for all identified patients, to find the underlying diagnosis leading to the drug prescription. Patients who were prescribed dopaminergic or anticholinergic medication for a non-PD diagnosis were excluded from further analysis (eg. dopamine agonists for pituitary tumours and restless legs syndrome; Levodopa for dopa-responsive dystonia; Amantadine for multiple sclerosis; anticholinergic medication for Huntington's disease and in patients prescribed neuroleptic medications).

The following information was recorded for each patient with a PD diagnosis, based on the review of the case record and prescription database:

- Relevant past medical and surgical history
- Current antiparkinson prescription
- Antiparkinson prescription 3 years preceding search date
- Date of diagnosis of PD
- Current or previous attendance at a hospital clinic for the PD diagnosis (and whether general or specialist movement disorder)

- Pharmacy refill data for antiparkinson drugs during the preceding 6 months (observed doses divided by expected doses, expressed as a percentage, where

    o observed= total dose obtained by the patient, using prescriptions which were issued in the time period, and

    o expected= total dose according to drug charting)

- Current and past drug history, including prescription of dopamine depleting drugs (eg. Metoclopramide, Prochlorperazine and neuroleptics)

- Documented evidence of clinical disease progression within GP notes or out-patient clinic letters

Step 2 – Selection for specialist out-patient review

Following case record review, patients prescribed antiparkinson medications for a PD diagnosis who met any of the selection criteria listed below were then invited for out-patient assessment:

- Treatment of PD with monotherapy for >5 years

- Low doses of antiparkinson therapy for >3 years (defined as daily doses within the initial starting range as described in the British National Formulary – doses up to and including - Levodopa 150mg, Ropinirole 3mg, Pramipexole base 0.54mg, Cabergoline 1mg, Bromocriptine 1.5mg, Selegiline 10mg)

- No increase (defined as either increase in drug dose or addition of a further agent) in antiparkinson therapy over 3 years preceding the search date

- Pharmacy refill of <60% during 6 months preceding the search date

- No clinical progression documented

- Documented lack of clinical response to antiparkinson therapy

- Co-prescription of dopamine receptor antagonist, suggestive of possible drug-induced Parkinsonism

The following served as exclusion criteria:

- Significant co-morbidities (eg. metastatic carcinoma or end-stage cardiac, renal or liver disease)

- Documented cognitive impairment

- Duration of antiparkinson therapy <1 year

- Patient in nursing home or housebound

Step 3 – Specialist out-patient review

At out-patient review history focussed on progression of movement disorder symptoms and clinical response to antiparkinson medication. 'Wearing off' symptoms and response to antiparkinson medication was assessed using a 7-point motor fluctuation questionnaire (See Appendix 4.2). The patient was examined by 2 neurologists. The patients were then scored by a PD nurse specialist (blinded to the clinicians' clinical suspicion) on the Unified PD rating scale (UPDRS) parts 1 – 6 (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease 2003). The nurse specialist was certified for scoring patients using the UPDRS scale, based on a standard training video (Goetz & Stebbins 2004).

The diagnosis was based on UK Brain Bank criteria. If both neurologists agreed that the clinical diagnosis was PD the patient was offered follow-up in the routine movement disorder clinic and had no further role within the study. If both neurologists agreed that the patient was unlikely to have degenerative Parkinsonism, the patient was consented for gradual reduction and cessation of antiparkinson medication under supervision: these patients formed the intention to treat (ITT) group. Diagnostic revision and plans for medication withdrawal were discussed with the patients with sensitivity to previous diagnosis and management. The patient's clinician was involved in the process and given the opportunity to exclude the patient from the study if they were aware of adverse clinical issues which would be affected by the patient being involved.

In clinically uncertain cases FP-CIT SPECT imaging was requested to determine whether there was degenerative Parkinsonism and guide the decision on medication withdrawal. Alternative diagnoses were made according to established criteria and definitions: essential tremor (ET) (Bain et al. 2000); vascular Parkinsonism (VP)

(Zijlmans et al. 2004); dystonic tremor (DT) (Schneider et al. 2007); or indeterminate tremor (Deuschl et al. 1998).

Step 4 – Therapy withdrawal and follow-up

Patients who consented to medication withdrawal were given an individual protocol, which was detailed in writing to them and their GPs. Medications were reduced at a rate of 50mg every 2 weeks for Levodopa and 20-30% of total prescribed dose every 2 weeks for dopamine agonists. Therapy withdrawal rates were based on previously reported figures (Marshall et al. 2006) and were designed to minimise the risk of Parkinsonism-hyperpyrexia syndrome (PHS).

Consenting patients were given contact details for the research team. Patients were warned that there might be worsening of their movement disorder symptoms following medication withdrawal and were advised to contact the research team if there was any change in symptoms. The research team gave telephone advice and expedited out-patient appointments as necessary. If there was worsening of movement disorder symptoms following medication withdrawal, these drugs were promptly re-introduced.

Patients were followed up in 2-3 subsequent clinics over 6-9 months with full clinical assessment by 2 neurologists and repeat scoring on the UPDRS scale by the same PD nurse specialist (who remains blinded to whether medication had been withdrawn). Patients able to successfully withdraw antiparkinson medication without clinical deterioration constituted the per protocol (PP) group.

Assessment of the control group

Control group patients were identified from step 1 and had all been prescribed antiparkinson medication for a PD diagnosis. Control patients did not meet either the selection criteria, or the exclusion criteria described in step 2. Controls were matched to those patients assessed in step 3 for sex, age (±5 years) and time since diagnosis of PD (±3 years). Control patients were then invited for out-patient clinic assessment. Control group patients underwent the clinical assessment described in step 3 for active patients. If

a control patient was diagnosed as unlikely to have degenerative Parkinsonism, therapy withdrawal under supervision, again following the same procedure as active patients, was offered.

Results

92 of 120 (77%) GP practices contacted agreed to participate. Searches of prescription databases and case record review within participating practices were completed during December 2006 to August 2007. The total population covered by 92 GP practices was 511,927 (49.5% male, 50.5% female).

Patients with a Parkinson's disease diagnosis

610 patients (55.6% male, 44.4% female) taking antiparkinson medications for a PD diagnosis were identified. 428 of 610 (70.2%) patients regularly attended a hospital out-patient clinic for their PD: 354 (58.0%) a specialist movement disorder clinic and 74 (12.1%) a non-specialist clinic (general medical or general neurology). 47 of 610 (7.7%) had previously attended a specialist clinic but had no on-going clinic attendance for their PD. 116 of 610 (19.0%) had never attended a hospital clinic, and clinic attendance was unknown for 19 of 610 (3.1%).

Patients identified by selection criteria

89 of 610 (14.6%) fulfilled step 2 of the selection criteria and were invited for out-patient assessment. 64 of these 89 (71.9%) patients (33 male, 31 female) meeting selection criteria were assessed, either in an out-patient clinic or at home. The mean age of patients assessed was 76.3 years (SD 5.0) and mean time since PD diagnosis was 7.0 years (SD 5.0). 16 of 64 (25%) attended a specialist movement disorder clinic and 3 of 64 (4.7%) a non-specialist clinic. Clinical findings of patients assessed within the study group are detailed within Table 4.3.

Following clinical assessment (Step 3) there was clinical diagnostic uncertainty in 25 of 64 (39.1%) patients and FP-CIT SPECT imaging was performed in each of these cases. 10 of these 25 (40%) patients demonstrated reduced striatal uptake of FP-CIT, in

keeping with a diagnosis of degenerative Parkinsonism, while 14 (56%) patients had normal uptake, effectively excluding degenerative Parkinsonism. In the remaining one case, the scan was initially reported as abnormal but this was later amended to normal by the reporting clinician.

The diagnostic breakdown for patients meeting selection criteria and control group patients is in Table 4.1. Following initial assessment of patients meeting selection criteria (including FP-CIT SPECT imaging), 25 of 64 patients (39.1%) were considered to have PD. These patients were all offered routine follow-up within a movement disorder clinic. The ITT group comprised 39 patients, or 60.9% of the 64 patients who attended for assessment.

The revised diagnoses made in the ITT group were as follows: 15 essential tremor; 12 VP; 5 indeterminate tremor; 3 dystonic tremor; 3 drug-induced Parkinsonism; and 1 gait ignition apraxia.

Antiparkinson medication withdrawal

Antiparkinson medication withdrawal was discussed with all ITT patients. 36 of the 39 (92.3%) consented to therapy withdrawal under supervision. 1 patient declined supervised therapy withdrawal due to ill health, while 2 patients declined in case their movement disorder symptoms would worsen.

Patients who consented to therapy withdrawal were followed up for a mean of 8.2 months (SD 2.3 months). 1 patient initially consented to therapy withdrawal but withdrew consent after 3 months. 2 of 35 patients (5.7%) who reduced and stopped antiparkinson medication described deterioration in their movement disorder symptoms, and had an increase (worsening) in UPDRS part 3 of 16 and 17 points. The baseline diagnoses for these patients (prior to therapy withdrawal) were essential tremor and vascular Parkinsonism. Both patients experienced worsening of symptoms at 3 months following medication withdrawal. FP-CIT SPECT imaging was subsequently undertaken and proved abnormal in both cases. Antiparkinson medications were re-introduced in

both cases with resultant symptomatic improvement. The final diagnosis in both cases was PD.

33 of 35 patients (94.3%) successfully reduced and stopped antiparkinson medications without significant deterioration in UPDRS part 3 scores at serial follow-up appointments. The mean change in UPDRS part 3 scores between initial and final assessment in this group was an improvement of 2.2 points (95% CI: improvement of 0.5 to 3.8 points).

Patients who completed successful antiparkinson medication withdrawal (n= 33) had a mean motor fluctuation questionnaire score of 0.42 out of 7 (SD 1.0) compared with 0.69 out of 7 (SD 1.4) for patients who were confirmed as having PD (n=25). This difference was not significant (p=0.38).

At the time of writing therapy withdrawal has not been discussed with the patient whose FP-CIT SPECT scan result was changed from abnormal to normal.

Control group and remaining patients

97 patients were invited for assessment as part of the control group. 64 of 97 (66.0%) agreed to clinical assessment. The reasons for 33 of 97 control patients not agreeing were: non-response to invitation (n=20), too unwell (n=8) and unwilling (n=5). 61 of 64 (95.3%) of the control group patients assessed were considered to have PD following assessment. FP-CIT SPECT scanning was performed in 4 of 64 (6.3%) patients in whom there was clinical uncertainty. 3 of 4 scans (75%) demonstrated normal striatal uptake of the radioligand. 2 of 3 (66.7%) of these patients were diagnosed as ET and 1 of 3 (33.3%) was diagnosed as VP. All 3 patients consented to gradual therapy withdrawal under supervision and completed this without significant deterioration in movement disorder symptoms or change in UPDRS part 3 score, with a mean deterioration of 0.7 points (95% CI: deterioration of 4.5 to improvement of 3.1 points). 1 of 4 (25%) patients had abnormal DAT SPECT imaging and this patient was considered to have PD.

The criteria described in step 2 of the methods identified a significantly higher proportion of patients with a non-PD diagnosis, compared with the control group (odds ratio 16.0 (95% confidence interval 5.2 – 49.2), p<0.0001).

In addition to the cases identified through the above processes (ITT and control patients), further patients were re-diagnosed as not having PD, during the period in which the study was performed. Within the 610 patients identified by searches of prescription databases with GP practices, 3 patients were identified by the investigators in routine out-patient clinics as demonstrating clinical features which were not in keeping with a PD diagnosis. All three patients were attending a specialist movement disorder clinic and described a poor clinical response to antiparkinson medication and little progression of symptoms over time. However, none of these patients had fulfilled criteria for step 2 of the selection criteria. Clinical findings for these 3 patients are detailed in Appendix 4.4. FP-CIT SPECT scanning was normal in all 3 cases. 2 patients were diagnosed as essential tremor and 1 as VP. Antiparkinson medication was successfully withdrawn in all 3 patients without significant change in UPDRS part 3 score, with mean improvement of 2.3 points (95% CI: deterioration of 7.7 to improvement of 12.4 points).

Overall therapy withdrawal rates

The total number of patients in whom antiparkinson medication was successfully withdrawn (including patients meeting selection criteria, control group patients, and routine care patients) was 39 of 610 patients (6.4%). 17 of 39 (43.6%) were male and the mean age was 75.0 years (SD 8.9) (See Table 4.2). 25 of 39 (64.1%) had no current attendance at a specialist clinic and the mean time since diagnosis of PD was 6.8 years (SD 5.6). The mean time since PD diagnosis was longer for patient with no specialist clinic attendance (8.6 compared with 3.5 years, p<0.005), but there was no significant difference in age between the two groups (P=0.71). The total annual cost of antiparkinson medication for these 39 patients was £41,800.

Prevalence of inaccurate Parkinson's disease diagnosis

The total number of patients within the 610 with a non-PD diagnosis can be estimated from:

(a) 33 of 64 respondents (52%) in the active group who successfully stopped antiparkinson therapy. In the remaining 25 cases meeting selection criteria (but not responding to the invitation to study participation), assuming the same diagnostic 52% error rate, an additional 13 cases would exist. However, if the proportion of non-respondent patients who did not have PD was only 26% (ie. half that of the respondents) the additional case numbers who did not have PD would be reduced to six.

(b) The proportion of patients successfully stopping antiparkinson therapy within the control group (3/64, 4.7%) scaled up to the remaining 457 patients not meeting selection criteria, giving an additional 21 patients.

The range for the total number of cases who did not have PD amongst the 610 study population is therefore as follows:

(i) lower estimate: 63 (or 10.3%) (derived from 33+6=39 from (a) above, plus 21 from (b) above)

(ii) upper estimate: 70 (or 11.5%) (adding 7 cases from (i) above).

See Table 4.5 for tests of the selection criteria using these upper and lower estimates.

Discussion

In keeping with previous UK studies, this report indicates significant misdiagnosis of PD within the community. Diagnosis of PD can be difficult, but some cases of PD misdiagnosis are avoidable and diagnosis should be re-evaluated over time, preferably within a specialist clinic.

Reduction and cessation of antiparkinson medications is not without risk: movement disorder symptoms may worsen and in rare cases the patient may develop PHS, characterised by Parkinsonism, hyperpyrexia and autonomic changes. There is also a theoretical risk of PHS in patients who do not have degenerative Parkinsonism, although there are no cases in the literature describing this. Our findings suggest that supervised medication withdrawal is safe in patients thought to have an alternative diagnosis (further details are in chapter 6).

The most common alternative diagnoses found in this series were ET and VP, in keeping with previous community studies (Meara, Bhowmick, & Hobson 1999;Schrag, Ben Shlomo, & Quinn 2002). It may be difficult to clinically differentiate between benign tremor disorders and early PD, and FP-CIT SPECT may be useful in such cases (Benamer et al. 2000a). There was no clinical deterioration following medication withdrawal in any of the 21 patients with normal FP-CIT SPECT scans. The role of FP-CIT SPECT in facilitating the diagnosis of PD has been previously established (Scherfler et al. 2007). Dopamine transporter (DAT) imaging is abnormal in early degenerative Parkinsonism and its main role is in early differentiation between with isolated tremor symptoms not fulfilling PD or essential tremor criteria, drug-induced, psychogenic and vascular Parkinsonism as well as dementia with Lewy bodies. However, the mean time since initial PD diagnosis in the 32 patients who underwent FP-CIT SPECT in this series was 6.2 years (SD 4.7) suggesting that SPECT scanning also has a later diagnostic role in patients whose clinical features of PD are not clinically progressing over time as expected (See Chapter 5). This application of the test would likely decline over time as prevalent cases are tested, although there remains significant potential for this application as the rate of such scanning in new patients is low in many centres.

