Istradefylline's mechanism of action provides a unique and significant advantage in Parkinson disease treatment

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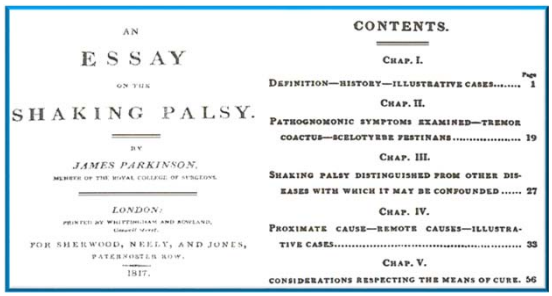
James Parkinson M.D. (1817)



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

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FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

CONTENTS.

…Until we are better informed respecting the nature of the disease, the employment of internal medicines is scarcely warrantable unless analogy should point out some remedy, the trial of which rational hope might authorize …

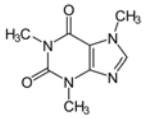
Overview

- Istradefylline, a CNS-penetrant antagonist of the adenosine A_{2a} receptor subtype, received FDA approval on August 29, 2019 for the treatment of PD patients experiencing “off” episodes
- The US release of istradefylline was preceded by the approval of the drug as a PD treatment in Japan
- Beyond its marketed indication and published randomized clinical trial data, several open-label studies suggest other uses for istradefylline in PD

Overview

- In addition to istradefylline, 4 other adenosine A_{2a} -selective receptor antagonists have undergone clinical testing, including ST-1535 and vipadenant (also known as V20006 and BIIB 014)
- Two compounds, preladenant and tozadenant, have undergone Phase 2 or 3 clinical trials in PD
- Considerable pre-clinical research was conducted with adenosine A2a antagonism before its translation into a therapeutic strategy for PD

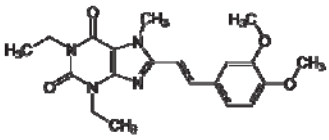
Adenosine receptor antagonists



Caffeine (Starbucks)

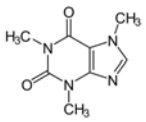
non-selective

Adenosine receptor antagonists



Istradefylline (KW-6002)

selective



Caffeine (Starbucks)

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Adenosine pharmacology and Parkinson disease

- Among the several classes of adenosine receptors, the A_{2a} receptor has limited distribution in the human brain – almost exclusively in striatum, globus pallidus externa, nucleus accumbens, and olfactory tubercle

  Mori A. *Int Rev Neurobiol* 2014; 119: 87-116

- With progression of Parkinson disease (and contrary to changes in striatal dopaminergic neurotransmission), the density of adenosine A_{2a} receptors increases

  Mishina M, et al, *Int Rev Neurobiol* 2014; 119: 51-69

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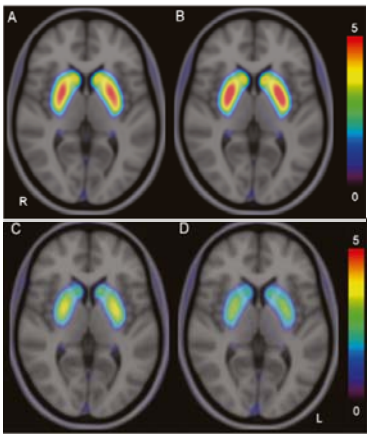
Positron-emission tomography imaging of adenosine A_{2A} receptors in basal ganglia

Healthy control



Parkinson disease (no istradefylline)

Parkinson disease (istradefylline 20 mg)

Parkinson disease (istradefylline 40 mg)

Ishibashi K, et al. Occupancy of adenosine A_{2A} receptors by istradefylline in patients with Parkinson's disease using ^{11}C-preladenant PET. *Neuropharmacology* 2018; 143: 106-112

Adenosine pharmacology and Parkinson disease

- **Istradefylline (KW-6002) is a highly selective inhibitor of the adenosine A_{2a} receptor, with a K_i of 12 nmol/L in human tissues**
  Saki M, et al, *Naunyn Schmiedebergs Arch Pharmacol* 2013; 386: 963-972
- **Beyond its high specificity for the adenosine A_{2a} receptor, istradefylline has no recognized affinities for any other neurochemical systems**
- The clearance half-life of istradefylline is ≈83 hours
- Istradefylline (Nourianz®) is dosed once-daily; most clinical experience to date hasn't differentiated between the anti-Parkinsonian effects of the available 20 mg and 40 mg daily doses
- Trials of istradefylline and preladenant as monotherapies did not detect an anti-Parkinsonian effect

