

## The Therapeutic Place of Duodopa – Choosing the Right Therapy for Individual Patients

a report by

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### Abstract

It is well established that motor fluctuations in Parkinson's disease (PD) to a large extent result from pulsatile dopaminergic stimulation, compounded by the short half-life and erratic absorption of oral levodopa therapy. Continuous dopaminergic stimulation (by means of intravenous or enteral infusions) has been shown to dramatically improve motor fluctuations, even in severely on-off-fluctuating patients. Recently, Duodopa therapy, which involves continuous delivery of a gel formulation of levodopa/carbidopa into the duodenum via a percutaneous tube and a portable pump, has become available in several European countries. Levodopa responsiveness is the most important predictor of beneficial response to Duodopa therapy. The same selection criterion applies to deep brain stimulation of the subthalamic nucleus (STN-DBS), which is an established surgical alternative for the treatment of

motor fluctuations and dyskinesias in patients with advanced PD. Patient selection is a key component in ensuring optimal outcomes for any treatment. Studies show that younger age, the absence of levodopa-resistant axial symptoms and normal cognitive status are associated with a better response to STN-DBS and a lower risk of surgery. Younger patients are also known to show a better psychosocial adaptation after movement disorder surgery. Contraindications for DBS surgery include unstable psychiatric conditions and medical co-morbidities. Duodopa therapy, on the other hand, is a relatively safe therapy with few contraindications, and it may even be tolerated by patients with unstable medical co-morbidities. Despite the lack of comparative trials, the current literature suggests that there may be subgroups of PD patients who will benefit from either Duodopa therapy or DBS. ■

This article will summarise many of the crucial points made in the previous papers regarding the therapeutic place of Duodopa. The aim is to put the evidence into a subjective perspective to enable physicians to individualise treatment decisions for patients with advanced Parkinson's disease (PD). PD is a multisystemic neurodegenerative disorder that, at least in the early stages, is predominantly characterised by a loss of dopaminergic functions, causing loss of motor functions. As PD progresses it causes non-motor symptoms as well. Levodopa is a good therapy for alleviating many of the symptoms of PD, but unfortunately the pharmacodynamic response to the drug changes over the course of the disease and the therapeutic window for oral levodopa becomes narrower.

There are limits to the time period available for considering advanced treatment in PD. Treatment of early PD is characterised by the levodopa honeymoon period, where most of the symptoms of PD can be well treated with oral medication. After a period of three to five years, depending on the age of the patient, motor complications eventually start to evolve. These complications may become more violent and require more advanced treatment strategies over time. Eventually, in the long term, levodopa-resistant symptoms develop and there is also cognitive decline, which may restrict treatment options for these patients (see *Figure 1*).

Thus, the questions are: When should alternatives to oral levodopa therapy be applied? Is there a 'too late' because of the levodopa-resistant symptoms and cognitive decline? Is there a 'too early'? Furthermore, once we have defined this period of more aggressive

treatment, which of the three available options – deep brain stimulation (DBS), dopamine agonist (apomorphine) infusion or levodopa infusion (Duodopa) – should we choose?

There are several ways to address the problem. One of the fashionable methods at the moment is to use evidence-based medicine (EBM). This provides guidance on which therapies are beneficial and have a good risk-benefit ratio in large populations of patients. One such example of EBM is the practice parameter review of the American Academy of Neurology published in 2006.<sup>1</sup> This states that there is moderate evidence in favour of DBS of the subthalamic nucleus (STN) being an effective therapy for improving motor function and reducing fluctuations and dyskinesias in advanced PD. It is therefore recommended in selected patients. Unfortunately, this review does not mention continuous dopaminergic stimulation because at the time of the review there were very few controlled clinical trials: only 11 long-term open-label studies on continuous subcutaneous apomorphine infusion existed, covering roughly 200 patients, and there were even fewer data on intestinal levodopa infusion or lisuride infusion. This is to be expected given that STN-DBS already had a 10–15-year history when levodopa infusions were introduced. Duodopa is currently at the same position that DBS was about 10 years ago: it is an orphan drug that is rapidly growing. Orphan drugs are, by definition, meant to be for the treatment of a relatively circumscribed small population, and therefore it is very difficult to find the large-scale evidence that is needed for an EBM review.

