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Therapy Concordance and Drug Adherence in Parkinson’s Disease

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Submitted for the degree of MD

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Faculty of Medicine
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Statement and Acknowledgements

The original research in this thesis was undertaken by me, involving design, conduct, and interpretation of the scientific material. I am grateful for the collaboration and guidance provided by clinical experts in neurology, clinical pharmacology, and health care psychology.

I would like to thank the Neurosciences Foundation for providing funding for the electronic monitoring bottles.

I am indebted to my supervisors Dr Donald Grosset and Professor John Reid for all their help, advice and support and most grateful to Professor Ian Bone for acting as my adviser.

I am also grateful to Professor Rob Horne for giving permission to use his beliefs about medicines questionnaire, and for assistance in the development of the Parkinson clinical questionnaire as described in the thesis.

I am most grateful to Parkinson Disease Specialist Nurses Angela O'Donnell and Tracy Murphy for help with clinical scoring and to Ms Elizabeth Jackson, Mrs Rosemary Tracey and to Ms Anna McMillan for secretarial support.

Finally, I am most grateful to all the patients for participating in the study.

Katherine Grosset

16th September 2005
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Global impression (patient/doctor or nurse)
Adverse events
Medical interview satisfaction scale (MISS)
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List of Abbreviations

DA - dopamine agonist
COMT - catechol-O-methyl transferase
CR - controlled release
EM - electronic monitoring
ESS - Epworth sleep Scale
GDS - Geriatric Depression Scale
H & Y - Hoehn and Yahr
IQ - interquartile range
IR - immediate release
MEMS® - medication event monitoring system
MISS 21 - Medical Interview Satisfaction Scale
MMSE - Mini-mental state examination
NMS – neuroleptic malignant syndrome
PD - Parkinson's disease
PDQ 39 - Parkinson's disease Quality of Life Scale
SD - standard deviation
S & E - Schwab and England (activities of daily living score)
SSRI - selective serotonin reuptake inhibitor
STC - simple tablet count
TD - tardive dyskinesia
UPDRS - Unified Parkinson's Disease Rating Scale
Therapy Concordance and Drug Adherence in Parkinson’s Disease

Summary and Overview

Oral drug therapy forms the mainstay of modern management of Parkinson’s disease. Consideration of how patients take prescribed medication is essential in understanding therapeutic response. Much is known about therapy adherence in many disease areas and about half of prescribed medicines are not taken as prescribed, but only limited information is available about compliance in Parkinson’s disease (PD).

Suboptimal therapy adherence has many consequences including poor symptomatic control resulting in worsening quality of life. This thesis forms a comprehensive study of drug adherence in Parkinson’s disease. Methods of assessing drug adherence are studied and compared, factors influencing drug-taking behaviour including patients’ beliefs are examined, and the effect of an educational intervention is tested.

Concordance describes the process of a patient/doctor interaction. The degree of patient involvement in therapy management decisions and satisfaction with the movement disorder service are examined in this thesis as an indication of concordance.

A cohort of 135 patients underwent several assessments for one year, of which subsets were evaluable in different aspects of the study, as described in individual chapters. A further 99 patients taking dopamine agonists formed an
additional cohort (Chapter 7). Finally, another 20 patients took part in the study developing a patient belief questionnaire.

Chapter 1 gives an overview of the relevance of studying therapy adherence in Parkinson’s disease. Variable medicine-taking behaviour can affect the clinician’s understanding of the diagnosis and rate of progression. Understanding medicine-taking behaviour is a first step in optimising therapy.

Chapter 2 examines drug induced neurological syndromes and considers the validity of patients' concerns about taking prescribed medications. Patients prescribed treatment for one movement disorder (e.g. the tremor and bradykinesia of Parkinson's disease) often find they develop another movement disorder (e.g. dyskinesia). Patients' concerns about long-term adverse effects are therefore valid, but this has to weighed against deteriorating quality of life associated with delaying treatment.

Chapter 3 compares different methods of assessing therapy adherence. One hundred and twelve cases of idiopathic Parkinson's were randomised to active monitoring (n = 69, simple tablet count and electronic monitoring conducted), or to no monitoring (n = 43, control group). All patients completed a self-report and visual analogue scale indicating therapy intake. Median adherence for self-report was 100% (interquartile range (IQ) 100-100) and for visual analogue was 100% (IQ 95-100), in both active and control groups. Patients taking ≥ 80% of prescribed medication had median total adherence of 98% (IQ 93-101) by electronic monitoring, which was similar to that from other methods: self-report (100%, IQ 100-100); visual analogue scale (100%, IQ 95-100); simple tablet count (98%, IQ 89-100). Median total adherence in patients taking <80% of medication was significantly lower by electronic monitoring (69%, IQ 44-74) than by other methods.
self-report 100% (IQ 100-100); visual analogue scale 100% (IQ 95-100); and simple tablet count 90% (IQ 78-100) (all p<0.0001). Self-report, visual analogue scale and simple tablet counts are insensitive predictors of sub-optimal medicine usage in PD.

Chapter 4 studies factors associated with sub-optimal medicine usage in 54 patients. Poorer compliance was associated with younger age (p = 0.007), with taking more antiparkinson tablets per day (p = 0.007), and with higher depression scores (p = 0.02) and poorer quality of life (p=0.002).

Chapter 5 reports a study of patient perceived involvement with management decisions and an assessment of satisfaction with the movement disorder service in 107 patients. Higher involvement was associated with increased satisfaction (r = 0.28, p = 0.003), particularly distress relief (r = 0.38, p < 0.0001). Communication scores correlated significantly with compliance intent (r = 0.6, p < 0.0001). Improved quality of life was significantly associated with higher compliance intent, and satisfaction.

Chapter 6 explores patients’ beliefs about antiparkinson medication in 129 patients. Parkinson’s patients held strong beliefs that their medicines were necessary but also had concerns about their medicines. Beliefs about medicines did not correlate with adherence. Although patients have concerns regarding medicine taking, this does not seem to affect medicine-taking behaviour.

Chapter 7 examines the effect on Parkinson’s patients of emerging data about drug side effects, specifically fibrosis due to ergot-based dopamine agonists. Ninety-nine patients taking ergot-derived dopamine agonists were informed about potential longer-term side effects and given therapy options. Out of 99 patients, 88
chose to switch to a non-ergot agonist (conducted overnight), 10 maintained therapy, and 1 stopped agonist therapy and increased levodopa.

Chapter 8 reports on an educational intervention designed to improve Parkinson drug timing compliance. Eighty-three patients were randomised, 43 to the active group (receiving the intervention) and 40 to the control group (no extra information). Prior to the intervention timing compliance was median 17% (interquartile range (IQ) 9-51) for the active group versus 21% (IQ 10-59) for the control group (difference not significant). Post-intervention timing compliance was significantly better in the active group at 39% (IQ 22-58) than in controls at 20% (IQ 10-47), (p=0.007). The UPDRS 3 motor score improved in the active group (mean change -0.5, SD 11) but deteriorated in controls (mean +5, SD 8) (p=0.03). In conclusion, timing compliance improves after providing patients with extra information, which is associated with better motor scores.

In summary, this thesis provides important new information about medicine taking in Parkinson's disease. A fifth of PD patients take less than 80% of prescribed antiparkinson medication. Electronic monitoring is the only reliable method of accurately detecting sub-optimal medication usage. Patients who take less than 80% of prescribed medicines are more likely to be younger, have concomitant depression, be prescribed more tablets per day and have poorer quality of life. Patients are more satisfied if they are involved in management decisions and have increased intention to comply with prescribed medication if there is better communication. Poorer quality of life is associated with less intention to comply with prescribed medication. Timing of medication intake is generally irregular but can be improved by informing patients of the continuous dopaminergic theory and
providing specific drug timings. Once daily drugs are taken more consistently than drugs with more frequent doses. Future research needs to evaluate further the true impact of sub-optimal compliance and explore methods to ease the process of medicine taking in Parkinson’s disease.
Chapter 1

The Importance of Concordance and Drug Adherence in Parkinson’s Disease
Background

Parkinson's disease (PD) is a common neurodegenerative disorder affecting approximately 1% of the population over 65 years. Prescribing medicines is the mainstay of modern management of PD. In recent years there have been many new therapeutic developments including the development of new dopamine agonists (Adler et al. 1997; Clarke & Guttman 2002; Geminiani et al. 1996; Hobson, Pourcher, & Martin 1999; Hubble 2002; Montastruc, Rascol, & Senard 1999; Olanow 2002; Shulman et al. 2000), slow release dopamine preparations (Koller et al. 1999), COMT (catechol-O-methyl transferase) inhibitors (Brooks & Sagar 2003; Fenelon et al. 2003) and combination preparations (Hauser 2004). There is increasing responsibility of the doctor to reach an accurate diagnosis and give up-to-date evidence-based advice. The management of PD is a complex area. There are multiple considerations in deciding the best course for individual patients (Bhatia et al. 2001). Understanding and agreement between the patient and doctor (concordance) should maximise benefit and requires patients then to comply with the prescribed therapy (Coons 2001; Mulleners, Whitmarsh, & Steiner 1998). The patient's decision to take treatment (or not) is based on a complex interplay of beliefs, knowledge, experience, symptoms, disease type, co-morbidity, culture, personality, social support and psychological state in addition to the interaction between patient and doctor. Adherence rates for prescribed medication across a wide spectrum of conditions, both symptomatic and asymptomatic, are typically around 50% with a range from 0% to over 100% (Sackett & Snow 1979). In chronic conditions about a third of medicines are not taken as prescribed (Horne R 1997). In a systematic review of 76 studies using electronic monitoring the mean total
compliance was 71% (standard deviation 17, range 34-97%) (Claxton, Cramer, & Pierce 2001). Non-compliance has significant loss of health gain and socioeconomic consequences. In the geographical setting of the current research, the annual drug budget was £199 million for a population of around 1 million (2002/3 figures). Fifty percent adherence rates equate to £100 of unused medication per head of population, and a much higher figure if considering only medicated patients.

**Adherence, Compliance or Concordance?**

**Compliance** measurements indicate whether patients take medication in accordance with prescriber's intentions; they reflect patient behaviour, and compliance may range from excellent to poor. The term adherence can be used synonymously with compliance. These terms are judgmental; non-compliance or poor adherence identify error (patients fail to follow instructions). Compliance measures include self-report, tablet counts, pharmacy refills, electronic monitoring, blood/urine samples or biological markers of drug effect. Compliance/adherence represent the theoretical intention of prescription, whereas concordance signifies the practical goal of treatment (Royal Pharmaceutical Society of Great Britain 1997).

**Concordance** is a descriptive term and patients cannot be non-concordant as the term refers to the process and outcome of the consultation rather than patient behaviour. The Medicines Partnership was created by the UK Department of Health to endorse concordance in several disorders including PD (Medicines Partnership 2003). The Royal Pharmaceutical Society of Great Britain multi-disciplinary working party defines concordance as follows (Royal Pharmaceutical...
Society of Great Britain 1997): Concordance is based on the notion that the work of the prescriber and the patient in the consultation is a negotiation between equals and the aim is therefore a therapeutic alliance between them. This alliance, may, in the end, include an agreement to differ. Its strength lies in a new assumption of respect for the patient's agenda and the creation of openness in the relationship, so that both doctor and patient together can proceed on the basis of reality and not of misunderstanding, distrust and concealment. Involving patients in their health care decisions is not a new concept; Szasz and Hollender described a model of mutual co-operation between physician and patient in 1956 (Szasz & Hollender 1956) and the World Health Organisation stated that patients as well as health care professionals have a right and a duty to participate in health care decisions in 1977 (World Health Organisation 1977). Increased patient involvement brings greater responsibility which not all patients desire, but it should be offered (Litva et al. 2002). Measuring concordance involves assessment of whether the consultation is patient centred, and whether the patient is satisfied with the process of care particularly relating to drug treatment decisions. Departure from the prescription represents at least in part failure to address the patient’s agenda. Increased concordance gives the clinician a better understanding of the patient, and enables optimisation of medicine taking, maximising health gain.

Research Aims

Therapy compliance and concordance are largely unpublished areas in PD. This research project aims to:

- Analyse the potential importance of compliance in PD and consider consequences of poor compliance (Chapter 1).
• Explore the risks of prescription medication from a general neurological perspective and the patient's understanding, thereby reviewing the 'necessity:concerns' ratio which is crucial to understanding therapy decision making by patients (Chapter 2).

• Define the level of compliance in PD using four methods of assessment of compliance (Chapter 3).

• Explore factors associated with sub-optimal medicine-usage (Chapter 4).

• Assess the level of patient involvement (concordance) in therapy decisions and satisfaction with the consultation in a movement disorder clinic setting (Chapter 5).

• Examine PD patients' beliefs about medicines and assess the impact of beliefs on therapy adherence (Chapter 6).

• Involve patients in change of therapy decisions (Chapter 7).

• Explore methods of supporting PD patients in medicine taking, by testing the effects of patient education on compliance (Chapter 8).

A cohort of 135 patients underwent several assessments for one year. Figures 1.1 and 1.2 give an overview of the study timeline and Table 1.1 indicates the timetable of study assessments. A CONSORT flowchart showing the flow of participants is shown in Figure 1.3.
**Figure 1.1:** Timeline of study visits. Patients were all seen at 3 monthly intervals over a period of 1 year.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>3m</th>
<th>6m</th>
<th>9m</th>
<th>12m</th>
</tr>
</thead>
<tbody>
<tr>
<td>STC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STC = simple tablet count, EM = electronic monitoring, SM = standard management

**Figure 1.2:** Timeline of educational intervention. At the 6 month visit half the patients (according to randomisation) received verbal and written information on the continuous dopaminergic theory and advice on optimal medicine dosage timings (the education pack).

<table>
<thead>
<tr>
<th>Baseline</th>
<th>6m</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CM = compliance monitoring (simple tablet count, electronic monitoring), SM = standard management with no compliance monitoring, EP = education pack, NEP = no education pack
Table 1.1: Overview and schedule of Study-Related Assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Measurement</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Brain Bank Criteria</td>
<td>Baseline</td>
</tr>
<tr>
<td>Cognition</td>
<td>MMSE</td>
<td>x</td>
</tr>
<tr>
<td>Consent</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PD stage</td>
<td>H&amp;Y</td>
<td>x x x x x</td>
</tr>
<tr>
<td>PD status</td>
<td>UPDRS 1-4</td>
<td>x x x x x</td>
</tr>
<tr>
<td>Depression</td>
<td>Geriatric Depression Scale</td>
<td>x</td>
</tr>
<tr>
<td>Functional Status</td>
<td>Schwab&amp;England</td>
<td>x x x x x</td>
</tr>
<tr>
<td>Functional Status</td>
<td>PDQ39</td>
<td>x</td>
</tr>
<tr>
<td>Side effects</td>
<td>Side effect sheet + global impression</td>
<td>x x x x x</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>UPDRS 4/PD/Goetz dyskinesia scale</td>
<td>x x x x x</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>Epworth sleep score</td>
<td>x</td>
</tr>
<tr>
<td>or if none</td>
<td>Patient Drug record</td>
<td>x x x x x</td>
</tr>
<tr>
<td>Compliance</td>
<td>VAS/Self-report</td>
<td>x</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>Medical interview satisfaction scale</td>
<td>x</td>
</tr>
<tr>
<td>Patient-centredness</td>
<td>Patient centredness score</td>
<td>x</td>
</tr>
<tr>
<td>Beliefs about medicines - General</td>
<td>Beliefs about medicines Questionnaire</td>
<td>x</td>
</tr>
<tr>
<td>Beliefs about medicines - PD specific</td>
<td>Beliefs about medicines Questionnaire - PD</td>
<td>x</td>
</tr>
<tr>
<td>Adherence self-report</td>
<td>Medicine Adherence Rating Scale</td>
<td>x</td>
</tr>
<tr>
<td>Satisfaction with information given on medicines</td>
<td>Satisfaction with information given about medicines questionnaire</td>
<td>x</td>
</tr>
<tr>
<td>for education cases</td>
<td>education pack</td>
<td>x</td>
</tr>
<tr>
<td>for STC and EM cases</td>
<td>pill count record</td>
<td>x x x x x</td>
</tr>
</tbody>
</table>

MMSE = mini mental state examination, H&Y = Hoehn and Yahr, UPDRS = Unified Parkinson’s Disease rating scale, PDQ39 = Parkinson’s Disease Quality of life questionnaire, STC = simple tablet count, EM = electronic monitoring, VAS = Visual analogue scale
Figure 1.3: Study Overview CONSORT Flowchart

Assessment of eligibility (n=135)

Excluded (n=6, all declined)

Randomised (n=129)

Allocated to active therapy monitoring (n=83)
- Received allocated intervention (n=81)
- Did not receive allocated intervention (n=2)
  - Reasons - withdrew consent

Lost to follow up (n=2)
- Discontinued intervention (n=10)
  - Reasons 9 had problems with monitoring bottles
  - 1 died

Analysed (n=69)

Allocated to educational intervention (n=33)
- Discontinued intervention (n=10)
  - Reasons
    - 3 declined re-run of monitoring bottles
    - 6 used monitoring bottles inconsistently
    - 1 system recording failure

Analysed (n=23)

Allocated to no active therapy monitoring (n=46)
- Received allocated intervention (n=45)
- Did not receive allocated intervention (n=1)
  - Reason withdrew consent

Lost to follow up (n=2)

Analysed (n=43)

Allocated to no educational intervention (n=36)
- Discontinued (n=7)
  - 1 declined re-run of monitoring bottles
  - 6 used the monitoring bottles inconsistently

Analysed (n=29)
Pharmacological Considerations in PD Compliance

To understand the effects and consequences of non-compliance in PD, a review of pharmacokinetic and pharmacodynamic properties of the antiparkinsonian medication is necessary.

**Levodopa Preparations**

Levodopa is a naturally occurring amino acid found in seedlings, pods and broadbeans. It is decarboxylated to dopamine and replenishes depleted striatal dopamine in PD. It is combined with an extracerebral decarboxylase inhibitor to reduce peripheral conversion of levodopa to dopamine. This limits side effects of nausea, vomiting and cardiovascular effects. Even combined with a decarboxylase inhibitor only 10% of the administered drug reaches the brain due to extensive peripheral metabolism by catechol-O-methyltransferase (COMT) (Deleu, Northway, & Hanssens 2002). Despite the introduction of new drug classes to treat PD, levodopa (meaning levodopa plus decarboxylase inhibitor) remains the most effective therapy in terms of symptom control (as measured by the Unified Parkinson’s Disease Rating Scale, the UPDRS). There are 12 different levodopa plus DCI preparations currently available in the UK. Dispersible, immediate release and controlled released formulations are used individually or in combination. Table 1.2 summarises the pharmacokinetic properties of levodopa preparations.

Dopamine metabolites are rapidly excreted in the urine.
Table 1.2 – Summary of Pharmacokinetic Properties of Levodopa

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Absorption</th>
<th>Time to maximum plasma concentration</th>
<th>Bioavailability</th>
<th>Elimination half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar Dispersible</td>
<td>rapid</td>
<td>1 hour</td>
<td>98%</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Madopar Immediate Release</td>
<td>rapid</td>
<td>1 hour</td>
<td>98%</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Madopar Controlled Release</td>
<td>slow</td>
<td>3 hours</td>
<td>60%</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Sinemet Immediate Release</td>
<td>rapid</td>
<td>0.75 hours</td>
<td>99%</td>
<td>1 hour</td>
</tr>
<tr>
<td>Sinemet Controlled Release</td>
<td>slow</td>
<td>2 hours</td>
<td>60%</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

**Motor Fluctuations**

Motor fluctuations (end of dose wearing-off, ‘on-off’ effects, dyskinesia and dystonia) occur in 50% of PD patients treated with levodopa after 5 years (Lees 1986; Marsden & Parkes 1976). Such complications are commoner in young onset patients (100% after 6 years in cases developing PD before age 40) (Clarke 2002). The mechanism of motor complications is complex but may relate partly to erratic absorption and short half-life of levodopa causing fluctuating serum and brain drug levels (Figure 1.4) and abnormal pulsatile stimulation (Figure 1.5) of striatal dopamine receptors (Bezard, Brotchie, & Gross 2001; Jenner 2000) contrasting with the more continuous neurone firing (Figure 1.6) under normal circumstances (Grace 1991; Onn, West, & Grace 2000). In early disease the dopamine neurones have the capacity to buffer variations in striatal dopamine levels, but as the disease progresses fluctuating plasma dopamine levels correlate with alternating high and low striatal dopamine levels causing pulsatile stimulation clinically manifesting as emerging motor fluctuations (Spencer & Wooten 1984).
Figure 1.4: Graph illustrating peaks and troughs of serum and brain levodopa levels in relation to dosing schedule

Figure 1.5: Diagram of abnormal fluctuating serum and brain levodopa levels causing pulsatile post synaptic stimulation resulting in motor fluctuations

Figure 1.6: Diagram of normal physiological tonic dopaminergic activity resulting in more continuous post synaptic stimulation
Controlled release preparations

In an attempt to prolong the clinical effect of levodopa, controlled release preparations were developed. Sinemet CR is designed to release active ingredients over a 4-6 hour period via a slowly dissolving polymeric matrix. Sinemet CR has approximately 70% bioavailability compared against IR; up to 30% more levodopa per day may be necessary. Dosing interval might theoretically increase by 30% (Hutton et al. 1989). Madopar CR is transformed in the stomach to a mucoid body which delivers its content through a hydrated layer by diffusion. Therapy should continue with the same dose frequency although in one study the average number of daily doses were 5.2 for patients on Madopar CR versus 6.2 for patients on IR (MacMahon et al. 1990). The CR preparations provide a more prolonged but lower peak plasma concentration of levodopa (they increase the area under the curve without increasing the maximum concentration of levodopa). In clinical trials there was no difference in the development of motor fluctuations between IR and CR preparations (Hutton, Morris, Bush, Smith, Liss, & Reines 1989; Koller, Hutton, Tolosa, & Capilldeo 1999). However patients taking CR had better activities of daily living and both patients and physicians preferred CR preparations scores (Grandas, Martinez-Martin, & Linazasoro 1998; Martinez-Martin et al. 1999).

Adverse effects

Levodopa is initiated at low dose to allow tolerance to peripheral dopaminergic effects of nausea, vomiting and postural hypotension; gradual increases then depend on clinical response. Domperidone (a peripheral dopamine antagonist which does not cross the blood-brain barrier) may be co-prescribed to counteract
these peripheral effects. In late disease symptoms of dopaminergic excess (dyskinesia, hallucinations and confusion) are often dose limiting. Unpredictable 'on-off' effects in advanced PD are inevitable after long-term therapy and are extremely difficult to control. Strategies of 'buying time' by delaying the initiation of levodopa have been developed.

**Dopamine Agonists**

Dopamine agonists (DAs) have a direct action on post-synaptic dopamine receptors. Although less potent than levodopa, DAs are proven in many independent trials (Hubble 2002; Rascol et al. 2000; The Parkinson Study Group 2000) to reduce and delay motor fluctuations and can delay the need to start levodopa (Hubble 2002). DAs are therefore commonly used early as monotherapy particularly in younger patients (Olanow & Koller 1998). There are seven agents in this class currently available in the UK. Bromocriptine, cabergoline, lisuride and pergolide are ergot-derived while pramipexole and ropinirole are non-ergot. Apomorphine is also non-ergot but requires parenteral administration (subcutaneous injection or infusion) because of extensive first pass metabolism (LeWitt 2004). Continuous waking day subcutaneous infusion benefits advanced PD patients with severe dyskinesia or 'on-off' fluctuations and allows a reduction or even discontinuation of oral therapy (Manson, Turner, & Lees 2002). DAs vary considerably in their pharmacological properties (Table 1.3). Several new DA products are under test, including the transdermal agent rotigotine, and ropinirole CR, both of which may reduce fluctuations by long duration of action.
Table 1.3: Pharmacokinetic properties of dopamine agonists

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Absorption</th>
<th>Time to maximum plasma concentration</th>
<th>Bio-availability</th>
<th>Elimination half-life</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine (sub-cutaneous)</td>
<td>very rapid</td>
<td>4-12 mins</td>
<td>100%</td>
<td>33 mins</td>
<td>extra-hepatic</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>rapid</td>
<td>1-3 hours</td>
<td>6%</td>
<td>15 hours*</td>
<td>hepatic</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>rapid</td>
<td>0.5-4 hours</td>
<td>50-80%</td>
<td>63-68 hours#</td>
<td>hepatic</td>
</tr>
<tr>
<td>Lisuride</td>
<td>rapid</td>
<td>0.2-1.2 hours</td>
<td>10-20%</td>
<td>1.3-2.5 hours hepatic</td>
<td></td>
</tr>
<tr>
<td>Pergolide</td>
<td>55% absorbed</td>
<td>1-3 hours</td>
<td>20-60%</td>
<td>27 hours</td>
<td>hepatic</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>rapid</td>
<td>1-3 hours</td>
<td>90%</td>
<td>8-12 hours*</td>
<td>renal</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>rapid</td>
<td>1.5 hours</td>
<td>50%</td>
<td>6 hours</td>
<td>hepatic</td>
</tr>
</tbody>
</table>

* Bromocriptine plasma elimination half life is 3-4 hours for the parent drug and 50 hours for the inactive metabolites. The elimination of parent drug from plasma occurs biphasically, with a terminal half-life of about 15 hours.

# In healthy volunteers

* 8 hours in the young to 12 hours in the elderly.

Selegiline

Selegiline is a monoamine-oxidase B inhibitor preventing dopamine breakdown in the brain. It also inhibits the re-uptake of dopamine at the pre-synaptic receptor. It can be used as an early monotherapy and prolongs the time before levodopa is needed by 9 months (The Parkinson Study Group 1993). In later disease when added to levodopa, it alleviates dose related fluctuations and end of dose deterioration. It is readily absorbed and maximum plasma concentrations are reached in 30 minutes. Bioavailability is low at 10%. It is lipophilic and quickly penetrates into tissues including the brain. Plasma selegiline is 94% reversibly...
bound to protein. Enzyme inhibition is irreversible and therefore resumes only after new enzyme has been formed. The mean elimination half-life is 1.6 hours.

Selegiline also comes in an oral lyophilisate formulation which dissolves completely within 10 seconds of being placed on the tongue. This is particularly indicated for patients with swallowing difficulties.