It has been suggested that there is a role for dopaminergic therapy in VP with doses of up to 1000mg/day Levodopa recommended. There is little evidence to support such high doses and in practice it may be difficult as patients experience dopaminergic side-effects such as nausea, confusion and postural hypotension. In one retrospective series of patients with pathologically confirmed VP, 12 of 17 reported an excellent clinical response to Levodopa (mean dose: 450mg/day; range: 100 – 1000mg/day) (Zijlmans et al. 2004). 3 of 17 patients in this series showed no response to Levodopa (300 - 400mg/day) and presumably were not able to escalate this dose further. All of the patients in the current study considered to have VP indicated little or no clinical response to Levodopa when assessed on the motor fluctuation scale. These patients were prescribed a mean of 275 Levodopa equivalents per day (SD 145) and there was no clinical deterioration following therapy withdrawal. It is possible that patients may have experienced symptomatic improvement at higher Levodopa doses, but this had not been undertaken clinically and was not attempted in this study.

The selection criteria described were effective at identifying misdiagnosed patients, with 16 times the likelihood of stopping antiparkinson therapy after fulfilling selection criteria compared to randomly selected patients. In practical terms, the current study required clinical assessment of 64 cases identified by selection criteria, while 576 cases selected at random would need to be assessed to achieve the same number of cases successfully stopping antiparkinson therapy. However, identification of further misdiagnosed cases (among those not fulfilling selection criteria) from the remainder of 546 patients within the control group and from the out-patient clinic (identified outwith study procedures) suggests that the criteria were unable to identify all misdiagnosed cases. These observations are reflected in the criteria having an estimated specificity exceeding 90% while sensitivity was only 62 to 66%. The main culprit amongst the exclusion criteria of step 2, for patients identified as not having PD, was an increased antiparkinson dose over time exceeding that specified. A greater number of misdiagnosed cases would be identified by assessing all 610 patients, but this would be far more labour intensive. We consider the selection criteria as defined to be the most appropriate starting point for testing in further populations; specific attention to the rate of dose escalation of

antiparkinson drugs would be appropriate, to determine whether a different threshold value improved case ascertainment.

Screening for misdiagnosis in PD and the supervised withdrawal of antiparkinson medication meets many of World Health Organisation (WHO) principles for a screening programme (Wilson & Jungner 1968). Usually sensitivity, specificity, predictive values and likelihood ratios are measures of the effectiveness of a diagnostic test in identifying a disease and are commonly applied to screening programmes. In this instance we used these measures to assess the value of the selection criteria in identifying misdiagnosis (or lack) of PD. These estimates made certain assumptions, namely that there would be further misdiagnosed cases within the patients meeting criteria who did not agree to clinical assessment, and that the 64 control group patients assessed were representative of the remaining cases. Whether these assumptions are accurate requires testing in a further population; in particular there may be variation in the rate of therapy withdrawal in control subjects, as the confidence interval is wide for only 3 patients within the 64 control subjects.

2 of 36 patients within the ITT group deteriorated clinically following medication withdrawal. Both cases subsequently had abnormal FP-CIT SPECT scanning and were re-diagnosed as PD. At initial assessment neither patient fulfilled Brain Bank criteria. This reinforces the evidence that the clinical diagnosis of PD can be problematic, even with the rigorous specialist assessment of a strict research protocol. However, the clinical deterioration was recognised early in both patients and was reversed without long-term sequelae.

The present study suggests that step 3 of Brain Bank criteria is not applied rigorously in routine clinical practice. The presence of one or more of the key factors had not alerted the treating clinician to diagnostic reconsideration. We deliberately omitted patients taking antiparkinson therapy for less than one year, since we considered the approach of a trial of antiparkinson therapy (as a diagnostic adjunct) much less likely

after this time. Moreover, we did not identify a single case of intercurrent therapy withdrawal occurring because of diagnostic reconsideration, outwith the processes of the study and its investigators. These observations collectively suggest that 'routine' diagnostic revision and treatment cessation is a rare event in clinical practice, for patients diagnosed as PD and established on antiparkinson treatment for more than a year.

The estimated total number of misdiagnosed cases within the study population was between 63 and 70 of 610 (10.3 to 11.5%). This compares with rates between 15 and 26% in previous UK-based community studies (Meara, Bhowmick, & Hobson 1999;Schrag, Ben Shlomo, & Quinn 2002) and 1.4 – 15% within the randomised controlled trials (Fahn 1999;Parkinson Study Group 2000;Whone et al. 2003;Seibyl et al. 2004). In the 39 patients successfully withdrawn from antiparkinson medications in the current study the mean time since PD diagnosis was 6.8 years. In the 2 previous UK-based community studies, the time since PD diagnosis was not declared. However, given that these studies were also cross-sectional, the average disease duration would also be expected to be at least 5 years. The much higher diagnostic error rate in the community studies, including the current study, compared to clinical trials, at a much later average duration since diagnosis, suggests that the patient population and diagnostic process differ, eg. selection criteria, frequency of review and proportion of specialist involvement.

It is for these reasons that the National Institute for Clinical Excellence emphasises that the diagnosis of PD may be difficult and recommends that all patients with a suspected diagnosis of PD attend a specialist clinic and that individual diagnoses are reviewed every 6 months (2006). Whilst we found a significant proportion of patients on therapy for PD not attending a specialist clinic, misdiagnosis amongst patients attending a clinic was significant, being 41% of the 39 patients in whom antiparkinson medications were successfully withdrawn. This demonstrates that it remains important for the PD diagnosis to be questioned over time in patients attending clinics. In those patients in whom antiparkinson drugs were successfully withdrawn who were attending

clinics, we did not specifically examine case records for evidence that the diagnosis was reconsidered at review assessments. However, by implication the absence of a record of disease progression, good therapy response, and increase in antiparkinson medication over time suggested that the process of diagnostic reassessment was not evident. A higher proportion of patients in the control group were attending a hospital clinic compared with the study group. This difference resulted from fulfilment of the selection criteria by the active patient group, since such patients were more likely to be non-clinic attenders. Whether the diagnostic error rate, and ability to stop antiparkinson therapy, would be greater in controls matched for clinic attendance, is not known, but again would be worth testing in further research.

Antiparkinson medications, especially dopamine agonists, are expensive. The annual cost of antiparkinson medications in patients who underwent successful therapy withdrawal in this series was £48,200 per year. The cumulative drug costs are much higher given the long duration of diagnosis and treatment. This cost must be offset against the study costs including medical, nursing and clerical personnel and the cost of FP-CIT SPECT scanning. The total cost of carrying out this study was £53,000 (FP-CIT SPECT: £19,200; new and return out-patient assessment: £28,200; clerical assistance: £5,000). There are also additional costs (return clinic appointments and increasing antiparkinson medications) for assessing patients previously managed by their GP. The cost of antiparkinson medication in patients misdiagnosed as PD (who do not gain benefit) represents a significant governance issue. Without this study, many patients in whom antiparkinson medications were successfully withdrawn may have stayed on these drugs for years, with the associated costs and potential of side-effects and drug interactions. A full cost-benefit analysis of this process was beyond the scope of the current work, but the outline data suggest that cost-savings would at least partially offset process costs (many of which are non-recurrent), particularly if similar results could be achieved outwith a full research protocol.

It is interesting to note that no patients identified in the study were rediagnosed as a Parkinson plus syndrome (eg. PSP and MSA). Brain bank studies have suggested that

this is the most common cause of misdiagnosis within the specialist clinic (Hughes et al. 1992b;Hughes et al. 2002). However, there is selection bias in patients coming to post-mortem examination and the criteria used here would not readily identify such patients because they have more rapid disease progression, and would likely have antiparkinson dose escalation. Further, control numbers were small to identify these rarer diagnoses.

Conclusion

This community study demonstrates that patients are often labelled as Parkinson's disease when the underlying diagnosis is essential tremor or vascular Parkinsonism. These patients can be identified from searches of prescription databases and GP case records, and can undergo supervised withdrawal of antiparkinson medications safely.

Table 4.1: Final diagnosis of patients in study and control groups

	STUDY (N=64)	CONTROL (N=64)
Degenerative Parkinsonism		
Parkinson's disease	26 (40.6%)	61 (95.3%)
Non- Parkinson's disease diagnosis		
Essential tremor	15 (23.4 %)	2 (3.1%)
Vascular Parkinsonism	11 (17.2%)	1 (1.6%)
Drug-induced Parkinsonism	3 (4.7%)	0
Dystonic tremor	3 (4.7%)	0
Indeterminate tremor	5 (7.8%)	0
Gait ignition apraxia	1 (1.6%)	0

Table 4.2: Clinical features in 39 patients successfully withdrawn from antiparkinson medication, according to clinic attendance

Type of clinic attendance	Number of cases (%)	Percentage male	Age in years	Years since PD diagnosis	Antiparkinson medication dose in Levodopa equivalents/day
Specialist clinic	14 (35.9%)	21.4%	76.3 (6.6)	3.5 (1.9)	200 (171)
Non-specialist clinic	1 (2.6%)	0%	86.9	5.0	400
No clinic attendance	24 (61.5%)	58%	73.8 (9.8)	8.8 (6.3)	302 (253)
All patients	**39**	**43.6%**	**75.0 (8.9)**	**6.8 (5.6)**	**268 (227)**

Data are mean (standard deviation) unless otherwise specified

Table 4.3: Clinical features of 64 patients meeting selection criteria for the study and undergoing clinical assessment

Patient number / age (yrs) / sex	Time since PD diagnosis (yrs)	Clinical features	Antiparkinson medication (doses per day)	FP-CIT SPECT	Preliminary diagnosis	Final diagnosis
1/63/F	12.0	Mild hypophonia and hypomimia; jaw tremor; moderate right hand and leg rest tremor; rigidity at neck and in upper limbs; mild bilateral bradykinesia; mild stoop; short steppage gait	Pramipexole 2.8mg	Abnormal	PD	
2/84/F	6.1	Mild resting, postural and kinetic tremor both hands; no rigidity or bradykinesia; mild stoop; preserved arm swing	Levodopa 400mg	Not done	ET	
3/84/M	2.9	No tremor, rigidity or bradykinesia; stooped, mild postural instability, hesitant gait	Levodopa 200mg	Not done	Gait apraxia	
4/86/F	5.0	Rest, postural and kinetic tremor of hands, no bradykinesia or rigidity, stooped, shuffling gait, postural instability	Levodopa 400mg	Not done	ET	
5/80/M	5.8	Mild hypomimia; mild right-sided rest and postural tremor; no rigidity or bradykinesia; stooped; gait slow with loss of arm swing	Pramipexole 0.804mg; Procyclidine 15mg	Abnormal	VP	PD
6/72/F	1.5	Resting and postural tremor of hands; no rigidity or bradykinesia; mild stoop; slowed gait	Levodopa 70mg	Abnormal	ET	PD
7/64/M	1.6	Rest, postural and kinetic tremor of hands, no rigidity or bradykinesia; slowed gait	Pramipexole 0.264mg	Abnormal	PD	
8/75/M	4.0	Hypomimia and hypophonia; chin tremor; rest tremor of hands; moderate limb rigidity; marked bilateral bradykinesia; stooped; short steppage gait with loss of arm swing	Levodopa 500mg	Not done	PD	
9/77/F	9.3	Hypophonia and hypomimia; jaw tremor; moderate rest tremor right hand and leg; increased tone in limbs; moderate asymmetrical bradykinesia; stooped; short steppage gait with loss of arm swing	Orphenadrine 100mg	Not done	PD	
10/74/M	5.7	Hypomimia and hypophonia; mild rest tremor of right hand; bilateral postural tremor of arms; no rigidity; moderate bilateral bradykinesia; stooped; short steppage gait with loss of arm swing	Levodopa 600mg	Abnormal	PD	
11/83/F	3.6	Rest and postural tremor of hands; mild left leg rigidity; no bradykinesia	Levodopa 280mg	Not done	ET	
12/69/M	10.1	Postural and kinetic tremor of arms; no rigidity or bradykinesia; mild postural instability	Levodopa 150mg	Not done	ET	
13/83/F	2.1	Hypomimia and hypophonia; resting, postural and kinetic tremor; mild rigidity right arm; mild asymmetrical bradykinesia; stooped; short steppage gait with loss of arm swing	Procyclidine 15mg	Not done	PD	

14/77/F	3.5	Hypomimia and hypophonia; rest tremor both hands and right leg; postural tremor right arm;	Levodopa 200mg	Not done	PD	
15/84/F	8.0	Cognitive impairment; jaw tremor; bilateral rest, postural and kinetic tremor of arms; no rigidity or bradykinesia	Levodopa 280mg	Not done	ET	
16/56/M	12.4	Postural and kinetic tremor of arms; increased tone at neck and in right arm no bradykinesia; mild stoop	Levodopa 150mg	Normal	DT	
17/86/M	5.2	Hypomimia and hypophonia; rest tremor right hand, right leg and left leg; postural tremor right arm; symmetrical moderate bradykinesia; stooped; shuffling gait with freezing and loss of arm	Levodopa 200mg	Not done	PD	
18/86/M	4.4	Hypomimia and hypophonia; chin tremor; increased tone right arm, right leg and left leg; moderate asymmetrical bradykinesia; stooped; short steppage gait with reduced arm swing	Levodopa 520mg	Not done	PD	
19/90/F	8.6	Mild hypomimia; rest tremor right leg; increased tone limbs; mild bilateral bradykinesia; short steppage gait with preserved arm swing	Levodopa 300mg	Abnormal	PD	
20/69/F	10.2	Hypomimia and hypophonia; postural tremor of arms; increased tone all limbs; moderate bilateral bradykinesia; stooped	Levodopa 520mg	Not done	PD	
21/70/M	7.2	Bilateral kinetic tremor arms; no rigidity or bradykinesia; mild stoop; gait slowed	Levodopa 100mg	Not done	Indeterminate tremor	
22/71/F	3.9	Jaw tremor; rest, postural and kinetic tremor of arms; no bradykinesia or rigidity; mild stoop	Levodopa 100mg	Not done	ET	
23/78/M	15.2	'No-no' head tremor; jaw tremor; bilateral rest tremor of hands; marked bilateral postural and kinetic tremor of arms; increased tone at neck; no bradykinesia; mild stoop; mild postural instability	Levodopa 300mg; Selegiline 10mg	Normal	ET	
24/80/M	9.6	Hypomimia and hypophonia; dyskinetic movements of limbs; bilateral postural tremor of arms; mild rigidity; moderate asymmetrical bradykinesia; stooped; shuffling gait with reduced arm swing	Levodopa 700mg	Not done	PD	
25/84/M	7.8	Postural and kinetic tremor both arms; pyramidal weakness right arm and leg; stooped; gait slowed; mild postural instability,	Levodopa 400mg	Not done	ET	
26/45/M	1.4	Rest, postural and kinetic tremor of arms; no rigidity or bradykinesia	Levodopa 70mg	Not done	ET	
27/65/F	2.1	Postural and kinetic tremor arms; increased tone lower limbs; no bradykinesia; stooped; reduced arm swing	Pramipexole 0.54mg	Normal	VP	
28/75/F	3.9	Jaw tremor; mild rest and postural tremor of arms; no bradykinesia; tone increased at neck; posture stooped; gait slowed with reduced bilateral arm swing	Pramipexole 2.1mg	Normal	VP	
29/80/F	2.1	Rest, postural and kinetic tremor of arms; mild rigidity in upper limbs; no bradykinesia; short steppage gait with reduced arm swing; moderate postural instability	Levodopa 300mg	Abnormal	PD	

