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Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: http://www.tandfonline.com/loi/iern20

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To cite this article: Roongroj Bhidayasiri, Nobutaka Hattori, Beomseok Jeon, Rou-Shayn Chen, Moon Keen Lee, Jawad A Bajwa, Vincent CT Mok, Baorong Zhang, Thamrin Syamsudin, Louis Chew Seng Tan, Roland Dominic G Jamora, Apichart Pisarnpong & Werner Poewe (2015): Asian perspectives on the recognition and management of levodopa 'wearing-off' in Parkinson's disease, Expert Review of Neurotherapeutics, DOI: 10.1586/14737175.2015.1088783

To link to this article: http://dx.doi.org/10.1586/14737175.2015.1088783

Published online: 21 Sep 2015.

EXPERT REVIEWS

Asian perspectives on the recognition and management of levodopa 'wearing-off' in Parkinson's disease

Expert Rev. Neurother. Early online, 1–13 (2015)

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Most Parkinson's disease patients will receive levodopa therapy, and of these, the majority will develop some levodopa-induced complications. For many patients, the first complication to develop is the decline in the duration of therapeutic benefit of each levodopa dose, a phenomenon commonly termed 'wearing-off'. There is already extensive literature documenting the epidemiology and management of wearing-off in Parkinson's disease patients of western descent. However, data derived from these studies might not always apply to patients of Asian descent due to genetic variations, differences in co-morbidities or non-availability of certain drugs. This review summarizes the current literature regarding the epidemiology of wearing-off in Asian (including Arab) patients and discusses the management issues in the context of drug availability in Asia.

Keywords: Arab • Asia • fluctuations • non-motor • Parkinson's disease • screening tools • wearing-off

It is well documented that levodopa is the most effective pharmacological treatment for Parkinson's disease (PD), and that it is generally well tolerated at all stages of the disease [1]. Although the choice of initial therapy varies depending on age, disease severity, co-morbidities and patient preference, levodopa is eventually required in most cases and is usually associated with sustained improvements in motor disability. The first few years of levodopa therapy are often referred to as the 'honeymoon phase' [2], but with disease progression and longer and higher exposure to levodopa, many patients develop a range of levodopa-induced complications, which include both motor and non-motor symptoms. For many patients, the first sign of these levodopa-induced complications is when they begin to notice a decline in the duration of therapeutic benefit with each levodopa dose, a phenomenon commonly termed 'wearing-off'.

There is an extensive literature documenting the epidemiology and management of wearing-off fluctuations [3–8]. Based on robust evidence from randomized controlled clinical trials, catechol-*O*-methyltransferase (COMT) inhibitors, monoamine oxidase type B (MAO-B) inhibitors and dopamine agonists are all indicated for adjunct use with levodopa to reduce motor fluctuations [9,10]. However, the vast majority of available studies have been conducted in the western (European and US) population, and there is generally less information regarding issues specific to the Asian population. In addition, western guidelines for the management of wearing-off fluctuations [3,10–12] might not necessarily apply to other ethnicities due to genetic variations (e.g., genetic polymorphisms in the *COMT* gene [13–15] or genetic causes of PD [16–18]), differences in co-morbidities, cost issues or non-availability of certain drugs.

In November 2014, an expert group of neurologists, specializing in movement disorders from the Asian (including Arab) regions, met to discuss region-specific issues of wearing-off; other authors took part in email discussions. The aims of the expert group were to identify the treatment gaps in wearing-off detection and management among Asian and Arab countries and help bridge these gaps by providing effective guidance to enhance

