Off time will disappear with longer acting levodopa formulations. NO

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Fluctuations in Parkinson's Disease (PD) are levodopa (LD)-related phenomenon. The decreasing number of dopaminergic cells within SN (the anatomical and biochemical substrate to converse LD to dopamine) results in loss of initially smooth response to LD after 3-5 years from treatment onset. Remaining cells and other neurons (e.g. serotoninergic) do not have capacity to store (buffer) the dopamine and it is released „without" control. The pharmacodynamic phase of LD activity is also related to hypersensitivity of dopamine receptors. But most of all pharmacokinetic phase with delayed gastric emptying and food protein load change dramatically the LD absorption and ability to cross blood brain barrier. Gastroparesis is the symptom related to pathological process within enteric nervous system which is progressing in PD over time. The novel formulations of extended release LD formulations as well with combination with COMT inhibitor (Stalevo) did not prevent the wearing off phenomenon in clinical trials. Also the newly marketed form (Rytary and IPX203) although result in longer duration of LD beneficial effect they do not prevent totally from offs. Moreover, due to erratic bioavailability they produce more peak-of-dose dyskinesias. The intrajejunal LD (Duodopa) administration improves pharmacokinetics of LD, but in clinical settings we know that patients need sometimes a booster injections as a result of wearing off. The mechanism of fluctuations is probably complex (both at the pharmacokinetic and pharmacodynamic levels, but also related to BMI, gender, ethnicity, genetic form of PD e.g. *PARK2* mutation) and to my opinion total dissapearing of OFF is not possible to achieve.