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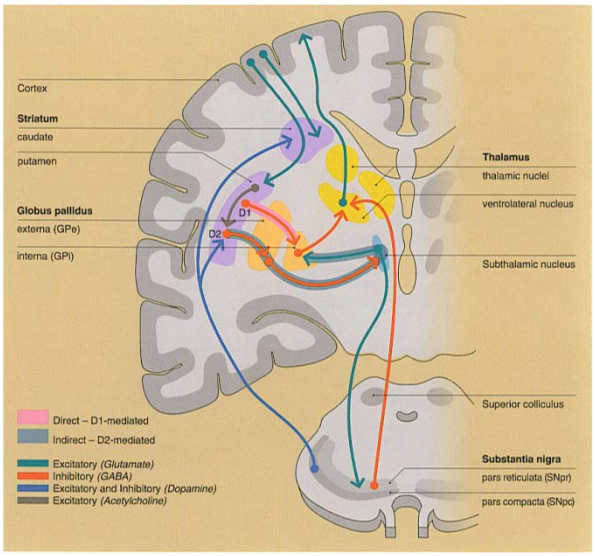
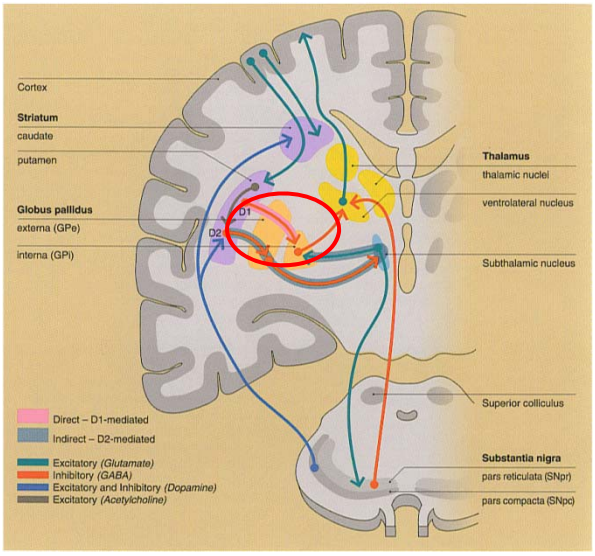
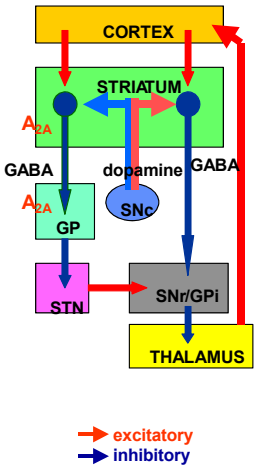




Rationale for adenosine A2a antagonism

Restoration of balance in a GABAergic output pathway from the striatum

Normal



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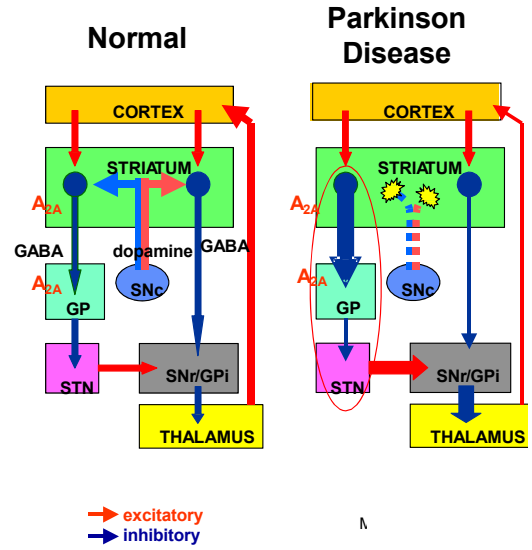

