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REVIEW

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Patient Diaries As a Clinical Endpoint in Parkinson's Disease Clinical Trials

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SUMMARY

Parkinson's disease (PD) is the second most common neurodegenerative disorder with an estimated 4 million patients worldwide. L-dopa is standard, and often initial, therapy for patients with this condition; however, with continued dopaminergic treatment and as the disease progresses, the majority of patients experience complications such as "wearing-off" symptoms, dyskinesias, and other motor complications. These complications may become disabling and profoundly affect quality of life. Treatment modification and combination therapies with L-dopa, dopamine agonists, monoamine oxidase type B inhibitors, and catechol-O-methyltransferase inhibitors are commonly used to manage complications. In recent years regulatory agencies, clinical researchers, and sponsors have widely accepted and utilized changes in "ON" and "OFF" time measured by Patient Hauser Diaries as endpoints for measuring efficacy of therapeutics seeking approval for symptomatic treatment of PD. Successful antiparkinsonian medications have been associated with treatment effects of more than 1 h in either reduction of "OFF" time of increase in "ON" time. Accurate "ON" and "OFF" time registration during clinical studies requires rigorous patient training. Reduced compliance, recall bias and diary fatigue are common problems seen with patient diary reported measures. Electronic diaries may help reducing some of these problems but may be associated with other challenges in large, multicenter studies.

Introduction

Idiopathic Parkinson disease (PD) is a multisystem disorder with a multifactorial etiology and diverse clinical phenotype. Disease prevalence is age-associated, with approximately 1–2% of the population being affected at 65 years, increasing to 4–5% in 85-year olds [1]. More than 1.5 million people in the United States (4 million people worldwide) are believed to have PD [2]. The prevalence of PD is expected to double by 2030 [3]. The mean age of onset is about 70 years, although 4% of patients develop early-onset disease before the age of 50 [4]. The main clinical phenotype of PD is parkinsonism, a movement disorder that is characterized by tremor at rest, bradykinesia, rigidity, and postural instability [5]. Typically, the onset of PD is insidious, asymmetrical, and steadily progressive as neuronal dysfunction and cell death lead to a profound depletion of the neurotransmitter dopamine in the striatum, a central component of the basal ganglia that is responsible for the initiation and control of movement caused by degeneration of dopaminergic neurons in the substantia nigra [6].

Introduced in the 1960s by George Kotzias, L-dopa revolutionized the treatment of PD. As a dopamine replacement therapy, L-dopa is still the standard of care for PD patients [7]. Although L-dopa remains the most effective drug in the symptomatic treatment of PD, the emergence of motor response complications, particularly motor fluctuations characterized by "wearing-off" and "ON"–"OFF" mobility patterns and dyskinesias, limits its usefulness [8]. After L-dopa treatment for 3 to 5 years, motor complications occur in approximately 50% of patients, and after 10 years in >80% of patients [9]. Treatment options have recently expanded; during the last decade new drugs based on dopamine replacement strategies have been licensed and deep brain stimulation surgical procedures continue to be refined. However, treatment-emergent complications continue to have a devastating impact to patient health-related quality of life [10] with consequences to pharmacoeconomic parameters and increased healthcare expenditures [11], indicating the clear unmet need in the long-term management of PD.

"Wearing-off", defined as a generally predictable recurrence of motor and nonmotor symptoms preceding scheduled doses of antiparkinsonian medication, has been attributed to declining dopamine storage capacity and usually improves after the next those with L-dopa [12]. "Wearing-off" can develop gradually or suddenly and may be predictable or random similar to the "ON"–"OFF" effect [8]. "Wearing-off" is usually linked to low plasma concentrations of L-dopa. Most symptoms improve in about 30–60 min after dosing administration, but in some

cases the latency may be markedly delayed (delayed-on) or no response occurs (no-on) [13]. Improvement may be followed by the emergence of dyskinesias, which usually coincide with higher plasma concentrations of L-dopa, followed by an improved state without dyskinesias. This improvement-dyskinesia-improvement pattern is the most frequent form of motor fluctuations in PD. "ON"–"OFF" motor fluctuations are rapid changes in mobility during which patients report sudden shifts from adequate mobility to mobility, usually within a few seconds or minutes. The pathogenesis of these changes is not well understood [14]. Other less, common forms of motor fluctuations apparently unrelated to plasma and brain L-dopa concentrations also exist. However, these uncommon forms of motor fluctuations do not respond well to pharmacological adjustments.

