Levodopa-Induced Dyskinesias in Parkinson’s Disease: Etiology, Impact on Quality of Life, and Treatments

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Introduction

Parkinson’s disease (PD) is a degenerative disorder characterized by the loss of substantia nigra pars compacta dopaminergic neurons and the subsequent loss of dopaminergic input to the striatum. As the degenerative process evolves, dopamine replacement therapy becomes necessary to help alleviate motor dysfunction. Four decades after its introduction, levodopa remains the most effective agent to improve parkinsonian motor symptoms, but chronic use is associated with the emergence of motor complications that include response fluctuations and dyskinesias. This has raised the question of how best to use levodopa in the management of PD.

The pathophysiologic mechanisms that underlie motor complications are not completely understood, but substantial support has been garnered for the idea that nonphysiologic pulsatile stimulation of striatal neurons and abnormal firing patterns in the basal ganglia. Dyskinesias have been associated with decreased quality of life, and a number of methodologies to evaluate severity of dyskinesias are now available. Strategies to avoid, reduce, or eliminate dyskinesias include providing more continuous dopaminergic stimulation, administering an antidyskinetic agent, and surgery. Several new compounds that may provide an antidyskinetic effect are also under investigation.

Key Words
Dyskinesia / Levodopa / Management / Parkinson’s disease / Quality of life / Treatment

Abstract
Levodopa is the most effective agent to alleviate motor dysfunction in Parkinson’s disease but its long-term use is associated with the development of dyskinesias. Although the pathogenic processes behind the development of levodopa-induced dyskinesias are still being elucidated, it appears that chronic administration of this short-lived agent results in nonphysiologic pulsatile stimulation of striatal neurons and abnormal firing patterns in the basal ganglia. Dyskinesias have been associated with decreased quality of life, and a number of methodologies to evaluate severity of dyskinesias are now available. Strategies to avoid, reduce, or eliminate dyskinesias include providing more continuous dopaminergic stimulation, administering an antidyskinetic agent, and surgery. Several new compounds that may provide an antidyskinetic effect are also under investigation.

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Dyskinesias are usually choreiform but may resemble dystonia, myoclonus, or other movement disorders [4]. Peak-dose dyskinesias are the most common type of dyskinesia. They occur during peaks of levodopa-derived dopamine in the brain, when the patient is otherwise experiencing a beneficial response (the ‘on’ state) [4]. Peak-dose dyskinesias worsen with increases in dopaminergic therapy and lessen with reductions in dopaminergic therapy. Some patients exhibit diphasic dyskinesia or dyskinesia–improvement–dyskinesia, which occurs when levodopa-derived dopamine concentrations are increasing or decreasing and the patient is turning ‘on’ and ‘off’ [4]. Diphasic dyskinesias are usually more dystonic and preferentially involve the lower extremities compared to peak-dose dyskinesias.

When patients experience motor fluctuations without dyskinesias, it is usually a relatively simple matter to smooth out the clinical response. Levodopa doses can be given closer together, or adjunctive medications that reduce ‘off’ time can be added. However, once a patient has motor fluctuations and peak-dose dyskinesias, it becomes difficult to smooth the clinical response. Increases in dopaminergic treatment then increase dyskinesias, and decreases in dopaminergic treatment reduce dyskinesias but worsen parkinsonian motor symptoms. Although for many patients dyskinesias are not disabling, they create a barrier to adequate treatment of fluctuations and parkinsonian symptoms. This review provides an update on dyskinesias; specifically, their etiology, underlying mechanisms of development, and impact on quality of life (QoL). It also considers pharmacologic and surgical strategies to reduce their development and frequency.