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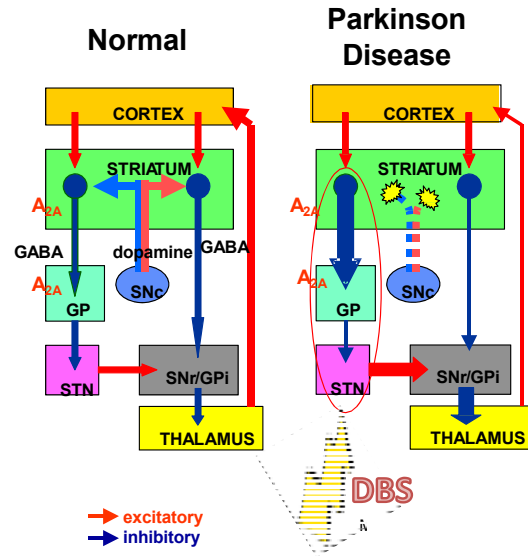

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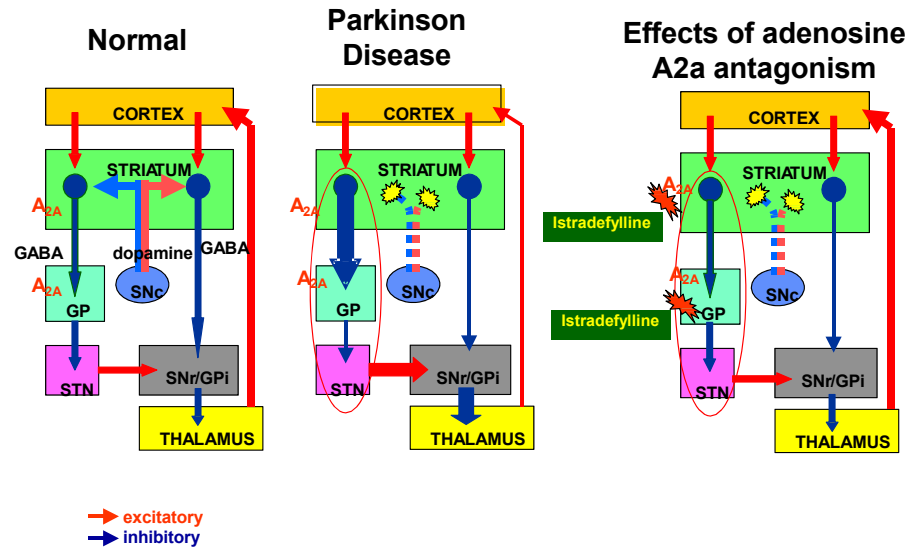


Overview of the 4 clinical trials leading to FDA approval of istradefylline

- The FDA review chose 4 of the 8 12-week randomized, multi-center, double-blind, placebo-controlled clinical trials
- Two studies were conducted in North America:
  - Study 1 (LeWitt et al, *Ann Neurol* 2008: 63: 295-301)
  - Study 2 (Stacy et al, *Neurology* 2008; 70: 2233-2240)

  and two in Japan:
  - Study 3 (Mizuno et al, *Mov Disord* 2010; 25: 1437-1443)
  - Study 4 (Mizuno et al, *Mov Disord* 2013; 28: 1138-1141)
- For enrolled patients, mean PD duration: 7.7 - 9.9 years
- Enrolled patients needed to experience at least 2 hours/day of "off" time; mean duration was 6.3 - 6.6 hours/day

Mean levodopa intake (mg/day) and concomitant medications (% of enrollees receiving each drug)

	Study 1 (n=195)	Study 2 (n=225)	Study 3 (n=357)	Study 4 (n=366)
Daily levodopa dose (mg/day)	785.1	775.1	416.2	429.1
Dopaminergic agonist (%)	76.9	76.0	92.4	86.9
COMT inhibitor (%)	41.0	44.9	14.8	50.0
Selegiline (%)	16.9	11.6	52.1	50.3
Amantadine (%)	28.2	31.1	35.6	36.6
Anticholinergic (%)	4.6	9.3	17.9	13.7

Primary end-point: change in "off" time from baseline to Week 12 (home diary data)

	Study 1	Study 2	Study 3	Study 4
Placebo (n)	-0.60 hours 65	-0.85 hours 113	-0.66 hours 118	-0.23 hours 123
Istradefylline 20mg/day (n)	---------- 126	-1.58 hours 112	-1.33 hours 115	- -0.99 hours 120
Istradefylline 40mg/day (n)	-1.76 hours 126	----------	-1.58 hours 124	-0.97 hours 123
Net difference 20mg 40mg	---------- -1.16 hours	-0.73 hours ----------	-0.67 hours -0.92 hours	-0.76 hours -0.74 hours
p value 20 mg 40 mg	---------- 0.05	0.025 ----------	0.028 0.002	0.006 0.008