30/86/F	6.4	Vocal and chin tremor; mild bilateral rest and postural tremor of arms; no rigidity or bradykinesia; stooped; gait slowed with reduced arm swing	Levodopa 150mg	Not done	VP	
31/84/M	9.5	Hypophonia; chin tremor; rest and postural tremor of arms; increased tone at neck and in limbs; moderate asymmetrical bradykinesia; stooped	Levodopa 420mg	Not done	PD	
32/72/M	4.0	Moderate hypophonia and hypomimia; jaw tremor; bilateral resting tremor of hands; bilateral postural tremor of arms; mild symmetrical bradykinesia; stooped; shuffling gait with bilateral loss of arm swing	Levodopa 600mg; Selegiline 10mg	Normal	Drug-induced Parkinsonism	
33/75/M	7.1	Hypomimia; postural and kinetic tremor of arms; rigidity at neck; no bradykinesia; stooped; slow gait with reduced arm swing	Levodopa 100mg; Pramipexole 2.1mg	Abnormal	PD	
34/64/M	4.5	'Yes-yes' head tremor; postural and kinetic tremor of arms; rigidity in lower limbs; no bradykinesia; stooped; short steppage gait with reduced arm swing	Levodopa 300mg	Not done	VP	
35/76/M	4.3	Hypophonia and hypomimia; chin tremor; mild neck and left arm rigidity; moderate asymmetrical bradykinesia; stooped; short steppage gait with reduced arm swing	Levodopa 300mg	Abnormal	PD	
36/77/M	6.5	Hypophonia; dyskinetic movements of neck and limbs; moderate limb rigidity; moderate asymmetrical bradykinesia; stooped; short steppage gait with loss of arm swing	Levodopa 750mg; Entacapone 600mg	Not done	PD	
37/62/M	8.9	Hypophonia and hypomimia; rest tremor left hand; postural tremor of arms; neck and limb rigidity; marked asymmetrical bradykinesia; stooped; short steppage gait with loss of arm swing	Levodopa 540mg	Not done	PD	
38/71/M	10.7	Mild hypophonia and hypomania; chin tremor; moderate rest tremor both hands; increased tone at neck and in limbs; moderate symmetrical bradykinesia; stooped	Levodopa 1260mg	Normal	Drug-induced Parkinsonism	
39/79/M	7.7	Rest tremor both hands and left leg; postural and kinetic tremor of arms; increased tone in limbs; moderate asymmetrical bradykinesia; stooped; short steppage gait with frequent freezing and loss of arm swing	Levodopa 420mg	Not done	PD	
40/82/F	4.8	Cognitive impairment; rest tremor right hand; bilateral postural and kinetic tremor of arms; no bradykinesia; difficulty standing; stooped; mild postural instability	Levodopa 400mg	Normal	VP	
41/79/F	5.7	Chin tremor; rest and postural tremor of left arm; no bradykinesia; stooped; Gait slowed with reduced arm swing	Pramipexole 1.08mg	Not done	Indeterminate tremor	
42/79/M	2.7	Hypomimia and hypophonia; jaw tremor; rest tremor left hand; rigidity at neck and in limbs; marked bilateral bradykinesia; stooped; short steppage gait with reduced arm swing	Levodopa 300mg; Entacapone 600mg	Not done	PD	

43/71/F	2.0	Mild hypomimia and hypophonia; jaw tremor; moderate rest tremor all 4 limbs; moderate bilateral bradykinesia; mild stoop; slow gait with reduced arm swing	Pramipexole 0.264mg	Normal	Drug-induced Parkinsonism	
44/74/F	3.9	Mild rest tremor right hand; bilateral postural and kinetic tremor arms; no rigidity or bradykinesia	Levodopa 400mg	Not done	ET	
45/75/M	5.4	Mild hypomimia; dyskinetic movements of limbs; jaw tremor; intermittent rest tremor right hand; moderate postural tremor of arms; increased tone at neck; no bradykinesia; mild stoop; reduced right-sided arm swing	Levodopa 300mg; Ropinirole 15mg	Abnormal	PD	
46/87/F	6.0	Jaw tremor; rest tremor left hand and both legs; mild postural tremor of arms; mild asymmetrical bradykinesia; stooped; short steppage gait with absent arm swing	Levodopa 150mg	Not done	PD	
47/87/F	4.2	'No-no' head tremor; bilateral postural and kinetic tremor of arms; no rigidity or bradykinesia	Levodopa 100mg	Not done	ET	
48/73/M	6.1	Mild rest tremor left hand; bilateral postural and kinetic tremor of arms; no rigidity or bradykinesia	Levodopa 100mg	Not done	ET	
49/79/F	24.7	Intermittent 'no-no' head tremor; mild bilateral postural and kinetic tremor of arms; no rigidity or bradykinesia; slowed gait with preserved arm swing	Levodopa 300mg	Not done	ET	
50/72/M	2.0	Dysarthria and expressive dysphasia; right-sided pyramidal weakness of arm and leg; increased tone at neck and in right arm and leg; no bradykinesia; stooped	Levodopa 150mg	Not done	Indeterminate tremor	
51/56/M	11.8	Dysarthria; bilateral postural tremor of arms; no rigidity or bradykinesia; mild stoop	Levodopa 200mg	Not done	Indeterminate tremor	
52/81/M	4.5	Mild bilateral rest tremor of hands; bilateral postural and kinetic tremor of arms; increased tone at neck; no bradykinesia; stooped; slowed gait with preserved arm swing	Levodopa 300mg	Not done	DT	
53/81/M	6.9	Bilateral postural and kinetic tremor; tone increased at the neck; no bradykinesia; mild stoop	Levodopa 400mg	Not done	DT	
54/76/M	5.7	Mild dysarthria; hypomimia; no tremor; rigidity in all limbs; symmetrical bradykinesia; stooped; unsteady gait	Levodopa 400mg	Normal	VP	
55/80/M	18.7	Jaw tremor; rest tremor right hand; bilateral postural and kinetic tremor of arms; no rigidity or bradykinesia; mild stoop	Levodopa 300mg	Not done	Indeterminate tremor	
56/72/F	8.7	'No-no' head tremor; bilateral rest tremor of hands; moderate bilateral postural tremor of arms; mild bilateral bradykinesia; stooped; gait slow with reduced arm swing	Levodopa 50mg	Normal	VP	
57/74/F	5.2	'No-no' head tremor; intermittent rest tremor both hands; bilateral postural and kinetic tremor; bilateral bradykinesia; markedly stooped; gait slow with loss of arm swing	Levodopa 200mg	Normal	VP	

58/77/F	23.3	Rest, postural and kinetic tremor of arms; increased tone at neck and in limbs; mild symmetrical bradykinesia; stooped; slowed gait with reduced arm swing	Levodopa 200mg; Bromocriptine 30mg	Abnormal	PD	
59/82/F	6.4	Mild hypomimia; jaw tremor; rest, postural and kinetic tremor of arms; increased tone at neck; mild symmetrical bradykinesia; stooped; slowed gait with reduced arm swing	Levodopa 300mg	Abnormal	PD	
60/76/M	5.4	Mild hypomimia and hypophonia; rest tremor both hands; increased tone at neck and in right arm; moderate symmetrical bradykinesia; stooped; short steppage gait with reduced arm swing	Levodopa 400mg	Not done	PD	
61/77/F	8.1	'No-no' head tremor; jaw tremor; rest tremor both hands; bilateral postural and kinetic tremor; mild left-sided bradykinesia; moderate stoop; preserved arm swing	Levodopa 300mg	Normal	VP	
62/72/F	8.4	Rest tremor left hand; bilateral postural tremor of arms; increased tone at the neck; mild bilateral bradykinesia; stooped; slow, unsteady gait	Levodopa 300g/day	Normal	VP	
63/84/F	23.2	'No-no' head tremor; rest tremor right arm and leg; postural and kinetic tremor of arms; increased tone at neck; no bradykinesia; stooped; slow and unsteady gait; marked postural instability	Levodopa 400mg	Not done	VP	
64/84/F	4.9	Dyskinetic movements of neck and limbs; postural and kinetic tremor of arms; increased tone at neck; moderate symmetrical bradykinesia; mild stoop; slowed gait with reduced arm swing	Levodopa 560mg	Not done	PD	

PD= Parkinson's disease; DT= dystonic tremor; ET= essential tremor; VP= vascular Parkinsonism

Table 4.4: Clinical features of 3 patients identified in routine out-patient clinics who successfully underwent supervised antiparkinson medication withdrawal

Patient number / age (yrs)/ sex	Time since PD diagnosis (yrs)	Clinical features	Antiparkinson medications (doses per day)	FP-CIT SPECT	Diagnosis
1/75/F	1.9	Jaw and 'no-no' head tremor; bilateral rest tremor of hands; postural and kinetic tremor of outstretched arms; rigidity at neck; moderate symmetrical bradykinesia; stooped; unsteady gait with loss of arm swing	Levodopa 400mg; Entacapone 800mg	Normal	VP
2/74/M	6.7	No rest tremor; bilateral postural and kinetic tremor of outstretched arms; no rigidity or bradykinesia; gait normal with preserved arm swing	Pramipexole 1.08mg	Normal	ET
3/70/F	1.8	No rest tremor; mild bilateral postural and kinetic tremor of outstretched arms; no rigidity or bradykinesia; mild stoop	Pramipexole 2.8mg	Normal	ET

ET= essential tremor; VP= vascular Parkinsonism

Table 4.5: Comparison of estimates for prevalence of misdiagnosed cases among 610 Parkinson's disease patients

	Lower estimate *(63 of 610 cases misdiagnosed)*	Upper estimate *(70 of 610 cases misdiagnosed)*
Sensitivity	0.62 (0.49 – 0.74)	0.66 (0.53 – 0.76)
Specificity	0.91 (0.88 – 0.93)	0.92 (0.89 – 0.94)
PPV	0.44 (0.33 – 0.55)	0.52 (0.41 – 0.62)
NPV	0.95 (0.93 – 0.97)	0.95 (0.93 – 0.97)
Likelihood ratio	6.9 (4.9 – 9.4)	8.3 (5.9 – 11.5)

PPV= positive predictive value; NPV = negative predictive value

PD patients on antiparkinson medication, **n=610**

| Fulfilled screening criteria **n=89** (14.8% of 610) | Did not fulfil screening criteria **n=512** (85.2% of 610) | Not selected as controls n=**415** |

Selected as controls **n=97**

Agreed to assessment

| NO **n=25** No response n=10 Unwilling n=4 Unwell n=11 | YES **n=64** (10.6% of 610, 71.9% of 89) | YES **n=64** (10.6% of 610, 66.0% of 97) | NO **n=33** No response n=20 Unwilling n=5 Unwell n=8 |

Appropriate for therapy withdrawal

| NO **n=28** Probable PD n=25 No consent n= 2 Unwell n= 1 | YES n=**36** (56.2% of 64) | YES **n=3** (4.7% of 64) | NO **n=61** Probable PD n=61 (95.3% of 64) |

Completed therapy withdrawal

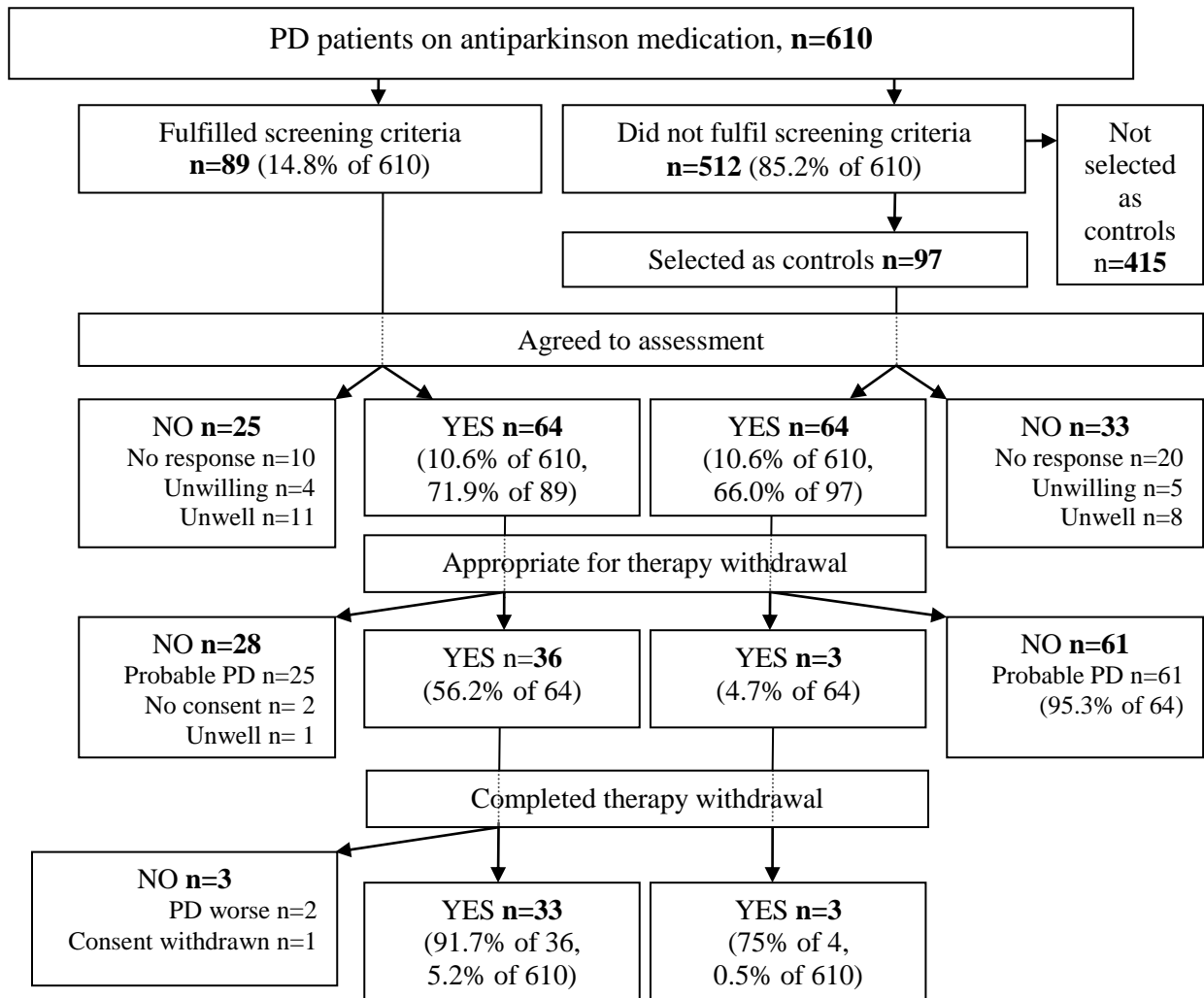| NO **n=3** PD worse n=2 Consent withdrawn n=1 | YES **n=33** (91.7% of 36, 5.2% of 610) | YES **n=3** (75% of 4, 0.5% of 610) |

Figure 4.1: Consort diagram for medication withdrawal in patients who do not benefit from antiparkinson medication

CHAPTER 5

FP-CIT SPECT IN PATIENTS WITH AN UNCERTAIN DIAGNOSIS OF PARKINSON'S

DISEASE

Introduction

The advent of *in vivo* imaging of the presynaptic dopaminergic system, disrupted in degenerative Parkinsonism, has given a new mechanism to test the accuracy of clinical diagnosis of Parkinson's disease (PD). Thus the earlier clinicopathological studies which reported significant misdiagnosis of PD in up to 25% of patients (Rajput et al. 1991b;Hughes et al. 1992a) can now be pre-dated in the living patient with a diagnostic test. It should be noted, however, that a proportion of the misdiagnosis of PD is for other degenerative parkinsonian conditions (eg. multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD)) in which presynaptic dopamine imaging is also abnormal (Scherfler et al. 2007). While postsynaptic dopamine receptor imaging might theoretically assist in differentiating among these conditions, in clinical practice the sensitivity and specificity of such testing has not been sufficiently high. In the present study, the main interest was in differentiating degenerative PD from non-degenerative conditions which are much commoner; hence these concerns were not of major significance. Some additional considerations regarding diagnostic accuracy are relevant to the material reported in the present chapter. Firstly, clinical diagnostic accuracy is greatest when Brain Bank criteria are strictly employed and when patients are assessed within a specialist movement disorder service (Hughes et al. 2002). Secondly, diagnostic accuracy improves when the patient is followed over time. Accordingly, the difficulties of differentiating PD from essential tremor (ET), especially with asymmetry of clinical features and rest tremor which are both recognised in ET (Louis et al. 1998;Cohen et al. 2003), should be reduced if patients have a long-standing diagnosis; and this differentiation should be enhanced in uncertain cases by applying presynaptic dopamine receptor imaging. Similar arguments apply to other non-degenerative movement disorders which may be difficult to differentiate from PD (eg. vascular Parkinsonism and dystonic tremor).