In recent years regulatory agencies, clinical researchers and sponsors have widely accepted and utilized "ON" and "OFF" time changes as an endpoint for measuring efficacy of symptomatic treatments for moderate and advanced stage PD as measured by Hauser Patient Diaries (detailed description of the diary is included in the Discussion) [15,16]. In the diaries "OFF" time is defined as a period when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness. Patients during this period experience relatively poor overall function with worsening of tremor, rigidity, balance, or bradykinesia. "ON" time is defined as the time when medication is providing benefit with regard to mobility, slowness, and stiffness. "ON" time can be classified as associated with or without troublesome dyskinesia that interfere with activities of daily living. It has been demonstrated that "OFF" time and "ON" time with troublesome dyskinesia are generally considered by patients to be "bad time" with regard to motor function, whereas "ON" time without dyskinesia and on time with nontroublesome dyskinesia are generally considered to be "good time" [16]. When "OFF" time is reduced one has to assume that it translates into "ON" time. However, "ON" time can be either good or bad. Both "OFF" time and good "ON" time have been used as primary endpoints in clinical studies and both have to be captured and interpreted to assure that treatment response is described sufficiently. Whether "ON" or "OFF" time is used as the primary endpoint depends on the trial objective, design, and mechanism of action of the experimental treatment. In most (but not all) cases reduction in "OFF" time is similar to "ON" time increase. For the purposes of this review data on both "OFF" and "ON" time change seen with PD therapeutics will be presented when available.

This review discusses how motor fluctuations are influenced by commonly prescribed oral therapeutic agents used as adjunctive to L-dopa therapies in the treatment of motor fluctuations and discusses advantages and caveats of "ON" and "OFF" time as a measure of treatment effect in PD for different approved drugs. An overview of the "OFF" time treatment effects of different approved therapeutics reduction is provided in Table 1.

Dopamine Agonists

Pramipexole

The major randomized controlled trials [17–20] that have compared oral doses pramipexole with placebo in 669 patients with moderate/advanced PD have already been the subject of a Cohrane review [21]. Two-phase III studies were medium term (24 weeks maintenance period) and two-phase II studies were short term (4 weeks maintenance period). The reduction in "OFF" time was significantly greater with pramipexole compared with placebo (weighted mean difference 1.8 h; 1.2, 2.3 95% CI). No significant changes were noted in a dyskinesia rating scale in any of the four studies, but dyskinesia as an adverse event was reported more frequently with pramipexole [21].

Ropinirole

The major double-blind, parallel group, randomized controlled trials [22–24] that have compared oral doses of ropinirole with placebo in 263 patients with moderate/advanced PD have already been the subject of a Cohrane review [25]. The two-phase II studies were relatively small, were conducted over the short term (12 weeks), and used relatively low doses of ropinirole (mean administered doses 3.3 and 3.5 mg/day) in a twice daily regime.

In a 16 week study comparing ropinirole to bromocriptine as an adjunct to L-dopa in the treatment of PD complicated by motor fluctuations patients in the ropinirole arm experienced 1.65 h (4.39 ± 3.13 to 2.74 ± 2.95) in "OFF" time reduction compared to 0.68 h (5.36 ± 3.12 to 4.68 ± 4.52) in the bromocriptine group [26].