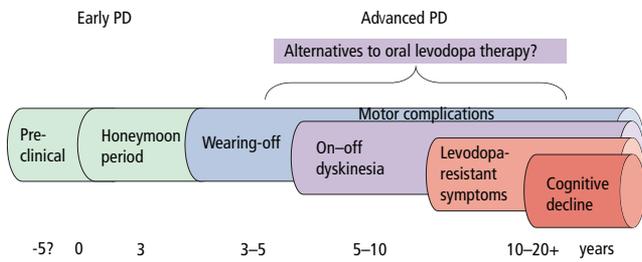
### Deep Brain Stimulation

As discussed in the article by Patricia Limousin, the major benefit of DBS is that it reduces the large gap between the best motor on state that patients experience with levodopa and the off state of parkinsonism

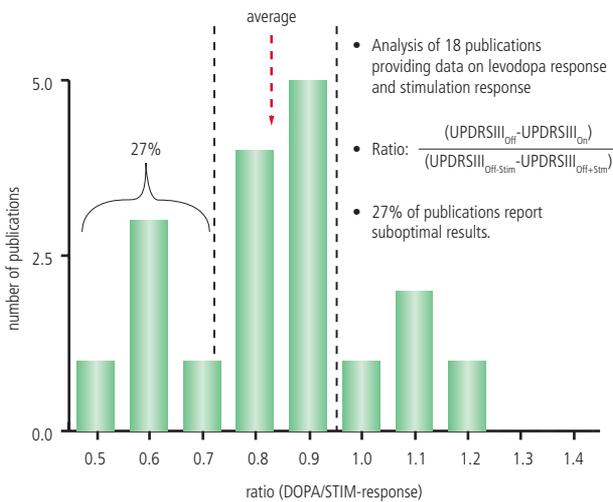
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# Continuous Dopaminergic Stimulation

**Figure 1: Progression of Parkinson's Disease**



**Figure 2: Quality Control in Deep Brain Stimulation of the Subthalamic Nucleus**



without needing to take dopaminergic drugs. This is quite a dramatic response. Ideally, it would mean that patients no longer fluctuate between the two extremes that existed pre-operatively, but instead they have two motor states that are difficult to perceive as being different.<sup>2</sup> Thus, there is a reduction in motor fluctuation, improvement in sleep, reduction in off time and, as a result of the 50–60% reduction in dopaminergic drugs, a reduction in dyskinesia.<sup>3</sup>

One of the most important predictors of outcome of STN-DBS is the levodopa response: the best possible STN-DBS effect ideally matches the effect achieved with a special levodopa challenge. Levodopa-resistant symptoms do not respond to STN-DBS, therefore it is not surprising that the benefit is at least equally effective when motor symptom severity is used as a primary outcome parameter.<sup>4</sup>

Most of the clinical studies now available, covering a large number of DBS patients, have demonstrated that it is a very effective therapy that can reduce motor fluctuations. However, the clinical reality is that there are many patients in the community who complain of being DBS failures. If the theoretical response in the clinical trials is so good, why are there these treatment failures?

Part of the issue is the difficulty in comparing clinical trial results from different centres: there are differences in patient selection, consideration of age or levodopa response and severity of symptoms. Most important is the quality of the surgical procedure, which is

decisive in determining how much of the patient's levodopa response is effectively transferred to STN-DBS. There are issues with electrode location and the surgeon's experience and learning curve. This therapy has spread into many centres in Europe; there are 35 in Germany alone. However, many centres perform fewer than five procedures per year. This is the reality beyond clinical trials. Many patients deemed DBS failures may, for example, have had an improperly positioned electrode.