Measuring DAT using SPECT

The main dopaminergic neurones are found within the substantia nigra pars compacta and the ventral tegmental area. The dopamine transporter (DAT) is a sodium chloride-dependent protein located on the presynaptic dopaminergic neurone. It controls

dopamine levels by active reuptake of dopamine after it interacts at the postsynaptic receptor (Jaber et al. 1997). Appropriate ligands, such as β-CIT: [^{123}I] 2-carboxymethoxy-3-(4-iodophenyl) tropane and [^{123}I]FP-CIT: [^{123}I]*N*-w-fluoropropyl-2-carbomethoxy-3-(4-iodophenyl)nortropane, bind to presynaptic DAT and therefore provide an indirect measure of dopaminergic neuronal degeneration when imaged using SPECT.

The time of optimal scan acquisition is 3-6 hours after injection with FP-CIT. Image analysis either uses quantitative region of interest (ROI) ratios and/or qualitative visual assessment. Striatal uptake of the radioligand is calculated in relation to a reference site with negligible DAT activity (commonly the occipital or cerebellar cortex). DAT imaging is considered safe and radiation doses acceptable being equivalents for an FP-CIT SPECT and a CT brain scan; and is also more widely available than positron emission tomography (PET) scanning.

Imaging using ^{18}F-dopa PET

Like SPECT, positron emission tomography (PET) imaging allows the *in vivo* assessment of the nigrostriatal system. The presynaptic radiotracer 18-fluorodopa (^{18}F-dopa) was first used in PD in 1983. Following intravenous administration ^{18}F-dopa is decarboxylated to fluorodopamine within dopaminergic nerve terminals. Region-of-interest (ROI) activity reflects the number of functional dopaminergic neurons, incorporating presynaptic dopa uptake, decarboxylation to dopamine and storage. The major reduction in striatal ^{18}F-dopa in PD is in keeping with post-mortem studies and correlates with bradykinesia and rigidity (Snow et al. 1993).

PET imaging can detect pre-clinical disease, such as in clinically unaffected co-twins of a patient with Parkinson's disease and asymptomatic subjects with a strong family history (Piccini et al. 1997;Laihinen et al. 2000). PET scanning has also been applied to neuroprotective studies, e.g. the REAL-PET study in which186 newly diagnosed patients were randomized to ropinirole or levodopa (Whone et al. 2003). After 2 years, putamen uptake declined by 13% for ropinirole cases compared to 20% for levodopa cases.

Within Europe FP-CIT is licensed as a radiotracer for diagnosis of PD. FP-CIT SPECT is increasing available for clinical use across the UK, whilst the more expensive PET scanning remains a research tool.

Clinical application of DAT imaging

DAT SPECT demonstrates significantly reduced asymmetrical striatal uptake in PD (Booij et al. 1997). Striatal uptake correlates with disease duration and motor severity (Benamer et al. 2000b). Abnormal radiotracer uptake progresses from putamen to caudate and matches contralaterally the more clinically affected side. The main clinical application of DAT imaging is in assessing patients in whom there is diagnostic doubt between degenerative Parkinsonism and other non-degenerative tremor disorders.

The conditions most commonly misdiagnosed as PD within the community are ET and vascular Parkinsonism (VP) (Meara, Bhowmick, & Hobson 1999). DAT imaging is normal in ET (Asenbaum et al. 1998;Benamer et al. 2000a). DAT imaging can assist the identification of VP in the presence of focal deficit which matches basal ganglia infarction often seen on CT brain imaging, distinct from the pattern seen in PD (Tzen et al. 2001). DAT SPECT is normal in drug-induced Parkinsonism (Lavalaye et al. 2001) and psychogenic tremor (Booij et al. 2001).

DAT SPECT in misdiagnosis of Parkinson's disease

DAT imaging is normal in a subset of patients clinically labelled as having PD (Benamer et al. 2003;Marshall & Grosset 2003a;Marshall & Grosset 2003b). Misdiagnosis of PD is recognised in randomised clinical trials with between 1.4 and 15% of patients in 3 large clinical studies having normal presynaptic dopaminergic imaging (The Parkinson Study Group 2002;Whone et al. 2003;Seibyl et al. 2004;Fahn et al. 2004).

Central to this thesis was a study in which patients, misdiagnosed as PD, were identified from searches of GP practice prescription databases and had antiparkinson medications gradually withdrawn under supervision (See Chapter 4). In the current chapter the results from FP-CIT SPECT scans performed as part of this larger study are

reported. The aim of the current study was to examine further the use of FP-CIT SPECT in the assessment of patients on antiparkinson therapy for a PD diagnosis in whom there is diagnostic doubt.

Methods

The patient identification process is described in detail in Chapter 4. In brief summary, searches of prescription databases and GP case records for patients prescribed antiparkinson medication for a PD diagnosis were completed in 92 West Scotland GP practices. Patients with features which raised the possibility that they did not have PD were invited for out-patient assessment, which amounted to 64 patients meeting selection criteria. In addition, 64 matching control patients were seen. Clinical assessment was undertaken in all cases by 2 movement disorder specialists. Patients considered to have PD were discharged from further follow-up and patients considered to have an alternate diagnosis were offered supervised antiparkinson medication withdrawal. Brain Bank criteria were used in assessment of the diagnosis of PD. Alternative diagnoses were made according to established criteria and definitions: ET (Bain et al. 2000); VP (Zijlmans et al. 2004); dystonic tremor (DT) (Schneider et al. 2007); or indeterminate tremor (Deuschl, Bain, & Brin 1998). FP-CIT SPECT scanning was performed in clinically uncertain cases, primarily in patients with overlapping features between different criteria (eg. patients with a prolonged history suggesting ET, but with emerging features raising the possibility of PD).

FP-CIT SPECT scanning was also performed in further patients labelled as PD, identified during the same time period as the above study, but within routine movement disorder clinics (by study investigators) as having clinical features inconsistent with degenerative Parkinsonism.

Data from the community study was compared with a subset (from the same centre as the present study) of patients who had serial FP-CIT SPECT scans part of a prospective 3-year multicentre European prospective FP-CIT study (Marshall et al. 2008). In that study, patients were recruited on the basis of clinical diagnostic uncertainty

between degenerative Parkinsonism and non-degenerative tremor disorders; patients were scanned at baseline and had repeat scans at 18 and 36 months. Data from patient scans at 36 months following initial scan were used as the comparator group to the patients in this study, since the patients in the present study had long duration diagnosis which was closest to the 3 year scan time-point in the prior work.

Age, sex and time from initial PD diagnosis to the date of the scan were recorded for all patients. All FP-CIT SPECT scans were performed using the same scanner (Institute of Neurological Sciences, Glasgow) and were interpreted by the same radiologist using standardised methodology, with measurement of the ratio of striatal radioligand uptake (divided into its anterior area representing the caudate, and its posterior area representing the putamen) to the uptake within the occipital cortex. The primary area of interest was defined as the lower of right or left sided uptake ratios for putamen, since this is the area which degenerates first in PD.

Statistical analysis

Mean putamen uptake between scans from the community and European prospective FP-CIT studies were compared using unpaired t-tests. Change in mean putamen uptake over serial scans for patients within the European prospective FP-CIT study was compared using one-way ANOVA.

Results

Community study

FP-CIT SPECT scans were performed in 37 patients (22 female, 15 male):

- 24 of 64 (37.5%) of the active group;
- 4 of 64 (6.3%) of the control group; and
- 9 patients identified within out-patient clinics, as follows:

Patients identified within out-patient clinics (n = 9) had features inconsistent with degenerative Parkinsonism:

- 3 of 9 patients (33%) were also among those identified from GP practice database searches, but neither fulfilled selection criteria nor were selected as controls.
- 6 of 9 patients (67%) originated from outwith the catchment area of the GP practice searches.

Mean age at time of FP-CIT SPECT scanning was 74.0 years (SD 7.3 years). Time since initial PD diagnosis was positively skewed; median time was 4.4 years (interquartile range: 1.9 to 7.5 years). Clinical features, scan results and final diagnosis are detailed in Table 5.1.

25 of 37 (67.6%) scans were reported as normal and 12 of 37 (32.4%) were reported as abnormal. All patients with abnormal FP-CIT scans were diagnosed as PD (diagnosis was based on clinical plus imaging features of PD). 13 of 25 patients (52%) with normal scans had a clinical plus imaging diagnosis of VP; 6 of 25 (24%) were diagnosed as ET; 3 of 25 (12%) were diagnosed as drug-induced Parkinsonism; 2 of 25 (8%) were diagnosed as dystonic tremor and 1 of 25 (4%) was diagnosed as indeterminate tremor.

All patients with normal scans were offered supervised antiparkinson medication withdrawal. 24 of 25 patients (96%) consented to therapy withdrawal. 23 of 24 patients (95.8%) completed therapy withdrawal and 1 patient (4.2%) withdrew consent. Patients were followed up for a mean period of 7.2 months (SD 3.1 months). The mean change in UPDRS motor score after therapy cessation was an improvement of 1.3 points (95% confidence interval: deterioration of 0.3 to improvement of 3.0 points). (*Note for clarification:* These UPDRS scores represent all patients who had normal FP-CIT SPECT and stopped antiparkinson therapy successfully during the current work. This includes 23 patients, 19 of whom are already included in Chapter 4, and in addition a further 4 patients identified in out-patient clinics. The present figures differ slightly from those in Chapter 4 because those results did not include the additional 4 out-patient cases).

Data from the European prospective FP-CIT study

This work was not performed as part of the present thesis but is summarised briefly as a framework for understanding and comparison with the present study. 32 patients (20 male, 12 female) with a clinically uncertain Parkinsonism / tremor disorder (which could be either degenerative or non-degenerative) underwent 3 FP-CIT SPECT scans (at baseline, 18 and 36 months). 14 of 32 scans (43.8%) were reported as normal. Mean minimal putamen uptake was 3.17 (SD 0.38) for scans reported as normal and 1.35 (SD 0.43) for scans reported as abnormal.

Figure 5.1 demonstrates the change in minimal putamen uptake over the 3 scans. The scan result did not change from normal to abnormal (or vice versa) in any case. There was no significant change in mean uptake over 3 scans for patients with normal scans ($p=0.48$) and although the mean uptake show a trend to decreasing over 3 scans in abnormal scans, this change was not significant ($p=0.63$).

Figure 5.2 compares minimal putamen uptake for scans from the community and European prospective FP-CIT studies. Mean minimal putamen uptake ratios for normal scans was 2.94 (SD 0.58) in the community study patients and 3.17 (SD 0.43) in the European prospective FP-CIT study (36 month scans). Mean minimal putamen uptake ratio for abnormal scans was significantly less for patients within community study than patients from European prospective FP-CIT study (scanned at 36 months following baseline) (0.75 (SD 0.29) versus 1.03 (0.38), $p<0.05$).

Examples of FP-CIT SPECT images from the current study are in Figures 5.3-5.5.

Discussion

This community study further confirms the tendency for overdiagnosis of PD, observed in previous community and clinicopathological studies (Hughes et al. 1992b;Meara, Bhowmick, & Hobson 1999;Schrag, Ben Shlomo, & Quinn 2002). Normal DAT imaging has also been reported in a subset of patients (labelled as PD) entering clinical trials of antiparkinson therapies (Fahn 1999;The Parkinson Study Group

2000;Whone et al. 2003;Seibyl et al. 2004). These patients have previously been referred to as SWEDDs (subjects with scans without evidence of dopamine deficiency) and there is debate as to the underlying pathology. Either these patients:

a) Do not have PD; or

b) Do have PD without presynaptic neuronal degeneration; or

c) Have nigrostriatal degeneration that is not detectable on SPECT or positron emission tomography (PET) scanning.

In clinical trials a higher proportion of SWEDDs is found in early disease. In ELLDOPA 14% of cases were SWEDDs (mean disease duration, 6.5 months), versus 11% SWEDDs (16-month duration) in REAL-PET, 4% SWEDDs (18-month duration) in CALM-PD, and 1.4% (23-month duration) in NIL-A-CIT. If misdiagnosis is more common in earlier disease this argues against a non- nigrostriatal form of PD in which the proportion would remain constant over time. There are no clinicopathological correlates for SWEDDs in the literature.

Given that abnormal DAT imaging has been reported in patients with olfactory disturbance who go on to develop clinical Parkinsonism (ie. patients in the pre-motor phase of PD) (Stiasny-Kolster et al. 2005) and that more than 50% of dopaminergic neurones are lost at the time of presentation of motor symptoms of PD it is unlikely that a normal scan could represent early PD. Gradual reduction in putamen DAT uptake has been described in PD patients, with 6 to 13% annual reduction compared to 0 to 2% in healthy controls (Scherfler et al. 2007). Therefore, a normal scan in a patient with a long-established PD diagnosis (a median of 4.4 years in the present study and an upper range of 23.3 years ago) is even less likely to represent PD.

The present study gives the highest proportion of SWEDDs (25 of 37 scans, 67.6%) ever reported. It should be realised that this was in a highly selected population, specifically identified through clinical criteria which were designed to identify patients unlikely to have PD despite being on established therapy for this diagnosis. However, even considering that only 19 patients out of 610 (the population of patients on

antiparkinson therapy for a diagnosis of PD identified from GP practice searches) had normal scans, this still amounts to 3.1% of SWEDDs in a community series. The real proportion of SWEDDs is clearly much higher; we did not submit patients for FP-CIT unless there was either baseline uncertainty or an unexpected deterioration following antiparkinson therapy withdrawal. Accordingly, it is perhaps appropriate to define a new entity, combining the clinically rediagnosed case (who does not undergo FP-CIT or similar scanning) with the SWEDD patients, for which we have invented the acronym SEDAPs (subjects erroneously diagnosed as PD). The proportion of community patients in this capacity has already been described and discussed in Chapter 4.

