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Debating Current Controversies and Discussing Recent Advances

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Istradefylline's Non-Dopaminergic Mechanism of Action Provides a Unique and Significant Advantage in PD Treatment?

Yay!

Nay!

Peter LeWitt MD
Henry Ford Hospital
Detroit

Michael Schwarzschild, MD PhD
Massachusetts General Hospital
Boston

Battle of Ideas!
January 23, 2021

Parkinson Study Group (PSG)

Investigators, 1987

Peter LeWitt, MD

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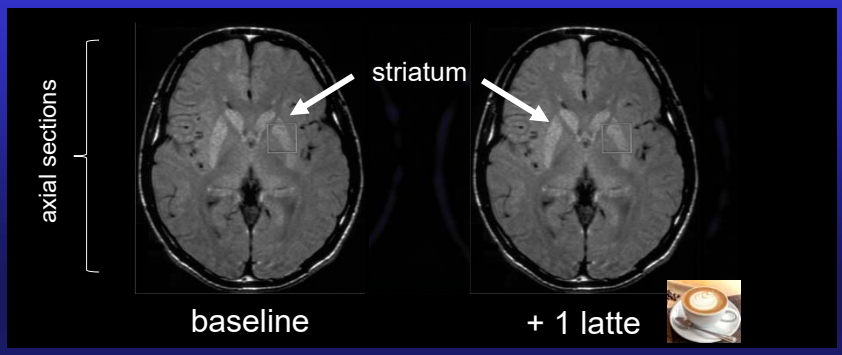
Quiz!: Brain PET/SPECT imaging of **? target** -/+ **? drug**



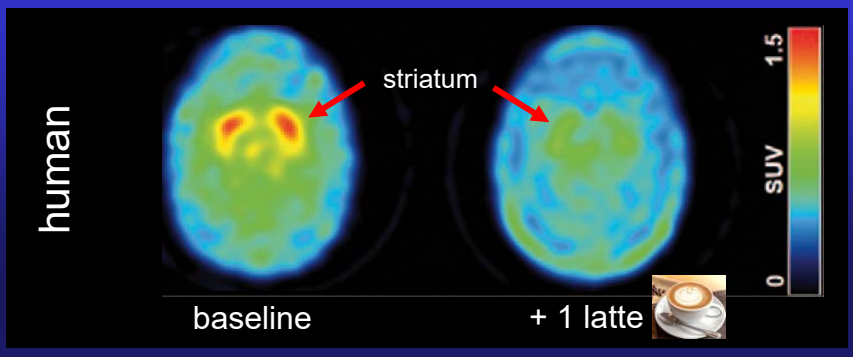
Tavares *et al.* (2015) M. Morelli et al. (eds.) The Adenosinergic System, *Current Topics in Neurotoxicity* 10:207-232.

a) DaT (Dopamine Transporter) ? .... + cocaine ?

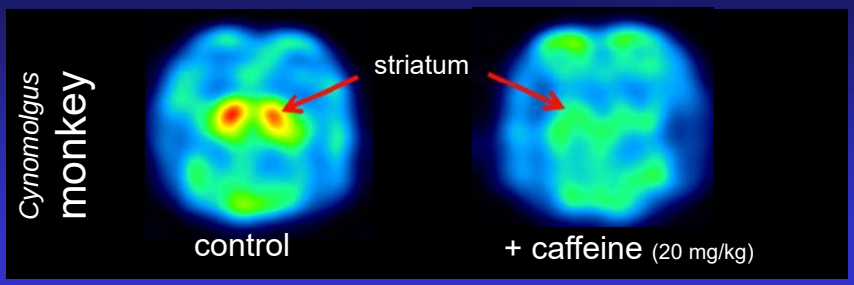
b) VMAT2 (Vesicular Monoamine Transporter 2) ? .... + tetrabenazine ?

c) $A_{2A}R$ (Adenosine 2A Receptor) ? .... + caffeine ?

