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Identification and treatment of wearing off in Parkinson's disease

Authors:
James M Fisher (St5 Geriatric Medicine, Northumbria Healthcare NHS Foundation Trust) & Richard W Walker (Consultant Physician and Honorary Professor of Ageing & International Health, Northumbria Healthcare NHS Foundation Trust/Newcastle University)

Correspondence to:
Richard Walker: Richard.walker@nhct.nhs.uk

Abstract:
Parkinson's disease (PD) is a neurodegenerative disorder classically characterised by motor symptoms. In recent years there has been increased recognition of the non-motor symptoms of PD. 'Wearing off', worsening of a patient's symptoms before the next dose of their medication is due, may be seen with advancing disease. Management of wearing off may include modification of a patient's levodopa medication regimen or prescription of an additional agent. The onset of such motor complications may be delayed by the use of levodopa-sparing agents or by keeping levodopa doses to a minimum. Wearing off may be evaluated via patient histories, diaries, rating scales or questionnaires. The efficacy of these assessment methods is however limited by recall bias and their inherent subjectivity. A number of potential objective methods of symptom assessment in PD have been explored, with body-worn accelerometers showing the most potential. The application of advanced computational algorithms to the data captured by accelerometers may enable the complexity of human movement to be appreciated. Such technology may, in future, allow objective identification of wearing off and thus provide the clinician with vital additional information on which to base clinical decisions.

Key Words:
Parkinson's Disease; Wearing off, Motor Fluctuations

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease with selective loss of dopaminergic neurones in the basal ganglia. When there has been loss of 70 – 80% of neurones the motor features of PD, resting tremor, cogwheel rigidity and bradykinesia, become evident. This is generally when the condition is diagnosed. There are currently no proven disease modifying agents and treatment for the disease is aimed at alleviating the symptoms. Generally, patients respond well to treatment early on in the disease but as more and more of the dopaminergic reserve in the basal ganglia is lost they develop motor side effects. These include dyskinesia which manifests as choreiform jerky movements

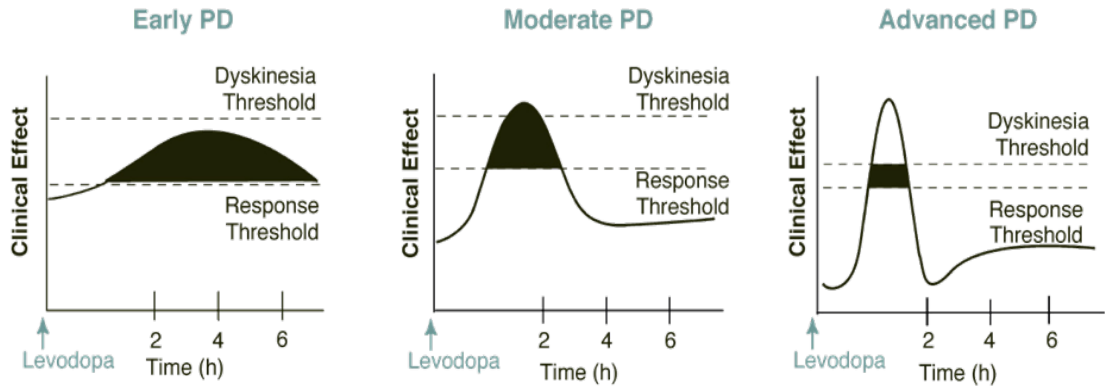
which can involve the limbs, trunk and face and are usually worse at peak dose. They also include wearing off, whereby the patient's symptoms deteriorate before the next dose of medication is due so, for example, the tremor may increase and they may slow up.

It is now increasingly recognised that patients with Parkinson's disease suffer from non-motor symptoms as well as motor symptoms. These include constipation, drooling, pain and neuropsychiatric symptoms including hallucinations, anxiety and depression. All of these symptoms can also occur as a manifestation of wearing off, and not necessarily at the same time as the motor symptoms.

What causes wearing off?

As demonstrated in Figure 1, as the disease progresses the buffering effect of the patient's own dopamine decreases, and they become more dependent on the drugs they take[1]. The short duration response (SDR) to each dose of drug decreases and the therapeutic window narrows such that the time spent controlled, with neither wearing off or peak dose dyskinesia, becomes shorter. In addition to the SDR there is also a long duration response (LDR) which can last for days to weeks but over time the LDR decreases more than the SDR thus leading to fluctuations[2].