In a recent double-blind, placebo-controlled, 24-week study, to evaluate the efficacy of ropinirole 24-h prolonged release in 393 subjects with PD there was a mean reduction in daily "OFF " time of 2.1 h in the ropinirole 24-h group and 0.3 h with placebo (adjusted treatment difference of 1.7 h) [27]. At week 24, the mean dose of ropinirole 24-h was 18.8 mg/day with a mean reduction in daily L-dopa of 278 mg. The decrease in "OFF" time in the ropinirole 24- h group was accompanied by an average increase in "ON" time of 1.6 h (treatment difference of 1.7 h). At study end (week 24), there was a significant treatment difference in favor of ropinirole 24-h for "ON" time without troublesome dyskinesia.

In contrast, the mean "ON" time with troublesome dyskinesia decreased by 0.04 h in the ropinirole 24-h group and by 0.23 h in the placebo group. Thus, the decrease in "OFF" time and increase in "ON" time seen in the ropinirole 24-h group did not result in an increase in troublesome dyskinesia.

However, the reduction in troublesome dyskinesia is most likely secondary to the reduction in L-dopa dose in both groups [27].

Rotigotine

The effect of rotigotine in "OFF" time reductions has been investigated in two major trials; Quinn et al. investigated rotigotine as adjunctive therapy to L-dopa for 7 weeks in patients with PD and L-dopa-induced motor fluctuations [28]. These results have only been published in abstract form and details are missing. In the second 24-week maintenance trial by LeWitt et al. [29] (PREFER) decrease in "OFF" time for patients receiving placebo was 0.9 h, compared with 1.81 h in the shorter trial by Quinn et al. [28], and the reduction in "OFF" time for those receiving rotigotine 8 mg/24 h was 60% greater than in the trial by Quinn. "ON" time

Table 1 Treatment effects of approved therapeutics on "OFF" time[a]

