

NEW PARKINSON DRUGS

- - -

HOW THEY ARE DEVELOPED
AND APPROVED

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OBJECTIVES

Provide overview of Federal drug regulation by Food & Drug Administration

Discuss steps in new Parkinson's drug development and testing

Introduce the concept and impact of the placebo effect in clinical trials and medicine

Federal Drug Regulation

- 1906 Food and Drugs Act = accurate labels
- 1938 Federal Food, Drug & Cosmetic Act = established the FDA
- 1962 Kefauver-Harris amendment = drugs must be safe & effective
- 1972 Review of OTC drug ingredients = active drug must be approved
- 1984 Drug Price Competition / Patent Restoration Act = generic drugs
+17yrs patents
- 1994 Federal Dietary Supplement Health & Education Act = direct
advertising to public & hands off non-medical supplements

How are New Drugs Discovered / Developed?

Drug Sources

Traditional / folk medicine

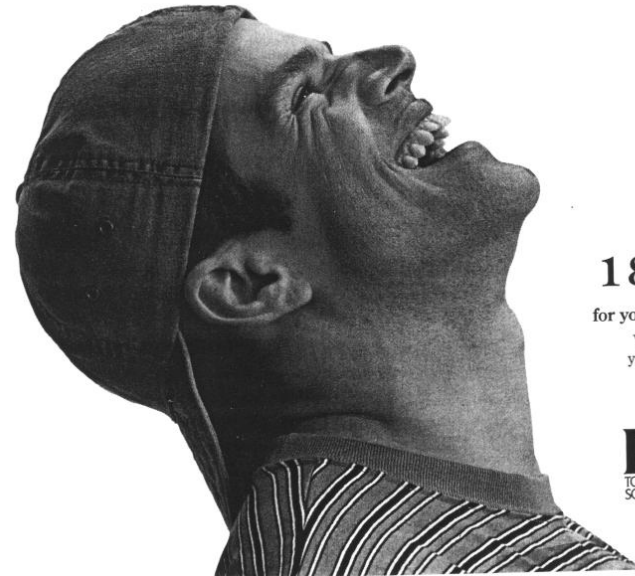
Novel plant & animal materials

Serendipitous discovery of new uses of existing drugs

Screening of new synthetic chemicals \
or biological products

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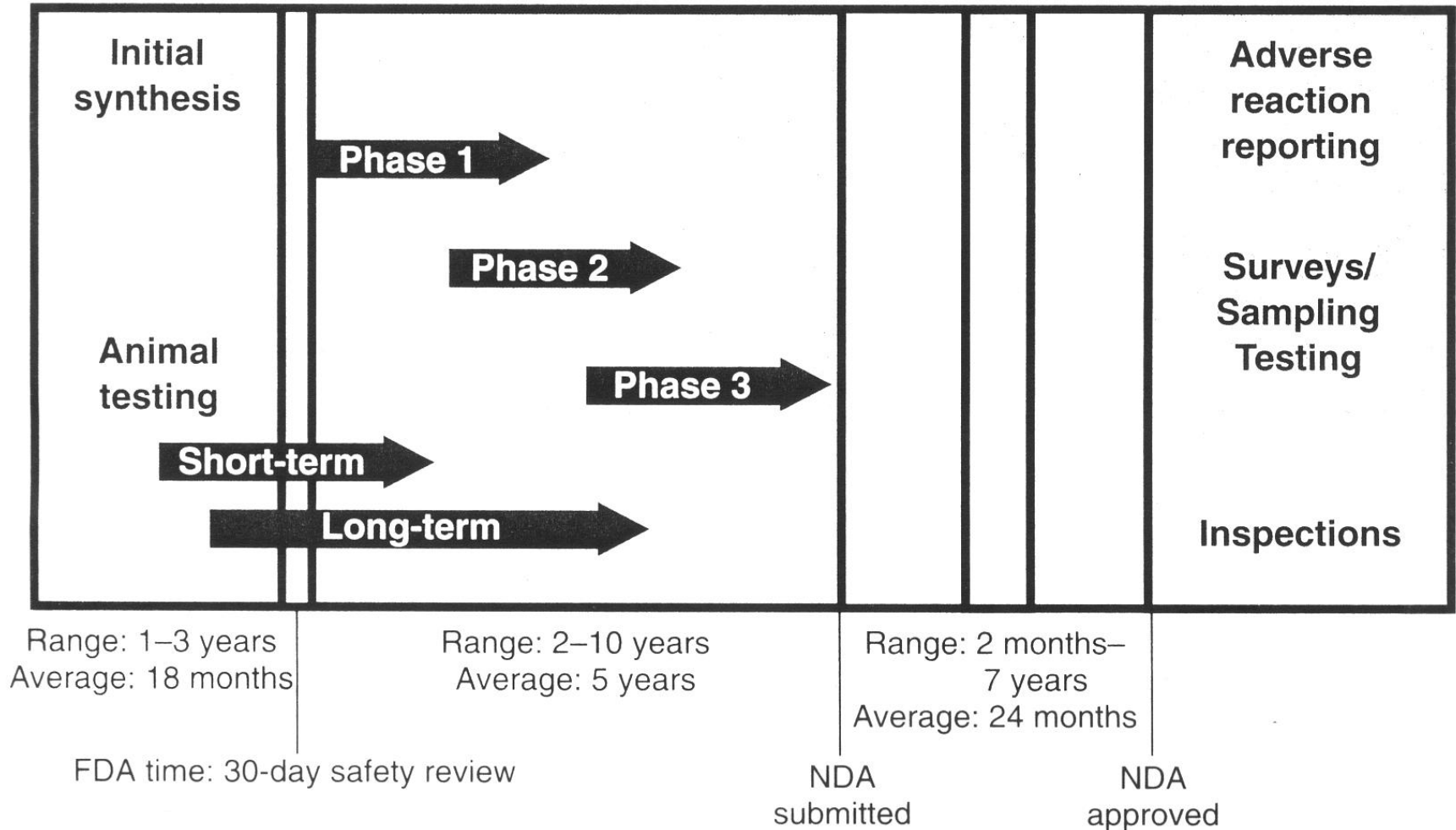
IND - Investigational New Drug