Brain SPECT of **adenosine A_{2A} receptors** with [^{123}I]MNI-420

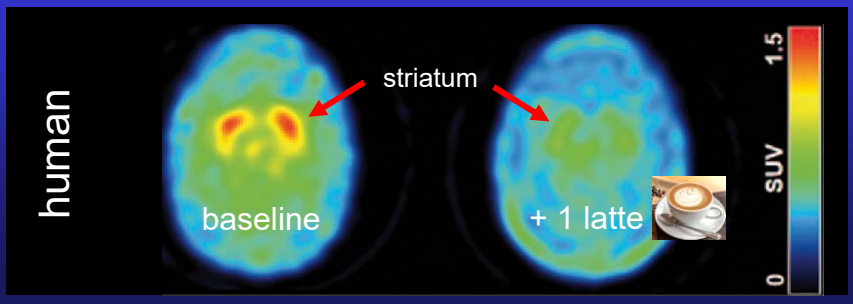


Tavares *et al.* (2015) M. Morelli et al. (eds.) The Adenosinergic System, *Current Topics in Neurotoxicity* 10:207-232; D. Russell, personal communication.



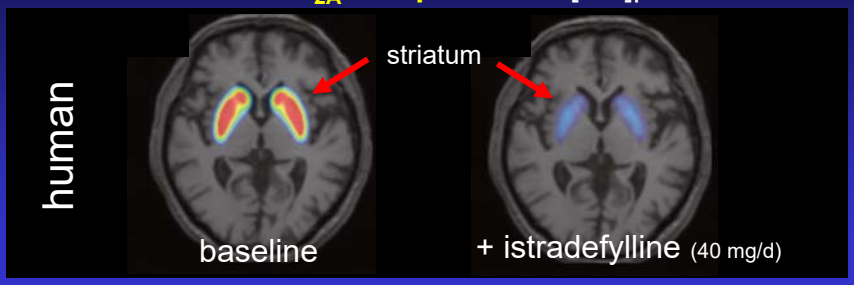
Tavares *et al.* (2013) *Nuclear Med. Biol.* 40:403-9.

Brain SPECT of A_{2A} receptors with [^{123}I]MNI-420



Tavares *et al.* (2015) M. Morelli et al. (eds.) The Adenosinergic System, *Current Topics in Neurotoxicity* 10:207-232.

Brain PET of A_{2A} receptors with [^{11}C]preladenant



Adapted from Ishibashi *et al.* (2020) *Mov. Dis.* Nov-16-2020 (online).

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Caffeine's Caveats (*vs* istra.)

- faster PK
- ? greater tolerance
- ? off-target (non-A_{2A}) effects
- ? less clinical support

Nay!

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OK, by class

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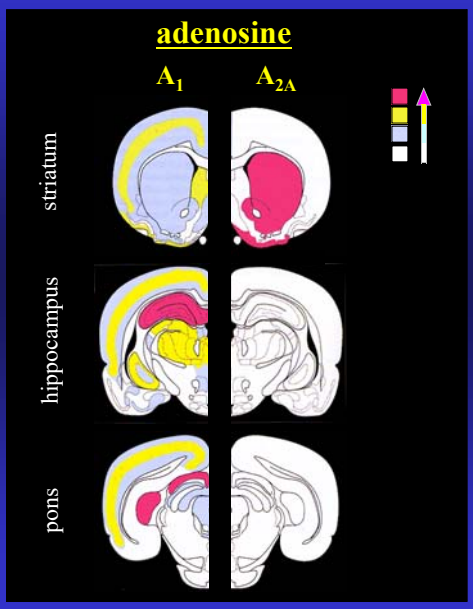
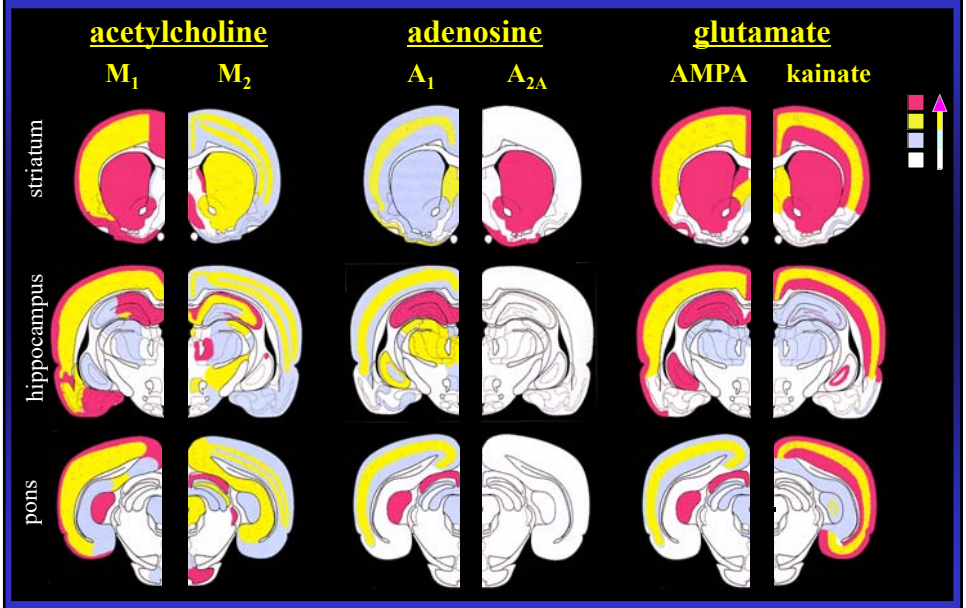
Brain distribution of adenosine receptors