	Studies	Phase/N	Duration[b]	Off-time reduction active arm (hours or %)[c]	Off-time reduction Placebo arm (hours or %)	Difference (95%CI) or *P* value
Dopamine Agonists						
Pramipexole	(Guttman 1997)	162	24 weaks	2.60 (4.30)	0.30 (4.40)	2.30 [0.89, 3.71]
	(Lieberman, Ranhosky et al. 1997)	360	24 weaks	2.40 (3.40)	0.70 (3.70)	1.70 [0.95, 2.45]
	(Pinter, Pogarell et al. 1999)	78	4 weaks	2.30 (2.70)	−0.40 (3.50)	1.90 [–0.92, 2.12]
	(Wermuth 1998)	69	4 weaks	1.20 (2.90)	0.60 (3.00)	2.70 [1.12, 4.28]
Ropinirole	(Lieberman, Olanow et al. 1998)	149	26 weaks	1.53 (4.28)	1.22 (3.70)	0.31 [–1.02, 1.64]
	(Perezaharon, Abbot et al. 1994)	68	12 weaks	1.33 (2.35	0.75 (2.81)	0.58 [–0.79, 1.95]
	(Rascol, Lees et al. 1996)	46	12 weaks	1.74 (2.36)	2.22 (3.00)	–0.48 [–2.04, 1.08]
	(Im, Ha et al. 2003)[d]	76	16 weaks	1.65	No data	No data
	(Pahwa, Stacy et al. 2007)	393	24 weaks	2.1 (0.64)	0.3 (0.64)	1.6 [–2.30, –0.85]
Rotigotine	(Quinn and For the European and South African Rotigotine CDS Study Group 2001)	324	7 weaks	2.44 (n/a)	1.81 (n/a)[e]	No data
	(LeWitt, Lyons et al. 2007),	351	24 weaks	2.7 (n/a)	0.9 (n/a)[f]	1,8 [–2.6, –1.0]
	(Poewe, Rascol et al. 2007).	506	16 weaks	22.6% (45.2)	10.7% (43.0)2	1,58 [–2,27, –0,9]
Cabergoline	(Ahlskog, Wright et al. 1996)	188	24 weaks			1.32 (no additional data)
	(Miguel, Obeso et al. 1993)	43	6–10 weaks	3.33 (2.10)	2.47 (2.86)	0.86 [–1.10, 2.82]
	(Steiger, El-Debas et al. 1996)	37	12 weaks	2.00 (2.30)	0.70 (2.25)	1.30 [–0.21, 2.81]
MAO-B Inhibitors						
Zydis Selegiline	(Waters, Sethi et al. 2004)	161	12 weaks	2.2 [13.2% (15.1)]	0.6 [3.8%(10.3)]	1.6 [$P < .0001$]
	(Ondo 2006)[d]	148	12 weaks	No data	No data	$P = .467$
Rasagiline	(2005)	472	26 weaks	1.85 (29%)	0.91 h (15%)	0.94 (–1.36, –0.51)
	(Rascol, Brooks et al. 2005)	687	18 weaks	1.18 (0.15)	0.40 (0.15)	0.8 [–1.20, –0.41]
COMT Inhibitors						
Entacapone	(1997)	205	24 weaks	0.80 (2.80)	0.10 (2.10)	0.70 [0.02, 1.38]
	(Rinne, Larsen et al. 1998)	171	6 months	1.30 (2.28)	0.10 (3.40)	1.20 [–0.87, 3.27]
	(Poewe, Deuschl et al. 2002)	301	6 months	1.60 (2.50)	0.90 (3.40)	0.70 [–0.19, 1.59]
	(Brooks and Sagar 2003)	300	6 months	1.10 (2.40)	0.60 (2.40)	0.50 [–0.43, 1.43]
Tolcapone	(Kurth, Adler et al. 1997)[g]	161	6 weaks	1.81 (1.85)	0.04 (1.75)	1.77 [0.98, 2.56]
	(Myllyla, Jackson et al. 1997)[h]	154	6 weaks	1.80 (2.80)	0.10 (2.60)	1.70 [0.41, 2.99]
	(Adler, Singer et al. 1998)[i]	215	6 weaks	2.50 (2.60)	0.30 (2.50)	2.20 [1.37, 3.03]
	(Baas, Beiske et al. 1998)[j]	177	12 weaks	2.00 (2.60)	0.70 (2.80)	1.30 [0.32, 2.28]

[a]Only approved dopaminergic medications are presented. Data on the effect of approved nondopaminergic medications (anticholinergics, amantadine) are limited and inconclusive.

[b]Titration and follow-up phases not included.

[c]Best response is presented.

[d]This study compared ropinirole to bromocriptine, there was no placebo arm.

[e]Results have only been published in abstract form and details are missing, pooled results analysis from combined data from Waters et al. and Ondo et al. only available in abstract format. Results from Ondo et al. did not show statistically significant reduction in ''off'' time with Zydis relative to placebo.

[f]The average treatment effect for the reduction of "off " time was 1.8 h for the 8 mg/24 h group (95% CI –2.6, –1.0; $P < 0.001$).

[g]Best result was seen with 400 mg dose of tolcapone.

[h]Best result was seen with 200 mg dose of tolcapone. Doses upto 400 mgs were tested.

[i]Best result was seen with 200 mg dose of tolcapone. Doses upto 200 mgs were tested.

[h]Best result was seen with 100 mg dose of tolcapone. Doses upto 200 mgs were tested.

with troublesome dyskinesias was not experienced by either rotigotine group.

In another double-blind, double-dummy, randomized controlled trial comparing rotigotine with placebo and with pramipexole in 427 patients experiencing motor fluctuations (CLEOPATRA-PD), the absolute change in "OFF" time from baseline compared with placebo was –1.58 h (95% CI –2.27 to –0.90; $P < 0.0001$) for rotigotine and –1.94 h (–2.63 to –1.25; $P < 0.0001$) for pramipexole. Responder rates were 67% (134 of 200 patients) for pramipexole, 59.7% (120 of 201 patients) for rotigotine, and 35% (35 of 100 patients) for placebo [30].