 10.1586/14737175.2015.1088783 ISSN 1473-7175

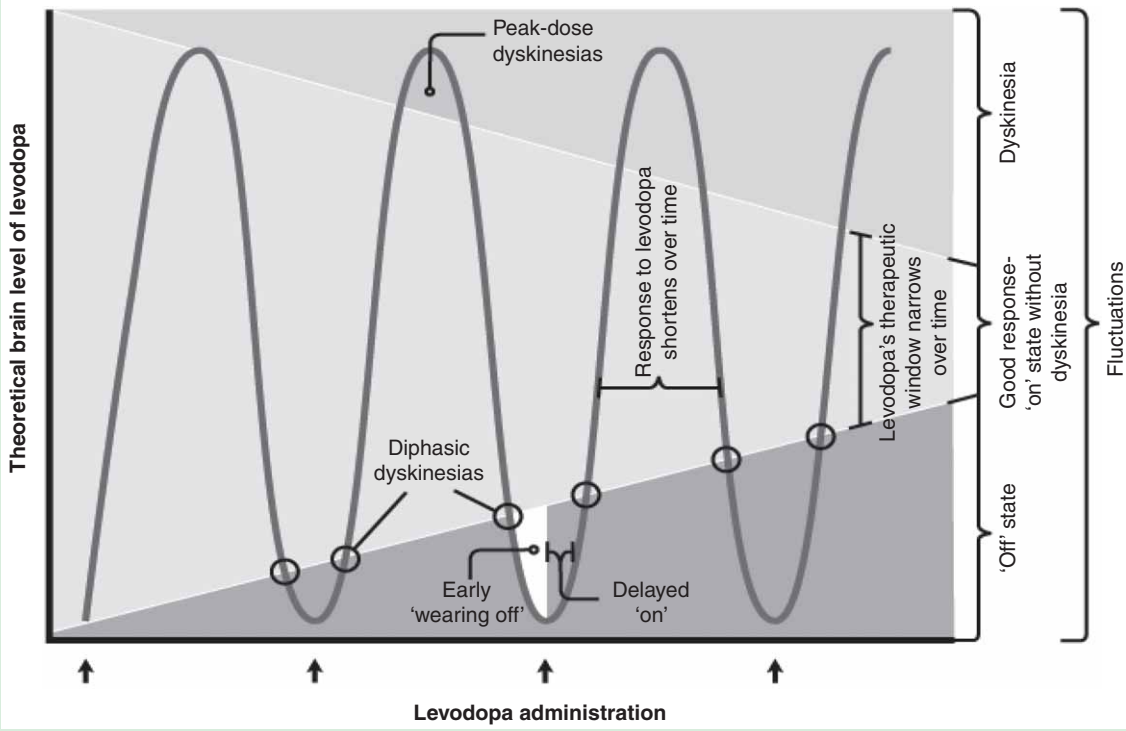

Figure 1. Relationship between levodopa administration and motor fluctuations.

recognition and proper treatment of wearing-off. This paper summarizes the key discussions at this meeting; due to the significant differences in data availability, the main focus of the paper is on the Asian populations and there is a separate discussion of the Arab perspective.

Emergence of wearing-off

Although there is no consensus definition of wearing-off, experts have previously defined it as *'A generally predictable recurrence of motor or non-motor symptoms that precedes a scheduled dose and usually improves with anti-parkinsonian medication'* [4,8]. According to this definition, it is the 'predictability' of wearing-off that differentiates it from ON–OFF phenomena, which are often unpredictable (Figure 1). To differentiate wearing-off from suboptimal titration (i.e., under dosing), it is also important that the patient should have had a period of stable response to levodopa.

It is generally accepted that the emergence of wearing-off is often one of the first clinical signs that the patient is entering a more complex phase of the disease; more patients in the CALM-PD and STRIDE-PD studies developed wearing-off before dyskinesia than *vice versa* [19,20]. The pathophysiology of wearing-off is known to be multifactorial, involving both the degeneration of the pre-synaptic dopaminergic terminals (and subsequent loss of dopaminergic storage capacity) and also post-synaptic mechanisms [21]. Key levodopa-related risk factors for the development of wearing-off fluctuations are discussed below.

Disease duration

Multivariate analyses of patients treated with levodopa in Ghana (where levodopa initiation is often delayed to many years after disease onset) and Italy indicate that disease duration (not duration of levodopa treatment) is significantly associated with the development of motor fluctuations [22].

The dose of levodopa

A secondary analysis of the STRIDE-PD study, which evaluated the risk of developing motor complications with levodopa/carbidopa versus levodopa/carbidopa/entacapone (LCE), showed that the risk of developing levodopa wearing-off increased in a dose-dependent manner [20]. This important finding has led the authors of that study to caution against large levodopa dose increases and to avoid doses greater than 400 mg/day when it is not clinically necessary [20].

Other factors

Several studies, including those conducted in the Japanese population [23,24], have shown that young age of onset and female gender confer a higher risk for developing motor complications [25–28].

Most studies to date support the idea that about 10% of patients per year develop motor fluctuations after the initiation of levodopa therapy, and thus, by 10 years, the majority of levodopa-treated PD patients will have developed signs and symptoms [1,29]. However, the reported annual incidence varies according to the definition of wearing-off used, and some

studies have reported that as many as 50% of patients can develop wearing-off within just 2 years of starting levodopa therapy [30]. By contrast, the incidence of wearing-off in the Asian population is just starting to be properly investigated. To the best of our knowledge, only one study has looked at the time course of developing wearing-off in an Asian population. In this retrospective case review of 1768 Japanese patients, the percentages of patients who developed wearing-off fluctuations by the end of the 5th, 10th and 15th year after disease onset were 21.3, 59.4 and 73.2%, respectively [24]. Women developed wearing-off slightly, but significantly earlier than men ($p = 0.0064$). While this rate is considerably lower than the 10% per year reported by other studies, the authors themselves noted the limitations of a retrospective study [24].

It has been often suggested that the relatively low frequency of wearing-off among Japanese patients is due to a lower levodopa maintenance dose (a survey of Japanese movement disorders experts suggests that the maximum dose they will use is 300 mg/day even for advanced patients [31]); however, this did not seem to hold true in the Japanese study where the mean maintenance dose was 471.5 mg at the final evaluation [24]. Other studies have found that in Asian (but not Caucasian) populations, Val158Met polymorphisms in the *COMT* gene are associated with differing risks of developing PD [32,33], and recent studies conducted in the Chinese population have found that the Met/Met homozygosity of the *COMT* Val158Met polymorphism is related to a decreased risk of developing wearing-off [13] and that the Val-Val genotype may be the risk factor for wearing-off [15]. These results are still under much debate, and further work is required to clarify the hypothesis.

