Continuous dopaminergic stimulation minimizes levodopa-induced motor complications

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SW PADRECC
Prevalence of Motor Fluctuations

- Varies with
  - age of patient
  - duration of disease
  - type of therapy
Effect of Age on Motor Fluctuations

% Dyskinesia at 5 yrs of therapy

Age of Onset

Kumar N et al. (2005) Mov Disorders 20: 342-366
Effect of Disease Duration on Motor Fluctuations

Effect of Therapy on Motor Fluctuations

• Continuous dopamine stimulation (CDS)
  – Physiological
  – Reduces priming
  – Reduces fluctuations once primed
CDS is Physiological

Grace and Bunney, 1984
Dopamine is tonically released

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
Etiology of Fluctuations

- Presynaptic mechanisms
  - Loss of DA buffering capacity
  - Extraneuronal DA synthesis from levodopa
- Postsynaptic
  - Alterations in DA receptors (unlikely)
  - Plasticity
    - Increased PPE in indirect pathway
    - Altered glutamate receptors
Primimg with Postsynaptic Pulsatile Stimulation

Fig. 1. Dyskinesia scores in animals receiving daily apomorphine injections (2 mg/kg, s.c., open circles) versus apomorphine implants (filled squares). After a mean of 8.3 days of daily apomorphine injections, all animals developed dyskinesias (range 6-10 on the Involuntary Movement Scale), whereas none of the implanted animals developed dyskinesias over 6 months of study.

Maybe COMT-I will help.
Fluctuations are Dependent on Levodopa Levels

Figure 2. Changes in visual analog score mood ratings in

Maricle et al. Neurology 1998
Fluctuations improve acutely with CDS

Mouradian et al. (1990)
What's the evidence in clinical practice?


Fig. 1. Dyskinesias in MPTP monkeys. Frequency of dyskinesia in 1-methyl-4-phenyl-1,2,3,6-
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CDS with Duodopa

QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.
CDS with Continuous Apomorphine

Colzi, Turner, and Lees, 1998
Similarities to Kindling