Cabergoline

The major randomized controlled trials comparing cabergoline with placebo have been a subject of a recent Cochrane meta-analysis [31] of two-phase II (6–12 weeks) [32,33] and one-phase III randomized controlled trials (24 weeks) [34]. These were double-blind, parallel group, multicenter studies including 268 patients with PD and motor complications. The reduction of 1.14 h (WMD; 95% CI –0.06, 2.33; $P = 0.06$) in "OFF" time in favor of cabergoline was not statistically significant. Inadequate data on dyskinesia was collected either on rating scales or as adverse event reporting to allow a conclusion to be drawn. A small but statistically significant advantage of cabergoline over placebo was seen in one study for Unified Parkinson's Disease Rating Scale– Activities of Daily Living (UPDRS ADL or UPDRS part II) score and UPDRS motor score. No such advantage was seen in one other study due to small numbers of patients and the comparatively low doses of cabergoline used [31].

MAO-B Inhibitors

Selegiline

Although studies with selegiline have reported some improvement in motor fluctuations, the data are insufficient to quantify the impact particularly on endpoints such as "OFF" time [35–37]. This is especially true because the studies were conducted before PD home diaries gained wide acceptance.

More is known about a recently developed, rapidly disintegrating tablet formulation of selegiline (Zydis selegiline). Zydis selegiline tablets were evaluated in two 12-week, randomized, parallel-group, placebo-controlled studies [38,39]. In both studies, L-dopa-treated patients with motor fluctuations were treated with Zydis selegiline 1.25 mg/day for 6 weeks followed by a dosage increase to 2.5 mg/day for the final 6 weeks. In the first study (Zydis selegiline n = 94 and placebo n = 46) groups at baseline had mean daily ''OFF'' times were 6.9 and 7.0 h [39]. At study end, ''OFF' time was reduced by 2.2 h in the Zydis selegiline group versus 0.6 h in the placebo group. Dyskinesia-free time significantly increased with Zydis selegiline compared with placebo ($P = 0.008$). In the second study (N = 148), results did not confirm those of the first trial; there was no statistically significant reduction in ''OFF'' time with Zydis relative to placebo ($P = 0.467$) [38]. A pooled analysis of data from these two studies showed that the average reduction at weeks 10 and 12 in ''OFF'' time was 12.4% with Zydis selegiline versus 6.9% with placebo ($P = 0.003$) [38].

Rasagiline

Two trials, PRESTO and LARGO, have examined the effectiveness of rasagiline as adjunctive therapy to L-dopa in patients with more advanced PD and motor fluctuations. In both of these studies, the primary outcome measure was the change in the percent of the waking day spent in the "OFF" state. In both studies, patients were on a stable dose of L-dopa/carbidopa throughout the trial, and there were no dietary restrictions. The major difference between the two trials is that PRESTO tested two doses of rasagiline against placebo, whereas LARGO tested one dose of rasagiline against placebo and entacapone.

The PRESTO trial was a multicenter, randomized, double-blind placebo-controlled 26-week trial. Subjects (n = 472) were randomized to receive rasagiline 0.5 mg once a day, rasagiline 1 mg once a day, or placebo. During the treatment period, the mean adjusted total daily "OFF" time decreased from baseline by 1.85 h (29%) in patients treated with 1.0 mg/day of rasagiline, 1.41 h (23%) with 0.5 mg/day rasagiline, and 0.91 h (15%) with placebo. Patients treated with 1.0 mg/day of rasagiline had 0.94 h (95% confidence interval, 0.51–1.36 h; $P < 0.001$) less "OFF" time per day compared with placebo. Patients treated with 0.5 mg/day of rasagiline had 0.49 h (95% confidence interval, 0.08–0.91 h; $P = 0.02$) less "OFF" time compared with placebo. Compared with placebo, the clinical global impression, UPDRS ADL score during "OFF" time, and UPDRS motor score during "ON" time improved significantly during treatment in patients receiving either dosage of rasagiline [40].