Pre-clinical
research and
development

Clinical research and
development

NDA
review

Post-marketing
surveillance



Phase II Trials

Limited well-controlled disease-related tests

"Proof of Concept" trials - double blind (placebo controlled) is best

Conducted in 100-300 patients with target disorder

Establish therapeutic benefit vs side effect risk

~ 45% of drugs tested pass Phase II

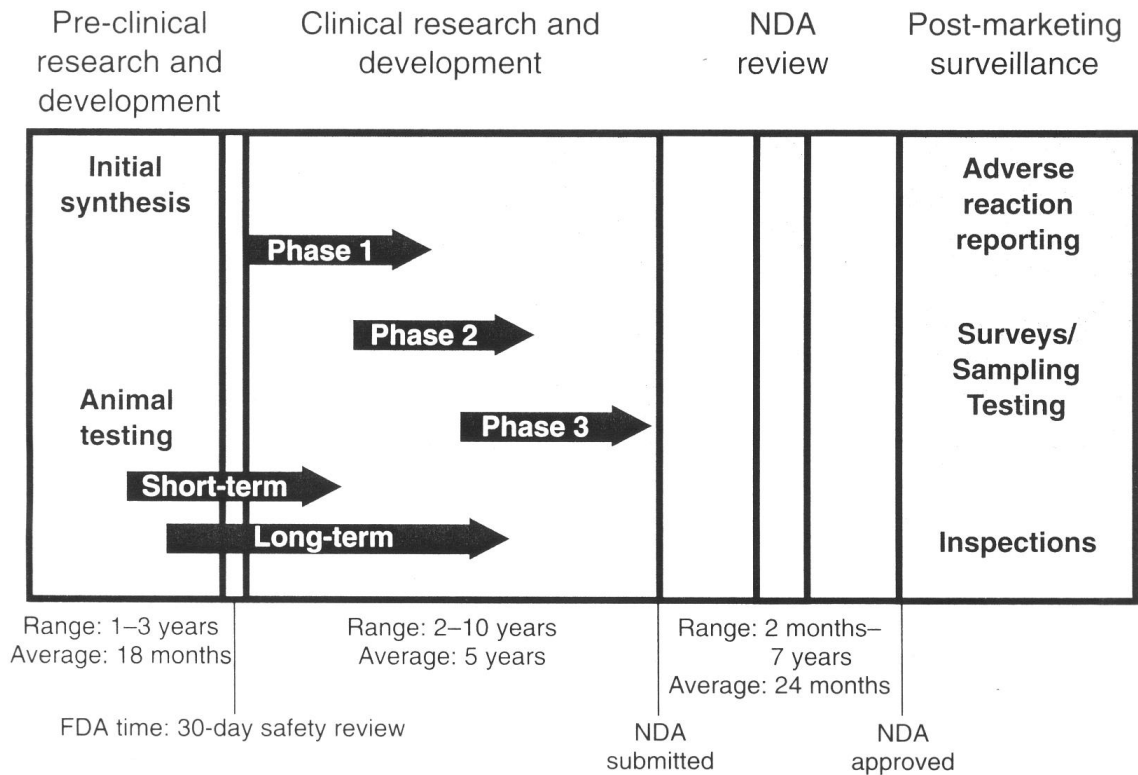
NDA - New Drug Application

- Relevant clinical safety / efficacy data

- Risk / benefit assessment - abuse potential

- Labeling / advertising claims

- Physicians can prescribe for “*off label*” use



- FDA review in 180 days with outside panel

Placebo Effect and Medicine

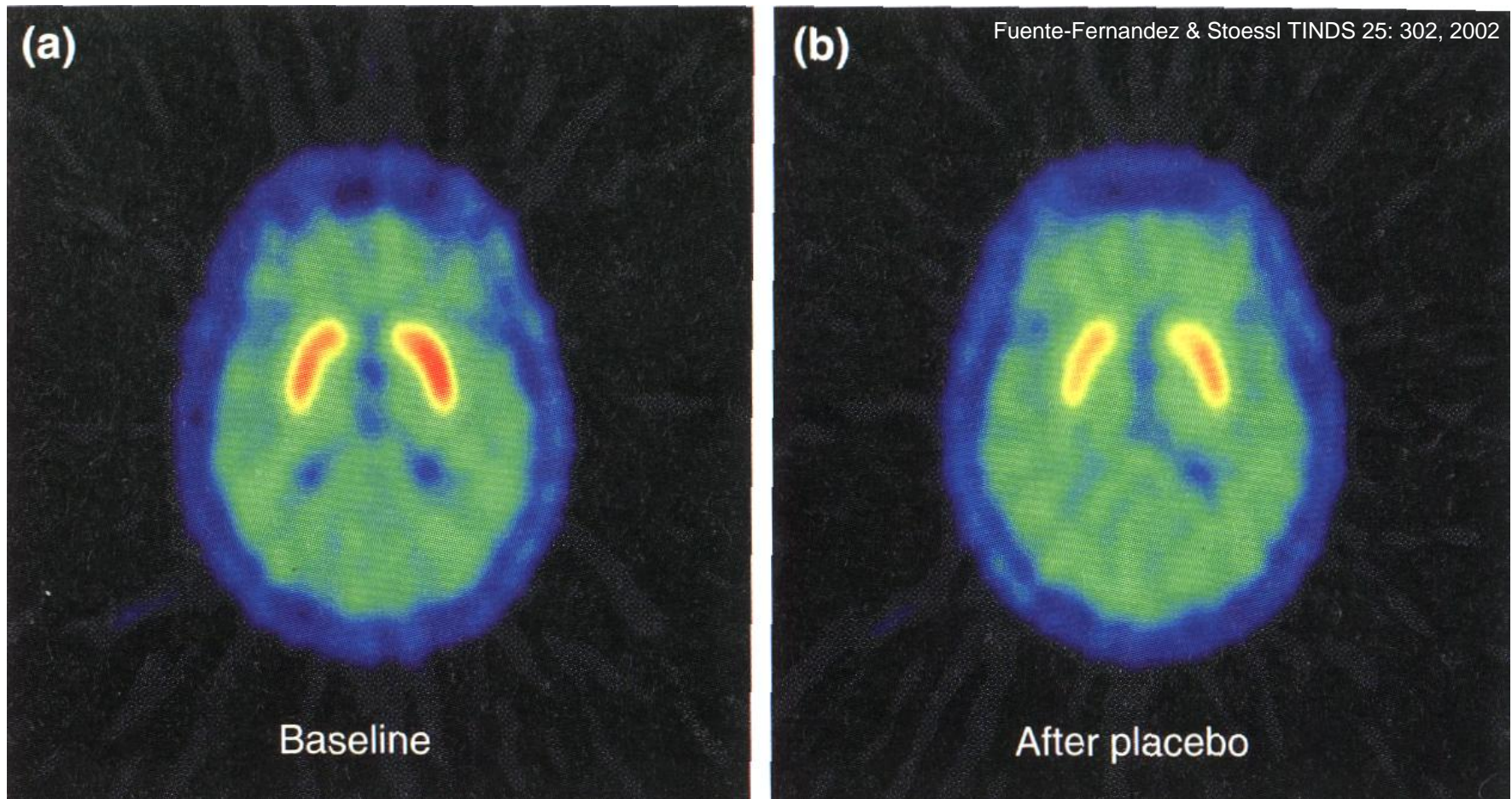
An inactive treatment that produces treatment-like effects

Expectation based psychosomatic actions

Important in double-blind randomized trials

Placebo use in medicine hotly debated

Axial [^{11}C]-raclopride PET scan showing dopamine D2 receptor localization in the striatum of a Parkinson's patient



Untreated binding

Saline / placebo injection

Placebo causes dopamine release that reduces labeling

PHASE II / III CLINICAL TRIAL - Istradefylline for OFF Time

A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease

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ABSTRACT

Background: The safety and efficacy of istradefylline, a selective adenosine A_{2A} receptor antagonist, was evaluated in a 12-week, double-blind study in levodopa-treated Parkinson disease (PD) subjects with motor complications.

Methods: Levodopa-treated PD subjects ($n = 395$) received istradefylline 20 mg/day ($n = 163$), istradefylline 60 mg/day ($n = 155$), or placebo ($n = 77$) at 40 sites. The primary efficacy variable was the change in the percentage of time per day spent in the OFF state. Secondary measurements assessed change in ON time, Unified Parkinson's Disease Rating Scale, and Clinical Global Impression. Safety monitoring included clinical laboratory, electrocardiograms, vital signs, physical/neurologic examinations, and adverse events (AEs).