In keeping with previous community studies the most common alternative diagnosis in patients with normal scans in the community series were ET and VP (Meara, Bhowmick, & Hobson 1999). The lack of deterioration in movement disorder symptoms following antiparkinson therapy withdrawal in these cases further supports the assumption of a non-PD diagnosis. DAT-imaging is abnormal in degenerative Parkinsonism and does not differentiate between different types (eg. PD, PSP, MSA, CBD). All patients with abnormal FP-CIT SPECT imaging in this study were considered clinically to have PD.

The lack of reduction in minimal putamen uptake ratio in the normal scans on serial imaging (over 3 years) in the European prospective FP-CIT study is in keeping with previously reported sequential scanning of SWEDDs (Whone et al. 2003;Fahn et al. 2004). Although we did not see a decline in uptake ratios over time in patients with abnormal scans at baseline, each patient showed persistence of an abnormal scan at repeat after 18 and 36 months. Collectively these observation reinforce the conclusions of the present study, specifically that patients with a normal FP-CIT SPECT are 'true negative' regarding the diagnosis of PD, and that patients in the current study with abnormal FP-CIT SPECT in the present study are 'true positive' regarding the diagnosis of PD. On this basis, we would argue that, in this patient population, a properly conducted FP-CIT SPECT scan can be used to 'over-rule' a contradictory clinical diagnosis.

Conclusion

       A subset of patients labelled as having Parkinson's disease and prescribed antiparkinson therapy have been misdiagnosed. FP-CIT SPECT is an extremely useful tool, if used appropriately, in the identification of such misdiagnosed cases, being able to differentiate degenerative Parkinsonism from non-degenerative disorders, in particular when the patient has carried the PD diagnosis for a prolonged time.

Table 5.1: Clinical features and FP-CIT SPECT result for 37 patients undergoing FP-CIT SPECT

Patient number / age (yrs) / sex	Time since PD diagnosis (yrs)	Clinical features	Minimal putamen uptake ratio	Report	Diagnosis
1/80/F	2.1	Rest, postural and kinetic tremor of arms; mild rigidity in upper limbs; no bradykinesia; short steppage gait with reduced arm swing; moderate postural instability	1.05	Abnormal	PD
2/63/F	12.0	Mild hypophonia and hypomimia; jaw tremor; moderate right hand and leg rest tremor; rigidity at neck and in upper limbs; mild bilateral bradykinesia; mild stoop; short steppage gait	0.71	Abnormal	PD
3/64/M	1.6	Rest, postural and kinetic tremor of hands, no rigidity or bradykinesia; slowed gait	2.17	Normal	ET
4/74/M	5.7	Hypomimia and hypophonia; mild rest tremor of right hand; bilateral postural tremor of arms; no rigidity; moderate bilateral bradykinesia; stooped; short steppage gait with loss of arm swing	0.49	Abnormal	PD
5/80/M	5.8	Mild hypomimia; mild right-sided rest and postural tremor; no rigidity or bradykinesia; stooped; gait slow with loss of arm swing	0.48	Abnormal	PD
6/75/F	3.9	Jaw tremor; mild rest and postural tremor of arms; no bradykinesia; tone increased at neck; posture stooped; gait slowed with reduced bilateral arm swing	2.68	Normal	VP
7/90/F	8.6	Mild hypomimia; rest tremor right leg; increased tone limbs; mild bilateral bradykinesia; short steppage gait with preserved arm swing	1.42	Abnormal	PD
8/56/M	12.4	Postural and kinetic tremor of arms; increased tone at neck and in right arm no bradykinesia; mild stoop	2.51	Normal	DT
9/78/M	15.2	'No-no' head tremor; jaw tremor; bilateral rest tremor of hands; marked bilateral postural and kinetic tremor of arms; increased tone at neck; no bradykinesia; mild stoop; mild postural instability	2.93	Normal	ET
10/65/F	2.1	Postural and kinetic tremor arms; increased tone lower limbs; no bradykinesia; stooped; reduced arm swing	2.76	Normal	VP
11/72/M	4.0	Moderate hypophonia and hypomimia; jaw tremor; bilateral resting tremor of hands; bilateral postural tremor of arms; mild symmetrical bradykinesia; stooped; shuffling gait with bilateral loss of arm swing	2.07	Normal	DIP
12/75/M	7.1	Hypomimia; postural and kinetic tremor of arms; rigidity at neck; no bradykinesia; stooped; slow gait with reduced arm swing	0.63	Abnormal	PD
13/76/M	4.3	Hypophonia and hypomimia; chin tremor; mild neck and left arm rigidity; moderate asymmetrical bradykinesia; stooped; short steppage gait with reduced arm swing	0.53	Abnormal	PD

14/71/M	10.7	Mild hypophonia and hypomania; chin tremor; moderate rest tremor both hands; increased tone at neck and in limbs; moderate symmetrical bradykinesia; stooped	3.43	Normal	DIP
15/82/F	4.8	Cognitive impairment; rest tremor right hand; bilateral postural and kinetic tremor of arms; no bradykinesia; difficulty standing; stooped; mild postural instability	2.57	Normal	VP
16/71/F	2.0	Mild hypomimia and hypophonia; jaw tremor; moderate rest tremor all 4 limbs; moderate bilateral bradykinesia; mild stoop; slow gait with reduced arm 0.53swing	3.36	Normal	DIP
17/75/M	5.4	Mild hypomimia; dyskinetic movements of limbs; jaw tremor; intermittent rest tremor right hand; moderate postural tremor of arms; increased tone at neck; no bradykinesia; mild stoop; reduced right-sided arm swing	0.53	Abnormal	PD
18/72/F	8.7	'No-no' head tremor; bilateral rest tremor of hands; moderate bilateral postural tremor of arms; mild bilateral bradykinesia; stooped; gait slow with reduced arm swing	2.96	Normal	VP
19/72/F	8.7	'No-no' head tremor; bilateral rest tremor of hands; moderate bilateral postural tremor of arms; mild bilateral bradykinesia; stooped; gait slow with reduced arm swing	3.54	Normal	VP
20/77/F	23.3	Rest, postural and kinetic tremor of arms; increased tone at neck and in limbs; mild symmetrical bradykinesia; stooped; slowed gait with reduced arm swing	0.65	Abnormal	PD
21/82/F	6.4	Mild hypomimia; jaw tremor; rest, postural and kinetic tremor of arms; increased tone at neck; mild symmetrical bradykinesia; stooped; slowed gait with reduced arm swing	0.96	Abnormal	PD
22/72/F	1.5	Resting and postural tremor of hands; no rigidity or bradykinesia; mild stoop; slowed gait	0.96	Abnormal	PD
23/77/F	8.1	'No-no' head tremor; jaw tremor; rest tremor both hands; bilateral postural and kinetic tremor; mild left-sided bradykinesia; moderate stoop; preserved arm swing	2.79	Normal	VP
24/72/F	8.4	Rest tremor left hand; bilateral postural tremor of arms; increased tone at the neck; mild bilateral bradykinesia; stooped; slow, unsteady gait	2.99	Normal	VP
25/80/F	2.0	Jaw tremor; rest, postural and kinetic tremor of arms; no rigidity or bradykinesia; stooped; slowed gait with reduced arm swing; mild postural instability	2.79	Normal	ET
26/77/F	1.6	Chin tremor; increased tone at neck and in all limbs; moderate symmetrical bradykinesia; mild stoop; slowed gait with reduced arm swing	3.64	Normal	VP
27/81/F	5.1	Rest tremor right hand; postural and kinetic tremor both arms; increased tone at neck; no bradykinesia; mild stoop; unsteady gait with mild postural instability	3.60	Normal	ET
28/88/F	7.8	Postural and kinetic tremor of arms; increased tone at neck; mild left-sided bradykinesia; mild stoop; slowed gait with preserved arm swing	0.61	Abnormal	PD

29/71/F	1.5	Jaw tremor; rest, postural and kinetic tremor both hands; increased tone at neck and in right arm and leg; moderate symmetrical bradykinesia; mild stoop; slowed gait with reduced arm swing	3.83	Normal	VP
30/67/M	0.1	'No-no' head tremor; rest, postural and kinetic tremor of arms (worse on left side); increased tone at neck and in lower limbs; no bradykinesia; mild stoop; slowed gait with reduced left arm swing; moderate postural instability	4.24	Normal	IT
31/59/M	1.1	'Yes-yes' head tremor; high frequency rest tremor; postural and kinetic tremor of outstretched arms; no bradykinesia; stooped; slowed and unsteady gait; mild retropulsion	3.04	Normal	DT
32/72/M	1.7	Dysarthric speech; postural and kinetic tremor of arms; increased tone at neck; no bradykinesia; mild stoop; reduced arm swing	2.41	Normal	VP
33/74/F	2.9	Chin tremor; postural and kinetic tremor of arms (worse on right); increased tone at neck and in both arms; no bradykinesia; mild stoop; slowed and unsteady gait with reduced arm swing; moderate postural instability	2.38	Normal	VP
34/70/M	1.2	'No-no' head tremor; rest and postural tremor right hand; no rigidity; mild right sided bradykinesia; mild stoop; slowed gait with reduced right arm swing; moderate postural instability	3.60	Normal	VP
35/74/M	6.6	Mild postural and kinetic tremor of arms; no rigidity or bradykinesia; preserved arm swing; no postural instability	2.42	Normal	ET
36/65/F	2.0	'No-no' head tremor; jaw tremor; rest and postural tremor of arms; increased tone at neck; no bradykinesia; mild stoop; short steppage gait with reduced arm swing; marked postural instability	2.61	Normal	VP
37/70/F	1.7	'No-no' head tremor; rest and postural tremor of arms; no rigidity or bradykinesia; mild stoop; normal gait with preserved arm swing; no postural instability	2.17	Normal	ET

PD = Parkinson's disease; ET = essential tremor; VP = vascular Parkinsonism; DIP = drug-induced

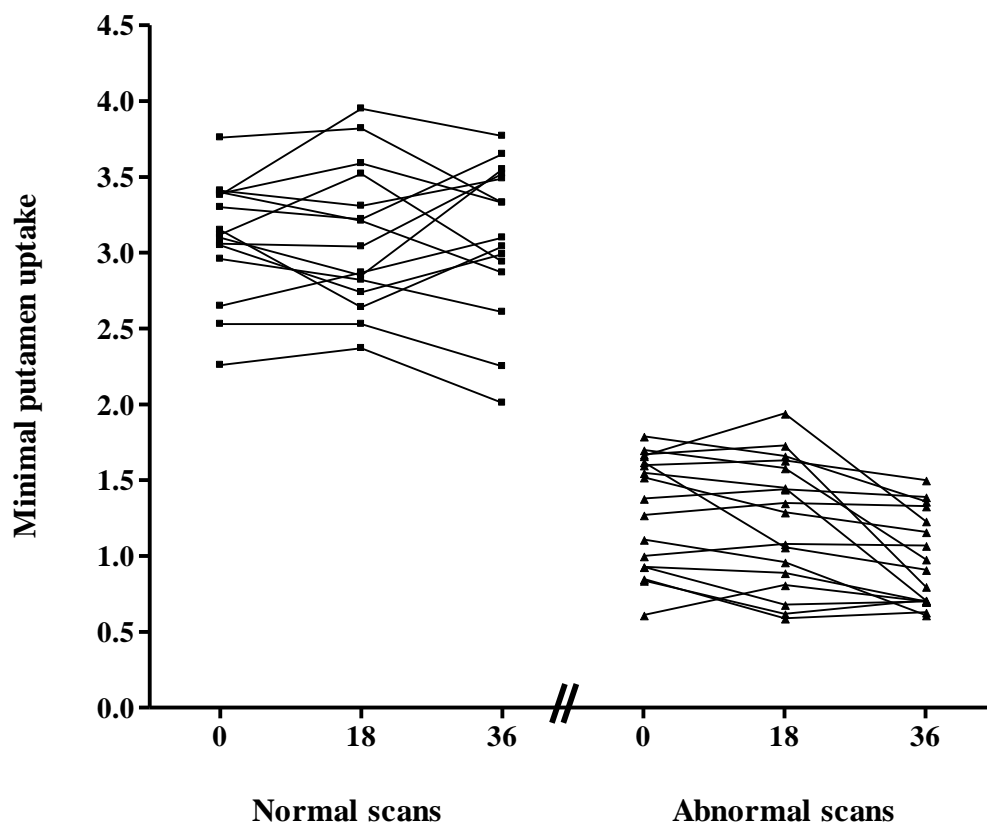Parkinsonism; DT = dystonic tremor; IT = indeterminate tremor

Figure 5.1: Minimal putamen uptake for patients undergoing repeat scans (at baseline, 18 and 36 months) according to scan report (normal or abnormal, graded blind to clinical presentation) as part of European prospective FP-CIT study.