Rasagiline, another monoamine-oxidase B inhibitor with a longer half life (and therefore given once daily) has recently become available and is effacious as early monotherapy (The Parkinson Study Group 2004) and later as an adjunct (Rascol et al. 2005).

Entacapone

Entacapone is a reversible, specific and mainly peripherally acting catechol-O-methyl transferase (COMT) inhibitor. There are large variations in the absorption of entacapone. The peak concentration is reached 1 hour after administration and the bioavailability is 35%. Entacapone is extensively bound to plasma proteins. It decreases the metabolic loss of dopamine to 3 O-methyl dopa. This increases the half-life of levodopa by 30-50% so that the levodopa total daily dose may be reduced (Fenelon, Gimenez-Roldan, Montastruc, Bermejo, Durif, Bourdeix, Pere, Galiano, & Schadrack 2003) with no significant effect on the C<sub>max</sub> (peak concentration) or T<sub>max</sub> (time to C<sub>max</sub>) . It is particularly useful for patients experiencing end-of-dose 'wearing off'.

Tolcapone is a more potent COMT inhibitor which acts centrally and peripherally, but was temporarily withdrawn in Europe because of hepatotoxicity. It requires extensive liver function monitoring.
**Stalevo** is a recently launched combination of entacapone, levodopa and carbidopa. It comes in three strengths containing 50, 100 and 150 mg of levodopa (Hauser 2004).

**Anticholinergics**

The use of anticholinergics in PD has declined in recent years due to adverse effects on cognition and the introduction of better alternative dopamine sparing agents. Structurally related to atropine, these drugs block muscarinic receptors in the striatum, inhibit the presynaptic carrier-mediated dopamine transport mechanism and are N-methyl-D-aspartate (NMDA) antagonists (reversing akinesia and potentiating levodopa in animal models). Table 1.4 summarises the pharmacokinetic properties.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Time to maximum plasma concentration</th>
<th>Bioavailability</th>
<th>Elimination half-life</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trihexyphenidyl</td>
<td>1.3 hours</td>
<td>100%</td>
<td>33 hours</td>
<td>renal</td>
</tr>
<tr>
<td>(Benzhexol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benztropine</td>
<td>7 hours</td>
<td>low</td>
<td>18-24 hours</td>
<td>renal</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>2-4 hours</td>
<td>95%</td>
<td>13-20 hours</td>
<td>renal</td>
</tr>
<tr>
<td>Procyclidine</td>
<td>1 hour</td>
<td>75%</td>
<td>8-16 hours</td>
<td>renal</td>
</tr>
</tbody>
</table>
Amantadine

Amantadine is a glutamate antagonist originally developed as an antiviral agent. It enhances dopaminergic transmission and has mild antimuscarinic activity. Absorption is slow and variable, and steady-state plasma concentrations are reached within 4-7 days (Aoki & Sitar 1988). The drug is extensively bound to tissues and 90% is eliminated by renal clearance. Its main use is in more advanced disease, as an antidyskinesia agent (Metman et al. 1999).

Categories of non-compliance, in relation to Parkinson's Disease

Compliance is the extent to which a patient's actual dosage administration corresponds to the prescribed regimen (Urquhart & de Klerk 1998). The patient needs to accept the treatment decided during the consultation, redeem the prescription, adhere to the dose (amount and frequency), and persist with the drug regimen.
Primary Non-compliance

In primary non-compliance, the patient fails to have the medication dispensed. In primary care, 5% of prescriptions are not filled (Beardon et al. 1993) and 80% of unredeemed prescriptions are for symptomatic conditions. Unclaimed prescriptions detected by automated transmittals to Swedish pharmacies found primary non-compliance in 2,171 out of 90,458 prescriptions (2.4%) in 3 months; the patient regarding the prescription as unnecessary was the commonest cause (Ekedahl & Mansson 2004). This may reflect mainly the patient’s rejection of the doctor’s diagnosis or advice and can be regarded as intentional non-compliance. Alternatively prescription charges may be a barrier. In PD, drug therapy is usually started when it is needed to help function as therapy is symptomatic and does not slow disease progression. Additionally, therapy initiation is often delayed due to inevitable future drug-related motor fluctuations. Balancing these judgements is often difficult for the patient and the prescriber. Primary non-compliance may occur if the doctor recommends drug treatment, but the patient feels it is not yet necessary. Patients weigh up the necessity of the treatment (in relation to their symptoms and disability) against concerns of adverse effects both short and long-term. Unintentional primary non-compliance may also be due to cognitive impairment (which exists in 10-20% of PD patients) or depression (present in about 40% of PD patients).

Secondary Non-compliance

This is when patients do not take medication as intended by the prescriber. There are a number of categories of secondary non-compliance, as follows.
Early Discontinuation

Adverse effects are the commonest reason for premature discontinuation in other disease areas such as depression (Bull et al. 2002b). Informing patients of potential adverse effects improves therapy continuation (Bull et al. 2002a). Antiparkinsonian medications are frequently associated with adverse effects. Initial application of levodopa in the 1960s after patients with PD were found to have deleted neostriatal dopamine was limited by severe peripheral effects of nausea, vomiting and postural hypotension. Discovery of decarboxylase inhibitors (DCI) in the late 1960s (Bartholini, Burkard, & Pletscher 1967) led to widening use and acceptability of the combined levodopa and DCI products. Further reduction in peripheral adverse effects can be achieved by co-prescribing domperidone. These measures anticipate and minimize early adverse effects, minimising unnecessary premature discontinuation.

Clinical trial discontinuation rates due to adverse events are high (Table 1.5).
Table 1.5: Early discontinuation rates due to adverse effects in PD clinical trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Discontinuation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Drug</td>
</tr>
<tr>
<td>Brooks et al (Brooks &amp; Sagar 2003)</td>
<td>Entacapone 19%</td>
</tr>
<tr>
<td>Larsen et al (Larsen et al. 2003)</td>
<td>Entacapone 14%</td>
</tr>
<tr>
<td>Parkinson Study Group (The Parkinson Study Group 2000)</td>
<td>Pramipexole 11%</td>
</tr>
<tr>
<td>Koller et al Hutton, Tolosa, &amp; Capilldeo 1999)</td>
<td>Levodopa IR 9%</td>
</tr>
<tr>
<td>Linazasoro (Linazasoro et al. 1999)</td>
<td>Levodopa CR 10%</td>
</tr>
<tr>
<td>Rinne et al (Rinne et al. 1997)</td>
<td>Cabergoline 7.7%</td>
</tr>
<tr>
<td>Shannon et al (Shannon, Bennett, Jr., &amp; Friedman 1997)</td>
<td>Pramipexole 13%</td>
</tr>
<tr>
<td>Adler et al Ropinirole 23% Placebo 10% (Adler, Sethi, Hauser, Davis, Hammerstad, Bertoni, Taylor, Sanchez-Ramos, &amp; O'Brien 1997)</td>
<td></td>
</tr>
</tbody>
</table>

IR = immediate release, CR = controlled release

**Lack of efficacy** also leads to early discontinuation. In depression, the time lag between therapy initiation and symptomatic improvement may lead to premature discontinuation especially in uninformed patients. In PD there are a number of issues relating to lack of efficacy. Patients frequently report no beneficial therapy effect because they expect an improvement in tremor, which occurs in only about half of cases (Brooks 2002) and is the most difficult feature to control from the classic triad of Parkinson's symptoms. Patients who are informed about realistic expectations of therapy goals (improvement in movements, muscle tone i.e. feeling less slow and stiff) may gain better realisation of therapy benefit. Initial low doses
to aid tolerability may compromise early efficacy. Scheduled titration such as with starter packs (ropinirole and pergolide) or follow-on packs (ropinirole) may assist. Lack of efficacy may drive a switch to an alternative preparation. Pharmacokinetic knowledge of the different types of levodopa preparations aids therapy conversion and appropriate use. The lower (70%) bioavailability of CR compared to IR needs to be taken into account in dose adjustments between the formulations. Modest increases in dosing interval can be achieved, but the main use is to lower peak plasma concentrations to limit peak-dose dyskinesia. However, patients who enjoy the relatively faster response to IR (and the increased mobility which accompanies dyskinesia) may dislike the slow time to peak from CR (Hutton, Morris, Bush, Smith, Liss, & Reines 1989). Dispersible preparations are useful with the initial morning dose to help patients 'get going' and can be taken to relieve wearing-off symptoms or for a more rapid onset response when there are unpredictable 'off' periods. Although CR prolongs the half-life of levodopa, and improves end-of-dose wearing-off and especially overnight control (benefiting the hypokinesia which prevents turning in bed), it does not delay the motor fluctuations inherent to PD, of which dyskinesia is the most troublesome (Hammerstad et al. 1994; Koller, Hutton, Tolosa, & Capilldeo 1999).

Effective switching from one DA to another requires careful calculation of dose equivalency (Bhatia, Brooks, Burn, Clarke, Grosset, MacMahon, Playfer, Schapira, Stewart, & Williams 2001) and where cabergoline is involved, its very long half-life must be taken into consideration.
Varying degrees of missed doses

These have been divided into 6 categories (Urquhart 1997): patients who

- remedicate punctually
- have timing variations but miss very few doses
- miss a few doses, rarely more than one at a time
- have occasional (3-4 per year) drug holidays (no medication for 3 or more consecutive days)
- take monthly drug holidays (medication missed for 3 or more consecutive days each month)
- take few or no doses

These patterns of non-compliance have not previously been published in PD.

Results of our study are presented in Chapter 3. A small study (Leopold, Polansky, & Hurka 2004) concluded that about 10% (4 of 39) of PD patients stick to their prescribed medication regimen. Compliance was measured for one month using a questionnaire and a computerised electronic monitoring system (Leopold, Polansky, & Hurka 2004). Venous levodopa levels have been used to assess compliance in PD patients (Copeland et al. 1994). In this study 103 samples from 53 patients were analysed and 3 were at or below the lower limit of the assay indicating poor compliance. Five values were above the therapeutic range and dyskinesia was more common in this group.

Complexity of drug regimen is inversely related to compliance (Claxton, Cramer, & Pierce 2001). Often in PD, patients are on several different antiparkinsonian drugs and on various formulations of the same drug in addition to other therapy for coexisting conditions. Adherence to such regimens requires significant effort.

Regimen simplification, perhaps using longer acting preparations such as
cabergoline or ropinirole CR (currently under trial) or combination products e.g. Stalevo (Hauser 2004) may ease the process of medicine taking.

Overuse of Medication

Overuse of medication is well recognized in many conditions, particularly with drugs possessing addictive properties. In PD, a small subgroup of patients use dopamine replacement therapy excessively and compulsively, and take increasing quantities of dopamine replacement therapy despite severe drug-induced dyskinesia and a cyclical mood disorder (Giovannoni et al. 2000; Lawrence, Evans, & Lees 2003). Overuse was also found in PD patients with punding (stereotyped repetitive manipulations of equipment or objects); 10 of 17 (59%) patients with punding compulsively overused medication, as assessed from drug history (Evans et al. 2004). A lesser degree of dopamine replacement therapy overuse to gain mobility despite worsening dyskinesia is common in clinical experience and merits quantification.

Consequences of non-compliance in PD

Loss of health gain Immediate consequences of non-compliance are lack of efficacy impairing function and quality of life. In the PD life study (Chaudhuri et al. 2004), patients who delay therapy initiation have worse motor scores and quality of life. Some drugs are more forgiving to non-adherence because of different pharmacokinetics and pharmacodynamics. Drug potency is a factor; there may be no noticeable effect from a missed dose of selegiline, but missing a levodopa dose is more likely to induce 'wearing-off'. A long elimination half-life such as cabergoline leaves residual activity when a single dose is omitted. The duration of effect is longer for agents with irreversible or non-competitive binding (e.g. selegiline) than for drugs that bind reversibly or competitively to enzymes or
receptors (e.g. COMT inhibitors). Additional complications may result from missed doses. In PD, withdrawal of antiparkinsonian medication (particularly if rapid) and especially for levodopa can very rarely trigger neuroleptic malignant syndrome (Takubo et al. 2003).

In the longer term, poor compliance may contribute to the development of motor fluctuations. Abnormal pulsatile stimulation of striatal dopamine receptors contributes to the development of motor fluctuations. Animal studies (Gagnon, Bedard, & Di Paolo 1990; Juncos et al. 1989; Pearce et al. 1998) indicate that continuous dopaminergic stimulation prevents motor complications. In PD patients similar conclusions come from clinical trials: initial therapy with a relatively long-acting DA have significantly fewer motor complications than short-acting IR levodopa preparations (Rascol, Brooks, Korczyn, De Deyn, Clarke, & Lang 2000; The Parkinson Study Group 2000). In advanced PD, continuous therapy reverses motor complications with apomorphine (Manson, Turner, & Lees 2002), duodenal levodopa (Kurth et al. 1993; Nilsson, Nyholm, & Aquilonius 2001) or lisuride (Stocchi et al. 2002), again mirroring similar work in animal models (Gagnon, Bedard, & Di Paolo 1990; Juncos, Engber, Raisman, Susel, Thibaut, Ploska, Agid, & Chase 1989; Pearce, Banerji, Jenner, & Marsden 1998).

Intermittent dopaminergic stimulation from erratic intake of medication through poor compliance will contribute to fluctuating plasma and brain levels of antiparkinsonian therapy. It seems likely from the above experimental and clinical evidence that such variations in the delivery of medication would contribute to the development of motor fluctuations. Electronic monitoring data (Figure 1.7) converted to estimated drug levels (Figure 1.8) shows how erratic drug timing exaggerates peaks and
troughs. The prospect of reducing fluctuations by regularising oral medication is appealing, but may be oversimplistic. Adequate thresholds for clinical effect in relation to compliance vary according to drug type and mode of action, but for PD are largely unknown.
Figure 1.7: Two-week chronology plot of co-careldopa 125 prescribed one tablet 5 times daily. Time windows for each dose (2 hours around the target) are marked. Data is taken from a 3-month monitoring period during which total compliance was 82%, daily compliance was 26%, and interval compliance was 25%.
Figure 1.8: *Estimated plasma L-dopa levels in a 5 times daily schedule.* Upper graph is derived from chronology plot shown in Fig 1.4. Reduced levels overnight reflect scheduling of medication during waking hours; daytime drug level fluctuations occur from erratic therapy intake including missed and extra doses. Lower graph is a theoretical perfect dose schedule, modelled from regular daytime intake, and shows more steady drug delivery.

Using therapy response as a diagnostic aid

In PD where there is a degree of diagnostic uncertainty, therapy response is used as a diagnostic tool. An excellent and sustained response to levodopa is one of the supporting features in step 3 of the UK Brain Bank Criteria (Gibb 1988); assuming that the poorly responding patient is fully compliant with medication may mislead the diagnostic process.
Clinical significance of therapy adherence in PD.

Subsequent management decisions in PD depend on response to therapy. Impaired therapy response points the clinician to an alternative tremor disorder or a Parkinson-plus condition, but may result from low drug intake. Decisions to titrate medication or combine treatments also depend on estimating the therapeutic response from prevailing doses; patients omitting doses may be incorrectly judged to have more rapid disease progression.

Clinical trials

Adherence measures help the interpretation of both biological and pharmacological aspects of drug trials (Rudd et al. 1990; Rudd et al. 1992). Nonadherence can therefore bias assessment of drug treatment efficacy (Gordis L 1979; Haynes & Dantes R. 1987). Cholesterol and coronary risk were reduced four times more effectively when patients took 5-6 of 6 prescribed doses of cholestyramine than in those taking only 1-2 doses (Lipid Research Clinics Coronary Primary Prevention Trial 1984). The investigators projected that adverse coronary events might be halved if all patients took the prescribed dose. In PD trials, adherence is usually measured by simple tablet count (Rascol et al. 1998; Shults et al. 2002) which may overestimate compliance. The lower limit usually applied is 80% of tablet intake but is arbitrary and does not have a strong pharmacological basis (Hughes et al. 2001). Compliance in clinical trials is generally higher than in 'real-life' due to patient selection (less concomitant disease and fewer co-administered drugs) and closer monitoring (Andrade et al. 1995; Fayers & Hand 1997).
Economic considerations

Potential economic costs of non-compliance include loss of work time due to poor symptom control, drug stockpiles, increased consultations, hospital admissions and higher levels of care. Increased motor complications may lead to earlier use of expensive therapies including apomorphine and surgery including stimulators.

Concordance in managing PD

In the management of PD there are several options of drug management at each disease stage. Timing and choice of first and subsequent drugs and their titration schedules represent some of the many considerations. Such variations in practice are being analysed in ongoing clinical research such as the PD MED study. Physicians are guided by knowledge gained from clinical trials, but ideally the therapy choice should result from a shared process, seeking the patient’s knowledge, views, understanding and attitudes. This requires the provision of accurate and concise information and ultimately giving the patient the management decision. The Medicines Partnership describe three pillars of concordance: (i) patient knowledge, (ii) involving patients as partners and (iii) supporting patients in taking medicines.

Conclusion

Knowledge of medicine-taking behaviour and clarifying the patient’s intentions through improved concordance is essential for a complete understanding of the patient’s clinical presentation and response. These factors impact on diagnostic accuracy and subsequent management decisions. Sub-optimal therapy intake has several potential consequences. Patients who under-dose may have increased disability and reduced quality of life. Mental state and behavioural problems occur from medication overuse. Those who take medication erratically may increase
clinical fluctuations. Research is needed to examine medicine-taking behaviour in PD to guide interpretation of therapy response in practice and in clinical trials.
Chapter 2

The risks of prescription medication from a general neurological perspective; What are patients concerns about prescribed medication?
Introduction

A therapy history is a fundamental part of the healthcare consultation. Current drugs (prescribed, over the counter, herbal remedies, drugs of misuse) and how they are being taken (frequency, timing, missed and extra doses), drugs tried in the past, reason for discontinuation, therapy response, adverse effects, allergies and intolerances should be taken into account. Recent immunisations may also be of importance. Knowledge of medicine-taking behaviour may clarify clinical presentations such as analgesic overuse causing chronic daily headache, or severe dyskinesia resulting from obsessive use of dopamine replacement therapy. Patients' beliefs about medicines have a close relationship to therapy adherence (Horne & Weinman 1999). Patients weigh up the balance between their personal necessity for medication (based on symptoms, disease perception, and expectations of therapy) against potential concerns over side effects (both short and long-term) and worries over becoming drug dependent. A questionnaire scoring levels of drug necessity against concerns has been validated for both general and disease specific versions (e.g. asthma, HIV, cardiac and renal disease). Patients with high necessity and low concern scores have higher therapy adherence; low necessity and high concerns correlate with low adherence; while high necessity together with high concerns provide patients with a dilemma resulting in partial adherence. How valid are patients' concerns about potential adverse effects? This chapter reviews drug-induced neurological problems in relation not only to Parkinson's disease but also to frequently associated problems (e.g. confusion and depression).
Movement Disorders

Drug induced movement disorders are common. In epidemiological studies between a third and a half of parkinsonism is caused by medication (Jimenez-Jimenez, Garcia-Ruiz, & Molina 1997). On the other hand dopaminergic excess results in hallucinations, chorea and dystonia (Figure 2.1).

Figure 2.1: Diagram of Dopaminergic System and Disease and Drug Effects

Therapy to replace deficient dopamine or otherwise stimulate the dopaminergic system in Parkinson's disease may cause hallucinations and paranoia, a form of drug-induced psychosis. Schizophrenia patients treated with neuroleptics may develop a movement disorder, such as tremor, parkinsonism, or tardive dyskinesia.

Neuroleptics are particularly likely to induce movement disorders. In one prevalence study, 62% of patients on neuroleptics developed movement disorders, encompassing a mix of akathisia (31%), parkinsonism (23%) and tardive dyskinesia (32%) (Janno et al. 2004). Extrapyramidal symptoms are associated to a lesser extent with all groups of antidepressants (tricyclics, monoamine oxidase
inhibitors and selective serotonin re-uptake inhibitors (SSRIs)) (Gill, DeVane, & Risch 1997), though this is based on case reports rather than controlled studies. The risk appears greater with the SSRIs than tricyclics. Complex interactions of dopamine, serotonin and noradrenaline between cortical structures and basal ganglia are the likely mechanism. Considering antidepressant treatment for patients with PD is complex. Depression affects at least a third of PD patients. Clinical experience suggests significant benefit from antidepressant therapy in selected patients, although some patients report worsened parkinsonism. A Cochrane systematic review concluded that there is insufficient data on the effectiveness and safety of antidepressant therapies in Parkinson's disease (Chung et al. 2003).

Akathisia (restlessness) may be induced by the antidepressants (Gill, DeVane, & Risch 1997), antipsychotics, antihistamines, calcium channel blockers, carbamazepine or metoclopramide. Akathisia is described as a sense of inner restlessness, a subjective need to move, such as shuffling of the legs, marching on the spot, pacing, rocking or crossing/uncrossing the legs. It is a frequent and early side effect of antipsychotic therapy (Miller et al. 1997) usually occurring within 2 weeks of initiation. If the offending drug cannot be stopped, propranolol or benzodiazepines may alleviate the symptoms.

Chorea is an adverse effect of dopaminergic excess. Thus in patients with PD, levodopa (Rascol, Brooks, Korczyn, De Deyn, Clarke, & Lang 2000), dopamine agonists (Hubble 2002) and COMT inhibitors (Fenelon, Gimenez-Roldan, Montastruc, Bermejo, Durif, Bourdeix, Pere, Galiano, & Schadrack 2003; Larsen, Worm-Petersen, Siden, Gordin, Reinikainen, & Leinonen 2003) may all contribute. About half of PD patients treated with levodopa will develop motor complications of
end-of-dose 'wearing off', dyskinesia (chorea/dystonia) and 'on-off' fluctuations within 5 years (Lees 1986; Marsden & Parkes 1976). Such motor complications are commoner in young onset patients (100% after 6 years in cases developing PD before age 40) (Clarke 2002). Dopamine agonists are now a frequent choice of initial antiparkinsonian medication (Montastruc, Rascol, & Senard 1999), based on strong evidence from many independent controlled studies that DAs delay the onset of motor complications and the need to initiate levodopa therapy for many months and even years (Hubble 2002). Selegiline is an alternative dopamine sparing agent which delays the need for levodopa by 9 months (Shoulson 1989).

Reducing antiparkinsonian medication lessens dyskinesia but increases 'off' time, and most patients prefer to maintain 'on' time despite the dyskinesia. Amantadine has some antidyskinetic activity in levodopa induced motor complications (Metman, Del Dotto, LePoole, Konitsiotis, Fang, & Chase 1999). A small subgroup of Parkinson's disease patients use dopamine replacement excessively and compulsively (Giovannoni, O'Sullivan, Turner, Manson, & Lees 2000; Lawrence, Evans, & Lees 2003), and take increasing quantities of dopamine replacement therapy despite severe drug-induced dyskinesia and a cyclical mood disorder.

Anticonvulsant induced chorea is rare but the risk increases with polytherapy perhaps due to an additive or synergistic effect on central dopaminergic pathways; the combination of phenytoin and lamotrigine in particular predisposes to drug induced chorea (Zaatreh et al. 2001). Other drugs such as amiodarone, amphetamines, antihistamines, anti-psychotics, oral contraceptives and metoclopramide may cause chorea.

**Tardive syndromes** are a group of delayed-onset abnormal involuntary movement disorders induced by dopamine receptor blocking agents (Fernandez & Friedman...
Tardive dyskinesia (rhythmic involuntary movements of tongue, face and jaw) is the best known and may occur even up to years after withdrawal of the drug. Tardive dystonia (usually of the face and neck), akathisia (which begins during neuroleptic therapy or within 3 months of discontinuation and persists for 1 month or more after drug discontinuation), tics (tardive Tourettism), myoclonus (of the neck or upper arms and particularly associated with high doses of neuroleptics) and tremor can also result from chronic antipsychotic use (Rodnitzky 2002). These syndromes also occur with the newer atypical antipsychotics but the risk is lower.

Informing and monitoring the patient may help to reduce malpractice claims which are common in the US in this therapeutic area (Kaye & Reed 1999). Kaye et al (Kaye & Reed 1999) describe the 4 commonest reasons for malpractice claims brought by patients with tardive dyskinesia (TD).

1. The risk of developing TD was not explained and consent was not obtained.
2. Diagnostic error, treatment with dopamine blocking drugs was not warranted.
3. The physician failed to monitor the patient.
4. The drug manufacturer and the doctor (as the manufacturer's agent) produced a drug with defective design, testing or warning information (product liability).

Onset of TD within 3 months of drug exposure is possible but uncommon. Some improvement after withdrawal of the offending drug occurs in a third of cases (Jeste & Wyatt 1979), but complete recovery is rare (Glazer et al. 1990). If antipsychotic therapy cannot be discontinued, an atypical agent or tetrabenazine may help (tetrabenazine is dopamine depleting and blocks postsynaptic dopamine receptors).

**Acute Dystonic reactions** can be induced by dopamine depleting drugs such as antihistamines, antipsychotics, antiemetics (domperidone, metoclopramide,
prochlorperazine), tetrabenazine and antimalarials. Domperidone and metoclopramide use is restricted in children and young adults (under 20 years) in whom acute dystonic reactions are commoner. The dystonia usually occurs on the first day of drug exposure and affects the head, neck and trunk muscles with neck retraction, tongue protrusion, trismus and oculogyric crisis. Acute dystonic reactions are treated with anticholinergics (benztropine) or benzodiazepines.

**Chronic dystonia** is associated with antiparkinsonian medication (levodopa and the dopamine agonists), phenytoin, phenobarbitone and tetrabenazine. The dystonia of Parkinson's disease, typically early morning calf or foot cramps, is a 'wearing-off' symptom which responds to DA or levodopa.

**Tremor** is caused by many drugs through several mechanisms (Smaga 2003) (Table 2.1). Drugs may enhance physiological tremor, typically a high frequency postural tremor. Dopamine depleting drugs cause a parkinsonian tremor typically the 4-6 Hz 'pill-rolling' rest tremor. Drugs causing a cerebellar syndrome cause an intention tremor; withdrawal tremors follow discontinuation of drugs of dependence or alcohol.