This kind of clinical reality is demonstrated by Okun et al., who examined the DBS failures referred to their US clinic from less experienced DBS centres. Of 41 patients deemed to be failures of STN-DBS, roughly half were selection failures, i.e. patients who had a poor neurological pre-operative work-out: either a wrong diagnosis of PD (multiple systems atrophy or supranuclear palsy, for example) or an inadequate medication trial, levodopa-resistant symptoms or even dementia. The remaining half had problems related to suboptimal placement of electrodes. Some could be repositioned, although not all patients fared better despite being treated a second time by an experienced DBS centre.<sup>5</sup>

The quality of DBS can be assessed numerically by taking the motor score element of the levodopa response and dividing it by the stimulation response the patient experiences. Therefore, the ideal DBS quality control ratio is as close to 1 as possible. A search within the literature reveals 18 papers that provide data on levodopa and stimulation responses, but this ideal figure of 1 is achieved by only a small group of studies. The average ratio is somewhere between 80–90%, and approximately one-third (27%) report an inferior outcome (see Figure 2).

The goal of DBS or drug infusion therapy in PD goes beyond purely symptomatic treatment for motor fluctuations and dyskinesia, and actually aims to improve activities of daily living (ADL) and quality of life (QoL). Motor symptoms, fluctuations and dyskinesia are only part of the overall impairment in PD. How they translate and what their weighting is in terms of disability restrictions to ADL, social or leisure activities is relatively unknown. Also relatively unstudied is the effect of subjective factors such as social support, coping ability, lifestyle choices and the

One of the most important predictors of outcome of STN-DBS is the levodopa response.

existence of social support services. There is evidence that young-onset PD patients suffer more than older patients, particularly in areas such as marital discord and stigma.<sup>6</sup> For these patients there is emerging evidence that early intervention with neurosurgery is beneficial.<sup>7</sup> Even with all of its limitations, the fact is that STN-DBS in well selected patients can make an impact beyond improving the motor symptoms of PD, and can appreciably improve QoL. This increase is in the order of 23%, not only for advanced PD but also for patients with a shorter PD duration and early onset of motor fluctuations.<sup>3</sup>

### Limitations of Deep Brain Stimulation

As discussed in the article by Patricia Limousin, there is a question regarding the safety of DBS in patients with psychiatric co-morbidities, mild cognitive impairment and axial on symptoms, and in those who are older. Up to 60 years of age the 'on' scores achieved prior to surgery with a levodopa challenge match those achieved afterwards with DBS; after 60 years of age this relationship starts to fail. Even adding levodopa does not enable these older patients to reach the best motor on state prior to surgery.<sup>8</sup> In addition, older patients face a greater risk of cognitive decline, especially in terms of executive function.

With strict criteria DBS leaves a lot of patients untreated for their severe motor fluctuations.

As shown in the study by Lees et al., the progression of PD may not be linear – a fact demonstrated by the appearance of extra symptoms in PD that are not linked with disease duration but rather with the patient's age and time of death. Approximately four to five years prior to their death, patients experience problems such as cognitive decline, falls and, ultimately, nursing home admission.<sup>9</sup> Therefore, in older patients the time period available to treat motor fluctuations with continuous levodopa infusion or DBS is relatively limited.

There is an issue with exactly how many patients are eligible for STN-DBS. An Italian study came up with a surprisingly low figure: in a group of unselected patients in a movement disorder clinic, the researchers found that while fluctuations were present to an extent that justified surgery in roughly 30% of patients, only 1.6% of patients fulfilled strict inclusion criteria for DBS. The exclusion criteria of age (<70 years) immediately removed 50% of people. With slightly more flexible severity and age criteria, the percentage of suitable patients rose to 4.5%.<sup>10</sup>

Those who are good candidates for DBS have: disabilities from motor fluctuations, dyskinesia or tremor; excellent levodopa response; no or few axial on symptoms; no cognitive impairment; and no uncontrolled psychiatric disease. Therefore, with strict criteria DBS leaves a lot of patients untreated for their severe motor fluctuations. This provides a starting point for deciding which patients should be primarily offered continuous dopaminergic stimulation.