The LARGO trial was a multicenter, randomized, double-blind placebo-controlled 18-week study in 678 subjects. Treatment with either rasagiline (1 mg) or entacapone (200 mg with every L-dopa dose), resulted in an approximately 25% reduction in "OFF" time ($P = 0.001$ for entacapone and $P < 0.001$ for rasagiline vs. placebo). Both rasagiline and entacapone reduced mean daily "OFF" time (–1.18 h rasagiline and –1.2 h entacapone vs. placebo –0.4 h; $P = 0.0001$, $P < 0.0001$, respectively) and increased daily "ON" time without troublesome dyskinesia (0.85 h vs. placebo 0.03 h; $P = 0.0005$ for both). These results were similar to those observed in PRESTO. Changes in UPDRS scores also significantly improved for activities of daily living during "OFF" time (–1.71 and –1.38 vs. placebo; $P < 0.0001$, $P = 0.0006$, respectively) and motor function during "ON" time (–2.94 and –2.73 vs. placebo; both $P < 0.0001$) [41].

COMT Inhibitors

Entacapone

The major studies comparing entacapone against placebo (1563 subjects) as adjunct therapy to L-dopa have been the topic of a Cochrane meta-analysis [42]. One study had a randomized double blind cross-over design [43], the remaining seven studies had a randomized, double-blind parallel-group design [44–50]. One was a phase II study [43], the remaining seven were phase III studies.

Not all the studies have included "OFF" time in their analysis. A complete data set for "OFF" time reduction data was only published in [48]. The authors of [46,49,50] provided data for the 2004 Cochrane meta-analysis [48]. The mean difference in the meta-analysis was 41 min (95% CI: 13 min, 1 h 8 min, $P = 0.004$) [42].

Tolcapone

The major studies comparing tolcapone as adjunct to L-dopa have also been the topic of a Cochrane meta-analysis [42]. In six parallel group randomized controlled trials examining tolcapone versus placebo in a total of 1006 patients have been studied [51–56]. Full data sets from some of these trials are not available. Furthermore, tolcapone trials used a variety of doses of the drug ranging from 50 to 400 mg. The dose that was common to them all was 200 mg tolcapone [42].

Full "OFF" time reduction data sets were available for four trials for inclusion in the Cochrane meta-analysis [51–53,55]. The weighted mean difference in "OFF" time reduction in the meta-analysis showed that the 50 mg dose was the least effective (1 h 25 min, 95% CI: 46 min, 2 h 3 min, $P = 0.00002$), whilst the remaining doses were equivalent: 100 mg producing 1 h 32 min "OFF" time reduction (95% CI: 54 min, 2 h 10 min, $P = 0.00001$), 200 mg giving 1 h 38 min (95%CI: 1 h 11 min, 2 h 5 min, $P = 0.00001$) and 400 mg giving 1 h 35 min (95% CI: 55 min, 2 h 16 min, $P = 0.00001$) reduction in "OFF" time [42].

In summary, tolcapone-treated patients experienced a 26–50% decrease in "OFF" time and a 20–30% increase in ''ON" time without dyskinesia. The addition of tolcapone also permitted a 29–40% reduction in total daily L-dopa dose [57].

Discussion

In recent years "ON" and "OFF" time changes captured in patient diaries have been the "gold-standard" in clinical trials studying the effects of drugs as adjunct to L-dopa for the improvement of treatment induced motor fluctuations. The PD patient diary has been reliably used as a clinical outcome measure, contributing to approval of antiparkinsonian medication that significantly improved patient care.