**Table 2.1: Mechanisms of Drug-induced Tremor**

<table>
<thead>
<tr>
<th>Enhanced Physiological</th>
<th>Parkinsonian</th>
<th>Cerebellar</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetics</td>
<td>Neuroleptics</td>
<td>Lithium</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Metoclopramide</td>
<td>Phenytoin</td>
<td>SSRI-Paroxetine</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Prochlorperazine</td>
<td>Chemotherapy-5FU</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Antidepressants</td>
<td>Chronic alcoholism</td>
<td>Opiates</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Calcium antagonists</td>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Sodium valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium valproate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SSRI = Selective Serotonin Reuptake Inhibitor; 5FU = 5 Fluorouracil
Parkinsonism can be drug induced and may be clinically indistinguishable from idiopathic Parkinson's disease (PD) (Arblaster et al. 1993). Although symptoms may be asymmetrical (Caligiuri, Bracha, & Lohr 1989), a symmetrical presentation is commoner than in idiopathic PD. Functional imaging using [123I]-FP-CIT (DaTSCAN, GE Healthcare, plc) single photon emission computerized tomography (SPECT), a measure of presynaptic dopamine transporters, differentiates drug induced parkinsonism (normal scan) from idiopathic PD (abnormal scan). Drug-induced parkinsonism is most commonly attributed to antipsychotics or prochlorperazine. Other implicated drugs are antidepressants, cinnarizine, metoclopramide and tetrabenazine. Atypical antipsychotics are less likely to induce extrapyramidal adverse effects (Baldessarini & Tazazi 2001), ranked in the following order: clozapine < quetiapine < olanzapine = zisprasidone (though this excludes akathisia and neuroleptic malignant syndrome) (Tarsy, Baldessarini, & Tarazi 2002). Antipsychotic induced parkinsonism is treated with an antimuscarinic (less correctly anticholinergic) usually procyclidine, if the antipsychotic medication cannot be discontinued. Sodium valproate can induce reversible parkinsonism (Armon et al. 1996). There are reports of calcium channel blockers such as diltiazem and verapamil causing drug-induced parkinsonism on rare occasions (Rodnitzky 2002).

Neuroleptic Malignant Syndrome (NMS) is caused by acute dopamine D2 receptor blockade (Pelonegro, Levenson, & Pandurangi 1998) in the corpus striatum, hypothalamus and spinal cord. It is an acute and severe form of drug-induced parkinsonism with a mortality of around 10% (Addonizio, Susman, & Roth 1987; Pearlman 1986; Rosenberg & Green 1989) due to rhabdomyolysis, disseminated intravascular coagulation and acute renal failure. Estimations of
incidence vary between 0.02% and 3.2% of patients on neuroleptics. Dehydration is an important predisposing factor. NMS is characterised by hyperthermia, fluctuating level of consciousness, muscular rigidity (often axial), dystonia, autonomic dysfunction and elevated levels of muscle proteins (creatine kinase and myoglobin) (Table 2.2). Several diagnostic criteria have been proposed; hyperthermia and muscle rigidity are cardinal features. Drugs causing parkinsonism may all produce NMS (particularly antipsychotic drugs, with a delay in onset for depot preparations) but withdrawal, particularly if rapid, of antiparkinsonian medication especially levodopa is also a trigger mechanism, as is rapid switch of dopamine agonists (Levenson 1985; Reimer, Kuhlmann, & Muller 2002; Takubo, Harada, Hashimoto, Inaba, Kanazawa, Kuno, Mizuno, Mizuta, Murata, Nagatsu, Nakamura, Yanagisawa, & Narabayashi 2003). Treatment involves stopping the causative agent (and lithium if the patient is taking this) and supporting with IV fluids, antipyretics and a cooling blanket. Several case reports demonstrate effective use of specific therapy such as dopamine agonists, levodopa, amantadine or dantrolene. Recovery usually occurs within 2 to 14 days.
Table 2.2: Characteristics of Neuroleptic Malignant Syndrome and Serotonin Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Serotonin Syndrome</th>
<th>Neuroleptic Malignant Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative Drugs</strong></td>
<td>SSRIs, TCAs, MAOIs</td>
<td>Neuroleptics, metoclopramide, amoxapine (a TCA), sudden dopaminergic therapy withdrawal</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>5-HT receptors overstimulation</td>
<td>D2 receptor blockade</td>
</tr>
<tr>
<td><strong>Onset of symptoms</strong></td>
<td>Within 24 hours</td>
<td>Within 7 days (longer with depot drugs)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Autonomic, Mental, Neurological</td>
<td>Autonomic, Mental, Neurological</td>
</tr>
<tr>
<td><strong>Differentiating Symptoms</strong></td>
<td>Myoclonus, diarrhoea, nausea, shivering</td>
<td>Dysphagia, hypersalivation, incontinence</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td>Dilated pupils, myoclonus, Hyper-reflexia</td>
<td>Temp &gt;38°C, akinesia, extrapyramidal rigidity</td>
</tr>
<tr>
<td><strong>Laboratory results</strong></td>
<td>↑WCC, ↑CK</td>
<td>↑WCC, ↑↑CK</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td>Wide spectrum mild - severe</td>
<td>More severe - most cases require intensive care</td>
</tr>
<tr>
<td><strong>Serious complications</strong></td>
<td>DIC, leukopenia, thrombocytopenia, seizures, multi-organ failure, rhabdomyolysis</td>
<td>DIC, acute renal failure, rhabdomyolysis myocardial infarction, sepsis cerebellar neuronal degeneration</td>
</tr>
<tr>
<td><strong>Main treatment</strong></td>
<td>Discontinue causative drug(s); supportive</td>
<td>Discontinue causative drug(s); supportive</td>
</tr>
<tr>
<td><strong>Specific Treatments</strong></td>
<td>Benzodiazepines, cyproheptadine, chlorpromazine</td>
<td>Dopamine agonists, amantadine, carbidopa-levodopa, dantrolene</td>
</tr>
<tr>
<td><strong>Recovery</strong></td>
<td>70% within 24 hours</td>
<td>2 - 14 days</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Total of 23 deaths to 1999</td>
<td>15 - 20% of cases</td>
</tr>
</tbody>
</table>

SSRIs = Selective Serotonin Reuptake Inhibitors, TCAs = Tricyclic Antidepressants, MAOIs = Monoamine Oxidase Inhibitors, 5-HT = 5-Hydroxytryptamine (serotonin), WCC = White Cell Count, CK = Creatine Kinase, DIC = Disseminated Intravascular Coagulation

Cognitive Impairment

Confusion, cognitive impairment and hallucinations are manifestations of relatively reduced cholinergic activity as illustrated in Figure 2.2.
Relative cholinergic excess in Parkinson's disease may be corrected by using anticholinergic drugs, but the risks of causing confusion and aggravating Parkinson's-related cognitive impairment or dementia means that these drugs are less commonly prescribed today. Acetylcholinesterase inhibitor drugs, used to treat Alzheimer's disease, have an opposite effect, and have tremor amongst the list of side-effects.
anticonvulsants, antidepressants, antituberculous drugs, antimalarials, anti-inflammatories, cardiac glycosides, diuretics, hypotensive agents, H2 antagonists, neuroleptics, opiates, sympathomimetics, and sedatives. Agitation and confusion may be part of a withdrawal syndrome from drugs of addiction and alcohol. Central neurotoxicity can result from chemotherapy (particularly methotrexate, cytarabine and ifosfamide used in the treatment of acute leukaemias) ranging from minor cognitive impairment to encephalopathy (Verstappen et al. 2003).

**Serotonin Syndrome** is an acute iatrogenic drug-induced condition, characterised by a triad of cognitive behavioural changes, autonomic instability and neuromuscular excitability (Ener et al. 2003). It is caused by overstimulation of 5-HT receptors (Birmes et al. 2003). However, the clinical similarity between serotonin syndrome and neuroleptic malignant syndrome (an acute dopaminergic blockade) indicates a more complex reciprocal interplay in the balance between serotonergic and dopaminergic systems rather than a simple serotonergic excess or dopamine deficiency. Since serotonin excess inhibits dopamine secretion, there is clinical overlap in the two syndromes (see Table 2.2). Different mechanisms of serotonin (5-HT) excess are summarised in Table 2.3 and Figure 2.3.
Table 2.3: Mechanisms of serotonin overstimulation

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs metabolised to serotonin or promoting serotonin release</td>
<td>Levodopa, Lithium, MAOIs, Tryptophan, Trazodone, Tetrabenazine</td>
</tr>
<tr>
<td>Inhibition of serotonin reuptake</td>
<td>SSRIs, TCAs, Trazodone, Tramadol, St John’s wort, Venlafaxine</td>
</tr>
<tr>
<td>Inhibition of serotonin metabolism</td>
<td>MAOI (phenelzine, isocarboxid, selegiline), St John’s wort</td>
</tr>
<tr>
<td>Postsynaptic receptor stimulation</td>
<td>Buspirone, Triptans, Lithium, Carbamazepine</td>
</tr>
</tbody>
</table>

MAOIs = Monoamine Oxidase Inhibitors; SSRIs = Selective Serotonin Reuptake Inhibitors; TCAs = Tricyclic Antidepressants

Figure 2.3: Mechanisms of Serotonin Syndrome
Metabolism of tryptophan to serotonin and release and recycling in the synaptic system is shown. Sites of potential disruption from exogenous drugs, which may be involved in generating a serotonin syndrome, are numbered (see key).

1 Increased substrate
2 Inhibition of serotonin metabolism
3 Increased release serotonin into synaptic cleft
4 Postsynaptic receptor stimulation
5 Inhibition of serotonin reuptake
The main causative drugs are selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) (Trindade et al. 1998) and monoamine oxidase inhibitors (MAOIs e.g. selegiline). The syndrome usually occurs after a dose increase or after adding a second serotonergic agent. Fortunately the risk of inducing this syndrome is low. For example, SSRI treatment of depression in patients with Parkinson's disease already on selegiline, found possible serotonin drug interaction in only 11 of 4568 patients (0.24%) (Richard et al. 1997). Serotonin syndrome has been reported as an interaction between St.John's wort (Hypericum perforatum, a herbal remedy used in depression) and SSRIs in several case reports (Ernst 2003). Theoretically the 5-HT agonists (the triptans) could cause a serotonergic overstimulation but there are no reports of serotonin syndrome when these drugs are prescribed as monotherapy although cases are described where a triptan has been combined with another serotonergic drug. Revised diagnostic criteria of serotonin syndrome are outlined in Table 2.4 (Radomski et al. 2000).

Serotonin syndrome should be considered in patients who present with an acute confusional state with mild pyrexia, sweating, agitation, nausea, tremor and diarrhoea. Symptoms typically occur rapidly after the medication change, within 2 hours in 50% and 24 hours in 75% of cases. Neuromuscular excitability (myoclonus, rigidity, tremor) occurs in 50% (Mills 1995) and changes in mental state (usually excitation) occur in 40% of cases. Elevated serum creatine kinase, white cell count, hepatic transaminases and lowered serum bicarbonate levels support the diagnosis. The serotonergic agent or agents must be discontinued. Supportive therapy should be given; 40% require intensive care admission and 25% need intubation. Benzodiazepines have been used to reduce anxiety.
Cyproheptadine (an antihistamine with antiserotonergic characteristics) and chlorpromazine (a 5-HT receptor antagonist neuroleptic) may be tried although their benefit is not proven. Deaths have been reported but the mortality rate is unknown.

Table 2.4: Diagnostic Criteria for Serotonin Syndrome

- Increase in dosage or addition of a second serotonergic agent
- Plus 4 major symptoms or 3 major and 2 minor symptoms

<table>
<thead>
<tr>
<th>Autonomic Symptoms</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>Tachypnoea, dyspnoea</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Hypo or hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mental Symptoms</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>Agitation, nervousness</td>
</tr>
<tr>
<td>Hypomania</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Coma or altered consciousness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological Symptoms</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td>Akathisia</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Impaired co-ordination</td>
</tr>
<tr>
<td>Tremor</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No recent introduction or dose increase of neuroleptic</td>
</tr>
<tr>
<td></td>
<td>Other causes (e.g. infective, metabolic, endocrine, toxic) excluded</td>
</tr>
<tr>
<td></td>
<td>No similar symptoms attributed to psychiatric condition prior to introduction of serotonergic agent</td>
</tr>
</tbody>
</table>

Cholinesterase Inhibitors indicated for mild to moderate Alzheimer’s disease have the potential to cause hypercholinergic effects either central (excitation, agitation) or peripheral (bradycardia, gastrointestinal symptoms) via drug interactions with psychotropics or antiarrythmics (Bentue-Ferrer et al. 2003).
Conclusion

A wide spectrum of neurological presentations may be caused or precipitated by drugs, both prescribed and non-prescribed. This can be at first presentation, or in cases with already established neurological disease. Doctors have responsibility in preventing iatrogenic symptoms by careful prescribing, and in identifying drug-induced syndromes. Failure to consider a drug-induced cause or incorrect attribution of the presentation to drug therapy may lead to inappropriate investigations and management.

Quantifying and summarising risk to guide patients in starting treatment and becoming aware of emerging side-effects is a key component of the concordance process. A European Union directive recommends qualitative descriptions for 5 bands of risk ranging from very rare (defined as <0.01%) to very common (>10%) (European Commission Pharmaceutical Committee 1998). However, when people are given qualitative descriptions of risk, the degree of risk is overestimated compared against risk information given in numerical terms. The patient is less likely to adhere to a drug regimen if they perceive side effects to be very common (Berry, Knapp, & Raynor 2002). Thus misplaced or exaggerated concerns about adverse effects may need addressed. In PD, treating one movement disorder (tremor, rigidity, bradykinesia) may result in another (chorea, dystonia). Benefits in terms of symptom control and improved in quality of life are weighed against potential adverse effects by both patients and clinicians. The patient’s perspective on risks of therapy will be reflected in their medicine taking behaviour.
Chapter 3

Measuring therapy adherence in Parkinson’s disease: a comparison of methods
Introduction

In this chapter four methods of assessing therapy adherence are compared with a view to practical use in day to day clinical practice and relevance for clinical trials. Consideration of how patients take their medication is vital in understanding the therapeutic response in any patient group. In Parkinson's disease, an excellent response to levodopa supports the accuracy of the clinical diagnosis (Hughes et al. 1992), while in other disorders poor adherence to drug therapy is often identified and accepted as a principal reason for impaired response (Urquhart 1994).

Evidence for excess medication intake by some Parkinson's patients is based largely on self-reporting (Lawrence, Evans, & Lees 2003) while electronic monitoring identified that only one in ten patients had complete schedule adherence (Leopold, Polansky, & Hurka 2004). Simple tablet counts, which are often used in clinical trials to indicate satisfactory adherence in Parkinson's (Rascol, Brooks, Brunt, Korczyn, Poewe, & Stocchi 1998; The Parkinson Study Group 1997) and elsewhere (Hughes, Bagust, Haycox, & Walley 2001) can be inaccurate when patients maintain multiple supplies (e.g. home, work) (Cramer et al. 1989; Stephenson et al. 1993) or discard drugs deliberately (Rand et al. 1992).

Measurement of compliance

There are 2 main categories, direct and indirect.

Direct Measurement of drug or metabolite levels in blood, urine or saliva is one approach. Measures of disease severity reflecting the drug mechanism are also considered direct e.g. lymphocyte subpopulation counts in assessing antiretroviral therapy, or glycosylated haemoglobin in diabetes. Serum and urine levels can be misleading because sampling is limited and compliance may improve at the time of measurement (e.g. in anticipation of a clinic visit) (Rudd, Ahmed, Zachary, Barton,
Bonduelle 1990; Urquhart 1994). Compared against electronic drug monitoring devices, serum drug concentrations had no significant relationship to compliance in epilepsy (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989). Also, non-drug effects may influence disease markers, such as diet in diabetes. Venous levodopa levels (Copeland, Dutton, Roberts, & Playfer 1994) in 103 samples from 53 PD patients suggested poor compliance in 3 (2.9%) whose levels were at or below the lower limit of the assay.

**Indirect Methods** include pharmacy refill data and appointment keeping (both of which are broad indicators) and self-reports, healthcare professional’s assessment, simple tablet count and electronic monitoring devices. Electronic monitoring assumes that medication is ingested, while it may simply be collected and stored or destroyed. Pharmacy refill data is useful in large population-based studies (Steiner & Prochazka 1997) but is of limited value in short-term studies. Self-reports vary from simply asking patients about compliance (avoiding a judgmental approach or prompting) to structured validated questionnaires. Careful questioning identifies over half of non-compliant patients (Stephenson, Rowe, Haynes, Macharia, & Leon 1993). There are structured validated self reports such as the brief medical questionnaire (Svarstad et al. 1999) and the Morisky self-report (Morisky, Green, & Levine 1986). Using blood pressure control as a measure of adherence, the Morisky scale has a sensitivity of 81% and specificity of 44%. Compared against pill counts, self-reports are 55% sensitive and on average 87% specific (Stephenson, Rowe, Haynes, Macharia, & Leon 1993). Self-reports of sub-optimal adherence are accurate (Hugen et al. 2002), but reports of full adherence may be misleading and self-reporting often overestimates true adherence behaviour (Melbourne et al. 1999). In PD studies of excess dopamine replacement therapy
intake, medication history was used to assess dosages taken (Evans, Katzenschlager, Paviour, O'Sullivan, Appel, Lawrence, & Lees 2004; Giovannoni, O'Sullivan, Turner, Manson, & Lees 2000; Lawrence, Evans, & Lees 2003). Clinical judgement of compliance is inaccurate and no better than chance (Gilbert et al. 1980; Roth & Caron 1978); in Primary Care sensitivity was 10% (Gilbert, Evans, Haynes, & Tugwell 1980) for patients well-known to the reporting physician. Simple tablet counts are easy and inexpensive for routine practice and indicate total dose compliance (ratio of total taken dose: recommended dose) but consistently overestimate compliance (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989; Paes, Bakker, & Soe-Agnie 1998; Pullar et al. 1989; Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990). Accuracy improves with unannounced “spot checks” in the patient's home (Haynes et al. 1980) which requires ethical consideration. Electronic monitoring devices are the gold standard for monitoring compliance (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989), but are expensive and impractical for routine care. Medication Event Monitoring Systems (MEMS®, Aardex, Switzerland) are pill bottles with microprocessors which record dose date and time (Figure 3.1).
In addition to total dose compliance, daily compliance (percentage of days when dose taken correctly) and time interval compliance (ratio of correct: incorrect doses by time interval) are calculated. Electronic devices are more accurate and detailed than other methods (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989; George et al. 2000; Hugen, Langebeek, Burger, Zomer, van Leusen, Schuurman, Koopmans, & Hekster 2002; Kruse et al. 1992; Lee et al. 1996; Olivieri et al. 1991; Rivers, Ardagh-Walter, & Wright 1998; Waterhouse et al. 1993). Electronic monitoring in 39 PD patients showed frequent under-compliance (Leopold, Polansky, & Hurka 2004).

The most appropriate compliance measurement method depends on the clinical situation; combining methods may improve accuracy. In depression electronic...
monitoring was the most accurate and serum levels had the least patient
acceptability of 4 methods tested (George, Peveler, Heiliger, & Thompson 2000).
The current study applied multiple techniques of assessing therapy adherence in PD, to define sensitivity of these methods against the gold standard of electronic monitoring (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989).

**Methods**

**Study Population**

Consecutive patients in a movement disorder clinic and with idiopathic PD fulfilling
UK Brain Bank Criteria were enrolled. Patients provided signed informed consent
and the local ethics committee approved the protocol. Patients were taking at least
one antiparkinson drug but were excluded if use of electronic bottles might
adversely affect care (e.g. patients relying on a dosette box or similar device).

**Study Design**

A prospective single blind randomised crossover design was undertaken (Figure
3.2). A computerised randomisation list was generated and group allocation was
inserted into opaque envelopes. The sealed envelopes were then given to the
investigator. A Parkinson's disease nurse specialist who remained blinded to group
allocation (active therapy monitoring or no active therapy monitoring) carried out
the clinical assessments.
Figure 3.2: Outline of study design in 129 patients with Parkinson's Disease. Patients were randomised to active therapy monitoring, with crossover between methods, but all patients completed self-reports of medicine intake.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>STC (n = 42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM+STC (n = 43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No added monitoring (n = 44)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STC = simple tablet count, EM = electronic monitoring

Two thirds of patients underwent active monitoring, consisting of 2 x 3 month periods of simple tablet count alone, or simple tablet count concurrent with electronic monitoring, in random order. The remaining one third received no additional therapy monitoring (control group). Data was tested for any order effect on electronic monitoring results (performed first or second in the crossover design). Baseline assessments were of Unified Parkinson's Disease Rating Scale (UPDRS) 1 to 4, Hoehn and Yahr, Schwab and England, Geriatric Depression Scale (GDS), Epworth sleep scale (ESS), Parkinson disease quality of life (PDQ 39), and mini mental state examination (MMSE). Current therapy and adverse events were noted and clinical scoring was blind to therapy monitoring method. Patients undergoing electronic monitoring had their PD medication dispensed into separate bottles for each drug type and strength.

At 3 months patients completed a validated self-report (Svarstad, Chewning, Sleath, & Claesson 1999) from which medication intake was calculated. They also
marked a visual analogue scale for each PD drug (range 0-120) annotated as follows:

- 50 representing about half of prescribed medication
- 100 meaning all medication taken exacted as prescribed
- 120 representing excess medication intake

Patients also answered two questions:

Please estimate how accurately you take your medication,

- 1. I miss a dose of medication
- 2. I take an extra dose of medication

- with choices of response for each of these two questions of:
  - frequently / sometimes / rarely / never.

- Patients recorded their opinion about being undertreated, overtreated or if antiparkinson therapy level was ‘about right’ and the clinician independently recorded a similar impression.

- UPDRS 1 to 4, Hoehn and Yahr, Schwab and England and adverse events were repeated at 3 and 6 months.

Patients unable to use the electronic monitoring bottles or who misused them were withdrawn.

**Outcome Measures**

The following definitions were applied, which follows standard methodology:

**Total adherence** refers to the amount of medication taken compared to the amount prescribed. In this study, total adherence was estimated by 4 different methods:

- self-report
- visual analogue scale
• simple tablet count
• electronic monitoring

**Days adherence** refers to the percentage of days the correct number of doses is taken.

**Timing adherence** is the percentage of doses taken at the correct time interval.
Timing adherence is calculated from time intervals which give an optimum pharmacokinetic profile, allowing for a 25% deviation in timing (e.g. for a drug taken three times a day time intervals of between 6 and 10 hours are satisfactory).

• Both days adherence and timing adherence were calculated from electronic monitoring.

One-way analysis of variance (ANOVA) was undertaken to compare methods of measuring compliance, using Bonferroni correction for multiple comparisons if overall significance was less than 0.05.

Average medicine intake was used to categorise actively monitored patients as follows:

• 'satisfactory adherence' meaning ≥80% intake, or
• 'underuse' meaning <80% intake

Electronic and tablet count methods were compared by McNemar’s test.

• The 80% cut off is commonly applied in compliance studies (George, Peveler, Heiliger, & Thompson 2000; Gilbert, Evans, Haynes, & Tugwell 1980; Haynes, Taylor, Sackett, Gibson, Bernholz, & Mukherjee 1980; Lee, Kusek, Greene, Bernhard, Norris, Smith, Wilkening, & Wright, Jr. 1996; Rosen et al. 2004; Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990) and clinical trials including PD (Hughes, Bagust, Haycox, & Walley 2001; Rascol, Brooks, Brunt, Korczyn, Poewe, & Stocchi 1998). Although this grouping would include patients with
medication overuse (another form of non-adherence) these numbers were expected to be small.

- The sensitivity and specificity of simple tablet count, self-report and visual analogue scale in detecting medicine underuse defined by electronic monitoring data were calculated. Statistical analysis used GraphPad Prism® (GraphPad® Software, San Diego, USA) and Statistica® (StatSoft, Bedford, UK).

Results

Of 135 patients approached, 6 (4%) declined mainly due to perceived disruption from using electronic monitoring bottles, leaving 129 cases randomised (Figure 3.3). There was no significant difference in age, gender, disease duration, type or dose of antiparkinson medication (levodopa, dopamine agonist) for patients who declined (data not shown). Seventeen patients (13% of randomised cases) were excluded from analysis, as follows:

- 3 withdrew consent
- 9 had problems with the electronic monitoring bottles (difficulty using, mainly due to dyskinesia n = 3; misuse eg. removing a full day’s medication in the morning n = 4; lost bottles n = 2)
- 4 patients were lost to follow up
- 1 died

This left 112 evaluable cases.

- There were no significant differences in baseline characteristics between patients completing versus drop-outs (data not shown) or between patients with active therapy monitoring versus controls (Table 3.1).

Median adherence rates for self-report and visual analogue were 100% for both actively monitored and control patients (Figure 3.4). More actively monitored
patients reported missed doses (39 of 69, 57%) than controls (17 of 43, 40%) but the difference was not significant, and extra doses were reported in 23% of cases for both actively monitored and control patients.
Figure 3.3: CONSORT flowchart of 135 eligible patients.