**Fig. 1.** Steps in the genesis of levodopa-induced motor complications [5].

**Etiology of Drug-Induced Dyskinesias**

**Levodopa**

The underlying pathophysiologic mechanisms responsible for the development of levodopa-induced dyskinesias are not fully understood, though both severity of the dopamine neuron loss and chronic intermittent administration of a drug with a short half-life, such as levodopa, are of critical importance (fig. 1) [1, 2, 5]. Under normal physiologic conditions, presynaptic dopaminergic neurons in nigrostriatal pathways fire tonically, resulting in a relatively continuous release of dopamine that causes a steady stimulation of postsynaptic striatal receptors [6, 7]. As PD advances, the loss of striatal dopaminergic neurons and terminals leads to a diminished ability to form, store, and regulate the release of dopamine, and the remaining receptors rely on the availability of exogenous dopaminomimetic agents [7, 8]. The short half-life (approximately 90 min) of levodopa, when administered with a peripheral dopa decarboxylase inhibitor such as carbidopa, causes intermittent (pulsatile) stimulation of striatal dopaminergic receptors [1, 7, 9]. This chronic pulsatile stimulation alters cell signals in striatal dopaminergic spiny neurons, causing potentiation of GABAergic efferents, particularly N-methyl-D-aspartate (NMDA) glutamate receptors [6, 7, 10]. Glutamate-mediated striatal sensitization, which results in nonphysiologic stimulation, triggers a cascade of events involving the induction of certain intracellular messengers and proteins, leading to abnormal basal ganglia firing patterns that result in dyskinesias [1, 9]. Thus, the proposal that continuous dopaminergic stimulation (CDS) leads to fewer motor complications has been the rationale for many new therapeutic strategies and interventions.

The overall duration of levodopa treatment [11, 12], disease severity [3, 11, 13], age of onset [12, 14–17], levodopa dosage [3, 17–19], and initial levodopa dosage [12, 14] are the most significant risk factors for the development of dyskinesias. Of these, the most influential factor associated with levodopa-induced dyskinesias is the duration of levodopa therapy [11, 12]. Dyskinesias occur in approximately 30% of patients by 5 years of treatment [14] and in 59–100% of patients by 10 years [12, 14, 20]. With respect to disease severity at the time levodopa is introduced, a review of the literature [13] showed that median dyskinesia frequency was 50% by 5–6 months of treatment when pre-levodopa era patients first received the medication but that it is slightly less than 40% by 4–6 years of treatment among levodopa era patients. The mean duration of disease was 6–10 years in the pre-levodopa era, in contrast...
to 2–3 years in modern-era patients [13]. Age of onset is also an important risk factor, with the 5-year incidence of dyskinesia greater than 50% when PD develops in patients 40–59 years of age and 16% when it develops in patients after age 70 [15]. The ELLDOPA (Earlier vs. Later Levodopa Therapy in Parkinson Disease) study showed the importance of levodopa dosage as a risk factor for dyskinesia. In this study, patients with early PD who were randomly assigned to levodopa 200 mg three times daily experienced significantly more dyskinesia than those who received a lower dose or placebo [18, 19]. Of note is the fact that motor fluctuations and dyskinesias appear to be interrelated because the presence of one is associated with the earlier development of the other [3].

**Other Agents**

Although more commonly associated with levodopa, dyskinesias can also occur with dopamine agonist mono-therapy [21–23]. The development of dyskinesia in some patients treated with dopamine agonists that have relatively long half-lives (ropinirole, 6 h; pramipexole, 8 h) or very long half-lives (cabergoline, 68 h) suggests that, to some extent, dopamine stimulation can cause dyskinesias even when provided in a continuous fashion.

Other medications can cause or worsen dyskinesias in patients already taking levodopa. In patients who are already exhibiting levodopa-induced dyskinesia, adjunctive medication that increases dopaminergic stimulation commonly increases dyskinesia. In addition, in some patients who have been treated with levodopa but in whom dyskinesia is not yet manifest, dyskinesia may emerge when the levodopa dose is increased or when adjunctive medications are introduced. In these cases, it is thought that the patient has already developed a lowered threshold for dyskinesia, which then becomes apparent when dopamine stimulation is increased. New or worsening dyskinesia has been reported in levodopa-treated patients when adjunctive medications are added, including dopamine agonists [24–26], the catechol-O-methyltransferase (COMT) inhibitors entacapone [27, 28] and tolcapone [29], and the monoamine oxidase type B inhibitors selegiline [30, 31] and rasagiline [32].

**Impact of Dyskinesias on Quality of Life**

**Quality of Life Scales**

Some scales used to evaluate dyskinesia depend on a rater assessment at a single point in time, while others gather historical information provided by the patient or caregiver over a period of time [33]. Some scales are dyskinesia specific, whereas others include an evaluation of dyskinesia as part of a multidimensional patient assessment.