Most of the other Asian studies of wearing-off have been of a cross-sectional design. One such study conducted in 137 Chinese patients found that of the patients who had received a levodopa preparation (72% of the overall population), 74.5% had motor fluctuations and 77.6% had dyskinesia [34]. A larger survey of 1558 patients living in mainland China has recently been reported and used the wearing-off questionnaire (WOQ) of nine symptoms (WOQ-9, see below) to screen for signs of wearing-off, which was further defined as the shortening of the duration of levodopa benefit to less than 4 h for every dose [35]. Using this relatively strict definition, the study estimated the overall prevalence of wearing-off to be lower at 46.5% (95% CI: 44.0–48.9%). While this prevalence is generally in line with the cross-sectional studies from other countries, the study also found that the dyskinesia rate of 10.3% was lower than previously reported [35].

Cross-sectional studies have also used the WOQ (19 symptoms; WOQ-19) to screen for signs of wearing-off [36]. One study conducted in 464 Japanese patients found that 69% of patients had motor signs of wearing-off and 40% had non-motor signs. Patients with both non-motor and motor fluctuations exhibited more severe motor symptoms, more non-motor symptoms and higher levodopa daily doses [36]. Finally, in a Thai cross-sectional study of 154 patients (98% of whom were taking levodopa), 79% of patients had wearing-off and 45% had on–off fluctuations. Once again, the factors associated with levodopa complications were earlier age of onset, long duration of disease, advanced stage, higher levodopa dosage and long duration of levodopa treatment [37].

Although such cross-sectional studies do not provide information about the time course of developing wearing-off, they confirm the high frequency of such problems and, thus, the need for effective management in this population. Further studies on the risk factors and development of wearing-off in different Asian populations are warranted.

Wearing-off: more than a motor complication

Traditionally, wearing-off has been referred to as a 'motor' complication of levodopa therapy. However, this view has been slowly changing to incorporate the increased recognition of non-motor fluctuations. When patients first develop the signs of 'wearing-off', they often start to notice subtle fluctuations in a broad variety of signs and symptoms [4]. Importantly, the early signs of wearing-off can vary considerably between patients; no single symptom has proven to be more important than others in predicting wearing-off [38]. For example, whereas some patients first notice the re-emergence of motor symptoms (e.g., tremor, bradykinesia), others might first complain of non-motor symptoms such as pain, anxiety, fatigue, mood changes, difficulty in thinking, restlessness or sweating [39].

Since non-motor symptoms can be very subtle, it might be difficult at first for patients to link them to their PD medication. This means that the patient is unlikely to discuss the emergence of the non-motor symptom with their physician, and as a result, the first signs of wearing-off might easily be missed until they become more prominent and disabling [4]. Moreover, many physicians do not currently associate 'wearing-off' with the predictable re-emergence of non-motor symptoms; several studies have shown that physicians underestimate the prevalence of non-motor symptoms in their patient population [40,41], and that less-experienced physicians are less likely to notice non-motor fluctuations in their patients [41].

In a study conducted in China, pain and aching were the most common non-motor symptoms experienced [35]; however, the choice of non-motor symptoms may have been limited by the use of the WOQ-9. Whereas the WOQ-32 included night-time symptoms [4], the WOQ-9 focuses on daytime symptoms that occur before the next dose [38]. However, night-time symptoms like nocturia can be a significant source of disability. There is some evidence that Asian males are at significantly greater risk of nocturia than other ethnicities [42], and a survey of Thai patients found that the most frequent and distressing night-time symptom was the interruption of sleep to pass urine (56.7%) [43]. Moreover, the omission of night-time symptoms could be an important limitation of the tool given that the Thai study identified presence of night-time symptoms (motor, sleep, urinary and neuropsychiatric symptoms) to be correlated with the presence of wearing-off [43].

Another Japanese study specifically used the WOQ-19 because it contains 10 non-motor items [36]. Using this version

doi: 10.1586/14737175.2015.1088783

Table 1. Sensitivity and specificity of wearing-off screening tools.

	WOQ-19		Q-10		WOQ-9	
	1+R	*2+R*	*1+R*	*2+R*	*1+R*	*2+R*
Sensitivity	95	88	96	90	96	90
Specificity	65	80	63	70	41	52
Positive predictive value	83	89	83	85	48	-
Negative predictive value	88	79	90	80	95	-
Accuracy	84	85	85	83	61	

1+R: One positive response; 2+R: Two positive responses; Q-10: Quick questionnaire 10-item; WOQ: Wearing-off questionnaire.
Adapted from [46].

of the WOQ, the study found that 53% of patients with motor fluctuations also had non-motor fluctuations, whereas 93% of patients with non-motor fluctuations also had motor fluctuations. Importantly, almost half (48%) of the patients with non-motor fluctuations exhibited more than one type of non-motor fluctuation. Interestingly, patients in the Japanese study had significantly higher fluctuation rates if they had psychiatric (49%) and sensory (45%) symptoms than patients with autonomic symptoms (32%, $p < 0.01$) [36]. Such findings are consistent with the Non-Motor Fluctuations in PD study, which also found that psychiatric non-motor symptoms (i.e., anxiety and depression) fluctuate more frequently and severely [44].

Tools to aid the recognition of wearing-off

In the routine office setting, poor patient education, limited physician evaluation time and communication difficulties can often hinder the timely recognition of wearing-off. Therefore, there has been much work in recent years to improve the early recognition of wearing-off.