### Continuous Dopaminergic Stimulation

Participants in our DBS study in Germany<sup>3</sup> who experienced an improvement in QoL following DBS were, on average, five to six years younger than those who experienced similar improvements in two of the larger Duodopa studies, by Antonini et al.<sup>11</sup> and Nyholm et al.<sup>12</sup> (see Table 1). Disease duration was also less than in the Italian study.

Motor fluctuations can be improved by Duodopa therapy, as outlined in the article by Francesc Valldeoriola. Can QoL also be improved in this older patient group? Compared with the Duodopa study by Antonini et al., our DBS study shows overall differences in the type of impairments the patients experience, which is to be expected as the Italian study was

Table 1: Comparison of Age and Duration of Disease

	Nyholm, 2005	Antonini, 2007	Deuschl, 2006
Number	24	9	156
Age (years)	68	66±10	60±8
Duration of Parkinson's disease (years)	12	18±6	13±6
LEDD (mg)	NA	1,283±308	1,176±517

LEDD = levodopa-equivalent daily dose.

Table 2: Kiel Experience with 13 patients on Duodopa

	n	Median	Min	Max
Age (years)	13	71	49	78
Duration of disease (years)	13	13	11	26
Hoehn and Yahr stage (Med ON)	12	3	2,5	4
Off duration (/24 hours)	9	5	2	8
On duration (/24 hours)	10	0.5	0	8
LEDD (mg)	12	1,000	300	1,500
Mattis score	8	128	105	136
Delusions	9/13	–	–	–
Use of antipsychotic medication	10/13	–	–	–

LEDD = levodopa-equivalent daily dose.

in a more advanced PD group with higher Parkinson's Disease Questionnaire (PDQ) scores in general. However, there were similar profiles of improvement for both therapies.

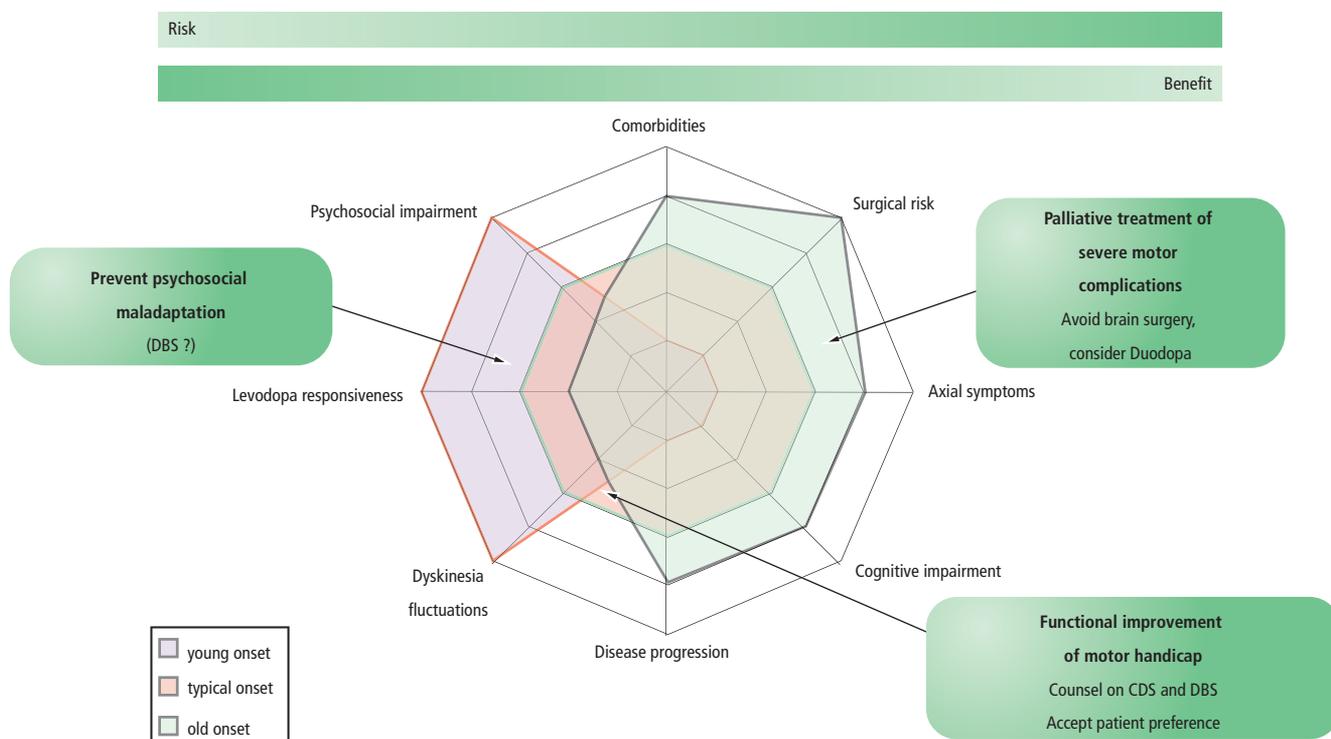
At Kiel, our experience with Duodopa started by taking those patients who did not fulfil the eligibility criteria for STN-DBS. Table 2 shows the inclusion criteria for the 13 patients treated with Duodopa since 2006. The median age of 71 years is clearly higher than for STN-DBS and, as an additional factor compared with the Italian and Spanish groups (discussed in the article by Francesc Valldeoriola), we also noted patients with cognitive impairment, as measured by the Mattis score, and took an overall count of patients with delusions and/or who were taking antipsychotic medication. In terms of QoL, we have five patients with at least six months of follow-up data. Their QoL scores (PDQ-39) with Duodopa are comparable to those achieved with DBS.<sup>3</sup> Emotional wellbeing, stigma and social support all scored lower than other measures, such as mobility and ADL.