Figuure 1: Development of Motor Fluctuations with Advancing Disease (adapted from Obeso et al.[1])



Treatment

Pulsatile delivery of traditional Levodopa leads to pulsatile stimulation of dopamine receptors making motor complications more likely, whereas continuous delivery of Levodopa by infusion reverses motor complications by maintaining the patient for a longer time within the therapeutic window[3]. Treatments aimed at continuous delivery of Levodopa, such as duodenal infusion with Duodopa, do produce improved symptomatic control but are very expensive.

Generally, when a patient who is on Levodopa presents with wearing off, options include increasing the dose frequency, changing to a controlled release preparation but these have variable absorption and an unpredictable effect, rescue therapy with fast acting agents such as dispersible Madopar (a form of Levodopa) or adding in other agents. Standard Levodopa includes a dopamine decarboxylase inhibitor (DDCI) which prevents breakdown of Levodopa

in the peripheral circulation, but which does not cross the blood brain barrier, thus allowing breakdown to dopamine once inside the brain. Dopamine agonists, such as Ropinirole, Pramipexole and Rotigotine (given as a patch), directly stimulate the post synaptic receptor and can reduce off time by approximately 20%, or 1 and a half hours per day. Monoamine oxidase-B (MAOI-B) inhibitors such as Selegiline and Rasagiline have also been shown to decrease wearing off as have the catechol-O-methyl transferase (COMT) inhibitors, Entacapone and Tolcapone. These drugs act by slowing the breakdown of dopamine and therefore prolonging the action of Levodopa.

Prevention

Ideally, motor complications should be prevented or, more realistically, delayed by appropriate management. Levodopa doses should be kept low, generally not higher than 600mgs per day. Levodopa sparing agents such as dopamine agonists, MAOI-Bs and COMT inhibitors should be utilised. There is evidence from previous drug trials, and the recently published PD MED study, that initial treatment with dopamine agonists compared to Levodopa leads to less motor side effects at 5 years, at the expense of poorer symptomatic control otherwise (PD MED 2011). There are now once daily preparations of both Ropinirole and Pramipexole available.

Identifying Wearing Off

Since wearing off can include such a variety of signs and symptoms it is thought that the condition may be under-recognised by clinicians[4]. It is therefore imperative that patients are educated about wearing off and are regularly asked about, and given ample time to describe, symptoms that may suggest wearing off. Reliance on patient recall of symptoms (perhaps with relative/carer input) is prone to recall bias which may be exacerbated by the duration of time between appointments and the fluctuant nature of the condition itself. A common description given by patients that should alert clinicians to the possible onset of wearing off, is that the duration of effect of their medications no longer lasts until their next medication is due.

Direct observation of wearing off by clinicians is simply impractical, given the long duration of time over which such fluctuations occur. Various attempts have therefore been made to improve the detection and measurement of wearing off. One of the most commonly used and simplest methods is a patient completed symptom diary. A symptom diary requires patients to record their current disease state, be it on, off or dyskinetic, usually at hourly intervals. Patients are typically asked to complete symptom diaries for a period of several days whilst at home, thus enabling prolonged recording of disease state and its fluctuation. Wearing off may be recognised by increasing amounts of off time occurring before the next dose of medication is due. Central to the validity of diaries is patient compliance with their completion and accurate disease state recognition by the patient. The nature of symptom diaries is such that they are open to recall bias. Evidence suggests that patient self-assessment, when compared to clinician assessment, often results in incorrect identification of their disease state, particularly when their disease is fluctuant[5].

In attempts to provide more objective, valid measures, a variety of clinical rating scales are in use for patients with PD. The most well known and widely used is the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[6]. This is an extensive assessment used widely in clinical research that includes both clinician and patient completed sections. The MDS-UPDRS consists of four sections, part four of which is designed to capture data on motor complications. Specifically relating to wearing off, the MDS-UPDRS has only two questions. Firstly it asks the patient, with clinician supervision, to quantify off time as a percentage of time spent awake in a typical day in the last week. Secondly it asks patients to categorise the functional impact of off time in terms of its impact on their activities and social interactions. Whilst this assessment method standardises the question asked and the choice of possible responses, it is ultimately limited by recall bias and inherently subjective.

Questionnaires have been specifically designed to detect both motor and non-motor symptoms of wearing off; the 32 item wearing off questionnaire, WOQ-32[4] and its abbreviated form, WOQ-9[7] (Table 1). Evidence suggests these tools may be more sensitive in the detection of wearing off when compared to clinician assessment; they are however limited by relatively low specificity[8].