Assessment of eligibility (n= 135)

Excluded (n=6, all declined)

Randomised (n= 129)

Allocated to active therapy monitoring (n=83)
Received allocated intervention (n=81)
Did not receive allocated intervention (n=2)
Reasons - withdrew consent

Lost to follow up (n=2)
Discontinued intervention (n=10)
Reasons 9 reported problems with monitoring bottles
1 died

Analysed (n= 69)

Allocated to no active therapy monitoring (n= 46)
Received allocated intervention (n=45)
Did not receive allocated intervention (n= 1)
Reason withdrew consent

Lost to follow up (n=2)

Analysed (n=43)
Table 3.1: Patient characteristics by group

<table>
<thead>
<tr>
<th></th>
<th>Active Therapy Monitoring</th>
<th>No Additional Therapy Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 69)</td>
<td>(n = 43)</td>
<td></td>
</tr>
<tr>
<td>Percentage male</td>
<td>57%</td>
<td>70%</td>
</tr>
<tr>
<td>Age</td>
<td>64 (12)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Number prescribed levodopa</td>
<td>46 (67%)</td>
<td>30 (70%)</td>
</tr>
<tr>
<td>Mean levodopa dose</td>
<td>526 mg (333)</td>
<td>427 mg (262)</td>
</tr>
<tr>
<td>Number on dopamine agonist</td>
<td>50 (72%)</td>
<td>30 (70%)</td>
</tr>
<tr>
<td>Number of PD drugs</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Number of PD administrations</td>
<td>4 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Number of PD tablets per day</td>
<td>9 (5)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Number of non-PD drugs per day</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Number of tablets per day</td>
<td>12 (5)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Number on &gt;4 levodopa daily doses</td>
<td>15(20%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>Number usually use compliance aid</td>
<td>18 (26%)</td>
<td>19 (44%)</td>
</tr>
<tr>
<td>Number carer helps with medication</td>
<td>13 (19%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Duration of PD (years)</td>
<td>7 (5)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>UPDRS 2</td>
<td>14 (6)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>27 (12)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Number with dyskinesia</td>
<td>21 (30%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Number with &quot;wearing off&quot;</td>
<td>33 (48%)</td>
<td>23 (53%)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.4 (0.6)</td>
<td>2.5 (0.6)</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td>78 (13)</td>
<td>74 (16)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28 (4)</td>
<td>28 (3)</td>
</tr>
<tr>
<td>Geriatric depression score</td>
<td>11 (7)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>PDQ 39 SI</td>
<td>28 (16)</td>
<td>31 (16)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) or number (percentage). PD = Parkinson’s disease, UPDRS = Unified Parkinson’s disease rating scale, MMSE = mini mental state examination, PDQ 39 SI = Parkinson’s disease quality of life summary index. There were no significant differences between groups.
For the 69 active monitoring patients data was available as follows:

- 142 drugs had electronic monitoring data
- 205 drugs had simple tablet count data (simple tablet counts were performed both alone and simultaneous with electronic monitoring).
- Paired data for simple tablet count and electronic monitoring was available for 111 drugs.
- Overall, the median total adherence measured by simple tablet counts was 97% (interquartile range (IQ) 84-100) versus 96% (IQ 82-100) using electronic monitoring.
- Median daily adherence was 77% (IQ 41-89)
- Median timing adherence was 18% (IQ 9-54) (Figure 3.4, daily and timing results only available from the electronic monitoring technique). There was no evidence of any order effect on electronic monitoring results.
Figure 3.4: Therapy adherence in 112 patients according to monitoring method. Self-report, visual analogue score, simple tablet count, and total adherence by electronic monitoring all showed high adherence rates. Days and timing adherence rates were lower, indicating irregular and erratic medicine intake. Data are median and interquartile range.

Of the 69 actively monitored patients medication intake was as follows:

- 56 (81%) taking 110 PD drugs took ≥80%
- 13 (19%) prescribed 32 PD drugs took <80% of prescribed medication (Figure 3.4).

- Considering the <80% group, self-report (median 100%, IQ 100-100), visual analogue (median 100%, IQ 95-100) and simple tablet counts (median 90%, IQ 78-100) all significantly overestimated median total adherence when compared to the result of electronic monitoring (69%, IQ 44-74, p<0.0001, ANOVA) (Figure 3.5).
Figure 3.5: Therapy adherence in 56 patients with good adherence and 13 patients with poor adherence, based on 80% threshold by electronic monitoring. Each of the 3 other methods reflects intake well in patients with good adherence, but significantly overestimates intake in the poor adherence group (p<0.0001 against electronic monitoring). Data are median and interquartile range.

- Considering those with ≥80% adherence, self-report (median 100%, IQ 100-100), visual analogue (median 100%, IQ 95-100) and simple tablet counts (median 98%, IQ 93-100) were not significantly different from electronic monitoring adherence (98%, IQ 93-101).

- Categorisation of medicine intake as ≥80% or <80% showed a significant difference between electronic monitoring and simple tablet count (p<0.0001, McNemar test).

In patients reporting sub-optimal adherence, electronic monitoring confirmed underuse indicating high specificity (self-report 100%; visual analogue score 97%), but sensitivity was low (self-report 10%; visual analogue score 17%). The broader adherence question of reporting any missed doses increased sensitivity to 77%, but at the expense of low specificity (46%), compared against electronic
monitoring. The sensitivity of simple tablet count was 50% and specificity was 76%, compared to electronic monitoring. The sensitivity of self-report against simple tablet count was 23% with 100% specificity. There was no significant difference in the proportion of patients with electronic monitoring showing <80% adherence who scored positive on the sub-optimal adherence questions (10 of 13 cases, 77%) versus those with good (≥80%) adherence (36 of 56 cases, 64%). Of the 112 patients, 45 (40%) reported never missing or taking an extra dose (from the two adherence questions), which would represent 100% daily adherence in these cases, while in fact no patients achieved 100% daily adherence, and only 3 cases (3%) had daily adherence >95%. Median daily adherence of those who reported missed doses was 70% (IQ 36-88) which just reached significance compared to those reporting perfect adherence (81%, IQ 70-89) (p = 0.05).

One quarter of patients reported a global impression of ‘under-treatment’, less than 5% ‘over-treatment’, and the remainder regarded their medication level as ‘about right’ (see Appendix 2, page 203). Patients taking less than 80% of their medication (by electronic monitoring) were more likely to report undertreatment (5 of 13, 38%) than those adhering to the prescribed regimen (13 of 56, 23%) (not significant). None of the underusers reported that they were being overtreated. Doctors were more likely than patients to judge that therapy levels were on the side of overtreatment (doctors 10%, patients 6%, not significant).

There were no significant differences between the number and types of adverse effects between those with active therapy monitoring and controls.
Discussion

Our finding that self-reports, visual analogue scale and simple tablet counts overestimate adherence compared against electronic monitoring in Parkinson's Disease is consistent with observations in depression (George, Peveler, Heiliger, & Thompson 2000), diabetes (Cramer 2004), hypertension (Hamilton 2003; Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990) and angina (Straka et al. 1997). Electronic monitoring is established as the reference technique in several diseases (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989; Cramer 2004; Lee, Kusek, Greene, Bernhard, Norris, Smith, Wilkening, & Wright, Jr. 1996), and has provided evidence of sub-optimal medication intake in PD (Leopold, Polansky, & Hurka 2004), but ours is the first Parkinson's Disease study comparing compliance assessment methods. The results challenge the assumption that symptoms motivate the Parkinson patient to adhere tightly to the drug regimen. This is consistent with poor compliance rates in other symptomatic diseases (de Klerk et al. 2003; Milgrom et al. 1996). Although Parkinson patients are often interested in their medication, and some chart drug intake and symptom fluctuation (at times obsessively), we found that many patients deviate from the prescribed regimen, and moreover are not accurate in reporting such behaviour. Simple questioning of the PD patient, or more detailed methods such as tablet counting, fails to identify around half of those Parkinson patients whose therapy compliance is poor. Blood levels or urinalysis were not conducted but are of limited validity in compliance studies (Urquhart 1994), nor did we apply other supporting methods (such as pharmacy refill data) which might be helpful in some clinical settings.
In our study patients were fully informed about the monitoring of their medication, which might artificially improve compliance. When study design was concealed from patients (Leopold, Polansky, & Hurka 2004) (who were told that a new pill bottle was under test), 15% had sub-optimal compliance below the 80% threshold, which compares to our rate of 19%. This suggests that blinding patients to electronic monitoring is not necessary to detect sub-optimal adherence. There may however be some effect of monitoring on self-reporting: missed doses tended to be declared more often by actively monitored patients than by controls.

Although the self-report had very low sensitivity (10%) for detecting patients taking their PD medication sub-optimally, it was highly specific and also quantifies underuse. Our adherence question of missed doses (sometimes or frequently) had a similar sensitivity (77%) to the Morisky self-report (72%) in depression (George, Peveler, Heiliger, & Thompson 2000) but neither approach quantifies non-adherence and the improved sensitivity comes at the expense of specificity. Some caution over such figures is needed; in a review of several studies self-reports were 55% sensitive and 87% specific (Stephenson, Rowe, Haynes, Macharia, & Leon 1993) but this was against pill counts, which themselves overestimate adherence compared to the electronic monitoring standard used in our study and elsewhere (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989; George, Peveler, Heiliger, & Thompson 2000; Paes, Bakker, & Soe-Agnie 1998; Pullar, Kumar, Tindall, & Feely 1989; Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990). In clinical practice in PD, when the self-report and/or visual analogue score are less than 80%, therapy intake is extremely likely to be sub-optimal. Occasional missed doses, or other minor deviations, which we commonly observed even in good
compliers, are of uncertain clinical relevance and are probably inevitable given the inherent complexity of today's antiparkinson drug regimens.

Around 40% of our patients declared never missing or taking an extra dose, which compares to 43% in hypertension (Morisky, Green, & Levine 1986) and 30% in HIV positive patients (Walsh et al. 2001), but 3 cases amongst our 40% declaring perfect adherence used less than 80% by electronic monitoring, and as in other studies (Macintyre, Goebel, & Brown 2005) none of our patients had perfect compliance. In diabetes, the sulphonylurea intake was 92% by self-report and 75% by electronic monitoring (Mason, Matsuyama, & Jue 1995), lower rates than ours of 100% for self report and 96% for electronic monitoring. The perception that Parkinson patients take their medication well is correct based on self-reporting, and is correct for overall medication intake, but disguises invariable deviation from the regimen, quite often at levels with potential therapeutic significance.

Simple tablet counts missed half of under-medicating patients, which has implications for this method in clinical trials (Hughes, Bagust, Haycox, & Walley 2001). In hypertension, 'near perfect' pill counts misclassified 22% as having satisfactory adherence (Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990) and pill counts were dismissed as offering little more than misleading reassurance. Another hypertension study found 68% of patients with acceptable adherence (80 to 100% of prescribed tablets taken) by pill count, but electronic monitoring indicated that almost half of these patients were non-adherent (Lee, Kusek, Greene, Bernhard, Norris, Smith, Wilkening, & Wright, Jr. 1996). In epilepsy, only 13% of patients with sub-optimal compliance were detected by pill count (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989), and in depression tablet counts were unreliable in 22% of patients (George, Peveler, Heiliger, & Thompson 2000). Since adherence
levels influence therapeutic efficacy (Gordis L 1979; Haynes & Dantes R. 1987), some adjustment may be appropriate in clinical trials. Additionally, while simple tablet counts are achievable in most patients (96% in one study in depression) they are often unreliable (22% of cases) (George, Peveler, Heiliger, & Thompson 2000). We were able to calculate accurate simple tablet counts in 78% of cases during the period when simple tablet count was carried out simultaneously with electronic monitoring, and 66% of cases when simple tablet count was done alone. Again, the complexity of PD therapy influenced this: patients requiring ready access to frequent doses often maintained supplies in more than one location, and in addition containers were often emptied before the return clinic visit, as experienced elsewhere (Myers & Calvert 1984; Rudd et al. 1986; Rudd et al. 1989). Although unannounced home visits improve the accuracy of simple tablet counts (Haynes, Taylor, Sackett, Gibson, Bernholz, & Mukherjee 1980) this approach in impractical.

Considering total adherence, 81% of our cases had very high rates of adherence. However, daily adherence is the more usual benchmark (Claxton, Cramer, & Pierce 2001) and was lower at 77% while time interval adherence was only 18%. Similar adherence rates occurred in hypertension (total 85%, daily 63% and time interval 34%) for a twice daily drug (Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990). There is no consensus on which one of the 3 electronic compliance measures provides the most useful information. In Parkinson’s Disease the proposed role of pulsatile rather than continuous dopaminergic stimulation in developing motor fluctuations would place greater significance on daily and particularly timing rather than total adherence, since wide variations between days could be missed by the total adherence measure. Accordingly we adopted timing
compliance as the main end point in our subsequent study designed to improve compliance in PD therapy (Chapter 8).

It was interesting that patients who take less medication than prescribed more frequently reported feeling undertreated. This clinical scenario can lead to a recommendation to increase therapy further, with the potential for further divergence between prescribed and actual medication intake. Unfortunately, identifying undermedicating patients amongst poor therapy responders is difficult through simple compliance approaches. In some instances where there are inadequate pointers to an alternative reason for poor therapy response (such as development of a Parkinson plus disorder) the application of more sophisticated compliance techniques such as electronic monitoring may be worthwhile.

In conclusion, self-report, visual analogue scale and simple tablet counts are insensitive in prediction of sub-optimal medicine usage in PD, but when these methods score positively this is likely to be accurate. Electronic monitoring devices show a subset of Parkinson patients who take less medication than prescribed, and indicate that most patients use their medication erratically, even when total tablet intake is correct. How patients take their medicines influences the interpretation of therapy response and consequent management decisions, with implications for clinical practice and clinical trial analysis.
Chapter 4

Sub-optimal medication adherence in Parkinson’s Disease: which factors are associated with medication ‘underuse’?
Introduction

The purpose of this chapter is to explore factors associated with sub-optimal adherence. Associated factors do not imply cause, but guide the clinician in recognising circumstances where therapy adherence may be an issue.

Oral drugs are the mainstay in Parkinson’s disease (PD) treatment. Although efficacy in controlling symptoms (Adler, Sethi, Hauser, Davis, Hammerstad, Bertoni, Taylor, Sanchez-Ramos, & O’Brien 1997; Brooks & Sagar 2003; Hammerstad, Woodward, Nutt, Gancher, Block, & Cyhan 1994; Shannon, Bennett, Jr., & Friedman 1997), and exploration of potential neuroprotective drugs (Shults, Oakes, Kieburtz, Beal, Haas, Plumb, Juncos, Nutt, Shoulson, Carter, Kompoliti, Perlmutter, Reich, Stern, Watts, Kurlan, Molho, Harrison, & Lew 2002; The Parkinson Study Group 1993) along with short and long term adverse effects are widely published, the way in which patients take their drugs has received little attention. In a study of 39 PD patients, adherence was monitored for one month using a questionnaire and electronic monitoring, and significant non-adherence occurred in 54% of patients while only 4 patients (10%) took medicines exactly as prescribed (Leopold, Polansky, & Hurka 2004). The present study was designed as a comprehensive examination of antiparkinson medication intake, and compared the characteristics of patients according to medicine intake using established parameters in the therapy compliance literature (George, Peveler, Heiliger, & Thompson 2000; Gilbert, Evans, Haynes, & Tugwell 1980; Haynes, Taylor, Sackett, Gibson, Bernholz, & Mukherjee 1980; Lee, Kusek, Greene, Bernhard, Norris, Smith, Wilkening, & Wright, Jr. 1996; Rosen, Rigsby, Salahi, Ryan, & Cramer 2004). Effects of medicine taking on clinical outcome (motor
scores and quality of life) were tested as well as influences of demographic factors and co-morbidities (impaired cognition and depression).

Methods

A single centre observational study was conducted in patients fulfilling UK Brain Bank criteria (Hughes, Daniel, Kilford, & Lees 1992) and prescribed at least one antiparkinson drug, but excluding patients on monotherapy with selegiline or amantadine. The study received ethics approval and signed consent was obtained. Patients unable to manipulate the electronic monitoring devices or using compliance aids (e.g. dosette box) where study participation would compromise their compliance were excluded. Out-patients were selected by randomisation (as previously described in Chapter 3) of two thirds of the caseload from two doctors’ lists in the movement disorder team. Baseline assessment included unified Parkinson’s disease rating scale (UPDRS) (Fahn, Elton, & members of the UPDRS Development Committee 1987), Hoehn and Yahr (H&Y), Schwab and England, mini mental state examination (MMSE) (Folstein, Folstein, & McHugh 1975), Geriatric depression score (GDS) (Yesavage et al. 1982), Epworth sleep score (ESS) (Johns 1991), quality of life assessment (PDQ39) (Peto, Jenkinson, & Fitzpatrick 1998), patient-perceived involvement in therapy management decisions (Makoul, Arntson, & Schofield 1995) and satisfaction (Meakin & Weinman 2002) with the movement disorder health care service. Prevailing antiparkinson medication was dispensed into electronic monitoring bottles (MEMS®, Aardex, Switzerland) (one bottle for each tablet type and strength) and patients were given verbal and written instruction. At 3 months, the electronic monitoring devices were collected and UPDRS, H&Y and Schwab and England were repeated.
Correlation between total dose compliance (total dose taken, expressed as a percentage of the total dose prescribed), daily compliance (percentage of days when correct number of doses taken) and time interval compliance (percentage of doses taken at the correct time interval) and other variables was examined using Pearson correlations (Prism 3, GraphPad®, CA, USA, and Statistica®, StatSoft, Bedford, UK). Patients were categorised according to medication use calculated from MEMS data:

- (1) Patients with medication underuse, defined as total compliance of less than 80%, or
- (2) Patients with satisfactory adherence, defined as total compliance of equal to or over 80%

The 80% threshold has been applied in several compliance studies as described in the methods section of Chapter 3. Since this threshold is not validated in PD we also applied a 70% threshold. Average compliance was calculated for patients on more than one antiparkinson drug.

**Results**

Of 68 patients asked to participate, 6 (9%) declined mostly due to perceived disruption of the electronic monitoring bottles, including one who used a compliance aid. There was no significant difference in age, gender, disease duration, type or dose of antiparkinson medication (levodopa, dopamine agonist) for patients who declined (data not shown). Of 62 patients issued with electronic monitoring bottles (EM), 8 dropped out, one with severe dyskinesia which precluded EM bottle usage, two lost the EM bottles, one died, one had prolonged hospital admission and three patient misused the EM. There was evaluable data for 54 patients. Baseline characteristics are shown in Table 4.1.
Table 4.1: Characteristics of 54 Parkinson patients undergoing compliance monitoring

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage male</td>
<td>56%</td>
</tr>
<tr>
<td>Age</td>
<td>61.9 (11)</td>
</tr>
<tr>
<td>Number taking levodopa</td>
<td>33 (61%)</td>
</tr>
<tr>
<td>Mean levodopa dose</td>
<td>533 mg</td>
</tr>
<tr>
<td>Number on DA</td>
<td>38 (70%)</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td></td>
</tr>
<tr>
<td>Number taking ropinirole</td>
<td>20</td>
</tr>
<tr>
<td>Mean daily dose</td>
<td>10.6mg</td>
</tr>
<tr>
<td>Number taking pramipexole</td>
<td>16</td>
</tr>
<tr>
<td>Mean daily dose (base)</td>
<td>2.2mg</td>
</tr>
<tr>
<td>Number taking pergolide</td>
<td>2</td>
</tr>
<tr>
<td>Daily dose</td>
<td>1.4mg</td>
</tr>
<tr>
<td>Number taking levodopa + DA</td>
<td>18 (33%)</td>
</tr>
<tr>
<td>Number of PD drugs</td>
<td>2.0 (1)</td>
</tr>
<tr>
<td>Number of PD administrations</td>
<td>4.1 (2)</td>
</tr>
<tr>
<td>Number of PD tablets per day</td>
<td>8.6 (4.7)</td>
</tr>
<tr>
<td>Number of non-PD drugs per day</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Number of tablets per day</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Duration of PD (years)</td>
<td>5.4 (3.9)</td>
</tr>
<tr>
<td>UPDRS 2</td>
<td>13.5 (6)</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>27 (13)</td>
</tr>
<tr>
<td>Number with dyskinesia</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>2.3 (0.6)</td>
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<td>Schwab &amp; England</td>
<td>79 (12)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28 (2)</td>
</tr>
<tr>
<td>Geriatric depression score</td>
<td>10.4 (7)</td>
</tr>
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<td>Epworth sleep score</td>
<td>8 (5)</td>
</tr>
<tr>
<td>PDQ 39 SI*</td>
<td>29 (17)</td>
</tr>
<tr>
<td>MISS-21</td>
<td>5.3 (0.8)</td>
</tr>
<tr>
<td>Patient-centredness</td>
<td>14.4 (3.6)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) or number (%).
DA = dopamine agonist, PD = Parkinson's disease,
UPDRS = Unified Parkinson's disease rating scale,
MMSE = mini mental state examination,
PDQ 39 SI = Parkinson's disease quality of life summary index,
MISS-21 = medical interview satisfaction scale.
*PDQ 39 SI data is based on 53 patients (see text).
Increased age was associated with better total compliance ($p = 0.007$, Pearson $r = 0.4$, 95% confidence interval [CI] 0.1 to 0.6), daily compliance ($p = 0.05$, Pearson $r = 0.3$, 95% CI 0.004 to 0.5) and timing compliance ($p = 0.04$, Pearson $r = 0.3$, 95% CI 0.006 to 0.5). Patients taking more medication had poorer daily compliance, considering PD medication alone ($p = 0.007$, Pearson $r = -0.4$, 95% CI -0.6 to -0.1) and all medication (for PD plus other disorders) ($p = 0.01$, Pearson $r = -0.3$, 95% CI -0.6 to -0.07). Total compliance was associated with worse depression ($p = 0.02$, Pearson $r = -0.3$, 95% CI -0.5 to -0.05) and with poorer quality of life ($p = 0.002$, Pearson $r = -0.4$, 95% CI -0.6 to -0.2). UPDRS (including sub-scores of bradykinesia, rigidity and tremor), MMSE and Epworth scores did not differ according to medicine usage. Similarly, there was no correlation between medicine usage with either patient-perceived involvement in therapy decisions or with satisfaction with the movement disorder service. Multivariate analysis was not performed as the study was exploratory and the sample size was insufficient in proportion to the number of variables tested.

Of the 54 evaluable patients, 11 (20%) receiving a total of 26 PD preparations (e.g. ropinirole 7mg taken as a 5mg plus a 2mg tablet represents 2 preparations) were underusers (< 80% total compliance) while 43 (80%) taking a total of 91 PD preparations showed satisfactory adherence. Patients were monitored for a mean of 88 days (SD 17 days). Antidepressant therapy was in place in 1 of the 11 patients (9%) in the underuse group (amitriptyline 50mg daily) and in 7 of the 43 patients (16%) with satisfactory adherence (6 selective serotonin reuptake inhibitors and 1 trazodone). All eight sub-domains of quality of life quality of life data (based on 53 patients, as one questionnaire was inadequately completed)
were worse (higher scores) in the underuse group, most markedly for social support (Mann-Whitney test, \( p < 0.0001, r^2 = 0.3 \)).

Compliance results consisting of total dose compliance, daily compliance and time interval compliance are shown in Figure 4.1.

**Figure 4.1:** Dotplot of adherence for individual drugs according to satisfactory adherence (91 drugs taken by 43 patients) and underusers (26 drugs taken by 11 patients). Daily and timing compliance was lower than total compliance, especially in underusers.
• Median total dose compliance was 98% (interquartile range IQ 93-102) in the satisfactory adherence group versus 65% (IQ 37 – 74) in underusers.
• Median daily compliance was 84% (IQ 67 - 90) for satisfactory adherence versus 27% (IQ 4 - 37) for underusers.
• Median time interval compliance was 25% (IQ 11 -73) for satisfactory adherence group compared to 11% (IQ 2 – 20) in underusers.

Timing compliance was better for drugs prescribed as once daily (14 of 25 drugs (56%) had time interval compliance over 80%) than for drugs taken more frequently (3 of 92 drugs (3%) had time interval compliance over 80%)(p < 0.00001). All drugs with time interval compliance over 90% were prescribed as once daily. None of the underuse patients overused (>100% total dose compliance) any individual drug (total dose compliance for individual drugs ranged from 19% to 95%). In patients with satisfactory adherence, underuse and overuse of individual drugs occurred (range 71% to 133%). Medication usage between 110 and 133% occurred for 8 preparations (3 selegiline, 2 levodopa, 2 amantadine and 1 dopamine agonist) in 5 patients, but none met criteria for the dopamine dysregulation syndrome (Lawrence, Evans, & Lees 2003). Removal of these patients from the analysis did not affect the results. A 70% compliance threshold classified 47 of 54 (87%) patients as having overall satisfactory adherence and 7 of 54 (13%) as underusers. Compliance results by drug class are shown in Figure 4.2a (satisfactory adherence) and Figure 4.2b (undersusers).
Figure 4.2a: Compliance measures according to drug type in 43 patients with satisfactory adherence. Compliance was good except in relation to the timing of intake of medications prescribed more than once daily.

Figure 4.2b: Compliance measures according to drug type in 11 patients with underuse of antiparkinson therapy. Daily and timing compliance rates were very low, indicating erratic medication intake with frequent missed doses.
Adverse events per patient did not differ between satisfactory adherence (mean 1.2, SD 1.3) and underusers (mean 1.4, SD 0.7), nor was there any difference in individual adverse events (in declining frequency: insomnia, sleepiness, dyskinesia, and nausea). Changes in UPDRS 2, 3, Hoehn and Yahr and Schwab and England between baseline and 3 months were not different between groups.

Discussion

Our study shows medication underuse in about one fifth of PD patients, which is a little higher than the 15% of 39 patients with compliance less than 80% using similar methodology (Leopold, Polansky, & Hurka 2004). We found an association between worse depression and poor total dose compliance although only one patient categorised as underusing PD medication was co-prescribed an antidepressant (which was at a subtherapeutic level). Depression has a high prevalence in PD (Rojo et al. 2003). In other diseases depressed patients are three times more likely to have poor adherence based on systematic review (Ciechanowski, Katon, & Russo 2000);(DiMatteo, Lepper, & Croghan 2000). The exclusion of depressed patients from the previous PD study (Leopold, Polansky, & Hurka 2004) is therefore a likely factor in our study having lower compliance rates. Given the major influence of depression on quality of life in PD (Schrag, Jahanshahi, & Quinn 2000; The Global Parkinson's Disease Survey Steering Committee 2002) and the deterioration in motor score and quality of life in patients who defer initiation of antiparkinson treatment (Chaudhuri, Taurah, MacMahon, Turner, Kelly, Burn, Forbes, Bowron, Foster, & PD LIFE Committee 2004), our results suggest that more detailed evaluation of the link between depression and medicine-taking behaviour in PD is needed.
The poorer quality of life in patients taking less medication than prescribed could not be explained by disease duration, since these two measures are not strongly associated (Schrag, Jahanshahi, & Quinn 2000). We found that lack of social support correlated significantly with poorer medicine intake, which is consistent with the known role of the carer in assisting PD patients with medication administration. The lower proportion of patients taking less than 80% of medication who had a carer (9%) compared to the satisfactory adherence group (21%) is consistent with the lack of social support identified through the PDQ39 questionnaire. The triad of depression, medication underuse and poor quality of life in socially isolated patients may be self-perpetuating, and runs counter to the often-assumed importance of education in optimising therapy intake (Heath 2003).