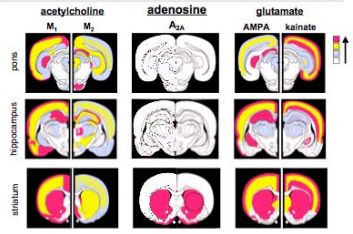
adapted from M Tohyama & K Takatsuji (1998)

Brain distribution of non-DA receptors targeted in PD



adapted from M Tohyama & K Takatsuji (1998)

(a) ***Regional*** → *low side effect potential*

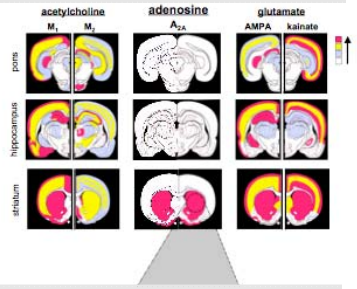


Taking advantage of the discrete localization of CNS A_{2A} receptors

(b) ***Cellular*** → *antiparkinsonian action*

(adapted from) Schwarzschild, Fuxe, Agnati, Chen & Morelli (2006) *TRENDS in Neurosciences*

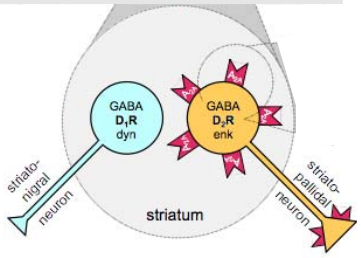
(a) ***Regional*** → *low side effect potential*



Taking advantage of the discrete localization of CNS A_{2A} receptors

(b) ***Cellular*** → *antiparkinsonian action*

(c) ***Molecular*** → *? Leveraged benefits*



(adapted from) Schwarzschild, Fuxe, Agnati, Chen & Morelli (2006) *TRENDS in Neurosciences*

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Stats & Regulatory

Istradefylline's Non-Dopaminergic Mechanism of Action Provides a Unique and Significant Advantage in PD Treatment?

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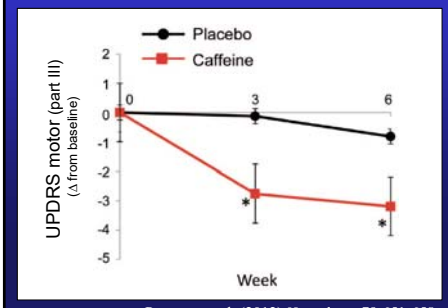
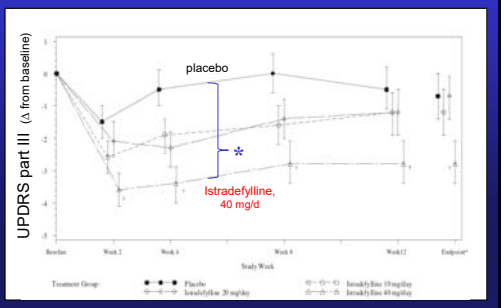
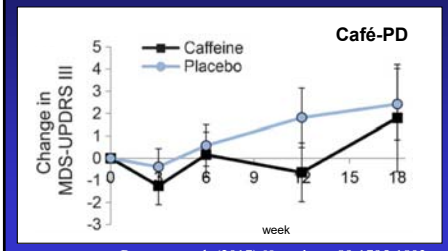
Adenosine antagonists' antiparkinsonian efficacy?



Postuma et al. (2012) *Neurology*. 79:651-658.



Pourcher et al. (2012) *Parkinsonism Relat Disord* 18:178-84.