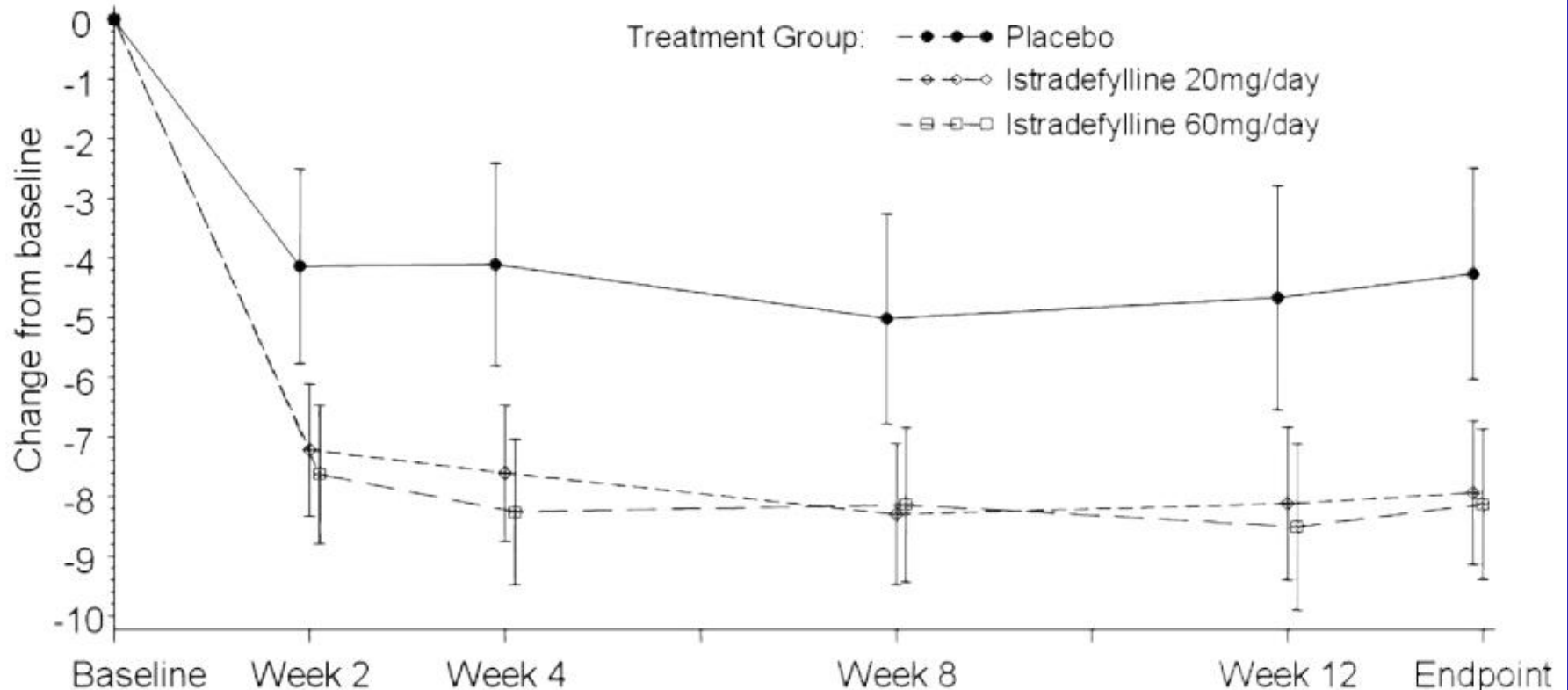
Results: Changes from baseline to endpoint in the percentage OFF time in the active groups compared with placebo were -4.35% (95% CI -8.16 to -0.54 ; $p = 0.026$) for istradefylline 20 mg/day and -4.49% (95% CI -8.35 to -0.62 ; $p = 0.024$) for 60 mg/day; these changes were significant (analysis of covariance). For total hours, istradefylline demonstrated mean differences from placebo of -0.64 hours (95% CI -1.30 to 0.01) for 20 mg/day and -0.77 hours (95% CI -1.44 to -0.11) for 60 mg/day ($p = 0.065$; overall treatment effect). Clinical response occurred by the second week and was maintained throughout the study. Istradefylline was well tolerated. The common AEs were dyskinesia, nausea, dizziness, and hallucinations.