In other disease areas, factors potentially influencing compliance show inconsistent results (Buck et al. 1997; Cramer 2004; Stephenson, Rowe, Haynes, Macharia, & Leon 1993). In PD, women estimate the frequency of missed dose more accurately than men, but men report more mistimed doses (Leopold, Polansky, & Hurka 2004).

We found that older PD patients had better therapy compliance. Varying effects of age are reported in other disease areas (Horne R 2001), with lower rates attributed to co-existing cognitive impairment and depression (Salas et al. 2001) while uncomplicated cases, particularly those termed the ‘young-old’ (i.e. those whose biological age is less than their chronological age) (Morrell et al. 1997) have higher adherence which may indicate greater caution about their health (Leventhal & Crouch 1997). Age, education level and disease severity did not individually correlate with compliance (assessed using a four point rating scale) in Parkinson’s patients participating in clinical trials (Dobson, Rodnitzky, & Uc 2004).
The finding of worse daily compliance with increasing numbers of PD and other medications is consistent with other studies (Claxton, Cramer, & Pierce 2001; Cramer 2004). Given that complexity of drug regimens detrimentally affects adherence (Claxton, Cramer, & Pierce 2001) and that drug regimen simplification improves adherence and outcome measures in other diseases (Richter et al. 2003), the use and development of longer-acting PD drugs appears warranted. Further evidence supporting this comes from our observation that once-daily drugs had better adherence rates than more frequently taken drugs.

Adverse effects are a widely recognised reason for non-adherence (Adler, Sethi, Hauser, Davis, Hammerstad, Bertoni, Taylor, Sanchez-Ramos, & O’Brien 1997; Brooks & Sagar 2003; Hughes, Bagust, Haycox, & Walley 2001), but neither the number or type of adverse events differed according to medication intake in our study. The fact that our patients were largely on established therapy may explain this, since adverse events are associated most strongly with early discontinuation (Hughes, Bagust, Haycox, & Walley 2001).

Daily adherence and time interval adherence levels were much lower compared to total adherence. Similar findings are reported in hypertension where total compliance was 90%, but the correct number of daily doses were taken on only 63% of days (daily compliance) and only 38% of doses were taken at the correct time interval (timing compliance) (Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990). Analysis of 76 studies across several disease areas reported total compliance of 71% (SD 17%, range 34 - 97%) and in studies where time interval adherence was measured, the rate averaged 59% (SD 24%) (Claxton, Cramer, & Pierce 2001). Rates declined as the number of doses increased for both compliance measures (Claxton, Cramer, & Pierce 2001). Poor timing compliance
was universal in our study, whether or not there was underuse, suggesting that erratic drug taking is the norm rather than the exception in PD. This is consistent with observations in hypertension (Rudd, Ahmed, Zachary, Barton, & Bonduelle 1990), epilepsy (Cramer et al. 1995) and the one other available PD study (Leopold, Polansky, & Hurka 2004). Given the significance attached to erratic and pulsatile stimulation of striatal dopamine receptors (Bezard, Brotchie, & Gross 2001; Grace 1991; Jenner 2000; Onn, West, & Grace 2000; Spencer & Wooten 1984) resulting in fluctuations and dyskinesia, our results suggest that irregular medication may be at least as significant as variable absorption in day-to-day and longer term fluctuations. Regularising oral medication using an educational intervention is reported in Chapter 8.

The present study is the largest of its kind in PD, and is unique in monitoring all doses and strengths of antiparkinson medication, rather than choosing one preparation (Leopold, Polansky, & Hurka 2004). We consider inclusion of all antiparkinson drugs important, especially in more advanced disease when different formulations are used concurrently by individual patients. None of our evaluable patients showed evidence of the dopamine dysregulation syndrome, even although there was intake exceeding 110%. The syndrome occurred in about 4% of cases in another UK clinic (Lawrence, Evans, & Lees 2003), which has a higher proportion of tertiary referrals. Further, we suspect that cases with dopamine dysregulation may decline or fail participation in therapy monitoring projects, which may explain why the syndrome has been defined without detailed compliance monitoring. One of our patients could not manipulate the EM bottles which is another practical difficulty in encompassing patient types in compliance studies in PD. Our longer
study duration of 3 months compared to 1 month (Leopold, Polansky, & Hurka 2004) should reduce any effect of monitoring on study results.

While the present study is large amongst compliance studies, it is appropriate to expand the project to multiple centres to allow more robust examination of associations found here. A limitation of the current study is that the data had inadequate power for multivariant analysis which would of interest in a larger study. Such a collaborative project is now underway in 5 European countries.

In conclusion, taking less medication than prescribed occurs in one fifth PD patients. Poorer compliance is more likely in younger patients and when drug regimens are complex, and is associated with worse depression and lower quality of life. Even patients who adhere well to their medication take drugs at erratic time intervals. Maximising gain from antiparkinson therapy requires consideration of these issues.
Chapter 5

Concordance: Patient-perceived involvement and satisfaction in Parkinson's disease: effect on therapy decisions and quality of life
Introduction

Concordance is descriptive of the process and outcome of the consultation rather than patient behaviour. Accordingly, patients cannot be non-concordant. Treating patients as partners in therapy decisions is crucial to the therapeutic process (Royal Pharmaceutical Society of Great Britain 1997). To maximise therapeutic benefit, healthcare consultations should share knowledge, beliefs and expectations and negotiate agreement on the best course of action. In concordant consultations, relevant understandable information should be given to enable active patient participation in management decisions. More involvement brings more responsibility, which is not welcomed by everyone. The only way to determine the degree of involvement desired by an individual is to ask them. Concordance is less easy than compliance to quantify, but is based on patient satisfaction with the process of care and the degree of patient-centredness of the consultation.

Departure from the prescription represents at least in part failure to address the patient’s agenda.

In diabetes (Kinmonth et al. 1998), primary care (Kinnersley et al. 1999) and headache clinics (Headache Study Group of The University of Western Ontario 1986) patient-centred consultation styles increase patient satisfaction. Active patient involvement is associated with improved health outcome in hypertension (Stewart 1995) and chronic disease (Michie, Miles, & Weinman 2003).

Dissatisfaction with communication is associated with non-compliance in headache (Fitzpatrick & Hopkins 1981), diabetes (Hulka et al. 1975), hypertension (Hovell et al. 1986), asthma (Wissow et al. 1998) and chronic disease (Bartlett et al. 1984), but has not been studied in PD.
In this chapter, patient-perceived involvement in PD therapy decisions in relation to consultation satisfaction (including communication and compliance intent), disease stage, co-morbidity (depression and cognitive impairment) and quality of life, using established methodology from other disease areas (Makoul, Arntson, & Schofield 1995; Meakin & Weinman 2002) is reported.

**Methods**

One hundred and seventeen patients attending the movement disorder clinic were enrolled. All fulfilled PD Brain Bank criteria (Hughes, Daniel, Kilford, & Lees 1992), except one with progressive parkinsonism despite stopping neuroleptics in whom the clinical diagnosis of PD was supported by abnormal presynaptic dopamine transporter imaging (DaTSCAN, GE Healthcare, UK). Unified Parkinson’s Disease Rating (UPDRS 1 to 6) (Fahn, Elton, & members of the UPDRS Development Committee 1987) and mini mental state examination (MMSE) (Folstein, Folstein, & McHugh 1975) were scored. The protocol received local Ethics Committee approval and signed consent was obtained. After the consultation, patients completed 4 questionnaires and were asked to base their responses based on their overall clinic experience:

- (1) An assessment of perception of involvement in therapy decisions, adapted by the Medicines Partnership (Medicines Partnership 2003) from Makoul et al (Makoul, Arntson, & Schofield 1995) with 4 questions graded for agreement on a Likert scale, then converted to a numerical score (4 to 25 representing low to high perceived involvement).
• (2) MISS-21 (medical interview satisfaction scale), a validated 21-question assessment of consultation satisfaction (Meakin & Weinman 2002) with 4 components:
  • a) distress relief (6 items e.g. the doctor seemed to know just what to do for my problem)
  • b) communication comfort (4 items e.g. the doctor did not allow me to say everything I had wanted about my problems)
  • c) rapport (8 items e.g. the doctor seemed warm and friendly)
  • d) compliance intent (3 items e.g. I'm not sure the doctor's treatment will be worth the trouble it will take).

Each component is converted to a numerical score between 1 and 7 (low through to high satisfaction).

• (3) Geriatric Depression Scale (GDS) (Yesavage, Brink, Rose, Lum, Huang, Adey, & Leirer 1982) to screen for co-morbid depression.

• (4) PDQ39, a validated quality of life tool in PD (Peto, Jenkinson, & Fitzpatrick 1998).

**Statistical analysis** Prism® (GraphPad®, San Diego, USA) and Statistica® (StatSoft, Bedford, UK) were used for unpaired t tests to compare patient characteristics, Fisher's exact test for categorical variables, and Pearson correlation to test association between variables. Due to the number of comparisons, statistical significance was accepted at $p < 0.005$ (applying the Bonferroni adjustment).
Results

Of 117 patients recruited, 2 withdrew before commencing questionnaires and 8 had incomplete data, leaving 107 (91%) evaluable cases (Table 5.1).

Table 5.1: Characteristics of 107 evaluated cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number male</td>
<td>64 (60%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (10)</td>
</tr>
<tr>
<td>Duration of Parkinson's disease (y)</td>
<td>6.7 (5)</td>
</tr>
<tr>
<td>Number on levodopa</td>
<td>67 (63%)</td>
</tr>
<tr>
<td>Duration of levodopa therapy (y)</td>
<td>3.1 (4.8)</td>
</tr>
<tr>
<td>Number on dopamine agonist</td>
<td>76 (69%)</td>
</tr>
<tr>
<td>Duration of dopamine agonist therapy (y)</td>
<td>3.8 (3.8)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.5 (0.6)</td>
</tr>
<tr>
<td>UPDRS 2</td>
<td>14 (6)</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>26.5 (11)</td>
</tr>
<tr>
<td>UPDRS total</td>
<td>47.6 (18)</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td>77 (12)</td>
</tr>
<tr>
<td>Mini-mental State Examination</td>
<td>27.8 (2)</td>
</tr>
<tr>
<td>PDQ 39 Summary Index</td>
<td>31 (17)</td>
</tr>
</tbody>
</table>

Data are means (standard deviation or percentage).
y = years; UPDRS = Unified Parkinson's disease rating scale; PDQ = Parkinson's disease quality of life

The 10 (9%) cases not completing were more likely to have dyskinesia and there was a trend to longer disease duration (Table 5.2), but there was no significant difference for age, sex, UPDRS, Hoehn and Yahr or Schwab and England (S&E).

Patient-perceived involvement is shown in Figure 5.1, which converts to a numerical score of 14.4 (SD 2.8) (scale range 4 to 25). The mean satisfaction score (MISS-21) was 5.3 (SD 0.7) (scale range 1 to 7).
Table 5.2: Characteristics of excluded versus included patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Excluded (n = 10)</th>
<th>Included (n = 107)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.7 (8)</td>
<td>62.2 (10)</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of PD</td>
<td>10.5 (7)</td>
<td>6.7 (5)</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Number with dyskinesia</td>
<td>6 (60%)</td>
<td>29 (27%)</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>UPDRS 2</td>
<td>14 (7)</td>
<td>14 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>27.8 (7)</td>
<td>26.5 (11)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation or percentage). PD = Parkinson's Disease; ns = not significant; UPDRS = Unified Parkinson's disease rating scale.
Figure 5.1: Patient-perceived involvement in 107 cases of Parkinson's Disease. Although patients scored favourably regarding responsibility, information, and opinion, almost half of patients reported that they were not asked to choose their treatment. This has implications for therapy compliance, disease control and quality of life (see text).

The doctor gave me responsibility for deciding how to deal with my health problem

- 74% Agree
- 19% Neutral
- 7% Disagree

I was asked to choose a treatment for my health problem

- 31% Agree
- 24% Neutral
- 45% Disagree

I was given enough information to make my own decision about treatment

- 74% Agree
- 17% Neutral
- 8% Disagree

The doctor did not ask my opinion about medicines

- 12% Agree
- 9% Neutral
- 79% Disagree
Higher involvement correlated overall with increased satisfaction \((r = 0.28, \ p = 0.003)\) shown in Figure 5.2, particularly the distress relief sub-component of the satisfaction scale \((r = 0.38, \ p < 0.0001)\) (Figure 5.3).

**Figure 5.2:** Patient satisfaction against involvement in 107 patients. Patient satisfaction was higher in those who felt more involved in therapy management decisions \((r=0.28, \ p=0.003)\).

![Figure 5.2: Patient satisfaction against involvement in 107 patients. Patient satisfaction was higher in those who felt more involved in therapy management decisions \((r=0.28, \ p=0.003)\).](image)

**Figure 5.3:** Distress relief scores in relation to perceived patient involvement in therapy management decisions. Higher involvement was associated with greater distress relief \((r=0.38, \ p<0.0001)\).

![Figure 5.3: Distress relief scores in relation to perceived patient involvement in therapy management decisions. Higher involvement was associated with greater distress relief \((r=0.38, \ p<0.0001)\).](image)
The communication sub-component correlated with compliance intent ($r = 0.6$, $p < 0.0001$) shown in Figure 5.4.

Figure 5.4: Communication in relation to intention to comply with therapy in 107 patients. Better communication was associated with higher intention to comply with therapy ($r=0.6$, $p<0.0001$).

Neither patient involvement nor satisfaction correlated with motor scores (UPDRS 3), depression (GDS), activities of daily living (UPDRS 2 and Schwab and England) or cognition (MMSE). Quality of life was inversely associated with depression ($r = 0.7$, $p < 0.0001$) (Figure 5.5) and disease severity (UPDRS) ($r = 0.5$, $p < 0.0001$) (Figure 5.6). Duration of PD, compliance intent and satisfaction correlated significantly with quality of life (Table 5.3). There was no statistically significant correlation of satisfaction and depression.
Figure 5.5: Depression in relation to quality of life. Higher levels of depression correlated with poorer quality of life (higher scores) \( (r=0.7, p<0.0001) \).

![Graph showing the correlation between Geriatric Depression Score and Parkinson's Disease Quality of Life Summary Index.](image)

Figure 5.6: Quality of life in relation to disease severity. Quality of life deteriorated with worsening disease severity, measured by higher scores in the total Unified Parkinson's Disease Rating Score \( (r=0.5, p<0.0001) \).

![Graph showing the correlation between Disease Severity and Parkinson's Disease Quality of Life Summary Index.](image)
**Table 5.3: Quality of life (PDQ39-SI) compared to other variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson r</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS</td>
<td>0.7 (0.6 to 0.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UPDRS total</td>
<td>0.5 (0.4 to 0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of PD</td>
<td>0.28 (0.1 to 0.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Compliance Intent</td>
<td>-0.28 (-0.4 to -0.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>-0.28 (-0.4 to -0.1)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data in brackets are 95% confidence intervals for correlation coefficients.
PDQ39-SI = Parkinson's disease quality of life summary index;
GDS = Geriatric depression scale; UPDRS = unified Parkinson's disease rating scale; PD = Parkinson's disease

**Discussion**

This cohort of PD patients reported involvement in therapy decisions and levels of satisfaction above the midpoint of the relevant scales, which is considered positively in such assessments (Horne R 2003). Involvement correlated with satisfaction, as seen in other disease areas (Kinnersley, Stott, Peters, & Harvey 1999; Simpson et al. 1991; Woolley et al. 1978), and our results were strikingly similar to those in a primary care study (Kinnersley, Stott, Peters, & Harvey 1999). Satisfaction was positively associated with quality of life, but neither involvement nor overall satisfaction correlated with motor score or co-morbidity (depression or cognition). Patient satisfaction is often linked to improved health status (Stewart 1995), (Patrick, Scrivens, & Charlton 1983) but this is not a universal finding, such as in a large study of recently hospitalised patients (otolaryngology, orthopaedics, cardiothoracic, transplant) where the relationship between satisfaction and physical and mental health was too weak to interpret (Welton & Parker 1999).

While patient-centred consultations improved communication and satisfaction in diabetic patients, paradoxically patient knowledge and glycaemic control worsened
in the patient-centred group (Kinmonth, Woodcock, Griffin, Spiegel, & Campbell 1998). A review of studies which tested associations between patient-centredness and health outcomes highlighted inconsistent results (Michie, Miles, & Weinman 2003) and suggested that different styles of patient-centredness have different effects. Active patient involvement (Kaplan, Greenfield, & Ware, Jr. 1989) compared against merely seeking patients’ views (Kinmonth, Woodcock, Griffin, Spiegel, & Campbell 1998) is more likely to positively associate with health outcome.

The Makoul questionnaire which we applied takes account of both perspectives, with items ‘I was asked to choose ......’ reflecting active involvement, and ‘the doctor did not ask my opinion ......’ reflecting patients’ views. The overall level of patient involvement which we found is similar to that in primary care (Makoul, Arntson, & Schofield 1995), and in both environments patients report being informed, having their opinion sought, and being given responsibility to decide on treatment but that they did not have the opportunity to choose their therapy. The last aspect is potentially the most active role of the patient, and lower scores may result in poorer outcomes such as quality of life. Incorporating such approaches into a health management programme (PROPATH) improved patient perception of general health and psychological wellbeing, but notably satisfaction was not increased (Mercer 1996). Further aspects are the added time needed for patient-centred consultations (Bissell, May, & Noyce 2004; Jones et al. 2004), often problematic in the neurology setting (Ringel et al. 2003), and the value to physician morale and job satisfaction which correlate with patient communication (Ringel, Vickrey, Schembri, & Kravitz 2003).
In our study, communication correlated with compliance intent. This is similar to observations in neurology out-patients (Fitzpatrick & Hopkins 1981), where dissatisfaction with communication was associated with non-compliance. Patient-centredness is linked to better compliance and is considered a marker of success in the doctor-patient interview (Stewart 1984). We found a relationship between compliance intent and quality of life, and report in Chapter 4 that there is an association between sub-optimal compliance and poorer quality of life. Further work is required to evaluate if improving compliance improves quality of life.

We found significant association between satisfaction and quality of life. This broadens the findings of the Global Parkinson's Disease Survey (The Global Parkinson's Disease Survey Steering Committee 2002) in which “satisfaction with the explanation of the condition at diagnosis” contributed significantly to health-related quality of life. Depression and disease severity correlated strongly with quality of life, again consistent with other studies (Schrag, Jahanshahi, & Quinn 2000; The Global Parkinson's Disease Survey Steering Committee 2002). Similarly, high satisfaction with information provided to PD patients was associated with better quality of life (Shimbo et al. 2004). Our study shows that patient involvement in therapy decisions is associated with patient satisfaction, and that satisfaction and compliance intent are associated with quality of life in PD. Since maximising quality of life is a key target agreed by patients, their representative organisations, and healthcare professionals from several disciplines, the factors which influence this, including the patient satisfaction components highlighted in the present study, deserve due consideration in the design and implementation of models of care.
Chapter 6

Parkinson’s Disease patients’ beliefs about medicines: how does this influence therapy adherence?
Introduction

In other disease areas beliefs about medicines are known to influence how patients take prescribed medication. The beliefs about medicines questionnaire assesses patient perceived necessity of, and concerns about, medication. There is a generic version of the beliefs about medicines questionnaire and also disease specific versions. In a Swedish pharmacy study where 2,171 prescriptions were unclaimed in a 3 month period, the patient regarding the prescription as unnecessary was the commonest reason given (Ekedahl & Mansson 2004). Acute conditions requiring short courses of medication are generally taken more consistently than long term medication for chronic conditions (Haynes, McDonald, & Garg 2002). In idiopathic Parkinson's disease it has traditionally been assumed that patients with a marked symptomatic benefit from levodopa would adhere to prescribed therapy. On the other hand, if adverse effects are experienced, patients may reduce or discontinue medication, and medication intolerance (both in the short and long term) is common with all types of antiparkinson medication as outlined in Chapters 1 and 2.

In this chapter, we describe a Parkinson's disease specific beliefs about medicines questionnaire which was developed in conjunction with Professor Rob Horne, Centre for Health Care Research, University of Brighton.
Background

Historically it has been assumed that most Parkinson's disease (PD) patients take their medication fastidiously, but there is more recent evidence of sub-optimal therapy adherence (Leopold, Polansky, & Hurka 2004). Sub-optimal therapy adherence may be unintentional, due to forgetfulness or co-morbid conditions such as cognitive impairment or depression, or may be fully intentional as some patients make positive decisions not to take prescribed medication. Factors that influence therapy adherence have been examined in many studies (McDonald, Garg, & Haynes 2002; Stephenson, Rowe, Haynes, Macharia, & Leon 1993). Social, demographic, disease or drug related associations are weak and inconsistent (Stephenson, Rowe, Haynes, Macharia, & Leon 1993). Beliefs about medicines may have a stronger influence on adherence than these other factors (Horne & Weinman 1999) and are related to adherence in HIV patients (Horne et al. 2004), asthma (Chambers et al. 1999) and other diseases (Horne & Weinman 1999). The beliefs about medicines questionnaire assesses patient-perceived necessity for prescribed medication, versus concerns about adverse effects and dependence (Horne, Weinman J., & Hankins 1999). Patients with high necessity and low concerns scores have associated high adherence rates; while those with low necessity and high concerns have low therapy adherence. The necessity-concerns differential is more strongly associated with therapy adherence than either necessity or concerns alone (Horne & Weinman 1999). We developed and tested a Parkinson's disease specific version of the beliefs about medicines questionnaire, and examined PD patients' beliefs about their antiparkinson medicines. We tested the association between the necessity/concerns score and therapy adherence, and
assessed patient satisfaction with the information they receive about antiparkinson medication.

Methods

PD patients’ beliefs about medicines were assessed by asking 20 consecutive patients from one doctor’s list attending a neurology movement disorder clinic using a semi-structured interview. All responses were collected and examined for common themes. These were used to form a PD specific beliefs about medicines questionnaire. This follows the methodology used in other diseases, and the exploratory approach used in developing patient rating scales in neurological and other disorders.

Consecutive patients from 2 doctors’ lists attending the movement disorder clinic were then asked to participate. Baseline assessments of demographic factors and disease severity were recorded using the following scales:

- Unified Parkinson Disease Rating Scale (Fahn, Elton, & members of the UPDRS Development Committee 1987)
- Hoehn and Yahr (Hoehn & Yahr 1967)
- Schwab and England (Schwab & England, Jr. 1961)
- mini-mental state examination (Folstein, Folstein, & McHugh 1975)
- Geriatric depression score (Yesavage, Brink, Rose, Lum, Huang, Adey, & Leirer 1982)

Amongst the patients completing the above assessments, electronic pill bottle monitoring data was available in a subset of patients.

Additional scoring was recorded as follows:
• At 3 months all patients were asked to complete the general version of the beliefs about medicines questionnaire (Horne, Weinman J., & Hankins 1999).
• At six months all patients were asked to complete the PD specific version of the beliefs about medicines questionnaire and a modified version of the medicine adherence rating scale (MARS) self-report.

Therapy intake was monitored over 3 months using electronic pill bottles with a microprocessor in the cap that records the date and time of bottle opening (MEMS®, Aardex, Switzerland). Clinical scoring was blinded to active or no monitoring.

• Patients were also asked to complete a questionnaire about their satisfaction about information received about medicines (Horne, Hankins, & Jenkins 2001).

Statistical analysis used linear regression to test association between variables using Prism® (GraphPad®, San Diego, USA) and Statistica® (StatSoft, Bedford, UK).

Results
Three themes emerged from the 20 semi-structured interviews exploring beliefs about medicines: concerns over

• (1) adverse effects
• (2) complicated drug regimens
• (3) lack of efficacy.

A fourteen point PD specific beliefs about medicines questionnaire was formulated (Appendix 1).
Of 135 patients approached, 6 (4%) patients declined mainly due to perceived disruption from active therapy monitoring bottles, leaving 129 cases. There was no significant difference in age, gender, disease duration, type or dose of antiparkinson medication (levodopa, dopamine agonist) for patients who declined (data not shown).

Data from the general beliefs about medicines questionnaire was evaluable for 119 patients and for the PD specific version for 111 patients due to 3 withdrawing consent, additional cases being either lost to follow up or having incomplete questionnaires (7 at 3 months, a further 8 at 6 months). Baseline characteristics are shown in Table 6.1.
Table 6.1: Characteristics of 119 PD patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage male</td>
<td>61%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (11)</td>
</tr>
<tr>
<td>Number prescribed levodopa</td>
<td>81 (68%)</td>
</tr>
<tr>
<td>Average levodopa dose</td>
<td>516 mg</td>
</tr>
<tr>
<td>Number on dopamine agonist</td>
<td>86 (72%)</td>
</tr>
<tr>
<td>Number of PD drugs</td>
<td>2.5 (1)</td>
</tr>
<tr>
<td>Number of non-PD drugs per day</td>
<td>2.5 (3)</td>
</tr>
<tr>
<td>Number of tablets per day</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Duration of PD (years)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>UPDRS 2</td>
<td>14 (6)</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.4 (0.6)</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td>78 (13)</td>
</tr>
<tr>
<td>MMSE</td>
<td>27 (4)</td>
</tr>
<tr>
<td>Geriatric depression score</td>
<td>11 (7)</td>
</tr>
<tr>
<td>PDQ 39 SI</td>
<td>28 (16)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) or number (percentage).

PD = Parkinson’s disease, UPDRS = Unified Parkinson’s disease rating scale, MMSE = mini mental state examination, PDQ 39 SI = Parkinson’s disease quality of life summary index.

On the general version of the beliefs about medicines questionnaire, scores were as follows:

- **mean necessity score was 20** (standard deviation (SD) 3) [the score ranges from 5=low necessity to 25=high necessity]
- **mean concerns score was 14** (SD 4) against a range of 4=low concerns to 20=high concerns
- **mean necessity-concerns differential of 6.7** (SD 5).