Postuma et al. (2017) *Neurology*. 89:1795-1803.

FDA label: NOURIANZ [istradefylline] is an adenosine receptor antagonist indicated as adjunctive treatment to levodopa/carbidopa in adult patients with PD experiencing "off" episodes. [@ 20 mg qd, 40 mg qd]

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Significant antiparkinsonian benefit beyond motor symptoms?!

K. Xu et al. / Pharmacology & Therapeutics 105 (2005) 267–310

A_{2A} antagonists in PD: Potential benefits and caveats

A. Motor system effects

✔ **symptomatic motor improvement** [mild benefit thus far]

? **attenuated dyskinesias** [*expression* effect in patients appears variable; *preventive* effect based on unsubstantiated animal models]

? **neuroprotection** [possible non-causal epidemiological link, the link for ↓risk ≠ a link for ↓ progression, unsubstantiated animal models of PD]

B. Non-motor CNS actions

? **psychosis** [not a problem in initial trials despite advanced patients; uncertain effect in preclinical PPI model]

? **antidepressant action** [uncertain validity of rodent depression models, human trial data not reported]

? **arousal** / ? **insomnia** [← ? Cognitive enhancement]

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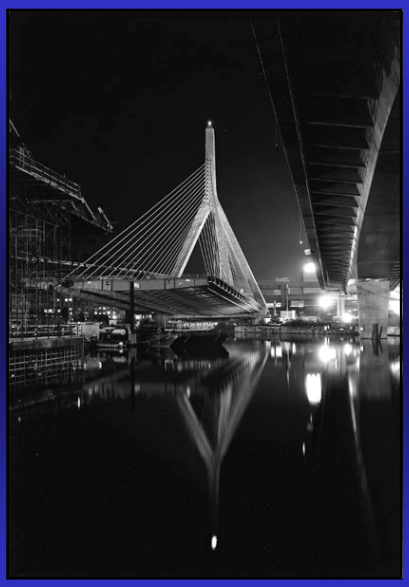
caffeine

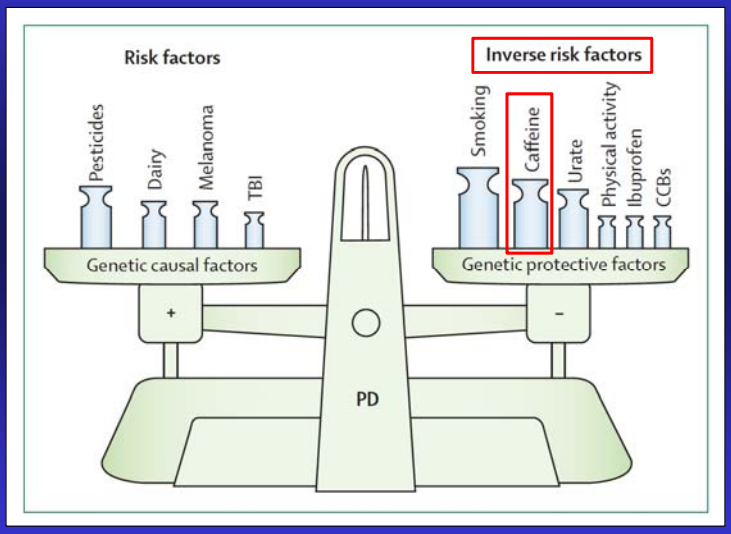
(trimethyl-xanthine)

(trimethyl-dioxo-purine)