A task force of the International Society for PD and Movement Disorders recently reviewed three diagnostic screening questionnaires for wearing-off, all of which are based on the same construct [8]. These questionnaires are known as the WOQs and are available in 32, 19 and 9 item formats [4,38,45]. The WOQ-32 was the first to be developed, and was based on a review of the literature and a consensus view [4]. To aid recognition in busy clinics, the WOQ authors then retrospectively designed two shorter forms, the items of which captured the majority of patients with wearing-off [38,45]. Both the WOQ-19 (also known as QUICK) and WOQ-9 have been found to possess adequate screening properties for the detection of wearing-off, and both have been recommended by the Movement Disorders Wearing-off Task Force as diagnostic screening tools for wearing-off in PD (Table 1) [8]. The main objective of WOQ-9 is to detect wearing-off and not to capture the greatest number of symptoms of wearing-off. In addition, the fourth questionnaire, the 10-item 'Q-10', has been developed by other authors [46].

The WOQ-19 and WOQ-9 scales have also been translated into Japanese [47], Chinese (Cantonese; WOQ-9 only) [48] and Thai versions [37]. The Japanese translation of WOQ-19 has been shown to have a high sensitivity of 82%, but a specificity of only 40% compared with a physician assessment [36]. The Chinese WOQ-9 (CWOQ-9) has good sensitivity (87%) and fair specificity (69%) [48].

The authors suggest that the WOQ-9 may facilitate earlier detection of wearing-off and allow therapy optimization to be implemented. It should, however, be noted that the WOQ-9 was not designed to be used as a diagnostic instrument, but should rather be used as an aid to guide the physician–patient conversation toward identifying a potential wearing-off problem in patients who have previously had a good response to their therapeutic regimen. It can also provide a useful aid in educating the patient (and/or caregiver, especially in cases of poor patient cognitive ability) on the signs and symptoms that may be associated with wearing-off. However, if wearing-off is suspected, the physician should ask about other symptoms, including night-time re-emergence of symptoms or early morning akinesia. The use of patient diaries (e.g., the Hauser diary [49]) is also recommended to further interrogate the relationship between the re-emergence of symptoms and medication timing.

Treatment of wearing-off

Given that wearing-off is often the first clinical complication to occur, it represents a critical time point to review the patients' medication [38]. Indeed, whereas wearing-off has been classically associated with the later stages of PD, it is now appreciated that even patients with early disease whose symptoms are apparently well controlled may already be experiencing changes in their response to levodopa [21]. The timely recognition of wearing-off is important as poor identification may lead to delayed management, potentially limiting the treatment options available to the patient. At this point in the disease course, the medication focus is on the optimization of dopaminergic therapy by improving the timing, dosage(s) and/or delivery of therapy. Table 2 provides an overview of the currently available medications in each of the main countries and the existing guidelines in each country for the treatment of wearing-off (if available).

Levodopa-modification strategies, such as increasing the total dose of levodopa or introducing a night-time dose of controlled-release levodopa, have traditionally been the first-line approach taken in the management of wearing-off [7,50]. Fractionating the levodopa dosage and changing the time intervals between dosages can also be useful. The main benefits of these strategies are their low cost and patient's familiarity with the drug. However, many patients find the introduction of an extra dose difficult to adhere to and often only experience short-term benefits, forcing frequent changes in the daily medication regimen [5]. Moreover, increasing the dose of levodopa increases the risk of developing dyskinesia (in those patients who have not already done so).

Table 2. Availability and formulations of Parkinson's disease medications in Asian countries.