Figure 5.2: Scatter plots comparing minimal putamen uptake in patients who underwent FP-CIT SPECT scans. (Upper) Results for patient scanned as part of the community study and (lower) results for 36 month scan for patients scanned as part of a European prospective FP-CIT study are shown in Figure 5.2. There was a striking similarity between the 2 series, and clear-cut differentiation of abnormal from normal in both datasets.
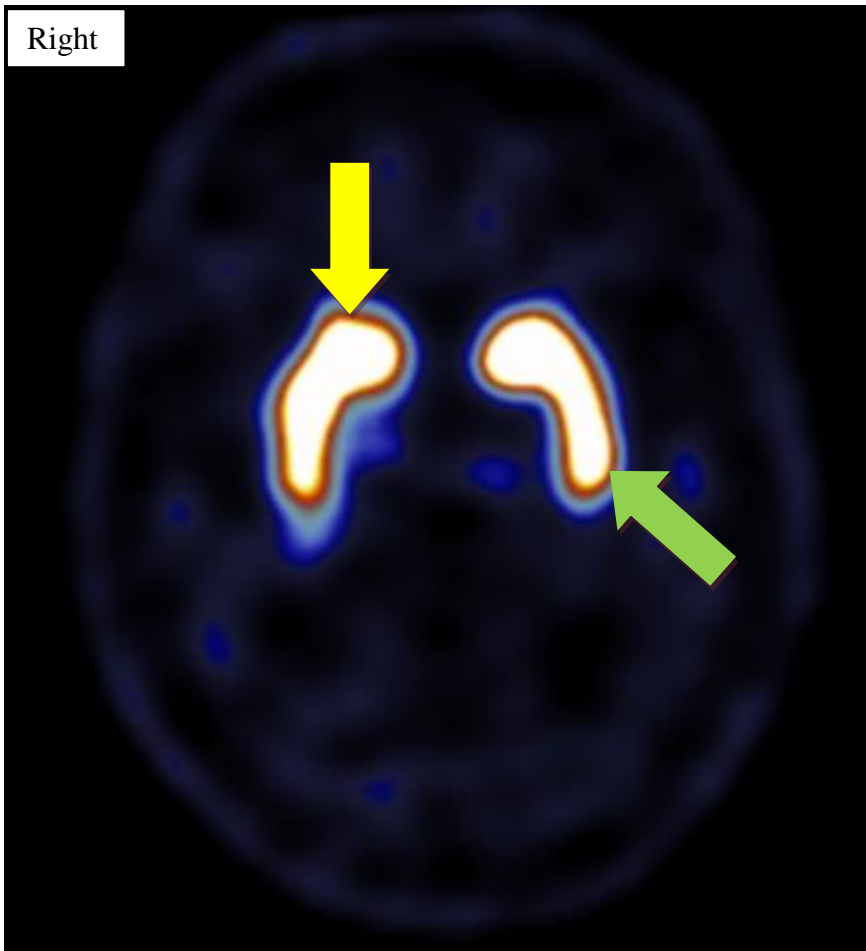
Figure 5.3: Image from normal FP-CIT SPECT scan demonstrating normal striatal uptake of the radioligand, in both putamen (green arrow) and caudate (yellow arrow).
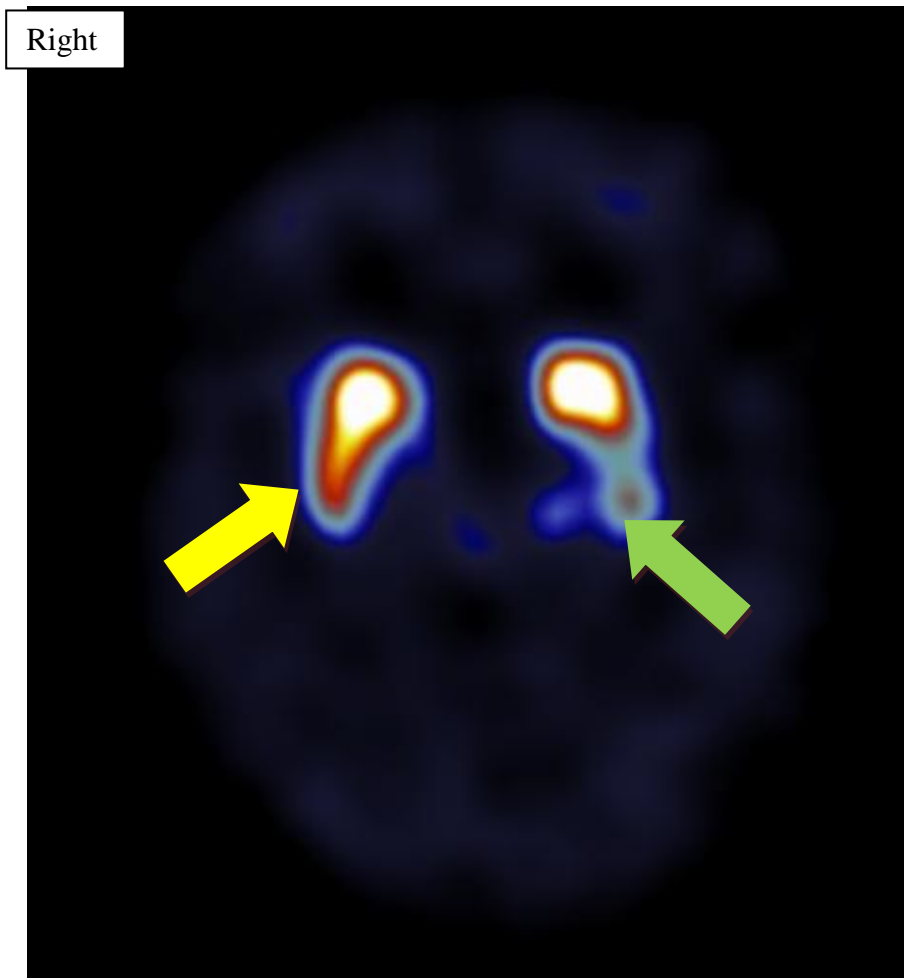
Right

Figure 5.4: Image from abnormal FP-CIT SPECT scan demonstrating reduced, asymmetrical radiotracer uptake within the putamen, most evident on the patient's left side (green arrow), but also showing early reduction on the patient's right side (yellow arrow).
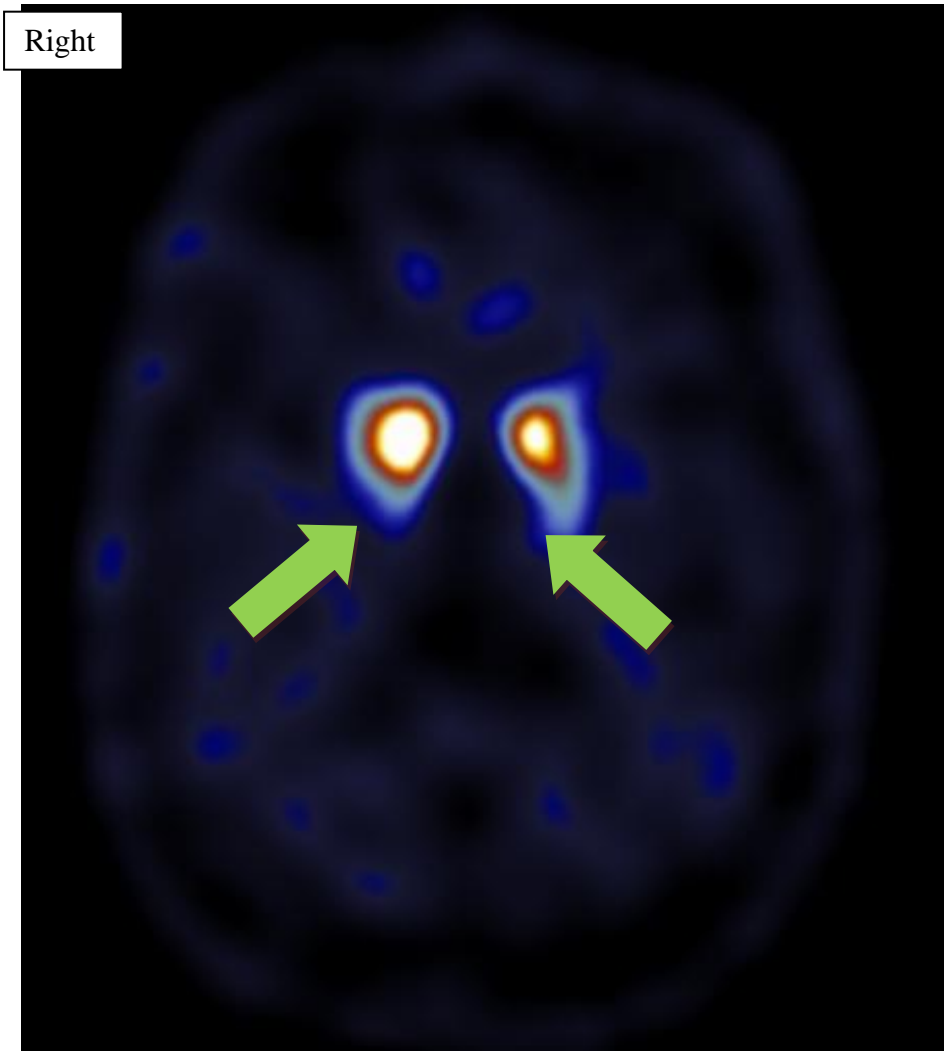
Right

Figure 5.5: Image from abnormal FP-CIT SPECT scan demonstrating gross presynaptic dopaminergic deficit with radiotracer uptake limited to the caudate bilaterally (absent putamen uptake highlighted by green arrows).

CHAPTER 6

RISKS OF WITHDRAWAL OF ANTIPARKINSON MEDICATION

Misdiagnosis of Parkinson's disease (PD) is recognised within cross sectional community studies and clinical trials (Meara, Bhowmick, & Hobson 1999;Fahn 1999;Schrag, Ben Shlomo, & Quinn 2002;Whone et al. 2003;Seibyl et al. 2004). None of these studies reported withdrawal of antiparkinson medication in these misdiagnosed cases. Successful medication withdrawal in patients with clinical signs of Parkinsonism and normal presynaptic dopamine transporter imaging has been reported (Marshall et al. 2006). It is appropriate, considering that antiparkinson medication withdrawal was a central component of the research in this thesis, to consider the potential risks of such a procedure. Two illustrative clinical vignettes highlight potential difficulties in this field. These are then used to discuss the issues in a wider context.

Clinical vignette 1: a patient with Parkinsonism in whom medication stoppage contributed to an adverse outcome

A 53-year old man without significant past medical history presented with a 12 month history of worsening tremor of the right hand and scuffing of his right foot when walking. Clinical examination demonstrated a mild rest and postural tremor of the right arm, increased tone in the neck and right arm and leg, and generalised bradykinesia. FP-CIT SPECT brain scanning demonstrated reduced striatal uptake of the radioligand, supporting the clinical diagnosis of degenerative parkinsonism. There was little clinical improvement with Madopar (increased to 125mg four times daily). Subsequent development of impaired speech and vertical eye movements raised the likelihood of progressive supranuclear palsy (PSP). He was admitted to the medical unit with acute confusion, visual hallucinations and agitation. Dehydration and chest infection were treated intravenously with fluids and Amoxicillin 1g three times daily and Clarithromycin 500mg twice daily. On admission, antiparkinson medication was stopped in view of his cognitive state; after 3 days the conscious level dropped, speech became incomprehensible, and he was unable to follow commands. There was a leucocytosis and a chest X-Ray showed lobar pneumonia. Despite high-flow oxygen and an adjusted antibiotic regimen (Ceftriaxone 2g once daily and Metronidazole 500mg three times daily), his conscious level dropped further over 48 hours, he became pyrexial (41˚C) and tone was increased axially and in all 4 limbs. Creatine kinase (CK) was markedly

elevated (>14,000) and Parkinsonism-hyperpyrexia syndrome (PHS) was diagnosed. Despite 400mg/day Madopar (via nasogastric tube) and intravenous fluids, he died 48 hours later with respiratory and renal failure.

Clinical vignette 2: Parkinsonism-hyperpyrexia syndrome in a PD patient treated with a dopamine antagonist

An 80-year old man presented with a 5-year history of rest tremor affecting his right hand and slowing of gait. He described difficulty getting washed and dressed and hypersalivation. Past medical history included hypertension, hypercholesterolaemia and several transient ischaemic attacks. His family had noticed recent memory disturbance, but the patient denied any visual hallucinations. Daily drug therapy comprised Clopidogrel 75mgs, Atorvastatin 40mgs and Perindopril 2mgs. He was the main carer for his wife who had advanced dementia. On examination speech was quiet and dysarthric, and facial expression slightly reduced. There was a mild and postural tremor of the right arm. Tone was increased at the axially and in both lower limbs. There was mild right-sided bradykinesia on finger taps and rapid alternating movements. Posture was good but gait was slowed with reduced arm swing. CT-brain scanning demonstrated previous lacunar infarcts and widespread small vessel disease. An FP-CIT SPECT scan demonstrated reduced striatal uptake of the radioligand and the diagnosis was therefore a combination of PD and cerebrovascular disease. He was commenced on Levodopa 200mgs/day resulting in moderate improvement. Over the next 12 months there was significant deterioration in his cognitive state and both he and his wife were moved into a nursing home. He became increasingly agitated and disorientated (especially at night), for which haloperidol 1mg/day was introduced, but without much improvement in his mental state. This dose was increased over a 4-week period to 5mgs/day. Over several days nursing staff found the patient to be increasingly confused. When his conscious level deteriorated further he was admitted to an acute medical ward. On examination eyes opened to pain, speech was incomprehensible and he could localise to pain. Tone was increased axially and in all 4 limbs. Temperature was 40.5˚C, CK was elevated (>8,000) and PHS was diagnosed. The patient was treated with intravenous fluids and 200mg/day Madopar (via nasogastric tube) and haloperidol was discontinued. His conscious level

improved within 48 hours. He was transferred to a rehabilitation unit where he received physiotherapy. He was subsequently transferred back to the nursing home after 3 weeks. As an in-patient his mobility improved but did not return to his pre-morbid state. He was commenced on Quetiapine 50mgs/day for agitation.

These 2 vignettes illustrate the risk of PHS in the PD patient. In the first case this resulted from abrupt withdrawal of antiparkinson medication and in the second case PHS was precipitated by prescription of a traditional dopamine depleting neuroleptic given at an escalating dose. The first case was observed during routine clinical practice by the movement disorder team, but was not part of the patient study groups reported in this thesis. The second case had been assessed as part of the medication withdrawal study described in Chapter 4, but his antiparkinson medication was maintained and the PHS complication occurred after study follow-up was completed.

The time profile of the therapeutic response is therefore now discussed, with particular reference to its evolution if antiparkinson therapy is discontinued.

Short and long-duration response to Levodopa

Withdrawal of antiparkinson medication in PD patients may result in the return of the 'off' symptoms of PD. Tremor, rigidity, gait, posture may all worsen and patients may develop dystonia. Patients may experience the return of non-motor symptoms such as depression, apathy, fatigue anxiety and pain (Schrag & Quinn 2000;Schrag 2006). Simple and choice reaction times are also slower for patients once Levodopa is withdrawn (Jahanshahi et al. 1992;Harrison et al. 1995).

In PD patients a single dose of Levodopa produces an immediate clinical improvement in symptoms known as the short-duration response (SDR). Chronic treatment with Levodopa induces a gradual improvement in motor symptoms that may take days to fully develop and lasts many days after discontinuation of treatment and is known as the long-duration response (LDR) (Stocchi et al. 2003a;Stocchi et al. 2003b). The LDR is not present in early PD and has been implicated in the development of motor

fluctuations (Nutt et al. 1997;Zappia et al. 1999). The LDR appears to be unrelated to Levodopa pharmacokinetics and has also been reported in patients treated with dopamine agonists (Stocchi et al. 2001). The underlying mechanism responsible for the LDR remains unknown, although it is thought to originate from pre-synaptic or post-synaptic mechanisms.

In one series Levodopa was deliberately withheld for a mean duration of 44 hours in 9 PD patients with 'on/off' fluctuations (Turjanski et al. 1993). All patients experienced a marked worsening of motor symptoms within 12 hours and a further mild delayed deterioration over days was also seen. One patient withdrew from the study following sudden onset of confusion and visual hallucinations after 23 hours. The minimum therapeutic dose of subcutaneous Apomorphine needed to produce improvement in motor symptoms was unchanged before and after medication withdrawal, providing no clinical evidence for alteration in dopamine receptor sensitivity following Levodopa withdrawal.

A report of 16 patients undergoing 3-5 days of Levodopa withdrawal also described a delayed response (Nutt et al. 1995) with gradual emergence of motor disability, as measured by change in tapping rate, occurring days after drug withdrawal. This LDR was not improved following intravenous Levodopa at the end of the therapy withdrawal period.

Drug holidays in PD

In the 1970's and 1980's the practice of 'drug holidays' in PD patients was commonplace. This involved acute and complete withdrawal of Levodopa for 4-10 days and was claimed to temporarily improve motor complications following re-introduction of Levodopa (Sweet et al. 1972;Friedman 1985). It had been thought that the down-regulation of striatal dopamine receptor sensitivity as a result of chronic dopaminergic drug therapy was temporarily reversed following Levodopa withdrawal (Weiner et al. 1980). Due to recognised complications of acute drug withdrawal and no clear demonstration of benefit, this practice is no longer recommended (Mayeux et al. 1985).

However, in a recent study of 12 patients with motor complications, Levodopa was withdrawn for 3 days and intravenous Amantadine was administered (Koziorowski & Friedman 2007). Follow-up demonstrated improved UPDRS parts 3 and 4 up to 4 months following the drug holiday.

Recognising Parkinsonism-hyperpyrexia syndrome

Neuroleptic malignant syndrome (NMS) was first described in early trials of haloperidol (Delay et al. 1960). It is a rare but potentially fatal side effect of drugs that block D2 dopamine receptors. Clinically it presents with fever, autonomic instability, muscular rigidity, reduced conscious level, diaphoresis and raised serum CK. It is commoner in young and middle-aged male patients and symptoms typically develop within the first week after introducing a neuroleptic agent. The incidence of NMS is less with atypical antipsychotics, but NMS affects 0.2% of patients started on all antipsychotic medications (Kipps et al. 2005). NMS is more likely when antipsychotic doses are relatively high, or titrated rapidly, or given parenterally (Keck, Jr. et al. 1989;Berardi et al. 1998) and results from an acute reduction in central dopamine transmission (Caroff et al. 2005).