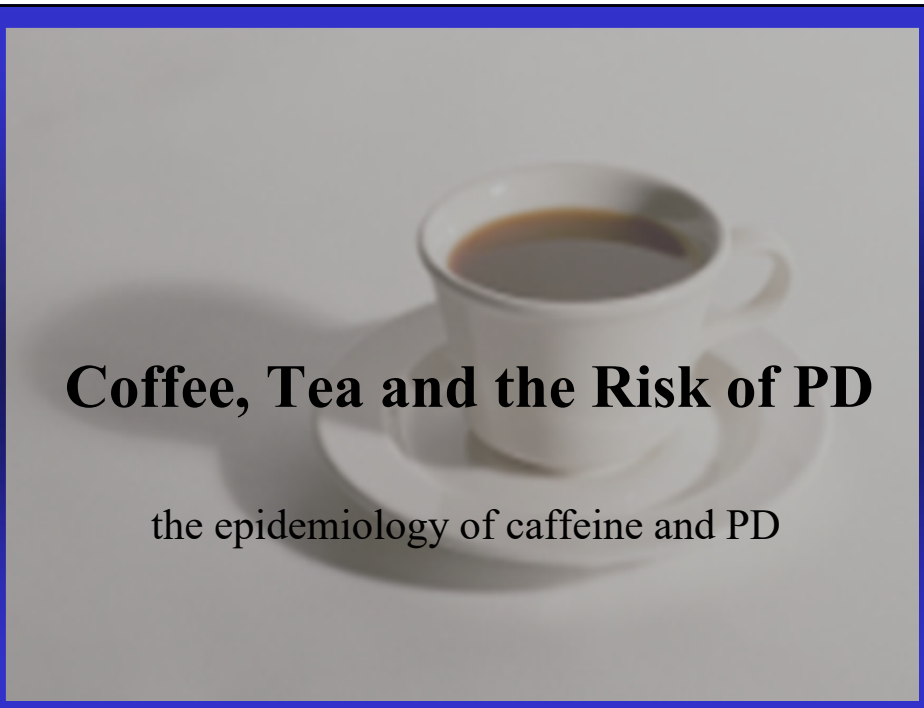


Don Eyles *November 2000*

Balance of environmental and genetic factors linked to PD occurrence



Ascherio A & Schwarzschild MA. *Lancet Neurology*. Nov. 2016. 15:1257-72.



Coffee, Tea and the Risk of PD

the epidemiology of caffeine and PD

ORIGINAL CONTRIBUTION

Association of Coffee and Caffeine Intake With the Risk of Parkinson Disease

G. Webster Ross, MD
Robert D. Abbott, PhD
Helen Petrovitch, MD
David M. Morens, MD
Andrew Grandinetti, PhD
Ko-Hui Tung, MS
Caroline M. Tanner, MD, PhD
Kamal H. Masaki, MD
Patricia L. Blanchette, MD, MPH
J. David Curb, MD, MPH
Jordan S. Popper, MD
Lon R. White, MD, MPH

Context The projected expansion in the next several decades of the elderly population at highest risk for Parkinson disease (PD) makes identification of factors that promote or prevent the disease an important goal.

Objective To explore the association of coffee and dietary caffeine intake with risk of PD.

Design, Setting, and Participants Data were analyzed from 30 years of follow-up of 8004 Japanese-American men (aged 45-68 years) enrolled in the prospective longitudinal Honolulu Heart Program between 1965 and 1968.

Main Outcome Measure Incident PD, by amount of coffee intake (measured at study enrollment and 6-year follow-up) and by total dietary caffeine intake (measured at enrollment).

Results During follow-up, 102 men were identified as having PD. Age-adjusted incidence of PD declined consistently with increased amounts of coffee intake, from 10.4 per 10 000 person-years in men who drank no coffee to 1.9 per 10 000 person-years in men who drank at least 28 oz/d ($P<.001$ for trend). Similar relationships were observed with total caffeine intake ($P<.001$ for trend) and caffeine from noncoffee sources

JAMA. 2000;283:2674-2679 www.jama.com

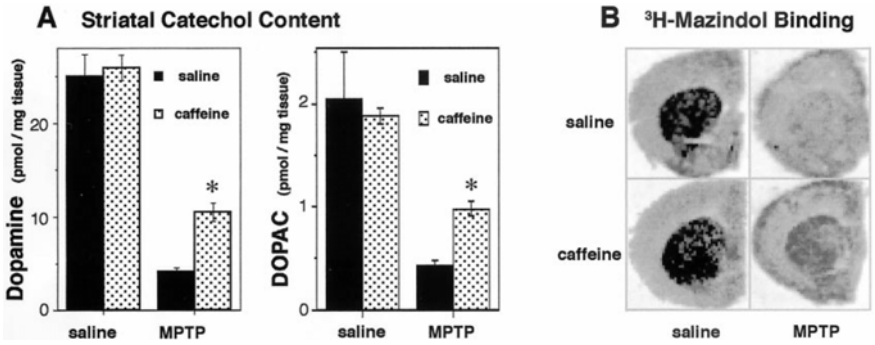
Prospective Study of Caffeine Consumption and Risk of Parkinson's Disease in Men and Women