All of the 119 (100%) patients believed their prescribed medication was necessary (indicated by a score higher than the midpoint of the scale), while 53% (63 of 119) had high levels of concerns (scores above the midpoint) regarding their medication.
Full adherence measured by a modified version of the medication adherence rating scale (MARS) was reported by 18% of patients, and 84% of patients had high levels of reported adherence with scores of 25 or over (scale ranging from 6 indicating low adherence to 30 representing perfect adherence). Adherence measured by the MARS self-report did not correlate significantly with beliefs (necessity, concerns or the necessity concerns differential), and there was no correlation between adherence measured by the MARS self-report and any of the adherence measures by electronic monitoring. For the subset of 66 patients undertaking electronic monitoring of medicine intake compliance results were as follows:

- **median total compliance** (the percentage of prescribed tablets taken) was 95% (interquartile range (IQ) 81-101)
- **median daily compliance** (the percentage of days the correct number of doses were taken) was 73% (IQ 38-88)
- **median timing compliance** (the percentage of doses taken at the correct time interval) was 19% (IQ 9-52).

The PD specific BMQ had a high level of internal consistency with a Cronbach’s alpha of 0.8. Cronbach’s alpha, which is a standard tool for this purpose, and is calculated from the formula:

\[ \alpha = \frac{\kappa}{\kappa-1} \left(1 - \frac{\Sigma s_i^2}{s_\tau^2}\right) \]

where \(\kappa\) is the number of items, \(s_i^2\) is variance of the \(i^{th}\) and \(s_\tau^2\) is the variance of the total score formed by summing all the items.
Patients’ main concerns were as follows:

- (1) potential future adverse effects (involuntary movements and drowsiness in particular)
- (2) not wishing to escalate doses or add medication until really necessary, and
- (3) worry about unresponsive symptoms and benefit wearing off (Figure 6.1).

**Figure 6.1:** Concerns about antiparkinsonian medication in 109 PD patients. The y-axis represents the percentage of patients who responded agree or strongly agree. The x-axis represents the individual questions (see Appendix 2). Patients’ main concerns centred around developing side effects in the future, increasingly complex dose regimens and lack of efficacy. The 50% level is highlighted as an arbitrary indicator of half of the study population.
For the 105 patients with evaluable data on the questionnaire on satisfaction with information received about medicines (Figure 6.2), overall satisfaction was high (mean score of 13 (SD 4), against a range 0=low satisfaction to 17=high satisfaction). Patients generally reported absent or inadequate information regarding medication as follows:

- effects on their sex life
- interaction with other drugs
- ability to take alcohol
- appropriate action for omitted tablets.

Figure 6.2: Satisfaction with information given about antiparkinsonian medication in 105 PD patients. Overall there were very high levels of satisfaction but a significant proportion of patients would like more information on how the medicine will affect their sex life and if the medicine interacts with other drugs.
Satisfaction with information about medicines did not correlate with beliefs about medicines, reported adherence or any of the adherence measures by electronic monitoring.

**Discussion**

Our study shows that PD patients believe their therapy is necessary but they have significant concerns about the effects of antiparkinson medication, which has similarities to other diseases such as asthma, diabetes and renal disease (Horne & Weinman 1999). We did not find a relationship between either reported adherence, or electronically monitored adherence, and beliefs. Previous studies report associations between reported adherence and beliefs about medicines (Horne & Weinman 1999) (Horne, Buick, Fisher, Leake, Cooper, & Weinman 2004), but the method of self report to estimate adherence is widely recognised to have limitations (Burney et al. 1996; Melbourne, Geletko, Brown, Willey-Lessne, Chase, & Fisher 1999; Straka, Fish, Benson, & Suh 1997; Waterhouse, Calzone, Mele, & Brenner 1993). In our study we found no correlation between adherence estimated by self-report and adherence assessed by electronic monitoring. Wider evidence of the relationship between beliefs and adherence measured using electronic monitoring is lacking. Reported adherence inherently has recall bias which itself may be influenced by beliefs about medicines. Overall, both necessity scores and total adherence were very high and this may reflect the typical PD personality (Bodis-Wollner 2003). Beliefs about medicines may influence the total amount of medicine taken rather than how it is taken.

Debate remains over initial drug choice in the management of PD. Less long-term dyskinesia with initial dopamine agonist monotherapy (Rascol, Brooks, Korczyn,
De Deyn, Clarke, & Lang 2000; The Parkinson Study Group 2000) has to be weighed against greater early symptom control from levodopa. In our study around 80% of patients were concerned about future adverse effects and 70% were worried about developing involuntary movements; such patients may prefer a dopamine agonist initially. Lack of efficacy is another main concern and these patients may opt for levodopa therapy. Taking individual patient's beliefs into account may therefore influence therapy choice.

Patients were generally satisfied with information provided about their antiparkinson medication with over two thirds stating that the level of information was appropriate or that information was not needed. Unlike previous studies (Horne, Hankins, & Jenkins 2001) where less satisfied patients had stronger concerns about medicines, we found no association between satisfaction and beliefs about medicines. There was no correlation between higher satisfaction with information about medicines and better reported adherence, unlike cardiac rehabilitation patients (Horne, Hankins, & Jenkins 2001), and there was no correlation with actual medicine taking behaviour measured by electronic monitoring. In our study this may be influenced by the high levels of both satisfaction with information about medicines, and the high levels of total adherence.

In conclusion, PD patients believe strongly in the necessity of their medicines, but also have significant concerns about them, in particular adverse effects, increasing quantities of medicines and lack of efficacy. However, beliefs do not affect medication adherence in PD.
Chapter 7

Patient involvement in therapy management decisions.

Switching from ergot to non-ergot dopamine agonists in Parkinson’s disease
Introduction
The Royal Pharmaceutical Society of Great Britain defined concordance as involving negotiation between equals (prescriber and patient) to form a therapeutic alliance and defined the three pillars of concordance as providing the patient with sufficient knowledge, involving patients in their management plan and supporting the patient in medicine taking (Royal Pharmaceutical Society of Great Britain 1997). This chapter describes a study based on these concepts of concordance whereby patients were provided with knowledge of potential drug adverse effects, allowed to choose between different management options and supported in their decision.

Dopamine agonists (DA) are now standard antiparkinson treatment both as early monotherapy (Adler, Sethi, Hauser, Davis, Hammerstad, Bertoni, Taylor, Sanchez-Ramos, & O’Brien 1997; Albin & Frey 2003; Clarke & Guttman 2002; Hubble et al. 1995; Montastruc et al. 1994; Montastruc, Rascol, & Senard 1999; Olanow 2002; Rascol, Brooks, Korczyn, De Deyn, Clarke, & Lang 2000; Schrag, Keens, & Warner 2002; The Parkinson Study Group 2000) and as a later adjunct (Guttman 1997; Hubble 2002; Lieberman et al. 1998; Lieberman, Ranhosky, & Korts 1997; Molho et al. 1995; Pinter, Pogarell, & Oertel 1999). In April 2002 the UK Committee of Safety in Medications (CSM) reported on 79 cases of fibrotic reactions in patients taking an ergot-based DA (49 on pergolide, 24 on bromocriptine, and 6 on cabergoline) which had been notified through their ‘Yellow Card’ scheme, a postal reporting system of clinically observed adverse events (Committee on Safety of Medicines (Medicines Control Agency) 2002). Many cases were advanced when discovered, 3 patients died and regular clinical monitoring was therefore recommended for earlier detection (Committee on Safety of Medicines (Medicines Control Agency) 2002). These reactions are well known.
but considered rare. Quantifying risk is not possible from the CSM process, or from clinical studies that are of relatively short duration. Ergot-related side-effects highlighted are pulmonary (Benard et al. 1996; Geminiani, Foton, Genitrini, Giovannini, Tamma, & Caraceni 1996; Ling et al. 1999; Saura, Aguilar, & Alio 1991; Shaunak et al. 1999; Todman, Oliver, & Edwards 1990), pericardial (Ling, Ahlskog, Munger, Limper, & Oh 1999; Saura, Aguilar, & Alio 1991; Shaunak, Wilkins, Pilling, & Dick 1999) and retroperitoneal (Jimenez-Jimenez et al. 1995; Kains et al. 1990; Kunkler, Osborn, & Abbott 1998; Sanchez-Chapado et al. 1995; Shaunak, Wilkins, Pilling, & Dick 1999) fibrosis. More recently pergolide and cabergoline have been associated with cardiac valvulopathy (Committee on Safety of Medicines (Medicines Control Agency) 2003; Pritchett et al. 2002; Van Camp et al. 2003). Fibrotic changes in the heart valves (particularly the tricuspid) of asymptomatic patients were found in a third of cases on pergolide (Van Camp et al. 2004). The definite advantages of DA therapy including a delay in the onset of fluctuations especially dyskinesia (Adler, Sethi, Hauser, Davis, Hammerstad, Berton, Taylor, Sanchez-Ramos, & O'Brien 1997; Albin & Frey 2003; Clarke & Guttman 2002; Hubble, Koller, Cutler, Sramek, Friedman, Goetz, Ranhosky, Korts, & Elvin 1995; Montastruc, Rascol, Senard, & Rascol 1994; Montastruc, Rascol, & Senard 1999; Olanow 2002; Rascol, Brooks, Korczyn, De Deyn, Clarke, & Lang 2000; The Parkinson Study Group 2000) need to be considered against such side-effects. The wide availability of two non-ergot oral DA drugs pramipexole and ropinirole (Hobson, Pourcher, & Martin 1999), both licensed for monotherapy and as an adjunct, and both with confirmed advantages over levodopa in reducing motor fluctuations (Rascol, Brooks, Korczyn, De Deyn, Clarke, & Lang 2000; The Parkinson Study Group 2000), leads to consideration of a switch away from ergot.
DA treatments. These factors need to be carefully balanced when guiding patients about side-effect issues, and the option to switch between DA drugs.

Adjustment of antiparkinson drugs is most frequently driven either by side effects which are more likely with DA drugs (such as hallucinations) or lack of benefit (such as the addition of levodopa to DA). Switching between DA drugs has primarily been conducted at a point of waning efficacy (Canesi et al. 1999; Goetz, Blasucci, & Stebbins 1999). We recognised that switching antiparkinson drugs in patients with good symptom control and no evidence of side-effects is against prevailing practice. However, we considered the fibrotic reaction issue as sufficient justification to inform patients of the issues, and offer a treatment change, thus involving the patient in their therapy management (Council of the European Communities. European Commission Council Directive. Brussels European Commission. 1992).

Methods

Patients with idiopathic PD attending the regional movement disorder clinic and taking an ergot-derived DA were identified. They were given verbal and written information about potential side effects and options to:

- (i) change to a non-ergot DA
- (ii) stop DA therapy and start or increase levodopa
- (iii) maintain treatment and be monitored per CSM recommendations (symptom enquiry, chest X-ray, urea and electrolyte levels, erythrocyte sedimentation rate, consideration of lung function tests and echocardiogram).
Patients electing to switch to a non-ergot DA underwent an overnight switch based on prior evidence that this was safe, and better tolerated than overlapping titration (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Goetz, Blasucci, & Stebbins 1999).

Dose equivalents were defined from a literature review and summary of product characteristics for each drug. Ratios used were as follows:

- 1:1 for pergolide to pramipexole (salt)
- 1:4 for pergolide to ropinirole (modified to between 1:4 and 1:5.3 at the upper end of the dose range)
- 4:3 for cabergoline to pramipexole
- between 1:3 and 1:4 for cabergoline to ropinirole
- 10:1 for bromocriptine to pramipexole
- between 2:1 and 3:1 for bromocriptine to ropinirole (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Goetz et al. 1989; Goetz, Blasucci, & Stebbins 1999; Hanna et al. 2001).

A conversion chart based on these ratios and providing example doses was applied (Table 7.1). Equivalent doses were used in most cases. Clinical judgement allowed doses at conversion to be adjusted upwards if the patient was undertreated, or downwards if there were any features suggesting dopaminergic excess (dyskinesia, hallucination, nausea, dizziness). Domperidone was maintained or commenced on clinical grounds. Concomitant antiparkinson therapy was recorded. Written switching instructions were handed to the patient.
### Table 7.1 Conversion chart; approximate dose equivalents for dopamine agonists

<table>
<thead>
<tr>
<th>Bromocriptine</th>
<th>Cabergoline</th>
<th>Pergolide</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg tid</td>
<td>0.5mg per day</td>
<td>0.125 mg tid</td>
<td>0.125 mg tid</td>
<td>Starter pack then 1 mg tid</td>
</tr>
<tr>
<td>2.5 mg tid</td>
<td>1 mg per day</td>
<td>0.25 mg tid</td>
<td>0.25 mg tid</td>
<td>1 mg tid</td>
</tr>
<tr>
<td>5 mg tid</td>
<td>2 mg per day</td>
<td>0.5 mg tid</td>
<td>0.5 mg tid</td>
<td>2 mg tid</td>
</tr>
<tr>
<td>7.5 mg tid</td>
<td>3 mg per day</td>
<td>0.75 mg tid</td>
<td>0.75 mg tid</td>
<td>3 mg tid</td>
</tr>
<tr>
<td>10 mg tid</td>
<td>4 mg per day</td>
<td>1 mg tid</td>
<td>1 mg tid</td>
<td>4 mg tid</td>
</tr>
<tr>
<td>12.5 mg tid</td>
<td>5 mg per day</td>
<td>1.25mg tid</td>
<td>1.25mg tid</td>
<td>6mg tid</td>
</tr>
<tr>
<td>15 mg tid</td>
<td>6 mg per day</td>
<td>1.5 mg tid</td>
<td>1.5 mg tid</td>
<td>8mg tid</td>
</tr>
</tbody>
</table>

*or 1.06mg if using 0.7mg tablet + (2 tablets x 0.18 mg)*

Follow-up was routinely at between 3 and 6 months but telephone advice and earlier clinic review were also available. Adverse events were classified as suggesting undertreatment (worsening PD), overtreatment (dopaminergic side-effects such as hallucinations or dyskinesia) or other side-effects (sleepiness, headache). DA doses were subsequently adjusted and/or levodopa added or adjusted on clinical grounds, on a balance between tolerability and level of symptom control. Results were stratified according to whether the dose at the time of switching was lower, equivalent, or higher than the conversion chart.

Pramipexole and ropinirole data for adverse events were combined due to small group sizes. The primary endpoint was retention of the new DA at last follow-up; retention of any DA at last follow-up was the main secondary endpoint.
Results

Patients Of 579 Parkinson's Disease patients attending the movement disorder clinic since October 1999, 383 (66%) had ongoing attendance at the time of the conduct of the study. Of these 383, 99 (26%) were on ergot DA agonists and 88 of these 99 (89%) opted to switch to a non-ergot DA. Ten patients (10%) chose to retain their existing DA; all underwent blood tests and chest X-ray with normal results. One patient increased levodopa and stopped DA treatment. Characteristics of the patients who switched therapy are shown in Table 7.2.

Table 7.2 Baseline characteristics of 88 patients undergoing Dopamine Agonist switch

<table>
<thead>
<tr>
<th></th>
<th>Pergolide</th>
<th>Cabergoline</th>
<th>Bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>69</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>1.4:1</td>
<td>4:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age in years</td>
<td>60 (8.3)</td>
<td>65 (8.8)</td>
<td>60 (10.8)</td>
</tr>
<tr>
<td>Duration of PD in years</td>
<td>6.2 (3.6)</td>
<td>8.7 (5.4)</td>
<td>9.5 (5.6)</td>
</tr>
<tr>
<td>Duration of DA therapy in months</td>
<td>26.5 (15.8)</td>
<td>26 (17)</td>
<td>74 (21)</td>
</tr>
<tr>
<td>Hoehn and Yahr at time of switch</td>
<td>2.2 (0.5)</td>
<td>2.4 (0.4)</td>
<td>2.3 (0.5)</td>
</tr>
<tr>
<td>Duration of follow-up in months</td>
<td>11 (9)</td>
<td>12 (6)</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>

Data are means with standard deviation in brackets; PD=Parkinson's Disease; DA=Dopamine Agonist

Reason for therapy switch. In 81% (71 of 88 cases) the reason for switching DA was the potential fibrosis issue highlighted by the CSM warning. Recognised ergot side effects were present in 4 cases (4%), and other side effects in 11 (12%) some of which might have been ergot-related (Table 7.3).
Table 7.3 *Reason for switching to a non-ergot Dopamine Agonist in 88 patients*

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of patients</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSM alert</td>
<td>71</td>
<td>Pleural effusion n=2</td>
</tr>
<tr>
<td>Ergot side-effects*</td>
<td>4</td>
<td>Pulmonary fibrosis n=2</td>
</tr>
<tr>
<td>Other side-effects</td>
<td>11</td>
<td>Respiratory symptoms n=3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluid retention n=3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea n=2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin rash n=2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation n=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness n=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flushing n=1</td>
</tr>
<tr>
<td>Patient request</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

CSM=Committee of Safety in Medicines
* Diagnosed by chest X-ray n = 4, Computed Tomography of thorax n = 3, lung biopsy n =1; all cases diagnosed by respiratory physicians and all improved after discontinuation of ergot.

Doses of Dopamine Agonists. DA doses at switch are listed in Table 7.4. The dose of non-ergot DA post-switch was relatively higher for pramipexole than for ropinirole, considering their respective dose ranges. At follow up DA doses were higher reflecting upward dose titration with progressing disease (Table 7.5).
Table 7.4 Baseline and post-switch doses of Dopamine Agonist in 88 patients

<table>
<thead>
<tr>
<th>Pergolide</th>
<th>Cabergoline</th>
<th>Bromocriptine</th>
<th>Baseline doses</th>
<th>Post-switch doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>69</td>
<td>15</td>
<td>4</td>
<td>74</td>
</tr>
<tr>
<td>Mean dose (SD)</td>
<td>2.1 (1.1)</td>
<td>3.2 (1.1)</td>
<td>28 (20)</td>
<td>2.3 (1.3)</td>
</tr>
</tbody>
</table>

All doses are total per day and expressed in milligrams (mg); SD=Standard Deviation; dose of pramipexole as salt

Table 7.5 Doses of Dopamine Agonist in 72 patients at follow-up

<table>
<thead>
<tr>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (SD)</td>
<td>3.0 (1.3)</td>
</tr>
</tbody>
</table>

All doses are total per day and expressed in milligrams (mg); SD=Standard Deviation; dose of pramipexole as salt

Adverse events. Overall 23 of 88 patients (26%) experienced adverse events suggestive of over or undertreatment (Table 7.6). The majority of patients were switched at equivalency (54 of 88, 61%); 20 of 88 (23%) had a lower than equivalent dose; and 14 of 88 (16%) had a higher than equivalent dose. Side effects were less common in patients on equivalent doses (11 of 54 cases, 20%) against 30% (6 of 20 cases) in the lower than equivalent dose group, and 43% (6 of 14 cases) in the higher than equivalent dose group. There were no adverse events suggestive of undertreatment in the 14 patients given a higher than equivalent dose. In the lower than equivalent dose group, adverse events were mainly symptoms of undertreatment.
**Table 7.6 Adverse events according to baseline DA and dose equivalency used at conversion**

<table>
<thead>
<tr>
<th>Baseline DA</th>
<th>Adverse events suggesting undertreatment</th>
<th>Suggesting overtreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conversion dose: Lower</td>
<td>Equal</td>
</tr>
<tr>
<td>Pergolide</td>
<td>5/14</td>
<td>3/45</td>
</tr>
<tr>
<td>(n=69)</td>
<td>(36%)</td>
<td>(6.7%)</td>
</tr>
<tr>
<td>Cabergoline (n=15)</td>
<td>0/5</td>
<td>2/7</td>
</tr>
<tr>
<td></td>
<td>(0%)</td>
<td>(29%)</td>
</tr>
<tr>
<td>Bromocriptine (n=4)</td>
<td>0/1</td>
<td>0/2</td>
</tr>
<tr>
<td>Total</td>
<td>5/20</td>
<td>5/54</td>
</tr>
<tr>
<td>(n=88)</td>
<td>(25%)</td>
<td>(9%)</td>
</tr>
</tbody>
</table>

DA=Dopamine Agonist; percentages omitted for bromocriptine due to small numbers; Lower, Equal, and Higher refer to doses chosen at switch (see text); adverse events not attributable to undertreatment or overtreatment are not shown
Additional side-effects are shown in Table 7.7. Overall side-effect rates were not statistically significant by dose group; small group sizes prevented more detailed analysis.

Domperidone was co-prescribed (pre-existing or started at therapy switch) in 35 of the 88 cases (40%) with no significant differences according to dose equivalency.

**Table 7.7: Adverse Events in 88 patients undergoing dopamine agonist switch**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening parkinsonism</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Excessive sleepiness</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Poor balance</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Feeling 'disconnected'</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Worsening dyskinesia</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Ankle oedema</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

*patients may have reported more than one adverse event

At the time of switch, levodopa was in place in 43 of the 88 cases (49%), which increased to 53 of 88 cases (60%) at follow-up. Considering levodopa usage at baseline according to dose equivalence for DA treatment at the time of switching, 25 of 54 (46%) at dose equivalence were on concomitant levodopa, 13 of 20 (65%) in the 'lower' group, and 5 of 14 (36%) in the 'higher' group. The mean total daily levodopa dose at
the time of switch was 506mg (95% confidence interval 413-600mg). At
follow-up 31 of 54 (57%) 'equivalent' cases, 15 of 20 (75%) 'lower' cases,
and 7 of 14 (50%) 'higher' cases were on levodopa.

Patients were more likely to remain on the switch DA if their switch was
at equivalent or lower doses (Table 7.8). Retention rates were 82% for
the switch DA and 93% for any DA.

Table 7.8: Retention of dopamine agonist therapy

<table>
<thead>
<tr>
<th>Conversion Dose</th>
<th>DA at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remains on switch DA</td>
</tr>
<tr>
<td>Equivalent (n=54)</td>
<td>44 (81%)</td>
</tr>
<tr>
<td>Higher (n=14)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>Lower (n=20)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Total (n=88)</td>
<td>72 (82%)</td>
</tr>
</tbody>
</table>

DA=Dopamine Agonist; Equivalent, Higher, and Lower refer to doses chosen at switch (see text)
Discussion

Prior DA switching reports are based mainly on waning efficacy (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Goetz, Shannon, Tanner, Carroll, & Klawans 1989; Goetz, Blasucci, & Stebbins 1999) unlike the present study in which switching was primarily a result of the CSM warning over ergot DA side-effect risks. Switching antiparkinson therapy because of a risk of ergot-related side-effects is a previously unreported territory. When provided with available information and potential options, the majority of patients chose to switch to a non-ergot agent, although a few delayed the switch for up to 9 months after initial discussions, and failing efficacy began to play a part in this decision. The rate of possible ergot related side effects (pleural effusion or fibrosis) in our series was 4%, which is classified as a common side effect by the European Union directive (European Commission Pharmaceutical Committee 1998). In three additional cases, symptoms of breathlessness may have been ergot-related, or alternatively due to co-morbidity (chronic obstructive pulmonary disease/congestive cardiac failure).

Pre-switch DA doses were near the midpoint of standard dose ranges for pergolide, comparable with other studies (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Goetz, Blasucci, & Stebbins 1999; Hanna, Ratkos, Ondo, & Jankovic 2001). The four patients on bromocriptine were in the upper dose range, while previous studies switched nearer the midpoint of the dose range (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Gimenez-Roldan, Esteban, & Mateo 2001); this reflected a longer duration of disease in our patients on bromocriptine. Overall, the mean duration of Parkinson’s disease was shorter in our study at around 8 years compared to 11 years (Gimenez-Roldan, Esteban, & Mateo 2001), 12.5 years (Hanna, Ratkos, Ondo, & Jankovic 2001), and 15 years.
(Goetz, Blasucci, & Stebbins 1999), reflecting our process of switching because of potential or actual ergot side-effects, rather than after efficacy had been exhausted. For the same reason, the duration of dopamine agonist therapy prior to switching in our cohort was shorter at 3.5 years versus 6 years (Goetz, Blasucci, & Stebbins 1999) and 7 years (Gimenez-Roldan, Esteban, & Mateo 2001), and 51% of our cases were on dopamine agonist monotherapy at the time of switch while other studies included a higher proportion of advanced cases (Gimenez-Roldan, Esteban, & Mateo 2001; Goetz, Shannon, Tanner, Carroll, & Klawans 1989; Goetz, Blasucci, & Stebbins 1999). Despite these differences, our mean post switch daily dose of 2.3 mg pramipexole was virtually the same as Goetz et al (2.2mg /day) (Goetz, Blasucci, & Stebbins 1999), although Hanna et al (Hanna, Ratkos, Ondo, & Jankovic 2001) converted patients over a one month period and with this optimisation the daily dose reached 3.2 mg. Our post-switch doses of ropinirole were lower than previously reported (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Gimenez-Roldan, Esteban, & Mateo 2001) for 2 main reasons: patients switched to ropinirole were on lower than average baseline agonist doses, and none was given higher than equivalent dose.

The dose conversions we applied were based on previous definitions, but there is variability amongst these. The reported ropinirole to pergolide ratio varies between 3:1 and 6:1 (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999). While arithmetically precise optimal conversion ratios were suggested at 0.77:1 for pergolide to pramipexole, and 10 to 1.5 for bromocriptine to pramipexole, the simple 1:1 pergolide to pramipexole, and 10:1 bromocriptine to pramipexole are more practical (Goetz, Blasucci, & Stebbins 1999). Since conversions need further adjustment because of available tablet sizes, we collated these suggestions into a
guide covering frequently encountered doses (Table 7.1). The individual patient response which is well-known in PD means that switching at ‘equivalency’ can still cause temporary worsening; 20% of our cases in this category had either under or over treatment, but we found the structured approach useful. Moreover, such observations are in keeping with known variations in affinity for dopamine receptor subtypes, reflected in studies combining two different DA drugs (Stocchi et al. 2003). However, detailed comparisons between switching and non-switching patients, or between equivalent versus non-equivalent switching, were not considered appropriate for the present study design and group sizes; these aspects may form the basis for a larger investigation.

We adopted an overnight switch in view of the comparative data against slow titration in other studies (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999; Gimenez-Roldan, Esteban, & Mateo 2001; Goetz, Shannon, Tanner, Carroll, & Klawans 1989; Goetz, Blasucci, & Stebbins 1999). Patients generally tolerated this process and maintained reasonable efficacy. The long half-life of cabergoline might theoretically cause overtreatment when switching to a new agent, and in support of this we observed overtreatment side-effects in all 3 patients switched from cabergoline to higher than equivalent doses. However, we did not find evidence of such a problem at equivalent, or lower than equivalent doses.