Other pertinent clinical experience with adenosine A_{2a} antagonists

Preladenant

- A 12-week randomized placebo-controlled Phase 2 clinical trial with 666 subjects showed improvement of "off" time (-1.7 hours) versus baseline, as compared to placebo (0.5 hours)
  Hauser RA, et al. *Lancet Neurol* 2011; 10:221-229)
- However, two subsequent Phase 3 studies failed to show efficacy
  Hattori N, et al. *Parkinsonism Relat Disord* 2016; 32:273-479
  Stocchi F, et al. *Neurology* 2017; 88:2198-2206

Tozadenant

- A 12-week randomized placebo-controlled trial with 420 subjects showed improvement of "off" time up to 1.9 hours versus baseline, as compared to placebo (0.76 hours)
  Hauser RA, et al. *Lancet Neurol* 2014; 13:767-776

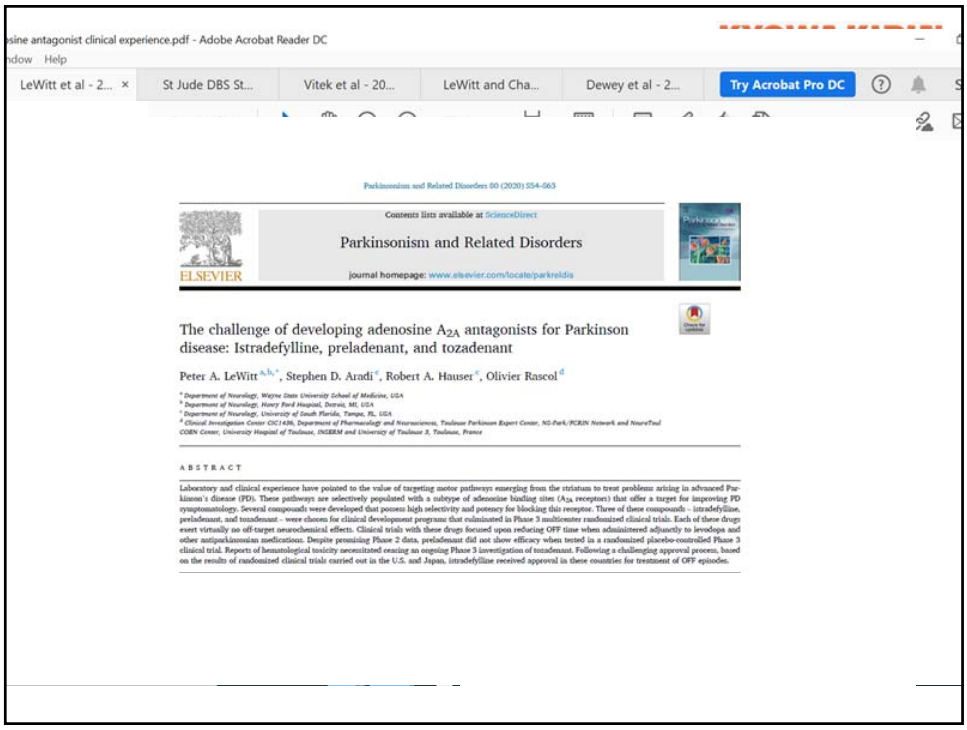
How to explain the lack of efficacy shown by istradefylline in clinical trials?

Clinical trials with adjunctive istradefylline and negative results

- **Pourcher E, et al. *Parkinsonism Relat Disord* 2012; 18:178-184**
  Randomized controlled 12-week clinical trial testing 10, 20, and 40 mg per day versus placebo (n = 584 subjects)
- **6002-EU-007 (unpublished clinical trial)**
  Randomized controlled 12-week clinical trial testing 10, 20, and 40 mg per day versus placebo (n = 311 subjects)
- **6002-014 (unpublished clinical trial)**
  Randomized controlled 12-week clinical trial testing 20 and 40 mg per day versus placebo (n = 609 subjects)