The Unified Parkinson’s Disease Rating Scale has proven to be reliable and valid [34], and it is the most widely used rating scale for measuring severity of parkinsonian symptoms in clinical research and practice [35]. It includes a patient- or caregiver-provided estimate of dyskinesia duration during the waking day (0, 1–25, 26–50, 51–75 or 76–100%) for the past week and a rating of its severity (not disabling, mildly disabling, moderately disabling, severely disabling or completely disabling) [36]. In clinical trials, dyskinesia has been considered present if the duration item response is at least 1–25% of the waking day [23]. The major limitation of the dyskinesia items of this rating scale is that they are rough estimates based on patient recall.

The Abnormal Involuntary Movement Scale [37] was originally developed to assess tardive dyskinesia, but it is also used to assess patients with PD and possible dyskinesia in clinical trials. It is a 12-item, clinician-administered scale that assesses the presence and severity of involuntary movements of the face, mouth, tongue, extremities, and trunk. Body parts are rated on a scale of 0–4, with 0 indicating no abnormal movement and 4 indicating severe symptoms [37]. It is familiar to clinicians, can be completed quickly, and can be used in routine clinical settings and clinical trials. Its major limitation is that it captures dyskinesia at one moment in time and does not assess functional impairment [36]. A modified version for use in patients with PD is commonly used in clinical trials [38, 39].

The Goetz Dyskinesia Rating Scale [40] is a physician- or study coordinator-completed scale in which the rater assesses severity and functional disability associated with the patient’s dyskinesias while observing the patient performing specific tasks. Its main advantage is the documentation of the functional impairment caused by dyskinesias at the time of assessment [36], and it has good interrater and intrarater reliability [40]. On the other hand, its disadvantages include only evaluating function over a short time period (minutes), and the office examination may not reflect the patient’s condition at home. In addition, completion of the scale is somewhat labor intensive and time consuming [36].

The Unified Dyskinesia Rating Scale is under development and is projected to be introduced, together with instructions and teaching tools, by early 2008. Its goal is to eliminate the use of disparate scales, relying on various clinical assessments in clinical research, and to increase the robustness of trials evaluating dyskinesia treatments.
A PD-specific home diary to assess functional status in patients with motor fluctuations and dyskinesia has been validated for use in clinical trials [41, 42]. The diary asks patients to indicate their predominant status over half-hour intervals based on the following categories: ‘asleep’; ‘off’; ‘on’ without dyskinesia; ‘on’ with nontroublesome dyskinesia, and ‘on’ with troublesome dyskinesia [42]. Time ‘on’ without troublesome dyskinesia was demonstrated to most strongly correlate with a patient’s perceived duration of a good response through the day and is an important outcome variable [42]. In recent years, home diaries have been routinely used in clinical trials investigating new treatments for PD. The major advantage of the diary is that it allows evaluation of the patient’s status through the course of the day in the patient’s own environment. It also allows the patient to determine whether the dyskinesia experienced during any time period is troublesome (interferes with activity or causes meaningful discomfort). A major limitation of the diary is that patients must be adequately trained to provide accurate responses and, despite this training, they may still make errors such as confusing the ‘off’ with tremor state and the ‘on’ with dyskinesia state. In addition, diaries are subject to patient compliance and recall.

Clinical Perspectives
QoL for PD patients is more impaired than it is for healthy elderly people [43] and for patients with chronic conditions [44]. Reduced QoL significantly correlates with disease progression [16, 45, 46] and duration [16]. Although it is apparent that PD patients have reduced QoL, the impact of dyskinesias on QoL remains controversial. An observational study of patients in 3 European countries found that dyskinesias do have a significant impact on the QoL of PD patients [47]. In addition, dyskinesias have been reported to adversely affect various dimensions of QoL – including mobility [48], activities of daily living [48, 49], stigma [48], communications [48, 49], and bodily discomfort [49] – as assessed by the PDQ-39 Parkinson’s Disease Questionnaire. Increasing severity of dyskinesias is also associated with increased depression [47]. Other studies have shown that dyskinesias can seriously interfere with the performance of activities of daily living [50], ambulation, and balance [51], and that they can be associated with increased falls [52] and unintended weight loss [53]. On the other hand, other investigators have reported that dyskinesias do not have a significant impact on QoL [16, 35, 54] and may not pose a major concern for patients [14, 55, 56]. Differences in QoL study results may be attributed to variability in methodology and to the patient populations studied.