Alberto Ascherio, MD, DrPH,[1,2] Shumin M. Zhang, MD, ScD,[1,3] Miguel A. Hernán, MD, DrPH,[2] Ichiro Kawachi, MD, PhD,[3,4] Graham A. Colditz, MD, DrPH,[2,3] Frank E. Speizer, MD,[3,5] and Walter C. Willett, MD, DrPH[1–3]

Results of case-control studies and of a prospective investigation in men suggest that consumption of coffee could protect against the risk of Parkinson's disease, but the active constituent is not clear. To address the hypothesis that caffeine is protective against Parkinson's disease, we examined the relationship of coffee and caffeine consumption to the risk of this disease among participants in two ongoing cohorts, the Health Professionals' Follow-Up Study (HPFS) and the Nurses' Health Study (NHS). The study population comprised 47,351 men and 88,565 women who were free of Parkinson's disease, stroke, or cancer at baseline. A comprehensive life style and dietary questionnaire was completed by the participants at baseline and updated every two to four years. During the follow-up (10 years in men, 16 years in women), we documented a total of 288 incident cases of Parkinson's disease. Among men, after adjustment for age and smoking, the relative risk of Parkinson's disease was 0.42 (95% CI: 0.23–0.78; p for trend < 0.001) for men in the top one-fifth of caffeine intake compared to those in the bottom one-fifth. An inverse association was also observed with consumption of coffee (p for trend $= 0.004$), caffeine from noncoffee sources (p for trend < 0.001), and tea (p for trend $= 0.02$) but not decaffeinated coffee. Among women, the relationship between caffeine or coffee intake and risk of Parkinson's disease was U-shaped, with the lowest risk observed at moderate intakes (1–3 cups of coffee/day, or the third quintile of caffeine consumption). These results support a possible protective effect of moderate doses of caffeine on risk of Parkinson's disease.

Ann Neurol 2001;50:56–63

Caffeine confers protection in PD models



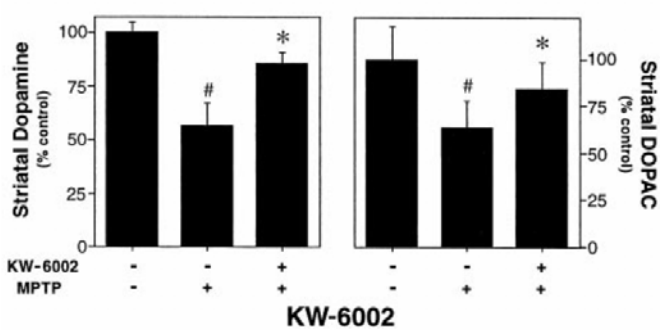
Chen, Xu, Petzer, Stahl, Xu, Beilstein, Sonsalla, Castagnoli, Castagnoli & Schwarzschild (2001) *J. Neurosci.*

Istradefylline confers protection in PD models

The Journal of Neuroscience, 2001, Vol. 21 RC143

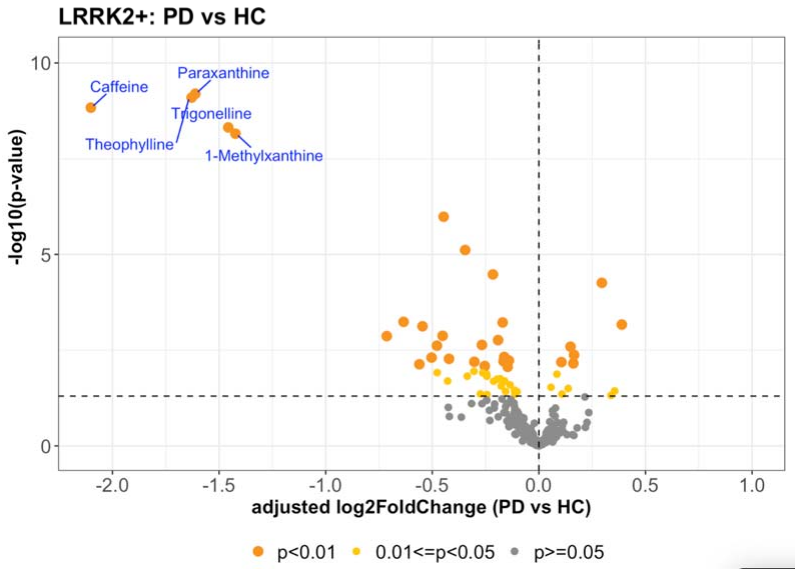
Neuroprotection by Caffeine and A_{2A} Adenosine Receptor Inactivation in a Model of Parkinson's Disease