Overall 82% of our patients retained the post-switch dopamine agonist and 93% remained on a dopamine agonist, after 11 months follow-up. Canesi et al (Canesi, Antonini, Mariani, Tesei, Zecchinelli, Barichella, & Pezzoli 1999) reported a 91% retention of new DA in 68 patients, but follow-up was short at only 4 weeks. With 6 months follow-up, 86% retention of new DA was reported in another study (Hanna,
Ratkos, Ondo, & Jankovic 2001). A longer follow-up captures patients who switch therapy for other clinical reasons, as also observed in comparative trials of DA versus levodopa, for example an 85% retention of pramipexole in the CALM-PD study (The Parkinson Study Group 2000).

Our findings guide the practising clinician in several important ways. When provided with verbal and written information balancing risks and benefits (and given prolonged consideration time if they wish it) most patients choose to switch from an ergot DA to a non-ergot DA. When switched, an equivalent dosage is less likely to result in adverse events. If a lower dose is used about a quarter of patients will have symptoms of undertreatment; up-titration is likely to become necessary. Retention of dopamine agonist therapy is more likely if a lower or equivalent dose is used.

Switching can be achieved as part of routine clinical care, aided by the conversion table in this chapter.
Chapter 8

Can an educational intervention improve adherence to prescribed medicines in Parkinson’s Disease?
Introduction

We have identified sub-optimal medicine usage in Parkinson’s disease; can this be improved? In this chapter we test the effect of an educational intervention to regularise medication timing. We hypothesize that irregular medicine intake contributes to pulsatile dopamine stimulation which contributes to motor fluctuations.

Although the majority (about 80%) of PD patients take almost 100% of prescribed medication, irregular timing of drug ingestion is almost universal (Chapters 3 and 4). The precise clinical effect of erratic drug ingestion are not known, but pulsatile dopaminergic stimulation in the basal ganglia (Stocchi et al. 2005) is implicated in the development and manifestation of motor fluctuations. Short drug half-life and erratic absorption both contribute to pulsatile stimulation, but irregular drug intake may be equally important. In other disease areas, interventions to assist patient adherence to prescribed medication include simplifying drug regimens (Girvin, McDermott, & Johnston 1999; Melikian et al. 2002), providing additional education (Henry & Batey 1999; Peveler et al. 1999), counselling and behavioural approaches (O’Donnell et al. 2003; Rosen, Rigsby, Salahi, Ryan, & Cramer 2004; Weber et al. 2004) and providing reminder packaging (Becker et al. 1986). We tested the effect on the timing of medicine ingestion of an educational intervention of informing patients about the continuous dopaminergic theory (Juncos, Engber, Raisman, Susel, Thibaut, Ploska, Agid, & Chase 1989; Stocchi, Vacca, Ruggieri, & Olanow 2005), to provide a reason for patients to take antiparkinsonian medication at regular time intervals.
Methods

Two out of every three patients attending the movement disorder clinic with idiopathic Parkinson disease (according to UK Brain Bank criteria) were invited to participate. Patients were prescribed at least one antiparkinson drug (including a dopamine agonist and/or levodopa). Patients were excluded if study participation, particularly use of the electronic monitoring bottles was potentially detrimental to their treatment. The study received ethics approval and signed consent was obtained. Baseline assessments of unified Parkinson’s disease rating scale (UPDRS) (Fahn, Elton, & members of the UPDRS Development Committee 1987), Hoehn and Yahr (Hoehn & Yahr 1967), Schwab and England (Schwab & England, Jr. 1961), mini-mental state examination (Folstein, Folstein, & McHugh 1975), geriatric depression scale (Yesavage, Brink, Rose, Lum, Huang, Adey, & Leirer 1982) and quality of life score (PDQ 39) (Jenkinson et al. 1997) were performed. Clinical scoring was performed in an ‘on’ state’ and was blinded to patient group. All antiparkinson medicines were monitored for three-months using electronic monitoring pill bottles (MEMS®, Aardex, Switzerland), the lid of which records the time and date of bottle opening. Patients were randomly assigned (method described in Chapter 3) to receive (the active group) or not receive (the control group) an educational intervention of verbal and written information about the continuous dopaminergic theory and written advice on optimal medicine timing tailored to the individual’s drug regimen. This was then followed by a further 3 months of antiparkinson electronic medicine monitoring. UPDRS and adverse events were recorded at each visit. The quality of life score (PDQ 39) was repeated at the final visit. Medication was adjusted according to clinical need. The increase in levodopa equivalent units during the study period was calculated according to
established formulas (levodopa + 1/3 if on entacapone + ropinirole x 20 + pramipexole or cabergoline x 67 + pergolide x 100 + bromocriptine x 10) (Parkin et al. 2002).

Total compliance (the total amount of prescribed medication taken), daily compliance (the percentage of days on which the prescribed number of doses were taken) and timing compliance (the percentage of doses taken at the correct time interval) were calculated from the electronic monitoring data. Timing compliance is calculated from time intervals which give an optimum pharmacokinetic profile, allowing for a 25% deviation in timing. For example a satisfactory interval between doses for a 3 times daily drug is between 6 and 10 hours; time intervals outwith this are unsatisfactory. Selegiline 5mg twice daily was excluded from this analysis as the second dose is taken at lunchtime to avoid sleep disturbance.

Longitudinal data of changes in compliance measures, UPDRS 3 and quality of life were calculated. Groups were compared using unmatched t-tests for parametric data and Mann-Whitney for non-parametric data. The primary end point was a difference in timing compliance between groups. Secondary end points were differences in UPDRS 2 and 3 and quality of life (PDQ 39) between groups. Statistical analysis used Prism 3 (GraphPad®, CA, USA).

Results
Of 89 patients asked to participate, 6 (7%) declined. Of the remaining 83, 43 were randomised to the active group and 40 to the control group. Baseline demographics and data are shown in Table 8.1. Fourteen patients dropped out during the pre-intervention stage as follows (Figure 8.1):
• 10 from the active group
  • 2 withdrew consent after baseline assessment,
  • 1 died
  • 7 had problems with the electronic monitoring bottles (e.g. being unable to manipulate the bottles due to dyskinesia, taking all the next day’s medication out the night before or losing the bottles), and
• 4 from the control group
  • 3 misused the bottles
  • 1 withdrew consent

There were no significant differences in baseline characteristics in patients who dropped out versus those continuing the study. Baseline compliance data was therefore available for 69 patients (33 in the active group and 36 in the controls).
Figure 8.1: CONSORT flowchart of 89 eligible patients.

Assessment of eligibility (n=89)

→ Excluded (n=6, all declined)

Randomised (n=83)

Allocated to intervention (n=43)
- Received allocated intervention (n=33)
- Did not receive allocated intervention (n=10)
  Reasons
    - 2 withdrew consent
    - 7 problems with monitoring bottles
    - 1 died

Discontinued intervention (n=10)
  Reasons
    - 3 declined rerun of monitoring bottles
    - 6 used the monitoring bottles inconsistently
    - 1 system recording failure

Analysed (n=23)

Allocated to no intervention (n=40)
- Received allocated intervention (n=36)
- Did not receive allocated intervention (n=4)
  Reasons
    - 1 withdrew consent
    - 3 problems using monitoring bottles

Discontinued (n=7)
  - 1 declined rerun of monitoring bottles
  - 6 used the monitoring bottles inconsistently

Analysed (n=29)
Table 8.1: Patient characteristics by group

<table>
<thead>
<tr>
<th></th>
<th>Pre-Intervention</th>
<th></th>
<th>Post-Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n = 43)</td>
<td>Control (n = 40)</td>
<td>Active (n = 23)</td>
<td>Control (n = 29)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>56%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (10)</td>
<td>62 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed levodopa (%)</td>
<td>28 (65%)</td>
<td>29 (73%)</td>
<td>18 (78%)</td>
<td>22 (76%)</td>
</tr>
<tr>
<td>Levodopa dose (mg)</td>
<td>508 (227)</td>
<td>607 (458)</td>
<td>511 (306)</td>
<td>670 (380)</td>
</tr>
<tr>
<td>Prescribed dopamine agonist (%)</td>
<td>30 (70%)</td>
<td>29 (73%)</td>
<td>18 (78%)</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>Change in levodopa equivalent units</td>
<td></td>
<td></td>
<td>51 (148)</td>
<td>70 (149)</td>
</tr>
<tr>
<td>Number of PD drugs</td>
<td>2.6 (1.2)</td>
<td>2.6 (1.3)</td>
<td>2.4 (1.2)</td>
<td>2.2 (1.5)</td>
</tr>
<tr>
<td>Number of PD daily doses</td>
<td>4.0 (2.3)</td>
<td>4.3 (2.2)</td>
<td>4 (0.8)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Number of PD tablets per day</td>
<td>9 (5)</td>
<td>9.5 (5)</td>
<td>9.5 (5)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Number of non-PD drugs per day</td>
<td>2.8 (3)</td>
<td>1.9 (2)</td>
<td>2.5 (3)</td>
<td>3.5 (4)</td>
</tr>
<tr>
<td>Total number of tablets per day</td>
<td>12 (6)</td>
<td>12 (5)</td>
<td>13 (7)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Carer helps with medication (%)</td>
<td>10 (23%)</td>
<td>10 (25%)</td>
<td>7 (30%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Duration of PD (years)</td>
<td>7.7 (6)</td>
<td>6.9 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS 2</td>
<td>14 (6)</td>
<td>14 (6)</td>
<td>14 (6)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>UPDRS 3</td>
<td>29 (11)</td>
<td>24 (13)</td>
<td>29 (14)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>UPDRS 4</td>
<td>3.2 (3)</td>
<td>3.5 (3)</td>
<td>3.2 (2.3)</td>
<td>3.6 (2.3)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>2.4 (0.6)</td>
<td>2.5 (0.7)</td>
<td>2.5 (0.7)</td>
<td>2.5 (0.7)</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td>78 (10)</td>
<td>76 (14)</td>
<td>71 (18)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28 (2)</td>
<td>28 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geriatric depression score</td>
<td>12 (6)</td>
<td>10 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDQ SI</td>
<td>31 (14)</td>
<td>31 (14)</td>
<td>36 (15)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Total compliance, median (IQ)</td>
<td>92% (72-99)</td>
<td>97% (87-102)*</td>
<td>96% (82-100)</td>
<td>94% (78-99)</td>
</tr>
<tr>
<td>Days compliance, median (IQ)</td>
<td>68% (30-87)</td>
<td>77% (56-88)</td>
<td>75% (48-88)</td>
<td>69% (36-86)</td>
</tr>
<tr>
<td>Timing compliance, median (IQ)</td>
<td>17% (9-51)</td>
<td>21% (10-59)</td>
<td>39% (22-58)</td>
<td>20% (10-47)**</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) unless otherwise stated. PD = Parkinson's disease, UPDRS = Unified Parkinson's disease rating scale, MMSE = mini mental state examination, PDQ 39 SI = Parkinson's disease quality of life summary index, IQ = interquartile range.

Compliance data is based on 33 patients in the active group and 36 patients in the control group in the pre-intervention phase.

*p=0.01. **p=0.007. There were no other significant differences between groups.
Baseline total compliance was significantly lower in the active group (median 92% (interquartile range [IQR] 72-99) versus median 97% [IQR 87-102] for control patients, p=0.01). The upper IQR's of 99 and 102 indicate that some medications were taken in excess of that prescribed. Although daily compliance was lower in the active group (median 68%, IQR 30-87) than in the control group (median 77%, IQR 56-88), as was timing compliance (active group median 17% [IQR 9-51] versus 21% [IQR 10-59] for controls), these differences were not significant. All other parameters did not differ significantly between active and control groups (Table 8.1).

In the post-intervention period 17 patients dropped out as follows:

- 10 from the active group
  - 3 did not wish to re-run the electronic monitoring bottles
  - 6 used them inconsistently
  - 1 failure of the recording system, and
- 7 from the control group
  - 1 declined to re-run the electronic monitoring
  - 6 did not use the bottles consistently

Post-intervention compliance data was evaluable for 52 patients (23 in the active group and 29 controls) (Table 8.1). Dosage as levodopa equivalent units increased by 51 (SD 148) in the active group versus 70 (149) in controls (not significant). After the intervention median total compliance was 96% (IQR 82-100) in the active group, versus 94% (IQR 78-99) in controls (not significant) and daily compliance was 75% (IQR 48-88) in the active group versus 69% (IQR 36-86) in controls, not significant. However, timing compliance was
significantly better in the active group at 39% (IQ 22-58) compared to controls 20% (IQ 10-47) (p=0.007). The changes in total and daily compliance, from pre- to post-intervention, were not significantly different between active and control patients, but timing compliance post-intervention improved by mean 11.4 (SD 28) in active group versus a deterioration (mean -7.4, SD 21) in controls, p=0.001. There was a worsening of all compliance measures in the control group for the second testing period compared to the first. There were no significant differences between UPDRS 3 or quality of life scores or adverse events between groups before the intervention (Table 8.1). The mean change in PDQ single index score was 8 (SD 11) in the active group versus – 2 (SD 15) in controls (not significant). However, UPDRS 3 improved in the active group (mean -0.5, SD 11) versus a deterioration in controls (mean +5, SD 8)(p=0.03).

There were no significant differences in frequency or type of adverse events between groups. In the active group there were 1.5 adverse events (SD 1.3) per patient, while in the control group there were 1.1 adverse events (SD 1.5) per patient. Dyskinesia, nausea, sleepiness and ankle swelling were the most frequent adverse events. Timing compliance was significantly better for once daily drugs such as selegiline 10mg (median 82%, IQ 70-93) than drugs prescribed twice daily (33%, IQ 4-47) or more frequently (p<0.0001)(Figure 8.2).
Figure 8.2: Compliance (median and upper quartile) against number of daily doses of antiparkinson medication. Compliance measures were lower with increasing number of daily doses, most notably for timing compliance. Timing compliance was significantly better for once daily drugs than drugs taken more frequently (p<0.0001). Data is from 69 patients in the pre-intervention phase of the study.

Discussion

We found improved timing of oral antiparkinson medicine intake after an educational intervention. However, there was variability in the response, which ranged within the active group from a worsening of 23% to an improvement of 96% in timing compliance, and there was an overall worsening of compliance measures in the control group. The initial 3-month compliance-monitoring period may provide artificially high levels of compliance, boosted by the novelty of the technique which diminished by the second three months of monitoring. Deterioration in control group compliance figures post-intervention is reported elsewhere: in compliance with antiretroviral therapy where a
cognitive behaviour intervention was tested in HIV positive patients (Weber, Christen, Christen, Tschopp, Znoj, Schneider, Schmitt, Opravil, Gunthard, & Ledergerber 2004) and in elderly patients prescribed cardiac medications (Fulmer et al. 1999). A small group of our patients (6 of 28 in the active group (21%) who entered the post-intervention phase) were highly motivated and improved timing dramatically, with a mean improvement in timing compliance of 53% (SD 27); 3 of these patients were prescribed only one drug and the other 3 were on two drugs, thus representing simpler drug regimens than average. The majority of our patients found regularisation of medicine-taking difficult. Although we did not explore the reasons for this, they are well documented in PD (Leopold, Polansky, & Hurka 2004) and other diseases (Chesney et al. 2000; Stephenson, Rowe, Haynes, Macharia, & Leon 1993) and include forgetfulness and leaving home without medication.

A significant proportion of our PD patients had a carer who helped with their medicines, and this is another potential influence on medicine taking behaviour.

We found no difference in adverse events between active and control groups. Drug side-effects influence compliance, in particular leading to premature therapy discontinuation (Bull, Hu, Hunkeler, Lee, Ming, Markson, & Fireman 2002a), but this is commoner after therapy initiation (Bull, Hunkeler, Lee, Rowland, Williamson, Schwab, & Hurt 2002b) whereas in our study patients were on established medication.

The dropout rate in this study was high as many patients found difficulty with the technique. Patients who dropped out of the study tended to be on higher doses of medication. Such patients may have lower medication compliance,
so that our figures may artificially elevate the ‘real-life’ situation of medicine intake.

A multitude of studies have tested interventions to improve therapy compliance (Haynes et al. 2002), but this is the first such study in Parkinson’s disease. The vast majority of studies in other disease areas used pill counts, self report or physician/nurse assessment (McDonald, Garg, & Haynes 2002) to measure compliance despite well-recognised shortcomings and inaccuracy of these methods (Cramer, Mattson, Prevey, Scheyer, & Ouellette 1989; Melbourne, Geletko, Brown, Willey-Lessne, Chase, & Fisher 1999; Paes, Bakker, & Soe-Agnie 1998; Pullar, Kumar, Tindall, & Feely 1989; Stephenson, Rowe, Haynes, Macharia, & Leon 1993). Many different types of intervention have been tested (Haynes, McDonald, Garg, & Montague 2002) most being complex involving multiple components, which leaves uncertainty as to which aspects have a positive effect. We therefore chose a simple one-dimensional intervention. In diabetes, when baseline electronic monitoring data was used to provide individualised cue-dose training (linking medicine taking to daily activities, including routine change such as weekends) timing compliance improved by a mean of 15% (Rosen, Rigsby, Salahi, Ryan, & Cramer 2004), similar to the improvement in timing compliance in our study. Other studies report either no benefit or only a modest improvement (McDonald, Garg, & Haynes 2002).

In our study drugs taken once daily were taken more regularly than complicated regimens, which is consistent with a systematic review of 76 electronic monitoring studies (Claxton, Cramer, & Pierce 2001).
Pharmaceutical development of more once daily antiparkinson preparations may help ease the process of medicine taking.

The improvement in motor score in active patients relative to controls occurred despite similar dose increases during the monitoring period, suggesting benefit of the intervention. Quality of life did not improve between active and control groups, nor was there an improvement in quality of life in the subset of patients whose compliance improved. This may be attributable to the stronger influence of factors other than motor score (e.g. depression) on quality of life (Schrag, Jahanshahi, & Quinn 2000). Another consideration is the well-known improvement in compliance immediately prior to the clinic visit, which may artificially improve the clinic UPDRS reading. More prolonged observation of clinical response may be more accurate, which we are now undertaking using ambulatory tremor readings. We speculate that longer-term regularisation of medicine intake might delay or reduce future motor fluctuations, but this is clearly beyond the scope of current work. Clinical indicators have sometimes improved in other diseases (e.g. epilepsy (Cramer, Glassman, & Rienzi 2002), hypertension (Leenen et al. 1997) and diabetes (Morris et al. 1997)) in association with better compliance, but such findings are not universal (Rosen, Rigsby, Salahi, Ryan, & Cramer 2004; Weber, Christen, Christen, Tschopp, Znoj, Schneider, Schmitt, Opravil, Gunthard, & Ledergerber 2004). Further larger, longer-term studies are necessary to evaluate the clinical significance of irregular medicine taking in Parkinson's disease. Other methods such as simplifying drug regimen, which is of proven value in other disease areas (Brun 1994; Eisen et al. 1990), may be more universally achievable and is another topic for further study.
Future developments

Our findings are based on observations from a single centre in the West of Scotland. The next step is to examine if these observations reflect medicine-taking behaviour in Parkinson's disease in a wider population. We are currently co-ordinating a study of medication adherence using electronic monitoring in Parkinson's disease across Europe. Five countries (the United Kingdom, France, Spain, Italy and Germany) are participating each with one or two centres and a total of 120 patients will be studied. The hypotheses being tested are:-

1. Drug taking in Parkinson's disease is erratic
2. The first dose in the day is taken more consistently than doses later in the day
3. Adherence is inversely related to the number of daily doses
4. Disease stage and the presence of fluctuations influence medicine taking behaviour
5. Poorly controlled patients consume more health care resources than well controlled patients

This study is scheduled to start in the autumn 2005 and is estimated to take a year to complete.

How does therapy intake relate to clinical response? Fluctuations in the clinical response to antiparkinson medication occur in virtually all patients in the later stages of disease, are difficult to manage, and cause significant functional impairment and morbidity. Pulsatile stimulation of the post-synaptic dopamine receptor is considered a key factor, and is contributed by pharmacokinetic properties of antiparkinson drugs (such as short half-life and variable absorption). We hypothesise that irregular drug ingestion contributes to motor fluctuations and that improved regularity of medicine intake will smooth the clinical response. The first step is to quantify the clinical response to individual doses of therapy using objective methods.

Tremor is the most commonly experienced 'wearing-off' symptom at the end of a dose of antiparkinson medication. We have planned a study which will use an accelerometer (a
small device attached to the limb via a Velcro strap) and relate tremor response to medication timing (measured using electronic monitoring bottles, Aardex®, Switzerland) over a 7 day period. The primary outcome measure is increase in tremor severity in relation to delayed doses of antiparkinson medication.

Conclusions

The work presented in this thesis shows that electronic monitoring is the most accurate method of measuring therapy adherence and gives detailed information on medicine-taking behaviour. About a fifth of Parkinson's patients take less than 80% of prescribed medication, and a tenth take medication in excess of that prescribed. The majority of patients take medicines at irregular time intervals. Taking less than 80% of prescribed medication is associated with depression, more tablets, younger age and poorer quality of life. Patients who are more involved in therapy management decisions are more satisfied and have higher intentions to comply with therapy, but this does not translate into actual therapy-taking behaviour. Parkinson's patients believe their antiparkinson medication is necessary and although they have concerns regarding medicine taking, this does not influence overall medicine intake. Parkinson's patients' main concerns are of adverse effects, increasingly complicated drug regimens and lack of efficacy of drug treatment. Timing compliance and motor scores can be improved by an educational intervention, and once daily drugs are taken more consistently than drugs prescribed more frequently.

There are significant implications of this work for clinical practice. Simplifying drug regimens and education on the continuous dopaminergic theory help to regularise medicine taking. Future work to evaluate the clinical significance is needed.
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Appendix 1: Patient Information Leaflets

Department of Neurology

**Information Sheet on Dopamine Agonists for Patients with Parkinson’s Disease**

A recent reminder from the Committee on the Safety of Medicines concerns some of the drugs used in Parkinson’s Disease. It reminds doctors that in a few patients taking a type of drug called a dopamine agonist (pergolide or Celance, bromocriptine or Parlodel, cabergoline or Cabaser), there have been side effects which may be serious unless treated appropriately. This information is not new, and has been known for many years, but as these drugs are being used more frequently instead of L-Dopa containing drugs, the reminder is timely.

Two members of this class of drug do not cause this problem as they are of a different formulation. They are ropinirole and pramipexole. It has always been our practice at review appointments to ask about side effects or problems with the drugs, but in line with the recommendations of the Committee on Safety of Medicines, we have introduced a more formal monitoring system with regular blood tests and chest x-rays. This is because the unwanted side effects may include breathing and circulation problems.

All dopamine agonists may cause nausea, drowsiness (including sudden onset of sleep) and hallucinations.

You have the following choices:

A. Change from your present tablet to either pramipexole or ropinirole.

B. Continue on your present medication but be monitored with regular blood tests and lung tests.

C. Come off the dopamine agonist completely and use alternative medication. This is a possible option if you have not had Levodopa or could manage with L-Dopa instead of dopamine agonist treatment.

We shall be happy to discuss this with you at your clinic visit.
WHY IT IS IMPORTANT TO TAKE MEDICATION FOR PARKINSON'S DISEASE ON A REGULAR BASIS

In Parkinson's disease, there is a loss of brain nerve cells containing a chemical called dopamine. The dopamine is needed to help control movements. Parkinson's medication either replaces the dopamine, boosts the dopamine by preventing its breakdown, or stimulates the brain in the same way as dopamine. Normally, the brain is stimulated by dopamine in a continuous fashion. In patients with Parkinson's disease, the dopamine levels are too low. When medication is taken, the levels of dopamine increase and are high after 30-60 minutes, the levels then gradually fall as the body breaks down the dopamine. This causes high and low levels of dopamine in the brain. If tablets are taken at regular intervals, there are smoother levels of dopamine in the brain giving smoother control of symptoms. Taking medicines at regular time intervals also helps prevent the development of long term side effects in the future.

Unfortunately, sometimes after taking medicine for Parkinson's disease for several years, variations or fluctuations occur in the control of the symptoms. When the symptoms are well controlled and you are able to function, this is termed "on", if the symptoms are poorly controlled and the movements are slow and stiff, this is termed "off". When the symptoms fluctuate this is called the "on/off" effect. If medications are taken on a regular basis, there is a steadier supply of dopamine to the brain and these fluctuations can be minimised.
Since its introduction in 1987, the UPDRS has been used extensively by researchers and clinicians around the world. The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. It comprises: Section 1: Mentation, Behavior, and Mood; Section 2: Activities of Daily Living; Section 3: Motor Examination. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible: 199 represents the worst (total) disability, 0 represents no disability.