Conclusions: Istradefylline demonstrated a significant reduction in the percentage of awake time per day spent in the OFF state, which resulted in a clinically meaningful reduction in OFF time, without an increase in ON time with troublesome dyskinesia, and was well tolerated as adjunctive treatment to levodopa in Parkinson disease. *Neurology*® 2008;70:2233-2240

PHASE II / III CLINICAL TRIAL - Istradefylline for OFF Time

Figure 2

Change from baseline to endpoint and by study visit in the percentage of awake time per day spent in the OFF state (intent-to-treat population)



OFF Time decreased ~ 8% for both Istradefylline groups,
but ~ 4% for Placebo group

PHASE II / III CLINICAL TRIAL - Istradefylline for OFF Time

Table 1 Baseline demographics and disease characteristics (intent-to-treat population)

	Placebo, n = 77	Istradefylline 20 mg/ day, n = 163	Istradefylline 60 mg/ day, n = 155
Age, mean (SD), y	63.0 (12.05)	65.0 (9.59)	63.5 (10.08)
Male, n (%)	54 (70.1)	104 (63.8)	106 (68.4)
Duration of PD, mean (SD), y	8.69 (5.002), n = 54	9.24 (5.275), n = 98	7.94 (4.017), n = 95
Time since diagnosis, mean (SD), y	3.81 (2.694), n = 40	3.71 (3.830), n = 74	3.27 (3.035), n = 84
Concomitant dopaminergic agent, n (%)	71 (92.2)	149 (91.4)	139 (89.7)
Entacapone, n (%)	27 (35.1)	67 (41.1)	69 (44.5)
Pramipexole, n (%)	36 (46.8)	63 (38.7)	63 (40.6)
Amantadine, n (%)	23 (29.9)	46 (28.2)	41 (26.5)
Ropinirole, n (%)	13 (16.9)	34 (20.9)	36 (23.2)
Selegiline, n (%)	13 (16.9)	25 (15.3)	25 (16.1)
Pergolide, n (%)	13 (16.9)	26 (16.0)	21 (13.5)

These individuals were taking many of the standard dopamine anti-Parkinson's meds

Pharmaceutical Business Review 2-28-2008

Kyowa Hakko: non-approvable letter for Parkinson's treatment

28th February 2008

By Charlotte Mackey

The FDA has issued a non-approvable letter for Kyowa Hakko's new treatment for Parkinson's disease.

The FDA's non-approvable letter is a major setback for the drug to gain approval for Parkinson's disease. However, it may reduce competition.



PARKINSON'S IN THE NEWS

June 3, 2008

Kyowa Pharmaceutical Suspends Development of Istradefylline in North America

Kyowa Pharmaceutical, Inc., has issued the following open letter to the Parkinson's community regarding its June 3 announcement that it will suspend development of istradefylline in North America:

On behalf of Kyowa Pharmaceutical Inc., I would like to thank you for your interest in the istradefylline (KW-6002) program, and I want to inform you of a change in the clinical development plan.

On February 25, 2008, Kyowa received a "Not Approvable" letter from the U.S. Food and Drug Administration (FDA) for istradefylline and subsequently had discussions with the FDA about options for further development. After reviewing these options, Kyowa has decided to suspend development of istradefylline in North America at this time. This decision was not related to any safety issues concerning istradefylline.

WHY DO PROMISING PARKINSON DRUGS FAIL?

- Inappropriate dose was studied
- Drug did not penetrate the brain very well
- Measures of disease were insensitive
- Treatment started too late in the course of disease
- Preclinical models were not good predictors of clinical success

Novel neurotrophic factor CDNF protects and rescues midbrain dopamine neurons *in vivo*

Päivi Lindholm¹, Merja H. Voutilainen², Juha Laurén¹†, Johan Peränen¹, Veli-Matti Leppänen¹,
Jaan-Olle Andressoo¹, Maria Lindahl¹, Sanna Janhunen²†, Nisse Kalkkinen¹, Tõnis Timmusk^{1,3}, Raimo K. Tuominen²
& Mart Saarma¹

Toxin alone

CDNF

GDNF