### Adverse Events

There were several adverse events related to the procedure. Concerning the percutaneous endoscopic gastrostomy (PEG), one patient had transient infection at entry site and three had transient fever and peritoneal signs. For the Duodopa infusion, six patients had no complications at all, but three had increased delusions and three increased dyskinesia. Overall, four patients did not complete the trial: three because they had died (for reasons unrelated to the therapy) and one who dropped out because of increased delusions.

The risk of DBS has been assessed in sufficiently large patient cohorts: 30-day mortality for DBS is around 0.4%,<sup>13</sup> and permanent morbidity, mostly caused by symptomatic intracranial haemorrhages, is around 1%. There is no register for adverse events in Duodopa-treated patients that can allow a reliable estimate of serious complications. However, PEG surgery is not a zero-risk procedure and may be associated with a mortality rate as high as 5.7% in a frail elderly population.<sup>14</sup> Nevertheless, Duodopa can be offered to many patients, even those who do not fulfil the strict inclusion criteria for DBS. It is not suitable for

**Figure 3: Indication for Drug Infusion and Surgical Therapies in Advanced Parkinson's Disease**



CDS = continuous dopaminergic stimulation; DBS = deep brain stimulation.

patients with severe dementia, who are non-compliant, have poor family support/nursing care or who are overall too frail.

It is therefore important to inform all patients with medically intractable motor fluctuations/dyskinesias who are eligible for DBS about the alternative of Duodopa. However, the preferences of patients must be respected, and many patients tend to prefer DBS, feeling for instance that there is a stigma associated with PEG and having to depend on a pump, or that there are too many logistical issues in terms of storing and carrying the Duodopa gel. QoL is highly subjective, and everyone puts different emphasis on its various aspects.

### Summary and Conclusions

Parkinson's disease is more than merely a motor condition, as it has an impact on many aspects of life. It affects people differently, with age at onset of the disease playing a large part in response to treatment.

What is needed is a multidimensional approach: an individual risk–benefit assessment. It is important to look at co-morbidities, surgical risks in individual patients, presence of axial symptoms, cognitive impairment, disease progression, levodopa responsiveness, psychosocial impairment and severity of dyskinesia and fluctuations. These are different in young-onset, typical-onset (50–60 years of age) and old-onset PD patients (see Figure 3).