In the Sydney Multicenter Study, Hely et al. [55] found that 94% of PD patients experienced dyskinesias by 15 years, and 46% considered their dyskinesia disabling. Conversely, 54% did not consider their dyskinesias disabling, and in only 12% were dyskinesias rated severe. Similarly, a clinical review of patients treated with levodopa for 5–10 years showed that only 12% had clinically significant dyskinesias [56]. More recently, a population-based study [14] revealed that dyskinesias can be expected to develop in nearly 60% of patients at 10 years and that in 43% they would be severe enough to necessitate medication adjustments. However, in only 12% could dyskinesia not be controlled with medication adjustments [14]. Nonetheless, it is unclear what effects these medication adjustments had on potential worsening of motor fluctuations and parkinsonian motor features. Dyskinesias have also been associated with significant increases in health care costs [47, 57], and strategies to delay the onset of dyskinesias or to alleviate them can significantly reduce health care expenditure.

From a clinical perspective, patients may have mild dyskinesias without apparent adverse impact on QoL. In fact, most patients prefer mild dyskinesias to being ‘off’ when they may feel immobile and constricted. However, marked dyskinesias can cause functional impairment and patient discomfort. Therefore, the effect of dyskinesias on QoL may very much depend on the severity of the dyskinesias. In addition, it must be recognized that the presence of dyskinesias limits the ability of the physician to increase PD medications to reduce ‘off’ time. Therefore, the actual impact of dyskinesias may come not only from disability caused by dyskinesia itself but also from motor fluctuations and ‘off’ time that cannot be adequately treated as a result.

Pharmacologic Strategies to Directly Address the Incidence of Dyskinesias
Restoration of striatal dopaminergic stimulation is the goal in the treatment of parkinsonian motor symptoms. Levodopa provides the greatest benefit for treating parkinsonian motor dysfunction, but because its use is associated with the development of motor complications, one of the great unmet needs for the treatment of PD is a medication that will match the efficacy of levodopa but not cause motor complications. Until such a medication is available, it is useful to identify treatment strategies...
that can provide adequate efficacy while minimizing motor complications.

The short half-life of levodopa and the resultant pulsatile dopaminergic stimulation appear at least in part to be responsible for the development of motor complications [1, 6, 7, 9, 10]. Therefore, CDS may delay the onset of dyskinesias in early disease and alleviate dyskinesias in advanced disease.

Early Disease: Avoiding the Development of Dyskinesia

Early disease strategies include administering a dopamine agonist as initial therapy, adding levodopa when the agonist alone is no longer able to adequately control parkinsonian symptoms, and using methods to deliver levodopa in a more continuous fashion.

Initiating Therapy with an Agonist and Adding Levodopa when Necessary

Animal data suggest that pulsatile stimulation with short-acting agents is the driving force in the genesis of dyskinesias [58]. Conversely, these short-acting agents do not induce dyskinesias when given in a continuous fashion [58]. In drug-naive, MPTP-lesioned monkeys, the administration of longer-acting dopamine agonists results in significantly less dyskinesia than does levodopa [59, 60]. However, once a long-acting agonist is administered to animals already primed to exhibit dyskinesias with levodopa, the resultant dyskinesias are comparable to those seen in the levodopa group [59]. An MPTP-marmoset study [60] evaluating the combination of ropinirole, a long-acting agonist, plus levodopa showed that the levodopa-dominant group (mostly levodopa) had increasing intensity of dyskinesias as the study progressed, whereas the ropinirole-dominant combination produced no greater intensity of dyskinesias than was produced by ropinirole alone.

Clinical studies randomly assigning patients to initial treatment with a dopamine agonist or levodopa have shown a lower risk for dyskinesias in the agonist-treated groups (agonists studied have included pramipexole [22, 61], ropinirole [23, 62], bromocriptine [63, 64], pergolide [65], and cabergoline [21]). Retrospective analyses have demonstrated that once levodopa is added, the rate of development of dyskinesias is the same regardless of whether or not the patient was already taking a dopamine agonist [62, 66]. Therefore, it appears that the benefit of initial treatment with a dopamine agonist in lowering the incidence of dyskinesias is related to the ability of the agonist to delay the need for levodopa [62, 66].