	China	Hong Kong	Indonesia	Japan	Malaysia	Saudi Arabia	Singapore	South Korea	Taiwan	Philippines	Thailand
Standard release levodopa	Levodopa benserazide 200/50 mg	Levodopa carbidopa 100/25, 250/25 mg, levodopa benserazide 200/50 mg, levodopa benserazide dispersible tablet 100/25 mg	Levodopa, benserazide 100/25 mg, levodopa benserazide dispersible tablet 100/25 mg	Levodopa carbidopa 100/10 250/25 mg, levodopa benserazide 100/25 mg	Levodopa carbidopa 100/25 250/25 mg, levodopa benserazide 200/50 mg	Levodopa carbidopa 100/25 250/25 mg, levodopa benserazide 100/25 200/50 mg	Levodopa benserazide 100/25 200/50 mg, levodopa carbidopa 100/25 mg, levodopa benserazide dispersible tablet 100/25 mg	Levodopa benserazide 200/50 mg, levodopa carbidopa 100/25 250/25 mg, levodopa benserazide dispersible tablet 100/25 mg	Levodopa carbidopa 100/25 250/25 mg, levodopa benserazide 100/25 200/50 mg	Levodopa carbidopa 100/25 250/25 mg, levodopa benserazide 200/50 mg	Levodopa carbidopa 100/25 250/25 mg, levodopa benserazide 200/50 mg, levodopa benserazide dispersible tablet 100/25 mg
Controlled-release levodopa	Levodopa carbidopa 200/50 mg	Levodopa benserazide 200/50 mg	NO	NO	Levodopa carbidopa 200/50 mg, levodopa benserazide 100/25 mg	Levodopa carbidopa 200/50 mg, levodopa benserazide 100/25 mg	Levodopa carbidopa 100/25 200/50 mg	Levodopa carbidopa 200/50 mg, levodopa benserazide 100/25 mg	Levodopa carbidopa 200/50 mg, levodopa benserazide 100/25 mg	Levodopa carbidopa 200/50 mg, levodopa benserazide 100/25 mg	Levodopa benserazide 100/25 mg
LCIG	NO	NO	NO	NO	NO	Levodopa (20 mg/ml) and carbidopa (5 mg/ml)	NO	NO	NO	NO	Levodopa (20 mg/ml) and carbidopa (5 mg/ml)
Bromocriptine	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Cabergoline	NO	NO	NO	0.25, 1.0 mg	0.5 mg	NO	NO	0.5 mg	0.5 mg	NO	NO
Pergolide	NO	NO	NO	50, 250 μg	NO	NO	NO	NO	NO	NO	NO
Piribedil	50 mg	NO	NO	NO	50 mg	NO	50 mg	NO	NO	50 mg	50 mg
Pramipexole IR ER	IR: 0.25, 1.0 mg	Only ER formulation available: 0.375, 1.5 mg	IR: 0.125, 0.25 mg; ER: 0.375, 0.75 mg	IR: 0.125, 0.5 mg; ER: 0.375, 1.5 mg	IR: 0.125, 1.0 mg; ER: 0.375, 1.5 mg	IR: 0.125, 0.25, 0.5, 1.0 mg; ER: 0.375, 1.5 mg	IR: 0.125; ER: 0.375, 1.5 mg	IR: 0.125, 0.25, 0.5, 1.0 mg; ER: 0.375, 0.75, 1.5, 3.0 mg	IR: 0.25, 1.0 mg; ER: 0.375, 0.75, 1.5 mg	IR: 0.25, 1.0 mg (only IR form available)	IR: 0.25, 1.0 mg; ER: 0.375, 1.5, 3.0 mg
Ropinirole IR ER; ER formulation is labeled as PD in some Asian countries	NO	Only ER form available (PD): 2, 4, 8 mg	Only ER form available (PD): 2, 4, 8 mg	IR: 0.25, 1, 2 mg; ER: 2, 8 mg	IR: 0.25, 1.0 mg; ER (PD): 2, 4 mg	NO	IR: 0.25, 1.0, 2.0 mg; ER (PD): 2, 4 mg	IR: 0.25, 1.0, 2.0, 5.0 mg; ER (PD): 2, 4, 8 mg	IR: 0.25, 1.0 mg; ER (PD): 2, 4, 8 mg	Only ER form available (PD): 2, 4, 8 mg	Only ER form available (PD): 2, 4, 8 mg
Rotigotine	NO	2, 4, 6, 8 mg patch	2, 4 mg patch	2.25, 4.5, 9, 13.5 mg patch	2, 4, 6, 8 mg patch	2, 4, 6, 8 mg patch	2, 4, 6, 8 mg patch	2, 4, 6, 8 mg patch	4, 6, 8 mg patch	2, 4, 6 mg patch	2, 4, 6, 8 mg patch
Apomorphine Pen injector Infusion pump	NO	Pen injector: 30 mg/pen;	NO	Only pen injector	Pen injector: 30 mg/pen;	Pen injector: 30 mg/pen;	Pen injector: 30 mg/pen;	NO	Only pen injector	Only pen injector	Only infusion pump

The information is as of August 2015, the dosage shown is per tablet/capsule unless indicated otherwise.
ER: Extended-release; GPi: Globus pallidus interna; IR: Immediate-release; LCE: Levodopa carbidopa entacapone; LCIG: Levodopa–carbidopa intestinal gel; NO: Not available; PD: Prolonged delivery; STN: Subthalamic nucleus; Vim: Ventral intermediate nucleus.

doi: 10.1586/14737175.2015.1088783

Table 2. Availability and formulations of Parkinson's disease medications in Asian countries. (cont.).

	China	Hong Kong	Indonesia	Japan	Malaysia	Saudi Arabia	Singapore	South Korea	Taiwan	Philippines	Thailand
		infusion pump: 5 mg/ml		available: 30 mg/pen	infusion pump: 5 mg/ml	infusion pump: 5 mg/ml	infusion pump: 5 mg/ml		available: 30 mg/pen	available: 30 mg/pen	available: 5 mg/ml
Entacapone	200 mg	200 mg	200 mg	100, 200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
LCE (each number confers the dosage of levodopa)	LCE 50, 100, 200	LCE 50, 100, 200	LCE 50, 75, 100,125, 150, 200	LCE 50, 100	LCE 50, 100, 150	LCE 50, 100, 150, 200 mg	LCE 100, 150, 200	LCE 50, 75, 100, 125, 150, 200	LCE 100	LCE 50, 100, 150	LCE 50, 100, 150, 200
Tolcapone	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Selegiline	5 mg	5 mg	5 mg	2.5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Rasagiline	NO	1 mg	NO	NO	NO	NO	NO	1 mg	1 mg	1 mg	1.0 mg
Amantadine	100 mg	100 mg	NO	50, 100 mg	100 mg	100 mg	100 mg	NO	100 mg	100 mg	NO
Istradefylline	NO	NO	NO	20 mg	NO	NO	NO	NO	NO	NO	NO
Zonisamide	100 mg	NO	100 mg	25 mg	100 mg	NO	NO	NO	NO	100 mg	100 mg
Deep brain stimulation	GPi, STN	GPi, STN	GPi, STN	GPi, STN	GPi, STN	GPi, STN, Vim	GPi, STN	GPi, STN	GPi, STN	GPi, STN	GPi, STN

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ER: Extended-release; GPi: Globus pallidus interna; IR: Immediate-release; LCE: Levodopa carbidopa entacapone; LCIG: Levodopa–carbidopa intestinal gel; NO: Not available; PD: Prolonged delivery; STN: Subthalamic nucleus; Vim: Ventral intermediate nucleus.

