DEBATE: ADJUNCTIVE THERAPY SHOULD BE INITIATED AS SOON AS WEARING-OFF IS DETECTED: NO

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Levodopa still remains the most effective dopaminergic agent for the main motor symptoms of PD since its introduction almost 50 years ago; therefore all patients with PD will eventually start using levodopa. However, the very well-known obstacle of long term levodopa treatment is its high potential of inducing motor complications, namely motor fluctuations and dyskinesias. Patients developing motor complications usually first experience gradual end-of- dose deterioration of motor response, so called "wearing-off" phenomenon (WO), which is sometimes accompanied, but most commonly followed by mild peak dose levodopa-induced dyskinesias. Although the underlying mechanisms are mutlifactorial, all types of motor fluctuations starting with WO and evolving to more complex ones such as unpredictable on-off periods and non-motor off phenomena are mainly thought to be related to non-physiological stimulation of denervated striatum with conventional levodopa/DDCI preparations. Since very short half-life and erratic peripheral pharmacokinetic profile of levodopa is the principal cause and hard to be optimized with available levodopa regimens, adjunctive therapeutical agents, such as COMT and/or MAO-B inhibitors and dopamine agonists are usually the first line of practical strategy to obtain more continuous dopaminergic replacement. However, there is still a space to optimize peripheral levodopa pharmacokinetics, to save time before starting these agents to restore the inaccurate central pharmacokinetics and pharmacodynamics of levodopa.

The more rational dosing tailored according to the patient's needs during the day, assuring all the measures to overcome the inter-and intra-personal variables of absorption and delivery of levodopa to the brain should be done according the known peripheral kinematics, including plasma levels of tmax, Cmax, Cmin, difference between them and AUC. The available data will be discussed according to frequent dosing regimens of levodopa/DDCI in comparison with use of concomitant COMT inhibitors.