Key considerations regarding istradefylline efficacy at improving "off" time

- Even through two of the clinical trials (Study 1 and 2) were originally classified as Phase 2b, their size, scope, and conduct qualified them to serve as pivotal studies for FDA approval (typically, at least two 12-week Phase 3 studies)
- The small improvements of "off" time need to be considered in the context of the polypharmacy most of the study patients were receiving
- The novel mechanism of action offered by istradefylline is similar to those of other non-dopaminergic "downstream" (post-striatal) PD treatments, deep brain stimulation and amantadine
- Istradefylline by itself has not been studied in the manner of study given to other levodopa adjunctive treatments



Hauser RA, et al. *JAMA Neurol* 2015; 72: 1491-1500

Original Investigation | CLINICAL TRIAL

Preladenant as an Adjunctive Therapy With Levodopa in Parkinson Disease

Two Randomized Clinical Trials and Lessons Learned

Robert A. Hauser, MD; Fabrizio Stocchi, MD; Olivier Rascol, MD; Susan B. Huyck, DrPH; Rachel Capece, BS; Tony W. Ho, MD; Peter Skiar, MD; Christopher Lines, PhD; David Michelson, MD; David Hewitt, MD

IMPORTANCE Preladenant is an adenosine 2A receptor antagonist that reduced "off" time in a placebo-controlled phase 2b trial in patients with Parkinson disease (PD). We sought to confirm its efficacy in phase 3 trials.

OBJECTIVE To evaluate preladenant as an adjunct to levodopa in patients with PD and motor fluctuations.

DESIGN, SETTING, AND PARTICIPANTS Two 12-week, phase 3, randomized, placebo-controlled, double-blind trials performed from July 15, 2010, to April 16, 2013. The setting included neurology clinics, clinical research centers, and hospitals in the Americas, the European Union, Eastern Europe, India, and South Africa. Participants included patients with moderate to severe PD taking levodopa who were experiencing motor fluctuations.

INTERVENTIONS In trial 1, a total of 778 eligible patients were randomized to the addition of preladenant (2 mg, 5 mg, or 10 mg twice daily), placebo, or rasagiline mesylate (1 mg/d) in a 1:1:1:1:1 ratio. In trial 2, a total of 476 eligible patients were randomized to the addition of preladenant (2 mg or 5 mg twice daily) or placebo in a 1:1:1 ratio.

MAIN OUTCOMES AND MEASURES The primary outcome measure was change in off time from baseline to week 12.

RESULTS In trial 1, neither preladenant nor rasagiline was superior to placebo in reducing off time from baseline to week 12. The differences vs placebo were −0.10 hour (95% CI, −0.69 to 0.46 hour) for preladenant 2 mg twice daily, −0.20 hour (95% CI, −0.75 to 0.41 hour) for preladenant 5 mg twice daily, +0.00 hour (95% CI, −0.62 to 0.53 hour) for preladenant 10 mg twice daily, and −0.30 hour (95% CI, −0.90 to 0.26 hour) for rasagiline mesylate 1 mg/d. In trial 2, preladenant was not superior to placebo in reducing off time from baseline to week 12. The differences vs placebo were −0.20 hour (95% CI, −0.72 to 0.35 hour) for preladenant 2 mg twice daily and −0.30 hour (95% CI, −0.86 to 0.21 hour) for preladenant 5 mg twice daily. Preladenant was well tolerated, with the most common adverse event that showed an increase over placebo in both trials being constipation (6%-8% for preladenant vs 1%-3% for

Supplemental content at jamaneurology.com

Author Affiliations: Parkinson's Disease and Movement Disorders Center, University of South Florida, National Parkinson Foundation Center of Excellence, Tampa (Hauser); Institute of Neurology,

Hauser RA, et al. *JAMA Neurol* 2015; 72: 1491-1500

Some Regions May Have Large Placebo Effects

In our trial 1, we observed a large placebo effect in Turkey, India, and Latin America. In a phase 3 preladenant monotherapy trial,[27] a large placebo effect was observed in Latin America, India, Turkey, and Eastern Europe. The reasons for this are not clear. Careful choice of sites and regions may help reduce placebo effects. Treatment stratification by region should be considered for smaller trials to assure balanced assignment of arms. Specialized training to mitigate placebo response is recommended for all sites.