Each of the currently available dopamine agonists has been proven as a useful adjunct to levodopa for reducing OFF time [51–58]. In practice, the dose of levodopa should be maintained until a clinical response to dopamine agonist is achieved. Later, the levodopa dose can be gradually lowered [59]. Physicians should also be aware of the risks associated with using dopamine agonists in the setting of dementia, hallucinations, autonomic dysfunction, impulse control and sleep disorders [60]. Also, ergot-derived dopamine agonists (e.g., bromocriptine, cabergoline and pergolide), which are still available in many Asian countries, are also associated with high risks of fibrotic reactions [60]. Where available, long-acting dopamine agonists that can be administered once a day have become more popular, and several Chinese [61–63] and Japanese [64,65] studies have shown good efficacy of these formulations. It should be noted, however, that studies conducted in Korea have shown that even these formulations often need to be administered more than once a day [66].

If the patient is already taking stable doses of levodopa, another option is to add an adjunct COMT inhibitor, which acts to increase the bioavailability of levodopa to the brain. Several controlled studies, including those specifically conducted in Asian populations [67–69], have demonstrated that adding COMT inhibitor is useful and has been shown to reduce OFF time. Depending on each country, the available options include entacapone alone as a single tablet and entacapone as part of LCE (a combination pill containing levodopa, carbidopa and entacapone). In practice, patients considering COMT inhibition should be advised that they may develop dyskinesia within 1 or 2 days of adding COMT inhibitor and that a 20–30% reduction in levodopa dose may be required [59]. Importantly, the Japanese dose-finding study reported by Mizuno *et al.* found no differences in the efficacy of entacapone given at a dose of 100 mg compared with the 200 mg dose (the standard dose in most countries) [67]. However, the safety and tolerability profile appeared more favorable for the 100 mg dose, and therefore, entacapone is available as a 100 mg tablet in Japan and is the standard initial dose. Although similar data are not available for other Asian ethnicities, the expert group confirmed that they share the Japanese experience and that, in practice, they tend to start entacapone at an initial dose of 100 mg, gradually titrating up to 200 mg if the signs and symptoms of wearing-off are not optimally controlled. The group also agreed that the introduction of LCE offers the opportunity to simplify the dosage regimen for patients already on entacapone. Patients who are stable on levodopa and entacapone given separately can be converted straight over to the equivalent dose of LCE.

Another option is to prolong the availability of central dopamine by inhibiting its breakdown by the enzyme MAO-B. At present, the main MAO-B inhibitor available in the Asian region is selegiline, which has comparatively

less robust evidence for its use in wearing-off [3,10]. The MAO-B inhibitor rasagiline, which does have good evidence for use as an adjunct therapy [70,71], has recently been launched in Hong Kong, Thailand, South Korea and Philippines. Rasagiline is currently being studied in clinical trials required for the registration of a drug in Japan and is being prepared for launch in other Asian markets. Safinamide, a highly selective and reversible MAO-B inhibitor with non-dopaminergic properties, was recently approved in some European countries as an add-on therapy in PD patients with motor fluctuations and has the benefit of increasing the ON time without troublesome dyskinesia [72]. However, it is not as yet available in Asia.

Finally, patients in Japan can also receive adjunct treatment with the antiepileptic zonisamide and the adenosine A2A antagonist istradefylline. Zonisamide is a benzisoxazole derivative with a long half-life that has multiple modes of action; relevant effects include activation of dopamine synthesis, inhibition of MAO, inhibition of T-type calcium channels and inhibition of an indirect pathway in the basal ganglia through the opioid δ-receptor. Zonisamide has been available in Japan since 2009 and national studies have indicated that the addition of adjunct zonisamide at 25–50 mg/day significantly improved cardinal symptoms in patients with advanced PD. These effects were maintained over more than 1 year even in patients with advanced disease [73]. Although tested in several Phase III trials [74–76], istradefylline has failed to gain US or European approval for use in PD. Studies in the Japanese population have reported reductions in OFF time from baseline of 1.3–1.6 h [77]. The most commonly reported adverse event was dyskinesia, which occurred in up to 9% of patients receiving istradefylline (20 mg or 40 mg once daily) [77]. These two agents are not generally available in other countries; zonisamide is available in Thailand, but its use is off-label.

Options for the management of advanced motor fluctuations

Failure of conventional pharmacotherapy should lead to a discussion with the patient about the potential risks and benefits of non-oral treatments. These include deep brain stimulation (DBS), apomorphine injections, and levodopa and apomorphine infusion strategies [78]. Again, the availability of these strategies varies widely by country. Apomorphine, given subcutaneously as a pen, is often used as a rescue therapy and is especially useful for patients who experience 'rapid' wearing-off symptoms or delays in the time taken to turn ON [79,80]. Unlike oral medications, apomorphine does not depend on gastrointestinal absorption and has been shown to provide patients with motor fluctuations a rapid and reliable levodopa-like ON effect usually within 8–15 min [81–83]. A recent study in the US indicates that apomorphine injections might be an especially useful strategy in patients with morning akinesia [84]. Apomorphine is also available as a continuous infusion therapy, and this may be considered in patients with more severe motor and non-motor fluctuations [85,86]. Contraindications to the use of continuous apomorphine infusion are severe dementia or neuropsychiatric symptoms and severe biphasic dyskinesia; however, unlike DBS, advanced age is not a contraindication [86].