A very similar syndrome, first described in 1981 in a PD patient who had not been exposed to neuroleptics, occurred after large doses of antiparkinson drugs were discontinued (Toru et al. 1981). Many further reports have followed, giving a variety of names including NMS, neuroleptic malignant-like syndrome, Levodopa-withdrawal hyperthermia, Parkinsonism-hyperpyrexia syndrome (PHS), dopaminergic malignant syndrome and acute dopamine depletion syndrome. The term PHS is preferred for the syndrome in the PD patient (by this author), since neither neuroleptic drugs nor Levodopa withdrawal are essential for its development. PHS also occurs in other forms of degenerative Parkinsonism (eg. progressive supranuclear palsy and multiple system atrophy) (Konagaya et al. 1997;Takubo et al. 2003).

The most common trigger for PHS is withdrawal of antiparkinson medication, especially Levodopa. 'Drug holidays' are no longer recommended, largely for fear of

inducing PHS (Mayeux et al. 1985). However, there remain circumstances in which dopaminergic medications are discontinued. The patient or carer may stop one or more drugs due to side-effects, or may omit one or more of their antiparkinson drugs through self-experimentation (Grosset D et al. 2008). Antiparkinson medication may be changed or stopped on hospital admission, often in the context of an alternative acute illness (which may be medical or surgical).

Other triggers to PHS are described in the PD patient, of which co-prescription of neuroleptic medication (exemplified in case vignette 2) is the most obvious. The importance of infection, dehydration, intestinal absorption changes, and pre-menstrual state (Mizuta et al. 1993;Gordon & Frucht 2001;Shimada et al. 2006;Douglas & Morris 2006) is less certain; changes in antiparkinson medication accompanying such events may be more relevant. PHS is also reported following bilateral subthalamic nucleus deep brain stimulation; again there was a rapid reduction of antiparkinson medications (Factor 2007).

Parkinsonism-hyperpyrexia syndrome (PHS): the clinical profile

Typically symptoms develop between 18 hours and 7 days following the trigger. The patient becomes rigid, sometimes with tremor, and over hours progresses to an immobile state (Ueda et al. 1999) (See Table 6.1). The clinical picture is one of severe acute Parkinsonism. Within 72-96 hours most patients develop pyrexia and a reduced conscious level, ranging from confusion to coma. Autonomic dysfunction with tachycardia, labile blood pressure and diaphoresis follow. Laboratory tests may reveal a leucocytosis, elevated CK and sometimes deranged liver function tests (elevated CK is not a pre-requisite for the diagnosis). Complications of PHS include aspiration pneumonia, deep venous thrombosis and pulmonary embolism, disseminated intravascular coagulation (DIC), rhabdomyolysis, acute renal failure and seizures. Poor prognostic indicators in PHS include older age and higher pre-morbid Parkinson severity (Sato et al. 2003).

In the largest reported series of PHS, 99 episodes occurred in 93 patients (72 patients with PD, 8 with PSP, 6 with MSA, 4 with vascular Parkinsonism, 2 with dementia with Lewy bodies and 1 with Parkinsonism secondary to vasculitis) in 5 Japanese centres (Takubo et al. 2003). The usual trigger (55% of cases) was cessation or withdrawal (by patient or carer) of dopaminergic drugs, most commonly because of confusion or hallucinations. Other triggers included infection, poor oral intake, dehydration and intestinal ileus; 69% of episodes resulted in recovery to the pre-morbid state and 4% of patients died. This compares with reported mortality from NMS of 11.6% (Shalev et al. 1989). In both PHS and NMS development of DIC and renal failure was associated with a poorer outcome.

A further series of 11 PD patients developed PHS following withdrawal of Levodopa and other antiparkinson medications (Serrano-Duenas 2003). Patients had mean disease duration of 9 years and developed symptoms of PHS on average 93 hours following medication withdrawal. All of the cases had increased rigidity as the presenting sign. No patients died in this series. These 11 cases occurred over 9 years and accounted for 3.6% of the total PD patient population regularly treated by the authors.

Hashimoto *et al.* described 16 episodes of PHS occurring in 14 PD patients between 1992 and 1999 (Hashimoto et al. 2003). Most cases resulted from discontinuation or withdrawal of dopaminergic drugs, but pre-morbid deterioration of parkinsonian symptoms, dehydration and infection were all considered to be risk factors.

As in NMS the underlying pathological mechanism for PHS is sudden suppression of central dopaminergic activity. A reduced CSF concentration of the dopamine metabolite homovanillic acid (HVA), which was attributed to abrupt medication withdrawal, has been found in PHS (Ueda et al. 1999;Ueda et al. 2001), but this is an expected biochemical change and does not imply a causative association.

Treating Parkinsonism-hyperpyrexia syndrome

The main key to treating PHS is early diagnosis, with the underlying cause being identified and corrected. Antiparkinson medications which have been discontinued should be promptly re-started. They can be given orally or via a nasogastric tube (See Table 6.2). If nasogastric feeding is contraindicated (e.g. because of ileus) Levodopa-based treatment can be administered intravenously (50-100mg of L-dopa infused over 3 hours), and this can be repeated four times daily until the patient can take medications orally. Patients should be given the same dose of Levodopa as taken prior to onset of PHS. If there has been no alteration in dopaminergic medication other causes should be sought (e.g. prescription of neuroleptic, infection, dehydration).

Patients often require high dependency or intensive care, with respiratory support and central venous pressure monitoring if necessary (Ikebe et al. 2003;Factor SA & Santiago A 2005). Supportive measures such as intravenous fluid replacement, anti-pyretics and cooling blankets are recommended. Patients are at high risk of aspiration pneumonia and antibiotics should be commenced early if infection is suspected. Renal function, coagulation factors and CK should be closely monitored. If CK is elevated urinary myoglobins should be tested for rhabdomyolysis.

Dantrolene is a skeletal muscle relaxant, inhibiting intracellular release of calcium from the sarcoplasmic reticulum and has been shown to be efficacious in cases of malignant hyperthermia (Rosenberg et al. 2007). Both Bromocriptine (5-10mg three times per day) and Dantrolene Sodium (10mg/kg per day in 3-4 divided doses) are traditionally recommended in treatment of PHS, although there are no studies demonstrating efficacy (Mueller et al. 1983;Ikebe et al. 2003). Other dopamine agonists (oral ropinirole or pramipexole, transdermal rotigotine, or subcutaneous apomorphine) have been used more recently.

Complications of PHS should also be managed. DIC may require intravenous heparin and platelet transfusion and acute renal failure may necessitate haemodialysis. In a randomised placebo-controlled trial, 3 days of 1g intravenous Methylprednisolone in 40

cases of PHS shortened the illness duration, but there was significant overlap between the active and placebo groups (Sato et al. 2003). All patients in this study also received Levodopa, Bromocriptine and Dantrolene Sodium.

Preventing Parkinsonism-hyperpyrexia syndrome

The most common trigger for the parkinsonian patient to develop PHS is reduction or cessation of antiparkinson medications (Takubo et al. 2003). The most common drug implicated is Levodopa, but PHS can be caused by acute reduction in any dopaminergic drug. Drug holidays are no longer practised, but patients and their carers often reduce dopaminergic drugs due to side effects (especially confusion and hallucinations). Patients should be advised not to suddenly stop antiparkinson medication. While dopaminergic drug dose reduction should generally be gradual, the circumstance of acute psychosis in PD patients with an intercurrent illness (typically infective) may necessitate stopping adjunctive dopaminergic therapy (eg. dopamine agonists, MAO-B inhibitors). Maintaining *some* antiparkinson medication (such as Levodopa-based treatment) will help prevent PHS. No specific guidelines inform the correct approach, and clinical judgement should assess the severity of the mental state, pre-existing cognitive problems, and the dose of different drug classes. However, the message should be clear: *complete and abrupt* cessation of established antiparkinson medication in a PD patient should almost always be avoided. The potential risks of neuroleptic drugs mean that they should be used sparingly in PD patients, but they are quite often beneficial in the more advanced PD patient with cognitive problems, hallucinations, and/or agitation.

The risk of PHS on admission to hospital is also pertinent. Retrospective audit of all acute hospital admission for PD patients in a District General Hospital in North Kent illustrated poor prescription and knowledge of antiparkinson medications (Magdalinou et al. 2007). While 26/35 (74%) of admitted PD patients had antiparkinson medications stopped, omitted or prescribed inappropriately, further details of this and the 'significant sequelae' in 16/26 (62%) were not reported, although 1 of their cases did require intensive care support. No case was specifically diagnosed with PHS.

Conclusions

        The risks of stopping antiparkinson therapy are one of the key considerations in managing a patient who may have an incorrect diagnosis of PD. The most serious consequence of acute medication withdrawal in PD patients is the Parkinsonism-hyperpyrexia syndrome (PHS). To minimise the risk of this potentially fatal syndrome, we tapered antiparkinson drugs slowly, and made arrangements for easy and early contact in the event of any uncertainty amongst patients and their carers about the effects of stopping treatment. This is essential as the early recognition of symptoms, replacement of dopaminergic medications, and introduction of supportive therapies and treatment of complications can improve patient outcome in the event of PHS. 2 of 41 (4.9%) patients undergoing therapy withdrawal clinically deteriorated and went back on therapy and an additional 1 case developed PHS remote from the study processes (See clinical vignette 2). While we cannot define exactly the risks of PHS due to the small numbers in our study coming off treatment, it is reassuring that no case of PHS attributable to study processes occurred.

Table 6.1: Clinical features of Parkinsonism-hyperpyrexia syndrome

Signs and Symptoms
- Muscle rigidity (with or without tremor)   - Pyrexia (>38˚C)   - Reduced conscious level (confusion to coma)   - Autonomic instability (labile blood pressure, tachycardia, diaphoresis, urinary incontinence)   - Dysarthria, dysphagia
Laboratory findings
- Raised creatine kinase   - Leucocytosis   - Deranged liver function tests   - Metabolic acidosis
Complications
- Acute renal failure   - Rhabdomyolysis   - Aspiration pneumonia   - Deep venous thrombosis / pulmonary thromboembolism   - Disseminated intravascular coagulation   - Respiratory failure

Table 6.2: Recommended treatment for Parkinsonism-hyperpyrexia syndrome

Replace antiparkinson medications   Levodopa (pre-morbid dose) orally, via nasogastric tube or via intravenous infusion (50-100mg infused over 3 hours)   Dopamine agonist therapy, oral or nasogastric: traditionally Bromocriptine 7.5 - 15.0mg three times daily (Ropinirole 1 – 2mg three times daily, or Pramipexole 0.18 – 0.36mg (base) three times daily may be preferred); transdermally: Rotigotine 2 – 4mg/24 hours; subcutaneously: Apomorphine 1.0 – 2.0 mg/hour (Grosset et al. 2004)
Supportive measures   Manage patient in high dependency or intensive care setting   Intravenous fluid replacement   Anti-pyretics and cooling measures   Dantrolene (10mg/kg per day in 3-4 divided doses) (if rigidity is severe and not responding to other measures)
Management of complications   Antibiotics for infection   Mechanical ventilation if respiratory failure   Haemodialysis for acute renal failure   Intravenous Heparin (5-15 units/kg per hour) and platelet transfusion if evidence of disseminated intravascular coagulation

CHAPTER 7

DISCUSSION AND INTERPRETATION

This work was undertaken against a background of recently emerging data about diagnostic accuracy in PD and movement disorders. The most important aspects of the findings in the current work are reviewed in this Chapter, and followed by discussions about next steps in such research programmes.

The main aims of this thesis were to:

1. Identify cases misdiagnosed as PD from searches of prescription databases and case records within primary care.

2. Undertake supervised antiparkinson medication withdrawal in this group, assessing for worsening of movement disorder symptoms during the follow up period.

The methodology employed in this study also allowed for an analysis of the prevalence of parkinsonian disorders and prescription of antiparkinson medications.

A number of features make this work unique:

- Searches of prescription databases and case records within 92 West Scotland GP practices allowed assessment of a population in excess of half a million, making this the largest UK-based PD prevalence study.

- Employing the same searching strategies across all practices allowed differences between primary care regions (community health partnerships) to be examined closely.

- Case record review, in addition to searches of prescription databases, ensured that the indication for antiparkinson medication was established in all cases. Previous PD prevalence studies using drug tracer methodologies have only estimated the proportion of patients prescribed antiparkinson drugs for non-PD diagnoses (eg. pituitary adenoma, restless legs syndrome, dopa-responsive dystonia).

- Antiparkinson drug costs and patterns of prescription within a large cohort of UK-based PD patients according to age, disease duration and clinic attendance were examined.

- A set of criteria were developed that successfully allows patients misdiagnosed as PD to be identified.

- A large number of patients, previously misdiagnosed as PD, underwent successful antiparkinson therapy withdrawal. There are no equivalent therapy withdrawal series in the literature.

- The use of FP-CIT SPECT imaging in patients, previously labelled as PD, in whom there is diagnostic doubt is examined.

The prevalence of Parkinson's disease in West Scotland

The prevalence of PD in the current study is in keeping with previous UK reports. We found crude prevalence to be 119.2 per 100,000 while the range in other UK studies was from 108 to 164 per 100,000 (Brewis et al. 1966;Mutch et al. 1986;Sutcliffe & Meara 1995;Porter et al. 2006). The prevalence age-adjusted to the population of Scotland was 129.5 per 100,000, indicating that the population studied was younger than the average for Scotland.

The use of prescription databases within prevalence studies of PD has been established (Menniti-Ippolito et al. 1995;van de Vijver et al. 2001;Lai et al. 2003;Brandt-Christensen et al. 2006). A major advantage of drug tracer methodologies is that a large population can be studied with relative ease. However, this type of study omits patients who have not yet come to medical attention and those who have been diagnosed as having PD (by GP or hospital specialist) but have not yet been commenced on antiparkinson therapy. In addition, many previous prevalence studies of this type have not included case record review. Case record review allows the clinical indication for prescription of antiparkinson drug to be established. PD prevalence would be significantly over-estimated if the real indication for drug prescription was unknown as we found that nearly 60% of patients prescribed antiparkinson drugs had non-PD diagnoses (the majority of whom were co-prescribed anticholinergics with antipsychotic medication). If patients prescribed anticholinergic monotherapy were omitted from database searches the proportion of patients prescribed antiparkinson medications for a

non-PD diagnosis was 25%. In future studies of large prescription databases, the PD prevalence could be estimated (without performing case record review) by omitting anticholinergic monotherapy from database searches and calculating 75% of the total number of patients prescribed antiparkinson medication, but this would not take account of differences in prescribing patterns in other regions in the prescription of antiparkinson drugs for alternative diagnoses (eg. greater use of such drugs for restless legs syndrome).

We described how 39 patients, previously misdiagnosed as PD, were identified and underwent successful antiparkinson medication withdrawal. Consequently, crude prevalence fell in our series from 119.2 to 111.5 per 100,000. The total number of misdiagnosed cases (among the 610 PD patients identified) was estimated at 63 to 70 patients. This would further decrease the prevalence to 105.5 - 106.9 per 100,000. Higher prevalence rates in previous studies may also result from overdiagnosis of PD. This has not previously been used to adjust rates in any of the reported prevalence studies but merits further investigation.