Table 1: The Wearing Off Questionnaire (adapted from Stacy et al.[7])

	COLUMN A Experience symptoms?	COLUMN B Usually improves after my next dose
Tremor		
Any slowness in movement		
Mood changes		
Any stiffness		
Pain / aching		
Reduced dexterity		
Cloudy mind / slowness of thinking		
Anxiety / panic attacks		
Muscle cramping		

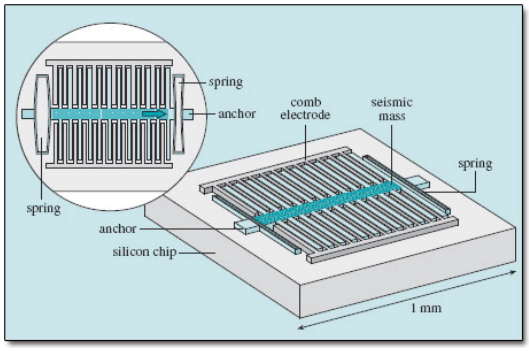
Moving towards more objective methods of assessment

Ultimately patient recall, questionnaires and even clinical assessment remain inherently subjective methods of assessment. As such they are limited by recall bias and the fact that symptoms may not be apparent during the brief period during which clinical assessment occurs. One might also argue that the very act of observing a patient in a clinical environment may in fact influence the signs and symptoms exhibited. There is therefore great need for a more objective method of symptom assessment capable of capturing data, unobtrusively, whilst the patient goes about their normal activities of daily living.

In attempts to objectively assess symptoms in PD, a wide variety of methods have been explored including lasers[9], electromagnetic sensors[10] and optoelectronic systems[11]. These systems have shown promise in a highly-controlled research setting but their clinical use has

been restricted as a result of their complexity and expense. Frequently they are only capable of short-lived assessment and evaluation of a patient in their own home has not been possible. The field that has seen the most work undertaken is that of accelerometry. Accelerometers are sensors that are capable of detecting and measuring acceleration, such as that generated by human movement. Accelerometers have been in existence for many years but recent advances in nano-technology have seen the development of micro-electromechnical systems (MEMS) accelerometers that are often less than a millimetre in size[12], an example of which is seen in Figure 2.

Figure 2: A typical MEMS accelerometer (adapted from [13])



Hoff et al.[14] used continuous ambulatory accelerometry in an attempt to identify on and off disease states in 15 patients with PD, all of whom exhibited fluctuations. Their system comprised 7 separate accelerometers located on the sternum, wrist and thigh, worn for a 24 hour period whilst patients simultaneously recorded a symptom diary. The objective measures generated by the authors' analysis showed inadequate sensitivity and specificity to consider this system an appropriate method of automated on-off detection. In this work human movement exhibited by participants was, for the purposes of analysis, mathematically described using small numbers of simple variables (e.g. mean acceleration). It is likely that the simplicity of such variables will fail to capture the complexity of human movement, hence the poor results seen in this work.

Keijsers et al.[15] collected data in a similar manner, with accelerometers placed at 6 sites on the body, but explored the use of more sophisticated analysis methods, neural networks. Artificial neural networks (ANNs) are mathematical models inspired by biological neural networks, capable of adaption and 'learning' as data are presented[16]. ANNs are capable of considering huge numbers of variables and, critically, can weigh up the complex interconnections between each. Their use in the field of speech recognition has proved extremely successful in improving it's accuracy. Keijsers' work showed that ANNs were able to distinguish the presence of dyskinesia from voluntary movement with high levels of sensitivity and specificity.

Accelerometers and analysis methods like ANNs have huge potential to provide a new, objective method to assess the symptoms exhibited by PD patients. This method may enable wearing off to be identified sooner and more accurately, thus more fully informing treatment decisions. The authors of this article are currently involved with research

exploring the use of similar analysis methods to accelerometer data, derived from wrist-worn sensors worn by patients with PD for prolonged periods at home. Looking further ahead, Rodriguez-Molinero et al.[17] hypothesised that in the future, body-worn sensors could be used in conjunction with drug infusion pumps to provide dynamic real-time dose adjustment in response to both the patient's disease state and their level of activity.

Conclusions

Wearing off is a major problem in later stage PD and has a significant impact on quality of life. Judicious use of drugs can help to delay the onset of wearing off and adaption of the drug regime can help to treat the motor symptoms but has less effect on the non-motor symptoms. In order to identify the problem healthcare professionals, patients and carers need to be aware, and scales and diaries can help. In the future it is likely that unobtrusive monitoring devices will become available clinically to guide management.

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