Levodopa infusion is not available in most Asian countries, but is available in Thailand and some Arab countries. At present, levodopa infusion can only be delivered directly into the duodenum, although subcutaneous routes of delivery are currently in development [87]. The most widely available levodopa delivery system is a concentrated levodopa/carbidopa intestinal gel. Several open-label studies [85,88,89] and one double-blind, double-dummy trial [90] have shown that levodopa/carbidopa intestinal gel reduces the OFF time and extends the ON time without troublesome dyskinesia in advanced PD patients. Serious adverse events can occur and are mainly related to the technique, primarily to the Percutaneous Endoscopic Gastrostomy (PEG) procedure. Relatively common ones are also infusion tube occlusions and dislocations.

Currently, there are no randomized controlled comparative studies of these treatments for more advanced disease [78]. There is, however, a wealth of collective evidence supporting the use of DBS in patients with severe motor fluctuations, and a recent long-term retrospective study found that compared with advanced PD patients managed on medical therapies, treatment with Subthalamic nucleus Deep Brain Stimulation (STN-DBS) shows a long-lasting superior clinical efficacy on motor fluctuations, with a significant reduction in the average percentage of the waking day spent in 'OFF' and in the duration and disability of dyskinesia [91]. Similar long-term efficacy has also been observed among Asians [92]. It should, however, be noted that DBS is only suitable for a subgroup of patients who meet well-defined criteria and, in general, the experience of the DBS team is a key factor in lowering the significant risks of surgical complications [93].

Treatment guidelines

Most western guidelines do not differentiate between the choice of adjunct therapy for the management of levodopa wearing-off, and all generally recommend dopamine agonists, COMT inhibitors (entacapone) and MAO-B inhibitors (rasagiline) as effective choices depending on the individual needs of the patient [3,9–12]. In general, the current guidelines for specific Asian countries are very much based on the current availability of the different PD medications in that country.

The evidence-based guidelines from Singapore [94] are very similar to those issued by the American Academy of Neurology and the European Federation of Neurological Societies. Based on availability of the medications, they recommend both dopamine agonists and entacapone for adjunct use in patients with motor fluctuations. The ergolinic dopamine agonists should be used with caution in patients with renal and heart problems [94]. Consensus guidelines from Malaysia recommend several approaches for reducing the OFF time, including levodopa dosing/frequency adjustments, dopamine agonists, entacapone (either as a separate pill or as part of LCE) and the MAO-B inhibitors, selegiline and rasagiline [95]. The Malaysian

doi: 10.1586/14737175.2015.1088783

guidelines note that controlled-release levodopa remains useful in addressing overnight wearing-off, but may be erratically absorbed, resulting in delayed ON or no ON responses and is, therefore, not the first choice to treat motor fluctuations. The guidelines further recommend that medication changes should generally be undertaken gradually, especially in a patient who is at higher risk of side effects (e.g., already experiencing significant dyskinesia, or when cognitive impairment is present) [95].

Consensus guidelines from Thailand and Japan present a more algorithmic approach [59,96]. The Thai guidelines currently recommend the following treatment strategy for wearing-off management: add entacapone; manipulate the dose of levodopa by shortening the interval between levodopa doses; add a dopamine agonist; other options (less frequently used) are water-soluble levodopa or addition of selegiline [59]. By contrast, the Japanese guidelines first recommend increasing the frequency of levodopa dosing (to three to four doses per day in case of under dosing) or to start/increase/switch a dopamine agonist. After this, the next choices depend on the presence of dyskinesia: if it is absent, the guidelines recommend the addition of entacapone, selegiline or zonisamide and if it is present, the guidelines recommend decreasing the dose of levodopa and the addition of entacapone or zonisamide. Finally, once further treatment modifications are made, the Japanese guidelines recommend either increasing the frequency of levodopa doses or increasing/switching the dopamine agonist. If these provide insufficient control, the patient should be counseled about the risks and benefits of surgery.

The Arab perspective

Like the so-called 'Asian' population, the Arab population is dynamically complex given unique ancestry and there are many genotype, environmental, cultural and lifestyle factors that may affect the phenotype of PD. For example, the incidence of familial PD is higher within certain subpopulations (e.g., Arab-Berber [16,17]) and many consume well water, which has been suggested to be a risk factor for PD [97]. A substantial proportion of the population is also vitamin D deficient [98], which increases the susceptibility to neurological diseases, including PD [99].

Although the current evidence is that the clinical features of PD in Arabs are not significantly different from other populations [100], very little is currently known about the development of wearing-off in the Arab population. There are currently no standard algorithm among Arab countries regarding the diagnosis and management of wearing-off. The overall management of PD depends on individual physician's experience, knowledge and preferences. This can vary quite considerably and physician (and patient) education on the management of wearing-off has been identified as a key unmet need for the region. Access to PD therapies is also relatively limited in certain countries. There are currently efforts to establish a center-based database to explore and collect comprehensive PD data regarding pre-clinical stage, genetics, epidemiology, disease progression and wearing-off.