Perhaps the most surprising finding was the difference in PD prevalence between areas studied. This difference was most pronounced when considering the age-adjusted PD prevalence for males in South Lanarkshire was more than double that for South Glasgow (202.7 per 100,000 versus 98.3 per 100,000). Methodological differences (eg. case finding, diagnostic error) are largely considered to be the explanation for differences between populations in previous prevalence studies. However, in this present study the methodology was the same in all regions studied. The age structure of the population may differ between areas, and prevalence of PD is known to increase exponentially with increasing age. When age-correction was applied in this study, the differences between regions became even more pronounced. Although other factors previously known to influence PD prevalence were considered (eg. cigarette smoking, education, access to services and rural living) these were felt unlikely to account for a difference of such magnitude.

One potential reason for the higher reported prevalence within South Lanarkshire is that misdiagnosis rates were higher in this region. Of the 39 misdiagnosed patients who underwent successful antiparkinson medication withdrawal, 27 (69%) were from South Lanarkshire compared with 10 (26%) from South Glasgow. Improved diagnostic accuracy has been reported within specialist movement disorder services (Hughes et al. 2002). A significantly higher proportion of patients in South Glasgow had on-going attendance at a hospital clinic for PD compared with those in South Lanarkshire (134 of 164 (81.7%) versus 197 of 323 (61.0%), p<0.0001) and there are likely to be more misdiagnosed cases among patients managed exclusively in primary care.

The correlation of poor access to specialist PD services with high misdiagnosis rates is of great importance, may partially explain the variation in prevalence reported in previous studies; and merits further investigation. In a period of greater de-centralisation of services within the NHS, patients with suspected PD must be able to access specialist out-patient clinics as recommended by NICE (2006). If an area with an unexpectedly high PD prevalence were identified (in a separate study) access to services for this region should be examined with a view to targeting future resources.

Prescription of antiparkinson medication

Analysis of prescription of antiparkinson medication suggested that, despite availability of a wide range of drugs, Levodopa remains the mainstay of drug therapy in PD. Within Scotland the Scottish Medicines Consortium (SMC) provide advice to NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) about all newly licensed medicines (NHS Scotland 2008). Both Rasagiline (a monoamine oxidase B inhibitor) and Duodopa (intestinal gel preparation of Levodopa) are not approved by the SMC as antiparkinson drug treatments. Although, individual cases can be made for each drug, the SMC ruling undoubtedly influences actual drug prescription with only 5 of 610 PD patients (0.8%) prescribed Rasagiline and no patients prescribed Duodopa in this study.

The greatest factor influencing choice of antiparkinson drug was whether the patient's PD was managed within primary care or a hospital clinic, with patients attending specialist clinics more likely to be prescribed:

- higher doses of antiparkinson drugs;

- more than one antiparkinson drug; and

- more expensive antiparkinson drugs

However, there were some differences between the groups of patients attending specialist clinics and those managed within primary care. These are addressed in the next section.

Previous European studies examining drug costs in PD have reported mean daily cost (LePen et al. 1999;Findley et al. 2003;Moller et al. 2005;Vossius et al. 2006). However, we found that drug costs were positively skewed and therefore we summarised these using medians and interquartile ranges. Previous studies have also reported costs for those patients attending a hospital clinic for the management of their PD and have largely excluded patients managed within primary care. In the present study we report costs for both categories and therefore have comparative data showing these differences. Whilst it is difficult to compare drug costs with other European countries (variable exchange rate and difference in costs of individual drugs between countries) we found there was significantly less expenditure on antiparkinson drugs than reported in previous German studies, probably largely relating to the co-prescription of dopamine agonists with Levodopa drugs from the earliest stages of the disease, while it is routine practice in the UK to maximise the dose (to either the manufacturer's maximum or to the maximally tolerated level) of one antiparkinson drug before the addition of another.

Newer dopamine agonists (eg. Apomorphine, Ropinirole and Pramipexole) were amongst the most expensive antiparkinson drugs available and significantly influenced overall drug costs. We found the cost of antiparkinson drugs changed with disease duration. Drug costs were highest for those patients 4-6 years following diagnosis and

then decreased thereafter, reflecting simplification of drug regimens and reduced prescription of dopamine agonists in advancing disease. These costs considered dopaminergic medications and ignored medications that may be co-prescribed in the patient with advanced PD (eg. Donepezil (an acetylcholinetserase inhibitor) for cognitive impairment, or Quetiapine (an atypical antipsychotic) for psychosis). However, by far the largest financial cost in a patient with advanced PD is the cost of social care required (Findley et al. 2003). Consideration of these costs was beyond the scope of this study.

Clinic attendance for management of Parkinson's disease

Only 70.3% of 610 patients studied had current attendance at a hospital clinic for management of PD; and 58.0% of 610 currently attended a specialist PD clinic. This falls short of national guidelines within England and Wales that have recommended that all patients with suspected PD are assessed within a specialist clinic and that the diagnosis is under regular review (2006).

Recently the Parkinson's disease Society (PDS) published results from a patient survey of over 13,000 members across the UK (Parkinson's Disease Society 2008). One of the key findings was that 15% of responders had never been seen by a movement disorder specialist, compared with 19% in our own study. Despite the obvious selection bias of a patient support group survey, this clearly suggests that problems with access to PD specialist services, and therefore misdiagnosis of PD, in West Scotland are replicated across the UK.

Several factors were found to influence specialist clinic attendance. There was a significant difference in specialist clinic attendance between regions studied, with the highest attendance rates within East Dunbartonshire (84.6%) and lowest within South Lanarkshire (41.8%). Therefore a higher proportion of patients is managed within primary care and non-specialist clinics within South Lanarkshire, reflecting poorer access to services in this area. We also found that age and sex influenced clinic attendance, with a greater proportion of younger and male patients being managed within a hospital clinic.

The reasons for this apparent selection bias are not clear from this study, but are deserving of further study.

Identifying misdiagnosis in Parkinson's disease

Misdiagnosis in PD is important. If the same rates of misdiagnosis were applied in cancer or heart disease, there would surely be a public outcry. Patients are often given incorrect prognostic information and are prescribed medications which may give rise to side-effects. The cost of these medications is also significant. We calculated the annual cost of antiparkinson drugs in the patients who underwent successful therapy withdrawal was £48,200. The cumulative drug costs for this group are much higher as misdiagnosed patients can remain on antiparkinson drugs for many years. The mean time since PD diagnosis in the group of patients in whom antiparkinson medication was successfully withdrawn was 6.8 years (SD 5.6). However, 1 patient had been taking Levodopa for 24.7 years, meaning a huge cumulative cost. We feel this represents a significant clinical governance issue.

The diagnosis of PD can be difficult at initial presentation. Patients with early disease may not yet fulfil diagnostic criteria (eg. they may have tremor and or rigidity without bradykinesia) and DAT imaging has been established as a valuable tool in the assessment of such patients. However, access to DAT imaging is variable. In West Scotland FP-CIT SPECT has been available since 2000 in South Glasgow, 2003 in North Glasgow and 2007 in South Lanarkshire. Many UK centres have availability of SPECT scans 'capped' on cost grounds. There is one-off cost for FP-CIT SPECT scanning of approximately £560 per patient which must be balanced against the annual and cumulative antiparkinson drug costs for patients misdiagnosed as PD.

PD is a progressive neurodegenerative disorder and if symptoms do not progress over years and there is little clinical response to Levodopa the diagnosis of PD should be questioned. All patients identified by searches of the GP prescription databases in this study were prescribed antiparkinson medication for a presumed PD diagnosis. We described criteria (devised by the authors) to help identify misdiagnosed cases from

searches within primary care. The criteria selected patients whose antiparkinson medication had not increased over time, in whom there was no recorded progression of disease or who were co-prescribed dopamine depleting drugs (relatively contraindicated in PD).We estimated that 63 to 70 of 610 (10.3 to 11.5%) PD patients identified were misdiagnosed. If these results were replicated elsewhere in the UK this would mean 630 to 700 misdiagnosed cases within Scotland and 7,700 to 8,500 misdiagnosed cases in the UK; with annual antiparkinson drug costs of £780,000 to £865,000 across Scotland and £9.5 to £10.5 million across the UK. Although this study clearly merits assessment in a separate population, all the evidence suggests that misdiagnosis is not a local issue. Not only in the local or UK setting is there a potential issue of failure to identify the non-progressing 'apparently benign' PD case – across Europe the process of referral of 'difficult to manage' cases would tend to miss the apparently benign patients who are misinterpreted as doing well and having a good response to medication. It appears most likely from the present work that this exact subset of patients is the major source of patients with a misdiagnosis of PD.

Unfortunately the selection criteria proposed were not able to identify all misdiagnosed cases. Some misdiagnosed cases were recognised within the control group (not meeting selection criteria) and a further 3 misdiagnosed cases were identified during routine out-patient clinic assessment (neither meeting selection criteria nor selected as controls). However 33 of 64 patients (51.6%) meeting selection criteria were considered to have an alternate diagnosis and underwent successful withdrawal of antiparkinson medication. The likelihood of undergoing successful antiparkinson medication withdrawal was 16 times higher in patients meeting selection criteria compared with randomly selected controls. These criteria are clearly valuable in screening for misdiagnosis, but require to be tested in a separate population.

Patients from nursing homes and long-term care institutions were excluded from the therapy withdrawal study. It may be difficult to judge therapy response, examine for bradykinesia or gain informed consent for such as study if patients are cognitively impaired. PD prevalence rates of 12,500 per 100,000 have been reported (ie. Almost 100

times the 'background' rate of 129.5 per 100,000 found in our study) in institutionalised patients in Germany (von Campenhausen et al. 2005). The diagnostic error rate in such patients has never been analysed. It is likely to be at least similar to the rates in the current study, but could be considerably greater. Confounding clinical features include the usually mild extrapyramidal features in Alzheimer's disease and the coexistence of tremor and/or Parkinsonism in vascular dementia. This certainly merits further examination.

Withdrawal of antiparkinson medication in patients considered to have a non-Parkinson's disease diagnosis

Clinical trials of antiparkinson drugs in which patients have had normal presynaptic dopaminergic imaging have not reported therapy withdrawal despite suggesting that these patients have an alternative underlying diagnosis such as ET (Whone et al. 2003;Fahn et al. 2004). It may be difficult for this to be achieved or collated in a multi-centre trial, perhaps requiring significant amendment to the study protocol. In addition, drug withdrawal is not the primary aim of the sponsors of such trials. There may also be concerns about the adverse effects of withdrawing treatment, such as the worsening of movement disorder symptoms or development of Parkinsonism-hyperpyrexia syndrome (PHS). Successful antiparkinson medication withdrawal has been reported in 11 patients with normal FP-CIT imaging (Marshall et al. 2006). We reported successful antiparkinson therapy withdrawal in 39 patients misdiagnosed as PD in a larger community study and a further 4 patients, identified within out-patient clinics outwith the main study. While apparently modest, this is the largest reported series.

We described 2 patients, both of whom were initially considered to have a non-PD diagnosis. Both patients consented to antiparkinson medication withdrawal. Following therapy withdrawal, both reported worsening of movement disorder symptoms and had increased UPDRS part 3 scores. Both subsequently had abnormal FP-CIT SPECT imaging and improved clinically following prompt re-introduction of antiparkinson drugs. These two cases illustrate that even movement disorder specialists can get the clinical diagnosis of PD wrong in the early stages. In both cases this would

have been avoided if FP-CIT SPECT imaging were carried out prior to medication withdrawal. No cases of PHS occurred within the medication withdrawal study. Given PHS is a potentially fatal complication; its occurrence in even a single patient would counterbalance any benefits for the remaining cases. More liberal use of FP-CIT SPECT is recommended for any future study as a safeguard to prevent PHS following therapy withdrawal. In the current study medication was initially withdrawn in 22 patients without FP-CIT SPECT scanning being performed. In the 2 of 22 patients (9.1%) who clinically deteriorated following medication withdrawal FP-CIT SPECT scanning was abnormal in both cases. If all 22 of these patients had undergone FP-CIT SPECT this one-off total cost would approximately be £12,320, which should be considered against the total annual antiparkinson drug cost of £4,930 in these 22 cases, and a much greater cumulative cost (to date) of £31,600 for the 22 cases.

The most common alternate diagnoses for patients who underwent successful medication withdrawal were ET and VP. The role of dopaminergic therapy in VP is unclear with reports of some patients deriving an excellent clinical response to Levodopa (Zijlmans et al. 2004). However, the ability of patients to tolerate higher doses of Levodopa treatment in this situation is poor. Although Zijlmans *et al.* suggested a trial of up to 1000mg/day Levodopa, most patients in their report were unable to tolerate a dose above 600mg/day. In the current study we found that patients diagnosed as VP did not clinically deteriorate when antiparkinson therapy was withdrawn. These patients may have derived symptomatic benefit from escalation of Levodopa dose, but this was not attempted in this study.

In dopa-responsive dystonia (DRD) there may be mild bradykinesia which improves with low-dose Levodopa. Patients usually present less than 12 years of age with foot dystonia or gait disorder. It is possible that a DRD patient could be misdiagnosed as juvenile PD, but no such cases were found in this series. FP-CIT SPECT is normal in DRD.

<u>Blueprint for further work</u>

1. <u>This study should be repeated in a separate population</u>

    The protocol could be modified as follows:

    - Patients in nursing home and long-term care institution should be a component of further work in this area. As commented above, they may have at least as high a diagnosis error rate and a careful study involving the patient, their families and carers is appropriate to assess this cohort.

    - FP-CIT SPECT could be applied more readily if there was concern about the risk of PHS following antiparkinson medication withdrawal. However, the cost of a greater number of FP-CIT SPECT scans has to be considered.

2. <u>Encourage referral of patients from primary care to specialist centres</u>

    - GPs should be made aware of the problem of misdiagnosis of PD in the community and the value of specialist input in PD patients.

    - GPs should be advised to refer all patients with suspected PD or new onset of tremor for specialist assessment.

These recommendations are already embodied within the NICE guidelines and are expected to feature prominently in the Scottish Intercollegiate Guidelines Network (SIGN) which are under current development.

The publication plan for the present thesis is for this study to appear in the wider general medical literature, rather than exclusively within the specialist PD and neurology journals, in order to publicise the results of the study and encourage GPs to understand the rationale for specialist involvement at an early stage in the diagnostic process, and the potential issues around maintaining ineffective antiparkinson therapy in erroneously diagnosed cases.

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Appendix 1: UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's disease

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Step 1: Diagnosis of a parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

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Step 2: Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crisis
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after three years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski's sign
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of Levodopa

Step 3: Supportive criteria for Parkinson's disease
(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to Levodopa
- Severe Levodopa induced chorea
- Levodopa for five years or more
- Clinical course of 10 years or more

Appendix 2: The Motor Fluctuation Questionnaire (Brooks et al. 2005)

Do you often experience the return of any of the following symptoms of Parkinson's Disease before you take your next dose of medication?		
An increase in tremor (shaking) of the hand	Y ☐	N ☐
Slowing of hand movements (e.g. buttons, tools, cutting food)	Y ☐	N ☐
Smaller or further slowing of handwriting	Y ☐	N ☐
Slower or increased effort at arising from sitting	Y ☐	N ☐
Smaller step, increased slowness at walking, or more shuffling	Y ☐	N ☐
Decreased volume or clarity of the voice	Y ☐	N ☐
Increased generalised stiffness of the muscles	Y ☐	N ☐