More Patients Is Not Always Better

In our trial 1, post hoc analysis found that if only the first 50% of enrolled patients were considered, both preladenant and rasagiline mesylate significantly reduced off time compared with placebo. Similar observations were made for paroxetine trials.[28] We hypothesize that sites enroll their most ideal patients first and then may "scrape the bottom of the barrel" to find additional patients to enroll. These patients may exhibit a larger placebo effect and may be less ideal in other ways, such as having less distinct motor fluctuations or more difficulty self-identifying their PD motor states. To mitigate this problem, one should avoid having to enroll more patients than are necessary (do not overpower the study and do not unnecessarily include dosage arms thought to be ineffective), consider more sites enrolling fewer patients if more competent sites are available, and avoid pressuring sites to enroll more patients or to enroll patients at a quicker pace.

Pressuring Sites to Increase Enrollment May Have Undesirable Consequences

Pressuring sites to enroll more patients or to enroll patients at a quicker pace may cause them to loosen their standards and enroll less ideal patients (as described above). In our trial 1, the second 50% of participants were enrolled in half the time it took to enroll the first 50%, suggesting that there may have been increased pressure to enroll during the second half of the study.

Avoid Unnecessary Exclusions

Unnecessary exclusions make enrollment more difficult, reduce the pool of eligible patients, and may increase the pressure on sites to enroll less ideal patients. This problem was not specifically identified in our studies but is commonly seen in clinical trials.

Active Control Arms Have Pros and Cons

Inclusion of an active control arm can be useful to confirm a trial's ability to detect efficacy using a medication known to be effective. In our trial 1, that the active control rasagiline did not exhibit efficacy compared with placebo suggested that there were problems with the design or conduct of the trial. This can be useful information to help interpret negative results regarding the active medication. On the other hand, because rasagiline was used as an active control, monoamine oxidase type B inhibitors were exclusionary, and this may have reduced the potential pool of eligible patients and placed an increased enrollment burden on the sites, leading to enrollment of less than ideal participants.

Understand Methodological Weaknesses and Institute Countermeasures Beforehand

In contemporary PD fluctuator trials, there are several responsibilities that are granted to the investigator and the patient such that trial data are dependent on the rigor with which the investigator and patient fulfill these responsibilities. First, the investigator is tasked with enrolling patients with a diagnosis of PD. This item could be strengthened by requiring the investigator or designate to complete a diagnosis criteria checklist that could be reviewed centrally. Second, eligible patients are required to have motor fluctuations, but there are often no clear criteria set. We suggest that UPDRS motor scores should be obtained in the clinic in the patient's usual on and off states, with a change criterion to be met to confirm the presence of motor fluctuations. Videotaped central ratings of on and off UPDRS motor scores would be even more rigorous but are more costly and time-consuming. Third, concordance diary testing to evaluate whether the patient understands the PD diary terminology and can self-identify his or her PD motor states is critically important. Unfortunately, this procedure is often conducted in an informal manner, with ongoing discussion between the rater and the patient. Strengthening this procedure by emphasizing that it is a test and that patient training should be completed before formal concordance testing is undertaken, with no discussion between the rater and patient regarding motor states during testing, should be emphasized. Fourth, receiving reliable data is dependent on the patient completely and accurately completing the diary in a timely fashion. A telephone call to the patient the day before the diary is completed to remind him or her to complete the diary and to review good practice completion instructions may be helpful. Sites should also exercise discretion and not enroll patients who are likely to be poorly compliant in diary completion. Electronic diaries may be helpful to remind patients to complete entries on time and limit entries to 1 per period.

Recommendations for avoiding ambiguity in PD clinical trials

adapted from Hauser RA, et al. *JAMA Neurol* 2015; 72: 1491-1500

- Some investigators (and some regions of the world) are associated with large placebo effect
- More patients enrolled is not always better for the study
- Pressuring enrollment may have undesirable consequences
- Avoid unnecessary exclusion for study enrollment
- Active control (treatment) arms for a study have pros and cons
- Understand methodological weaknesses and institute counter-measures proactively

Final considerations

In reviewing outcomes of clinical trials, meta-analysis or selectivity in choice of reviewed studies may obscure pharmacological and clinical “truths”

The metric of evaluating “off” time in a placebo-controlled trial with multiple anti-Parkinsonian medications in use is challenging (and has potential artifacts)

Responder-rate analysis was not carried out