If established, the Arab guidelines will have to be very specific, given the unique ancestry and co-morbidities of this underserved population. There is, therefore, a need for urgent action to better understand and manage PD in the Arab population. In particular, much more research is required to understand the influence of local ethnic, genetic, epidemiological and clinical factors on the development of wearing-off fluctuations. There is also a significant need for improved PD education in this region.

Expert commentary

The evidence reviewed in this paper highlights that wearing-off fluctuations are a common problem among Asian PD patients. As in other countries, there is a clear need to improve the recognition of wearing-off in Asian patients and there are several tools available to help with this. As a group, we recommend the WOQ-9 as a convenient screening tool that can be followed up by the use of a PD diary to get more information on the relationship of the dosing schedule and symptom re-emergence.

Although comparative data is lacking in terms of therapeutic trials between western and Asian patients, most existing guidelines in Asia adopt the American Academy of Neurology [3], the International Parkinson and Movement Disorder Society (MDS) [9] and European Federation of Neurological Societies-MDS [10] recommended therapeutic options for wearing-off. While this review has been mainly formulated to address the management of wearing-off in Asian patients, it also draws attention to the general need to tailor therapy to the individual patient. Physicians treating patients of Asian descent living in other countries can be reassured that the available treatments are also efficacious in these specific populations. There are, however, some important differences that should be noted, for example, the use of 100 mg entacapone in Japanese patients and the introduction of 100 mg (half the usual 200 mg size of entacapone) by many Asian experts. Zonisamide is also an option to treat wearing-off in Japan. We take this opportunity to call for more research in specific Asian and Arab PD populations to determine the optimal dosage and responses to various interventions.

Five-year view

The importance of wearing-off has long been recognized in the movement disorders community; however, potential differences between different populations have to date largely been ignored. This discrepancy has now been identified and several groups are now working to fill in the many information gaps present regarding the epidemiology of wearing-off in the Asian population. Likewise, there are several ongoing studies of the different therapeutic modalities in specific populations. As these data are released, awareness of the issues related to wearing-off will increase in Asia, facilitated by the work of specific groups such as the MDS Asian and Oceanic Section. It is to be hoped that within the next few years, such work will allow a more tailored approach to the management of wearing-off in Asian patients.

Financial & competing interests disclosure

This study was supported by the Ratchadapiseksompoj Endowment Fund of Chulalongkorn University (RES560530136 & RES560530137-HR), and research unit grant of Chulalongkorn University. We thank Anita Chadha-Patel for her assistance with literature searching, referencing and editing in the development of this report. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Key issues

- Most Parkinson's disease (PD) patients will receive levodopa therapy, and of these, the majority will develop some levodopa-induced complications. Wearing-off is often the first complication to develop and, as such, can be considered a signal that the patient is entering a more complex stage of the disease.
- There is already an extensive literature documenting the epidemiology and management of wearing-off in PD patients of western descent. However, data derived from these studies might not always apply to patients of Asian descent due to genetic variations, differences in co-morbidities or non-availability of certain drugs.
- Although the cross-sectional studies published have confirmed that wearing-off fluctuations are common in the Asian population, relatively little is known about the time course of developing this problem and further studies are warranted in the Asian populations.
- Non-motor fluctuations are a common problem in Asian PD patients, and it is important that physicians routinely ask their patients about all the possible signs and symptoms of wearing-off.
- Use of the wearing-off questionnaire-9 may facilitate earlier detection of wearing-off and allow therapy optimization to be implemented. However, in order to differentiate wearing-off from sub-optimal titration, it is also important to ascertain that the patient is experiencing a *change* in his/her response to levodopa (i.e., that the patient previously had a good response to his/her levodopa regimen).
- Other limitations of screening tools include the focus on day-time symptoms, when many Asian patients also suffer from nocturnal fluctuations.
- There are a number of medications available (including catechol-*O*-methyltransferase inhibitors, monoamine oxidase type B inhibitors, dopamine agonists) for the management of wearing-off. Although the level of evidence from randomized controlled trials in Asian populations is variable for each drug, routine clinical experience supports their general efficacy and safety.
- Options for advanced fluctuations (when oral therapies are not sufficient) include apomorphine, levodopa infusion and deep brain stimulation. However, there are little or no studies of apomorphine and levodopa infusion in the Asian population, and the Asian availability of these treatments is variable.
- Most Asian treatment guidelines follow the western guidelines, but there are some important differences. For example, patients in Japan can also receive adjunct treatment with the antiepileptic zonisamide and the adenosine A2A antagonist istradefylline, which are not generally available in other countries. Likewise, the initial starting dose of entacapone in Japan is 100 mg (and not 200 mg as in western guidelines).
- Although the current evidence is that the clinical features of PD in Arabs are not significantly different from other populations, very little is currently known about the development of wearing-off in the Arab population. There are currently no standard treatment algorithms among Arab countries regarding the diagnosis and management of wearing-off. If established, the Arab guidelines will have to be very specific, given the unique ancestry and co-morbidities of this underserved population.

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doi: 10.1586/14737175.2015.1088783