Delivering Levodopa in a More Continuous Fashion

Optimizing levodopa therapy by adding an agent that can prolong its half-life and deliver it in a less pulsatile manner is another promising way to achieve CDS. Levodopa is metabolized peripherally by aromatic amino acid decarboxylase and COMT. The combination of levodopa/carbidopa plus the COMT inhibitor entacapone can reduce the peripheral conversion of levodopa and extend the levodopa half-life to 2.5 h [67]. In MPTP-treated monkeys, Jenner [68] showed that coadministration of the same dose of levodopa 4 times a day with entacapone improved parkinsonian motor response and caused less dyskinesia than treatment with levodopa alone. Peak dose dyskinesia scores and dyskinesia duration were decreased [68]. Rat studies showed similar results [69], supporting the theory that reducing pulsatile delivery of levodopa leads to fewer motor complications. Clinical trials are now under way in which patients in need of levodopa therapy are randomly assigned to treatment with levodopa and carbidopa, or levodopa, carbidopa and entacapone. The aim is to determine whether the introduction of entacapone when levodopa and carbidopa are first administered will lower the rate of dyskinesia onset.

It was previously hoped that sustained-release levodopa and carbidopa might be able to decrease the rate of dyskinesia onset. However, a double-blind multicenter study comparing immediate-release carbidopa-levodopa twice daily (b.i.d.) with controlled-release carbidopa-levodopa therapy b.i.d. in patients with PD proved otherwise and showed no statistical difference in the incidence of dyskinesia between the 2 treatment groups during the first 5 years of treatment [70]. However, the dosing of controlled-release carbidopa-levodopa b.i.d. might have been insufficient to achieve continuous stimulation.

Advanced Disease: Reducing or Eliminating Established Dyskinesias

PD patients eventually need levodopa to help alleviate parkinsonian motor features. When dyskinesias emerges, one strategy is to dose levodopa so that it peaks just below the dyskinesia threshold and administer it frequently enough to avoid wearing off. This typically amounts to administering levodopa in smaller doses more often, which may be inconvenient and result in reduced compliance. At the extreme, liquid levodopa (which is not commercially available but can be easily prepared [71]) can be used to deliver very small doses of levodopa very frequently (usually every hour) [71, 72]; however, patients usually find this very inconvenient.
Another strategy is to use higher doses of a dopamine agonist to reduce both the total daily levodopa dose and its frequency [73] or to gradually substitute a dopamine agonist for levodopa [72]. Unfortunately, these strategies rarely work and typically reduce dyskinesias at the expense of less satisfactory control of parkinsonian symptoms.

Alternative routes of levodopa administration, such as intraintestinal [39, 74, 75] or intravenous infusion [76], provide more sustained levodopa delivery and reduce motor complications. Stocchi et al. [39] demonstrated significant reductions in ‘off’ time and dyskinesia after 6 months of intraintestinal levodopa infusion. Infusion was associated with continuously elevated levodopa concentrations that avoided wide fluctuations and especially low troughs [39]. This suggests that the benefits for dyskinesia may not be attributed to maintaining levodopa levels just below the dyskinesia threshold. Rather, by providing high concentrations that avoid levodopa troughs, desensitization may be induced over time. Continuous intraduodenal levodopa infusion has been evaluated in small trials [74, 75, 77, 78] and warrants further study. It may be an option for patients with marked fluctuations and dyskinesia in whom deep-brain stimulation (DBS) is contraindicated or not possible due to advanced age, or it may provide an alternative to DBS. Continuous subcutaneous infusion of apomorphine has also been used in Europe for almost 2 decades [51, 79–84].

Symptomatic Treatment of Dyskinesias

As the therapeutic window for levodopa narrows and the balance between alleviating dyskinesias without compromising motor status becomes more difficult, amantadine (200–400 mg/day, in 2–4 divided doses) can be considered [72]. Amantadine, a noncompetitive NMDA antagonist, appears to have antidyskinetic effects, and several studies have assessed its efficacy and safety [85–92]. Some studies suggest that the benefits of amantadine persist for only a few weeks [90] or months [87], but others suggest that amantadine has a more long-lasting effect [91]. An adequate trial of amantadine may be appropriate before surgery for severe dyskinesias is considered [91].