In the older population group, the emphasis is on palliative treatment of severe motor complications and fluctuations, which cause less impairment of QoL. For these patients, I would suggest avoiding brain surgery and recommending alternatives such as Duodopa. There is a large group of patients where the goal of advanced treatment is to improve their functional status, reduce motor handicap and improve ADL. These patients should be counselled on all alternatives, and patient preference accepted. ■

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**Improved quality-of-life and advanced Parkinson's Disease don't normally belong in the same sentence.**

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Duodopa® contains 1 ml contains 20 mg levodopa and 5 mg carbidopa monohydrate. 100 ml contain 2000 mg levodopa and 500 mg carbidopa monohydrate. **Pharmaceutical form:** intestinal gel. **Therapeutic indications:** Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. **Posology and method of administration:** the gel should be administered with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy with an outer transabdominal tube and an inner intestinal tube. A temporary nasoduodenal tube is recommended to find out if the patient responds favourably to this method of treatment. **Dosage:** the total dose/day of Duodopa is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses. **Morning dose:** The morning bolus dose is administered by the pump to rapidly achieve the therapeutic dose level (within 10-30 minutes). The total morning dose should not exceed 15 ml (300 mg levodopa). **Continuous maintenance dose:** The maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The continuous maintenance dose is adjusted individually. It should be kept within a range of 1-10 ml/hour (20-200 mg levodopa/hour). **Extra bolus doses:** To be given as required if the patient becomes hypokinetic during the day. The extra dose should be adjusted individually. Treatment must be monitored. **Contraindications:** hypersensitivity to levodopa, carbidopa or any of the excipients; severe liver and renal insufficiency; severe heart failure; severe cardiac arrhythmias; acute stroke. **Special warnings and precautions for use:** Duodopa should be administered with caution to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions. In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments. All patients treated with Duodopa should be monitored carefully. Patients with past or current psychosis and chronic wide-angle glaucoma can be treated with caution. Levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should therefore be exercised when driving and operating machines. Previous surgery in the upper part of the abdomen may lead to difficulty in performing gastrostomy or jejunostomy. **Interaction with other medicinal products and other forms of interaction:** Caution is needed in concomitant administration of Duodopa with the following medicinal products: antihypertensives, antidepressants, anticholinergics, COMT inhibitors, some antipsychotics and benzodiazepines. Duodopa can be taken concomitantly with the recommended dose of an MAO inhibitor, which is selective for MAO type B (for instance selegiline-HCl). Concomitant use of selegiline and levodopa-carbidopa has been associated with serious orthostatic hypotension. Amantadine has a synergic effect with levodopa and may increase levodopa related adverse events. Sympathomimetics may increase cardiovascular adverse events related to levodopa. Levodopa forms a chelate with iron in the gastrointestinal tract leading to reduced absorption of levodopa. As levodopa is competitive with certain amino acids, the absorption of levodopa can be disturbed in patients who are on a protein rich diet. The effect of administration of antacids and Duodopa on the bioavailability of levodopa has not been studied. **Pregnancy:** Duodopa should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus. **Lactation:** Levodopa is excreted in the breast milk. It is unknown whether carbidopa is excreted in human breast milk. Duodopa should not be used during breast-feeding. **Effects on ability to drive and use machines:** Caution should be exercised when driving or using machines. **Undesirable effects:** Undesirable effects that occur frequently with levodopa/carbidopa are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by levodopa dosage reduction. **The device:** Complications with the devices may occur, e.g. connector leakage and dislocation of the intestinal tube. Dislocation of the intestinal tube backwards into the stomach leads to reappearance of motor fluctuations. In general, relocation of the tube can be done using a guide-wire to steer the tube into the duodenum under fluoroscopy. Occlusion, kinks, or knots of the intestinal tube lead to high pressure signals from the pump. Occlusions are usually remedied by flushing the tube with tap water; kinking, knotting, or a tube displacement may need readjustment of the tubing. 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<sup>1</sup> Nyholm D. et al. Duodenal levodopa infusion monotherapy versus oral polypharmacy in advanced Parkinson's disease. *Neurology* 2005; 64: 216-223.



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