Estimation of Motor Fluctuations and Dyskinesias Using the PD Home Diary

Estimation of "ON" and "OFF" times heavily relies on accurate completion of patient diaries [58]. Both the UPDRS [59] and its newer version, the Movement Disorder Society (MDS)-UPDRS [60] provide a crude estimation of the type and duration of treatment-related complications. Currently available diaries are designed to record patient motor state for half-hour intervals over a 24-h period. These diaries are a way for patients to assess their own health status without clinician bias or interpretation. Diaries are especially useful in understanding symptoms' temporal dynamics, including triggers that exacerbate symptoms they also help individuals to evaluate the impact of their treatment [61].

For PD patient diaries, subjects participating in clinical studies receive training during screening from certified instructors (principle investigators, nurse coordinators) with hands-on explanation of the process and through the use of prerecorded video segments of patients in different stages of PD [15,16]. Not infrequently training videos of patients in late disease stages may have a negative impact on study participants and have to be presented with caution. At the end of the training session, the subject and a site rater concurrently complete separate training diaries during several half-hour periods. Usually, patients are required to reach a certain degree (i.e., 80%) of diary concordance with a site rater to qualify for the study. For the duration of a clinical study patients are requested to complete home diaries for 2–3 consecutive days preceding baseline and scheduled visits. For results interpretation previsit diary recorded "OFF" times are averaged and compared to baseline.

The most common primary efficacy variables in PD clinical trials are: (1) the change from baseline to endpoint(s) in "OFF" time (percentage and total hours) during waking hours and (2) the change in "ON" time (percentage and total hours) without troublesome dyskinesia (sum of "ON" time without dyskinesia and "ON" time with nontroublesome dyskinesia) during waking hour. Other endpoints include changes in total "ON" time and "ON" time according to other dyskinesia categories, including "ON" time with troublesome dyskinesia and "ON" time with nontroublesome dyskinesia. In general an "OFF" time reduction or "good ON-time" increase of 1 h may be considered clinically significant and has been used as an assumption in power calculations in clinical trials so far.

"OFF" and "ON" Time as Clinical Endpoints

But why is a measure of motor fluctuations so widely accepted as primary endpoint in late stage PD studies with therapeutics seeking regulatory approval for the symptomatic treatment of PD when patients also suffer from a variety of symptoms including nonmotor complications? Motor fluctuations may severely compromise mobility, activities of daily living, and emotional well being [62]. Patients with PD may suffer enhanced embarrassment, stigma, or depression arising from PD symptoms during "OFF" time, may further restrict their social activities, rate their home or family life far more impaired than healthy individuals, and may have a sense of loss of control over life, or a loss of confidence [63–65]. Patients clearly prefer less disease severity with no "OFF" time and would likely seek and benefit from treatment alternatives that improve their amount of "ON" time experienced per day. The presence of fluctuations influenced health state preference more than Hoehn & Yahr stage [66].

Paper/Pen versus Electronic Diaries

Although well accepted and widely used, traditional paper and pen forms of diaries have significant caveats including reduced compliance, recall biases, and diary fatigue. One can only rely on rigorous training and reminder messages (i.e., mail, email, text messages, and nurse visits) to improve compliance and reduce bias

by nonreal time completion of diaries. Delayed completion of PD dairies can affect study outcomes as the patients may have recall biases or errors during diary completion. In addition, other potential problems such as multiple entries for the same time period, incomplete diaries, or illegible diaries can lead to unusable data [67]. Similar biases are seen in other diseases that rely on diary completion like pain and headache [68]. Electronic diaries have some advantages over paper diaries in that they can remind the patients to complete the diary entries on time, allow only one answer per entry and record the exact time and date the data were entered, increasing compliance and reliability of outcomes. In addition, the data can be directly downloaded to a database for analyses reducing data entry errors [69]. However, electronic diaries require more rigorous training and caregiver participation, especially in an aged population with severe movement impairment. Other issues include device selection, hardware/software failures, and data extraction/management.