Clozapine is an atypical antipsychotic that has been assessed for the treatment of drug-induced psychosis in PD. It may also be effective in decreasing dyskinesias [72], and a few studies have focused on its antidyskinetic effect [93, 94]. However, the hematologic monitoring necessary with clozapine can be burdensome for both the patient and the physician and can limit its usefulness.

Many other available drug therapies have been evaluated for the treatment of dyskinesias, but nearly all studies were small and had other methodologic limitations [95]. Other noncompetitive NMDA antagonists, such as dextromethorphan [96, 97] and remacemide, have been studied. The latter was studied in a larger trial and was found to be safe and well tolerated but did not show any demonstrable anti-dyskinetic benefit [36]. Topiramate, an AMPA glutamate antagonist, significantly reduced levodopa-induced dyskinesias in the MPTP-lesioned marmoset model of PD [98]. In a small open-label study, the antiepileptic drug levetiracetam significantly improved the percentage of the awake day ‘on’ without dyskinesia or with nontroublesome dyskinesia but was frequently associated with somnolence [99]. Two ongoing randomized, double-blind, placebo-controlled studies in Europe are assessing the use of levetiracetam in the management of levodopa-induced dyskinesias. Buspirone, a 5-HT1A receptor partial agonist [100, 101], fluoxetine, a serotonin reuptake inhibitor [102], and idazoxan, an alpha-2 antagonist [103], may reduce dyskinesia without worsening parkinsonism. Mirtazapine – a 5-HT1A agonist, a 5-HT2 antagonist, and an alpha-2 antagonist – was moderately effective in reducing levodopa-induced dyskinesia, alone or together with amantadine [104]. A variety of novel compounds, such as adenosine A2A antagonists [105–107] and serotoninergic agonists [108–110], are also under investigation.

Diphasic dyskinesias are difficult to treat [72]. In theory, maintaining continuous high levels of dopaminergic stimulation should avoid the turning ‘off’ and turning ‘on’ phases of the levodopa cycle in which these dyskinesias occur. However, this is usually only partially successful, and using higher levodopa doses may encourage the development of peak dose dyskinesias and other levodopa-induced adverse effects. Amantadine and clozapine are only partially effective. Patients with severe, medically refractory peak dose dyskinesias or diphasic dyskinesias should be considered for DBS [72].

Surgical Treatment

Abnormal basal ganglia output neurons communicate inappropriate information to cortical and brain stem motor regions [111], and surgical procedures are thought to act by interrupting these abnormal neuron firing patterns [112]. Surgical approaches can be highly effective in reducing dyskinesias. Dyskinesias and motor fluctuations are the main reasons for surgery in patients with PD.
Levodopa-Induced Dyskinesias in Parkinson’s Disease

Conclusions

Levodopa continues to be the mainstay of medical therapy for PD, but it is associated with the emergence of dyskinesias. Because of its short half-life, its administration leads to pulsatile stimulation of striatal neurons with resultant intracellular events that are expressed clinically as dyskinesias. Risk factors for dyskinesias are disease duration, duration of levodopa therapy, levodopa dose, and age. The emergence of dyskinesias has been associated with decreased QoL and increased health care costs.

One strategy to address levodopa-induced dyskinesias is to attempt to provide CDS to delay the onset of dyskinesias in early disease and to alleviate dyskinesias in advanced disease. Strategies in early disease include using initial treatment with a dopamine agonist and adding levodopa later when parkinsonian motor symptoms progress, and delivering levodopa in a more continuous manner. Controlling troublesome dyskinesias once they emerge is usually difficult. As the therapeutic window for levodopa narrows, decreasing levodopa to alleviate dyskinesias often compromises motor function. An attempt can be made to administer smaller levodopa doses more frequently. Amantadine and clozapine can also be considered. Other nondopaminergic drugs have been shown to reduce dyskinesias in small trials, and some are undergoing evaluation. Surgery should be considered for patients with medically intractable motor fluctuations and dyskinesias. STN DBS is the most commonly performed surgical procedure. It improves parkinsonian symptoms, reduces response fluctuations, and allows for significant reductions of levodopa dose, which in turn alleviates dyskinesias.

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