ADJUNCTIVE THERAPY SHOULD BE INITIATED AS SOON AS WEARING-OFF IS DETECTED: YES

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For over 40 years, levodopa has been the gold-standard of treatment of PD, and patients unavoidably will require it during the course of the disease. When patients are initially started on levodopa therapy they experience a sustained clinical response throughout the day. As the disease progresses, the therapeutic effect shortens and many patients experience benefit only for a few hours after ingestion of the drug: this step is otherwise known as the WO. Despite several studies have been conducted in patients with fluctuations, it is difficult to infer from the available data a clear consensus on the prevalence, timing and characteristics of the WO phenomenon. For many years, doctors considered the WO as a late and even rare phenomenon. On the other hand, it is now widely recognized that the development of WO has a significant impact on patient's neurological disability and QoL

We recently conducted a study, based on an observational, cross-sectional, multicentre study called *Early DEtection of wEaring off in Parkinson disease* (DEEP Study). The primary goal was to look at the frequency of WO phenomena among a wide population of patients with PD, and secondarily to assess the impact of WO on patient's QoL. The diagnosis of WO was made both on the neurologist evaluation as well as on the basis of the patient self-assessment using the Italian version of the WOQ-19

617 patients with PD were included in the study. Neurologists identified 351 subjects (56.9%) with WO symptoms while 415 subjects (67.3%) were identified by the WOQ-19 ($p<0.0001$). The WOQ-19 was more sensitive particularly in subjects with <2.5 years disease duration, with 23 (41.8%) patients indicating ≥2 WO symptoms compared with 12 (21.8%) patients identified by neurologists ($p<0.001$), similarly for subjects with 2.5-5 years (54.6% vs. 36.2%; $p<0.001$), 5-10 years (69.3% vs.60.1%; $p<0.0001$), and >10 years disease duration (76.8% vs. 80.4%; $p<0.0001$; Fig. 1). For 489 (79.3%) patients there was agreement between neurologists and WOQ-19 for the absence in 170 (27.6%) or presence in 319 (51.7%) of WO. For 128 (20.8%) patients there was disagreement; 32 (5.2%) those in whom WO diagnosis by neurologists was not confirmed by WOQ-19, and 96 (15.6%) endorsed WO symptoms through WOQ-19, which their neurologists did not diagnose.

The DEEP study confirmed that WO is a very common phenomenon in PD and it appear early. Indeed 41% (according to the questionnaire 21.8% according to the neurologist) of patients with less than 2.5 years of disease already had WO symptoms.

In clinical practice, treatment is initiated once the compensatory mechanisms alluded to above have failed. As a result, there is a reduced capacity to compensate for the changes in dopamine availability associated with oral administration of levodopa and the basal ganglia-motor system network widely oscillates between various abnormal states. The critical and therapeutically relevant point is that standard levodopa formulations lead to oscillating and very unstable levels of striatal dopamine, which depart considerably from the prevailing operational model of the basal ganglia under normal conditions. Thus, standard levodopa administration at this stage does not restore the normal physiology of the basal ganglia, but induces, through 'pulsatile' stimulation, molecular abnormalities such as phosphorylation of NMDA subunits and up-regulation of AMPA receptors in medium spiny striatal neurons that sustain the 'wearing-off' response.

In summary, compensatory mechanisms in the brain allow dopaminergic striatal depletion to be asymptomatic until relatively high deficit are reached. At this stage, the basal ganglia becomes dysfunctional and clinical features become severe enough to allow the diagnosis of PD. Disease progression is associated with further SNc cell loss, augmented dopamine depletion and marked physiological changes in the output nuclei of the basal ganglia which loss their auto-regulatory capacity. Restoring dopaminergic deficit with short acting drugs will be soon be associated with a SDR and the induction

of dyskinesias, as pulsatile dopaminergic stimulation fails to come close to provide a physiological restoration of dopaminergic activity.
If pulsatile treatment continues then this can only lead to an even more unphysiologic situation in the basal ganglia. Thus the earlier fluctuations are managed, the better chance the patient has at improved long-term outcomes. It is therefore logical that treatment should be optimised from the very beginning: DAs should be long lasting (preferably better than those currently available), Levodopa treatment should always be optimised to have a longer half-life , the use of COMTi or MAOBi extend levodopa and dopamine half life reducing fluctuations in plasma levodopa level and brain dopamine levels inducing a more continuous dopaminergic stimulation. A combination of COMT and MAOB could be beneficial – if a patient is already on rasagiline then this doesn't preclude patients from taking Stalevo and vice versa.