While reactivity studies have shown no sign of consistent trend in recordings of electronic diaries over time, no study has reported on whether the variance of readings diminishes with time. It is possible, at least in theory that repeated use may lead to consolidation on a small number of points as the study progresses. Similarly, habituation to questions/prompts in the same order may have unwanted effects on data accuracy; despite the flexibility of programmable devices to randomize the order of questions, no study has been reported to perform this [68].

Furthermore, a number of additional disadvantages in using electronic diaries in multicenter, multiethnic, multisite clinical trials have been identified. The first is that participants need to be confident, willing, and able to operate them [68]. Cultural, educational, and socioeconomic differences may render the use of electronic diaries problematic. The cost is not insignificant, but can be set against savings in transcription time for data and the possibility of the reuse of devices in future studies. The risk of device failure should be considered in planning studies, and measures should be put in place to regularly back up data, ensure that batteries are adequately charged, and ensure that any problem can be quickly resolved. In PD motor impairment may be added to the list of disadvantages despite the results from a recent study showing that PD patients are capable of using electronic diaries to measure daily motor function [67]. The use of electronic diaries in PD may be considered in smaller studies with highly motivated patient populations and should be considered with caution in large multicenter settings.

Improvement of treatment induced motor fluctuations in PD varies with different therapeutics and between trials with the same therapeutic. When trying to interpret this variability one should consider several factors beyond pharmacology, inclusion/exclusion criteria, and study design. Although large randomized placebo controlled studies in moderate to advanced PD tend to have relatively similar patient demographics and baseline characteristics including an "OFF"-time ranging from 5–7 h subjects from different ethnicities may have different views on levels of tolerance for "ON" versus "OFF" and differences in familiarity with patient filled instruments like the home diary. Investigators from different geographies may also differ in prescribing patterns and best medical treatment approaches. The methodological consistency between studies using diaries [70] and the length of time that patients have kept diaries also varies considerably, ranging from a few days to virtually continuous data collection over several years [71]. The extent to which accurate diary data can be collected beyond a time period remains unknown.

Conclusion

Patient diaries have gained wide acceptance as a primary endpoint for clinical development of therapeutics aiming to reduce treatment-related motor complications. Table 2 provides an overview of PD home diary strengths and weakness. Motor fluctuations are associated with compromise in activities of daily living and health-related quality of life. Patient training to improve accuracy and compliance is essential. Electronic diaries have the advantage over traditional paper and pen forms of improving compliance and reducing recall bias. However, many challenges are

Table 2 Overview of PD home diaries pros and cons

Pros	Cons
• Endpoints for regulatory approvals of antiparkinsonian medication that have improved patient care.	• Patient compliance can be challenging: patients required to estimate their motor state every 30 min for 24 h for at least 1–3 days.
	• Recall bias and diary fatigue can occur.
• Contribute to rigorous evaluation of PD symptom temporal dynamics.	• Do not rate quality/severity of OFF time.
• Patient Reported Outcomes: Limit clinician bias or interpretation.	• Require rigorous training in a challenging population.
• Training resources to help improve compliance are available.	• Training videos of patients in late disease stages may be a source of distress for study participants.
• Provide a bimodal evaluation of dyskinesia severity to troublesome and nontroublesome.	• No continuous quantification or qualification of dyskinesia (severity and type). Assumes that all dyskinesias occur during "ON".
	• Has to be supplemented by additional outcome measures.
• Both pen/paper and electronic diaries are available.	• Challenges with missing data handling.
	• Not useful/reliable in measuring alterations in motor state when there are both ON and OFF episodes within a 30 min block. Small alterations may be relevant when considered collectively.

associated with electronic diaries, especially in large trials and diverse populations. A better definition of a "clinically significant" "OFF" and "ON" time reduction is warranted.

Conflict of Interest

Dr Papapetropoulos is an employee of Allergan Inc.

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