Fahn S, Elton R, Members of the UPDRS Development Committee.
In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2.
Florham Park, NJ.
Macmillan Health Care Information 1987, pp 153-163, 293-304

I - MENTATION, BEHAVIOUR, AND MOOD (max points 16)

1. Intellectual Impairment (max 4)
   - 0 none
   - 1 mild (consistent forgetfulness with partial recollection of events with no other difficulties)
   - 2 moderate memory loss with disorientation and moderate difficulty handling complex problems
   - 3 severe memory loss with disorientation to time and often place, severe impairment with problems
   - 4 severe memory loss with orientation only to person, unable to make judgments or solve problems

2. Thought Disorder (max 4)
   - 0 none
   - 1 vivid dreaming
   - 2 "benign" hallucination with insight retained
   - 3 occasional to frequent hallucination or delusions without insight, could interfere with daily activities
   - 4 persistent hallucination, delusions, or florid psychosis.
3. Depression (max 4)
   □ 0 not present
   □ 1 periods of sadness or guilt greater than normal, never more than a week
   □ 2 sustained depression for more than one week
   □ 3 vegetative symptoms (insomnia, anorexia, abulia, weight loss)
   □ 4 vegetative symptoms with suicidality

4. Motivation (Initiative) (max 4)
   □ 0 normal
   □ 1 less of assertive, more passive
   □ 2 loss of initiative or disinterest in elective activities
   □ 3 loss of initiative or disinterest in day to day (routine) activities
   □ 4 withdrawn, complete loss of motivation

II - ACTIVITIES OF DAILY LIVING (max points 52)

5. Speech (max 4)
   □ 0 normal
   □ 1 mildly affected, no difficulty being understood
   □ 2 moderately affected, may be asked to repeat
   □ 3 severely affected, frequently asked to repeat
   □ 4 unintelligible most of time

6. Salivation (max 4)
   □ 0 normal
   □ 1 slight but noticeable increase, may have nighttime drooling
   □ 2 moderately excessive saliva, may have minimal drooling
   □ 3 marked drooling
7. **Swallowing** (max 4)
   - 0 normal
   - 1 rare choking
   - 2 occasional choking
   - 3 requires soft food
   - 4 requires NG tube or G-tube

8. **Handwriting** (max 4)
   - 0 normal
   - 1 slightly small or slow
   - 2 all words small but legible
   - 3 severely affected, not all words legible
   - 4 majority illegible

9. **Cutting Food** (Handling Utensils) (max 4)
   - 0 normal
   - 1 somewhat slow and clumsy but no help needed
   - 2 can cut most foods, some help needed
   - 3 food must be cut, but can feed self
   - 4 needs to be fed

10. **Dressing** (max 4)
    - 0 normal
    - 1 somewhat slow, no help needed
    - 2 occasional help with buttons or arms in sleeves
    - 3 considerable help required but can do some things alone
    - 4 helpless
11. **Hygiene** (max 4)

- 0 normal
- 1 somewhat slow but no help needed
- 2 needs help with shower or bath or very slow in hygienic care
- 3 requires assistance for washing, brushing teeth, going to bathroom
- 4 helpless

12. **Turning in Bed** (Adjusting Bed Clothes) (max 4)

- 0 normal
- 1 somewhat slow no help needed
- 2 can turn alone or adjust sheets but with great difficulty
- 3 can initiate but not turn or adjust alone
- 4 helpless

13. **Falling** (Unrelated to Freezing) (max 4)

- 0 none
- 1 rare falls
- 2 less than one per day
- 3 average of once per day
- 4 more than one per day

14. **Freezing** (When Walking) (max 4)

- 0 normal
- 1 rare, may have start hesitation
- 2 occasional falls from freezing
- 3 frequent freezing, occasional falls
- 4 frequent falls from freezing
15. **Walking** (max 4)
- □ 0 normal
- □ 1 mild difficulty, may drag legs or decrease arm swing
- □ 2 moderate difficulty requires no assistance
- □ 3 severe disturbance requires assistance
- □ 4 cannot walk at all even with assistance

16. **Tremor** (max 4)
- □ 0 absent
- □ 1 slight and infrequent, not bothersome to patient
- □ 2 moderate, bothersome to patient
- □ 3 severe, interferes with many activities
- □ 4 marked, interferes with all activities

17. **Sensory Complaints** (Related to Parkinsonism) (max 4)
- □ 0 none
- □ 1 occasionally has numbness, tingling, and mild aching
- □ 2 frequent, but not distressing
- □ 3 frequent painful sensation
- □ 4 excruciating pain

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**III - MOTOR EXAMINATION** (max points 108)

18. **Speech** (4 max)
- □ 0 normal
- □ 1 slight loss of expression, diction, volume
- □ 2 moderate impairment, monotone, slurred but understandable
- □ 3 marked impairment, difficult to understand
- □ 4 unintelligible
19. **Facial Expression** (4 max)

- □ 0 normal
- □ 1 slight hypomymia, could be normal "poker face"
- □ 2 slight but definite abnormal diminution in expression
- □ 3 moderate hypomymia, lips parted some of time
- □ 4 masked or fixed face, lips parted 1/4" or more with complete loss of expression

20. **Tremor at Rest** (5 part question - 20 points max)

- □ **Face, lips, chin** (4 max)
  - □ 0 absent
  - □ 1 slight and infrequent
  - □ 2 mild and present most of time
  - □ 3 moderate and present most of time
  - □ 4 marked and present most of time

- □ **Left hand** (4 max)
  - □ 0 absent
  - □ 1 slight and infrequent
  - □ 2 mild and present most of time
  - □ 3 moderate and present most of time
  - □ 4 marked and present most of time

- □ **Right hand** (4 max)
  - □ 0 absent
  - □ 1 slight and infrequent
  - □ 2 mild and present most of time
  - □ 3 moderate and present most of time
  - □ 4 marked and present most of time
☐ **Left foot (4 max)**
  ☐ 0 absent
  ☐ 1 slight and infrequent
  ☐ 2 mild and present most of time
  ☐ 3 moderate and present most of time
  ☐ 4 marked and present most of time

☐ **Right foot (4 max)**
  ☐ 0 absent
  ☐ 1 slight and infrequent
  ☐ 2 mild and present most of time
  ☐ 3 moderate and present most of time
  ☐ 4 marked and present most of time

21. **Action or Postural Tremor of Hands** (2 part question - max points 8)

☐ **Left hand (4 max)**
  ☐ 0 absent
  ☐ 1 slight, present with action
  ☐ 2 moderate, present with action
  ☐ 3 moderate present with action and posture holding
  ☐ 4 marked, interferes with feeding

☐ **Right hand (4 max)**
  ☐ 0 absent
  ☐ 1 slight, present with action
  ☐ 2 moderate, present with action
  ☐ 3 moderate present with action and posture holding
  ☐ 4 marked, interferes with feeding
22. **Rigidity** (5 part question - max points 20) (judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

- **Neck** (4 max)
  - 0 absent
  - 1 slight or only with activation
  - 2 moderate
  - 3 marked, full range of motion
  - 4 severe

- **Left upper extremity** (4 max)
  - 0 absent
  - 1 slight or only with activation
  - 2 moderate
  - 3 marked, full range of motion
  - 4 severe

- **Right upper extremity** (4 max)
  - 0 absent
  - 1 slight or only with activation
  - 2 moderate
  - 3 marked, full range of motion
  - 4 severe

- **Left lower extremity** (4 max)
  - 0 absent
  - 1 slight or only with activation
  - 2 moderate
  - 3 marked, full range of motion
  - 4 severe

- **Right lower extremity** (4 max)
  - 0 absent
  - 1 slight or only with activation
  - 2 moderate
  - 3 marked, full range of motion
  - 4 severe
23. **Finger Taps** (2 part question - max points 8)
(Patient taps thumb with index finger in rapid succession)

- **Left hand** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform

- **Right hand** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform

24. **Hand Movements** (2 part question - max points 8)
(Patient opens and close hands in rapid succession)

- **Left hand** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform

- **Right hand** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform
25. **Rapid Alternating Movements of Hands** (2 part question - max points 8)
(Pronation and supination of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously)

- **Left hand** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform

- **Right hand** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform

26. **Leg Agility** (2 part question - max points 8)
(Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches)

- **Left leg** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform

- **Right leg** (4 max)
  - 0 normal
  - 1 mild slowing and/or reduction in amplitude
  - 2 moderately impaired, definite and early fatiguing, may have occasional arrests
  - 3 severely impaired, frequent hesitations and arrests
  - 4 can barely perform
27. **Arising From Chair** (4 max)
   (Patient attempts to arise from a straight-backed chair, with arms folded across chest)
   - 0 normal
   - 1 slow, may need more than one attempt
   - 2 pushes self up from arms or seat
   - 3 tends to fall back, may need to try more than once but can get up without help
   - 4 unable to arise without help

28. **Posture** (4 max)
   - 0 normal erect
   - 1 slightly stooped, could be normal for older person
   - 2 definitely abnormal, moderately stooped, may lean to one side
   - 3 severely stooped with kyphosis
   - 4 marked flexion with extreme abnormality of posture

29. **Gait** (4 max)
   - 0 normal
   - 1 walks slowly, may shuffle with short steps, no festination (hastening steps) or propulsion
   - 2 walks with difficulty, little or no assistance, some festination, short steps or propulsion
   - 3 severe disturbance, frequent assistance
   - 4 cannot walk at all, even with assistance

30. **Postural Stability** (4 max)
    (Response to sudden, strong, posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
    - 0 normal
    - 1 recovers unaided
    - 2 would fall if not caught
    - 3 falls spontaneously
    - 4 unable to stand
31. **Body Bradykinesia and Hypokinesia** (4 max)
(Combining slowness, hesitancy, decreased arm-swing, small amplitude and poverty of movement in general.)

- □ 0 none
- □ 1 minimal slowness, could be normal, deliberate character
- □ 2 mild slowness and poverty of movement, definitely abnormal, or decreased amplitude
- □ 3 moderate slowness, poverty, or small amplitude
- □ 4 marked slowness, poverty, or amplitude

**IV - COMPLICATIONS OF THERAPY** (In the Past Week) (max points 23)

32. **Dyskinesias: Duration** (max 4)
(What proportion of the waking day are dyskinesias present?) (Historical information)

- □ 0 none
- □ 1 1-25% of day.
- □ 2 26-50% of day.
- □ 3 51-75% of day.
- □ 4 76-100% of day.

33. **Dyskinesias: Disability** (max 4)
(How disabling are the dyskinesias?) (Historical information; may be modified by office examination)

- □ 0 Not disabling
- □ 1 Mildly disabling.
- □ 2 Moderately disabling.
- □ 3 Severely disabling.
- □ 4 Completely disabled.

34. **Dyskinesias: Pain** (max 4)
(How painful are the dyskinesias?)

- □ 0 No painful dyskinesias
- □ 1 Slight.
- □ 2 Moderate.
- □ 3 Severe.
- □ 4 Marked.
35. **Dystonia** (max 4)  
(Presence of Early Morning Dystonia?)

- □ 0 No.
- □ 1 Yes.

36. "Offs" **predictable** (max 1)  
(Are "off" periods predictable?)

- □ 0 No.
- □ 1 Yes.

37. "Offs" **unpredictable** (max 1)  
(Are "off" periods unpredictable?)

- □ 0 No.
- □ 1 Yes.

38. "Offs" **sudden** (max 1)  
(Do "off" periods come on suddenly, within a few seconds?)

- □ 0 No.
- □ 1 Yes.

39. "Offs" **duration** (max 4)  
(What proportion of the waking day is the patient "off" on average?)

- □ 0 none
- □ 1 1-25% of day.
- □ 2 26-50% of day.
- □ 3 51-75% of day.
- □ 4 76-100% of day.

40. Does the patient have anorexia, nausea, or vomiting? (max 1)

- □ 0 No.
- □ 1 Yes.

41. Any sleep disturbances, such as insomnia or hypersomnolence? (max 1)  
(Record the patient's blood pressure, height and weight on the scoring form)

- □ 0 No.
- □ 1 Yes.

42. Does the patient have symptomatic orthostasis? (max 1)

- □ 0 No.
- □ 1 Yes.
V - MODIFIED HOEHN AND YAHRT STAGING SCALE

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability, physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

VI - SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.
Mini Mental State Examination (MMSE)

ORIENTATION

Date 1__        Clinic 1__
Day 1__         Floor 1__
Month 1__       City 1__
Year 1__        County 1__
Season 1__      Country 1__

___out of 10

REGISTRATION Plant, Key, Ball (3) Score___

ATTENTION & CALCULATION
93, 86, 79, 72, 65

or

WORLD = DLROW out of 5 Score___

RECALL The 3 items above out of 3 Score___

LANGUAGE: NAMING: Point to and ask the name of: Pen, Watch: 2 Score___

REPETITION: repeat 'No ifs ands or buts' 1 Score___

COMMAND: take paper in R hand 1, fold it in half 1, place on lap/floor 1 = 3 Score___

READING: read and obey the command: 'Close your eyes' 1 Score___

WRITING: write a sentence (which makes sense) 1 Score___

DRAWING: pentagons 1 Score___

___out of 30
Due to having Parkinson’s Disease, how often during the last month have you…
(Please tick one box for each question)

1. **Had difficulty doing the leisure activities you would like to do?**

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Total Score

2. **Had difficulty looking after your home, for example, housework, cooking or gardening?**

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Total Score

3. **Had difficulty carrying shopping bags?**

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4. **Had problems walking half a mile?**

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Total Score
5. Had problems walking 100 yards (approximately one block)?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

6. Had problems getting around the house as easily as you would like

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

7. Had difficulty getting around in public places?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

8. Needed someone else to accompany you when you went out?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score
9. Felt frightened or worried about falling in public?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

10. Been confined to the house more than you would like?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

11. Had difficulty washing yourself?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

12. Had difficulty dressing yourself?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score
13. Had problems doing up buttons or shoe laces?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

14. Had problems writing clearly?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

15. Had difficulty cutting up your food?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

16. Had difficulty holding a drink without spilling it?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score
17. Felt depressed?

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Total Score

18. Felt isolated and lonely?

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19. Felt weepy or tearful?

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20. Felt angry or bitter?

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Total Score
21. Felt anxious?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

22. Felt worried about the future?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

23. Felt you had to hide your Parkinson’s from people?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

24. Avoided situations that involved eating or drinking in public?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score
25. Felt embarrassed in public?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

26. Felt worried about other people’s reaction to you?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

27. Had problems with close personal relationships?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

28. Have you lacked the support you needed from your spouse or partner?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score
29. Have you lacked the support you needed from your family or close friends?

0 [  ] Never
1 [  ] Occasionally
2 [  ] Sometimes
3 [  ] Often
4 [  ] Always

Total Score

30. Unexpectedly fallen asleep during the day?

0 [  ] Never
1 [  ] Occasionally
2 [  ] Sometimes
3 [  ] Often
4 [  ] Always

Total Score

31. Had problems with your concentration, for example, when reading or watching TV?

0 [  ] Never
1 [  ] Occasionally
2 [  ] Sometimes
3 [  ] Often
4 [  ] Always

Total Score

32. Felt your memory was failing?

0 [  ] Never
1 [  ] Occasionally
2 [  ] Sometimes
3 [  ] Often
4 [  ] Always

Total Score
33. Had distressing dreams or hallucinations?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

34. Had difficulty speaking?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

35. Felt unable to communicate effectively?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score

36. Felt ignored by people?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always
Total Score
37. Had painful muscles cramps or spasms?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always

Total Score

38. Had aches and pains in your joints or body?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always

Total Score

39. Felt uncomfortably hot or cold?

0 [ ] Never
1 [ ] Occasionally
2 [ ] Sometimes
3 [ ] Often
4 [ ] Always

Total Score
PD ASSESSMENTS Sleep/dyskinesia

Date: ________________________

Name: ________________________ DOB: ________________________

Time of assessments: ________________________

Unit No: ________________________

Time last dose of PD medication taken: ________________________

Dose the patient experience ON / OFF periods? Yes / NO

Epworth Sleepiness Scale.

Q - How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

Scale:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>2. Watching TV</td>
<td></td>
</tr>
<tr>
<td>3. Sitting, inactive in a public place (e.g., a theatre / meeting)</td>
<td></td>
</tr>
<tr>
<td>4. As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>5. Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>6. Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>7. Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>8. In a car, while stopped for a few minutes in traffic</td>
<td></td>
</tr>
</tbody>
</table>

total = 0

score > 16 equals severe daytime sleepiness

Parkinson Dyskinesia Scale

Scale:

0 = Normal
1 = Intermittent
2 = Generalized, mild but continuous, may not be obvious to untrained observer
3 = Moderate, generalized, definitely noticeable to untrained observer
4 = Incapacitating

<table>
<thead>
<tr>
<th>Head</th>
<th>RUE</th>
<th>LUE</th>
<th>RLE</th>
<th>LLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
<td>_____</td>
</tr>
</tbody>
</table>

Trunk total = ___

Goetz Dyskinesia Rating Scale

Score:

0 = Absent
1 = Minimal severity: no interference with involuntary motor acts involved in task
2 = Dyskinesias impair involuntary movements but patient is capable of efficiently completing the motor acts involved in the rated task
3 = Intense interference with movement control so that completing the rated motor task is greatly limited
4 = Violent dyskinesias, incompatible with completion of the rated motor task.

Type of dyskinesia present

<table>
<thead>
<tr>
<th>Chorea</th>
<th>Dystonia</th>
<th>Other, specify</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most disabling - tick only one</th>
<th>Severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorea</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>Other, specify</td>
<td></td>
</tr>
</tbody>
</table>

202
Concordance/Compliance Adverse Events Record

Any adverse events Yes/No

How much alcohol do you drink in a week? ______ units

Occupation

Does a carer supervise your medication? Y/N

Do you use a dosette box? Y/N

Global Impression: Score the approximate overall treatment 'estimate' as follows (this refers to symptoms - a patient with a lot of tremor or stiffness may score themselves undertreated; a patient with a lot of dyskinesia may be scored by the doctor/nurse as overtreated):

Patient's estimate: Undertreatment overtreatment about right

Doctor/Nurse estimate: Undertreatment overtreatment about right

Adverse Event Tick if present

Nausea

Dizziness

Confusion

Nightmares

Hallucinations

Ankle swelling

Sleepiness

Insomnia

Dyskinesia

Other Please detail
Medical Interview Satisfaction Scale

We are interested in your views about the consultation you have just had with your doctor.

If you could spend a few minutes completing this questionnaire it would be a great help.
Please think about the consultation you have just had and indicate whether you agree or disagree with each of the following statements.

Circle one number for each statement.

<table>
<thead>
<tr>
<th>Statement</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The doctor told me just what my trouble is.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2. After talking with the doctor, I know just how serious my illness is.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>3. The doctor told me all I wanted to know about my illness.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>4. I am not really certain about how to follow the doctor’s advice.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>5. After talking with the doctor, I have a good idea of how long it will be before I am well again.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>6. The doctor seemed interested in me as a person.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>7. The doctor seemed warm and friendly to me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8. The doctor seemed to take my problems seriously.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>9. I felt embarrassed while talking with the doctor.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>10. I felt free to talk to this doctor about private matters.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>11. The doctor gave me a chance to say what was really on my mind.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

PLEASE GO TO THE NEXT PAGE
12. I really felt understood by my doctor.  

13. The doctor did not allow me to say everything I had wanted about my problems.  

14. The doctor did not really understand my main reason for coming.  

15. This is a doctor I would trust with my life.  

16. The doctor seemed to know what (s)he was doing.  

17. The doctor has relieved my worries about my illness.  

18. The doctor seemed to know just what to do for my problem.  

19. I expect that it will be easy for me to follow the doctor's advice.  

20. It may be difficult for me to do exactly what the doctor told me to do.  

21. I'm not sure the doctor's treatment will be worth the trouble it will take.  

PLEASE CHECK THAT YOU HAVE GIVEN YOUR OPINION ON EACH STATEMENT

THANK YOU FOR YOUR HELP TODAY.
Please tell us about the discussion with your doctor/nurse about your treatment.

Read each statement and tick one box on each line.

<table>
<thead>
<tr>
<th></th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The doctor/nurse gave me responsibility for deciding how to deal with my health problem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. The doctor/nurse asked me to choose a treatment for my health problem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. The doctor/nurse gave me enough information to make my own decision about treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. The doctor/nurse did not ask my opinion about my medicines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please estimate how accurately you take your medication:

I **miss** a dose of medication: (circle one answer)

- Frequently
- Sometimes
- Never

I **take an extra** dose of medication: (circle one answer)

- Frequently
- Sometimes
- Never

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS
How do you take your medication for Parkinson's Disease?

Put an X on the line below to show roughly how much of your Parkinson's medication you took in the last month.

We would be surprised if this was 100% for most people:

0% means you have taken none of your Parkinson's medication

50% means you have taken half your Parkinson's medication

100% means you have taken every single dose of your Parkinson's medication

120% means you have taken a few extra doses of your Parkinson's medication
Satisfaction with Information About Medicines Scale

We would like to ask you about **the information you have received about your medicines**. Please rate the information you have received about each of the following aspects of your medicines. If you use more than one medicine, please give your overall feeling about information you have received about **all your medicines**.

<table>
<thead>
<tr>
<th>What your medicine is called</th>
<th>About right</th>
<th>Too little</th>
<th>None received</th>
<th>None needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>What your medicine is for</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>What it does</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>How it works</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>How long it will take to act</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>How you can tell if it is working</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>How long you will need to be on your medicine</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>How to use your medicine</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>How to get a further supply</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>Whether the medicine has any unwanted (side)effects</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>What are the risks of you getting side effects</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>What you should do if you experience unwanted side effects</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>Whether you can drink alcohol whilst taking this medicine</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>Whether the medicine interferes with other medicines</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>Whether the medicine will make you feel drowsy</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>Whether the medicine will affect your sex life</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
<tr>
<td>What you should do if you forget to take a dose</td>
<td>About right</td>
<td>Too little</td>
<td>None received</td>
<td>None needed</td>
</tr>
</tbody>
</table>
QUESTIONS ABOUT USING YOUR MEDICINES

- Many people find a way of using their medicines which suits them.

- This may differ from the instructions on the label or from what their doctor has said.

- We would like to ask you a few questions about how you use your medicines

Here are some ways in which people have said that they use their medicines

For each of the statements, please tick the box which best applies to you

<table>
<thead>
<tr>
<th>Your own way of using your medicines</th>
<th>Always</th>
<th>Often</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 I forget to take them</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2 I alter the dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3 I stop taking them for a while</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M4 I decide to miss out a dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M5 I take less than instructed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M6 I take them at regular time intervals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Depression Scale

Directions: Please choose the best answer for how you have felt over the past week.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you basically satisfied with your life?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2. Have you dropped many of your activities and interests?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>3. Do you feel that your life is empty?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4. Do you often get bored?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>5. Are you hopeful about the future?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>6. Are you bothered by thoughts you can’t get out of your head?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>7. Are you in good spirits most of the time?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>8. Do you often feel helpless?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>9. Do you get restless and fidgety?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>10. Do you prefer to stay at home rather than go out and do things?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>11. Do you frequently worry about the future?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>12. Do you feel happy most of the time?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>13. Are you afraid that something bad is going to happen to you?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>14. Do you feel you have more problems with memory than most?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>15. Do you think it is wonderful to be alive now?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>16. Do you feel downhearted and blue?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>17. Do you feel pretty worthless the way you are now?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>18. Do you worry a lot about the past?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>19. Do you find life very exciting?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>20. Is it hard for you to get started on new projects?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>21. Do you feel full of energy?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>22. Do you feel that your situation is hopeless?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>23. Do you think that most people are better off than you are?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>24. Do you frequently get upset over little things?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>25. Do you frequently feel like crying?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>26. Do you have trouble concentrating?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>27. Do you enjoy getting up in the morning?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>28. Do you prefer to avoid social occasions?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>29. Is it easy for you to make decisions?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>30. Is your mind as clear as it used to be?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>
**BRIEF MEDICATION QUESTIONNAIRE (BMQ 2003)**

1. Please list below all medications you took in the **PAST WEEK**. For each medication you list, please answer each of the questions in the boxes below. [Use additional page if necessary]

<table>
<thead>
<tr>
<th>a. Medication name</th>
<th>b. How many days did you take it?</th>
<th>c. How many times per day did you take it?</th>
<th>d. How much did you take each time?</th>
<th>e. How many times did you miss taking it?</th>
<th>f. For what reason were you taking it?</th>
<th>g. How well did this medication work for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

2. Do any of your medications bother you in any way? (Check one)  
   a. IF YES, please name the medication and explain how it bothers you.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>In what way does it bother you?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

3. How much problem or concern are you having in the following areas [circle one]  
   a. My medication causes side effects ...........................................  
   b. It is hard to remember all the doses .........................................  
   c. It is hard to pay for the medication .........................................  
   d. It is hard to open the container ..............................................  
   e. It is hard to get my refill on time .........................................  
   f. It is hard to read the print on the container ..............................  
   g. The dosage times are inconvenient .............................................  
   h. My medication causes other problem or concern ................................

If other problem or concern, please explain: ____________________________

4. Did you stop taking any medications in the **PAST SIX MONTHS**? (Check one)  
   a. IF YES, please list the medications you stopped. For each, answer the questions in the boxes below

<table>
<thead>
<tr>
<th>a. Medication name</th>
<th>b. For what reason were you taking it?</th>
<th>c. How well did the medicine work for you?</th>
<th>d. How much did it bother you?</th>
<th>e. For what reason did you stop taking it?</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>
Beliefs about Medicines Questionnaire

Your views about medicines prescribed for your Parkinson's Disease

We would like to ask you about your personal views about medicines prescribed for you. These are statements other people have made about their medicines. Please show how much you agree or disagree with them by ticking the appropriate box.

<table>
<thead>
<tr>
<th>Statement</th>
<th>strongly disagree</th>
<th>disagree</th>
<th>uncertain</th>
<th>agree</th>
<th>strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My health, at present, depends on my medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Having to take medicines worries me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My life would be impossible without my medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Without my medicines I would be very ill</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I sometimes worry about long-term effects of my medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My medicines are a mystery to me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My health in the future will depend on my medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My medicines disrupt my life</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I sometimes worry about becoming too dependent on my medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>My medicines protect me from becoming worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Your views about medicines in general

We would like to ask you about your personal views about medicines in general. These are statements other people have made about medicines in general. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.

<table>
<thead>
<tr>
<th>Statement</th>
<th>strongly disagree</th>
<th>disagree</th>
<th>uncertain</th>
<th>agree</th>
<th>strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors use too many medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>People who take medicines should stop their treatment for a while every now and again</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Most medicines are addictive</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Natural remedies are safer than medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Medicines do more harm than good</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>All medicines are poisons</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Doctors place too much trust on medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>If doctors had more time with patients they would prescribe fewer medicines</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Beliefs about Medicines for Parkinson’s Disease Questionnaire

Your views about medicines prescribed for your Parkinson’s disease

We would like to ask you about your personal views about medicines prescribed for your Parkinson’s Disease. These are statements other people with Parkinson’s Disease have made about their medicines. Please show how much you agree or disagree with them by circling the appropriate number.

<table>
<thead>
<tr>
<th>Belief</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no concerns about my Parkinson’s medication</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry that my Parkinson’s medicines will stop working</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>The side effects of my medicines are unpredictable</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry about having to take so many tablets</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I am concerned that the medication causes drowsiness</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I would like to delay any increase in my medication for as long as possible</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry about getting side effects in the future</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>These medicines will not help all of my symptoms</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry that I will need more and more medication as time goes on</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I am concerned about the medicines causing involuntary movements</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I would like to delay adding new medication for as long as possible</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry that the benefits of the medication will suddenly disappear</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Using this medicine regularly now will make it less effective in the future</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I worry that the medication worsens some of my symptoms</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>