Jiang-Fan Chen,[1] Kui Xu,[1] Jacobus P. Petzer,[2] Roland Staal,[3] Yue-Hang Xu,[1] Mark Beilstein,[1] Patricia K. Sonsalla,[3] Kay Castagnoli,[2] Neal Castagnoli Jr,[2] and Michael A. Schwarzschild[1]



(istradefylline)

Caffeine-related analytes distinguish PD from healthy controls (HC) among 233 *LRRK2*+ LCC subjects:



Crotty et al. (2020) *Neurology*. 95:e3428-e3437.

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Designing future A_{2A} trials toward a substantial benefit for people with Parkinson's

Parkinsonism and Related Disorders

Do caffeine and more selective adenosine A_{2A} receptor antagonists protect against dopaminergic neurodegeneration in Parkinson's disease?

Jiang-Fan Chen, Michael A. Schwarzschild

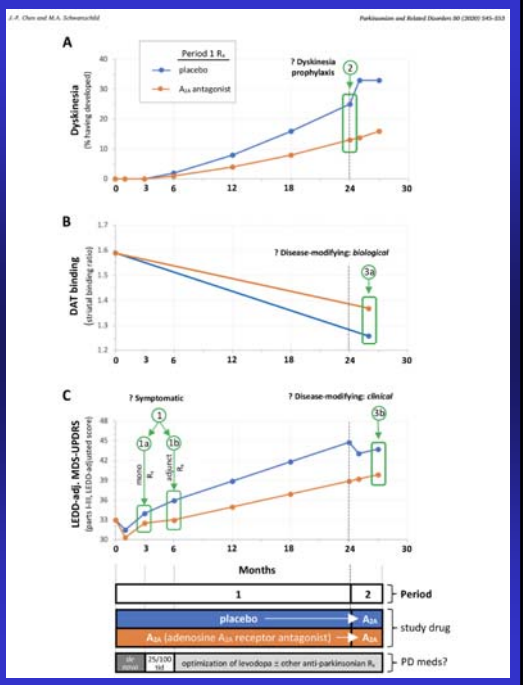

Fig. 1. Envisioned design for a phase 2, randomized, double-blind clinical trial of an adenosine A_{2A} receptor antagonist to investigate its multiple potential indications spanning short-term symptomatic and long-term, disease course benefits in PD.

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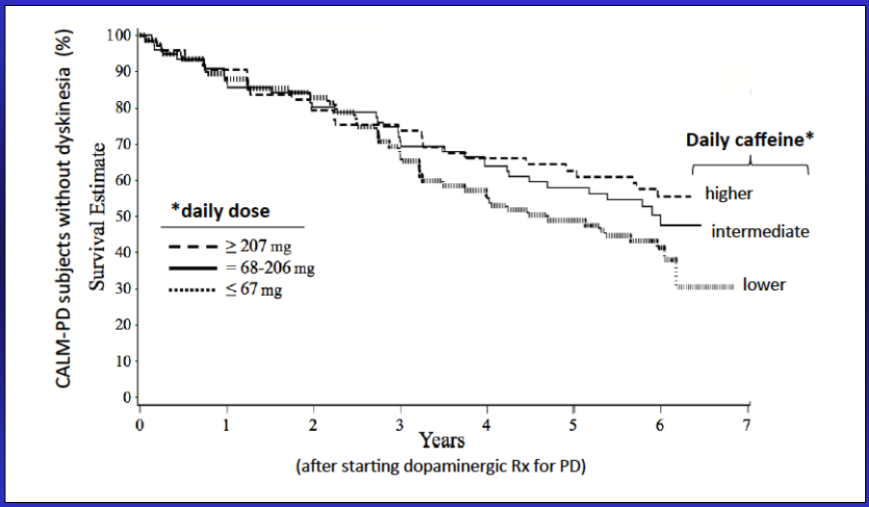
Thank you.

Questions?

Caffeine consumption & the risk of dyskinesia in PD



Wills AM, Eberly S, Tennis M, **Lang** AE, Messing S, Togasaki D, Tanner CM, Kamp C, Chen JF, Oakes D, McDermott MP, Schwarzschild MA; Parkinson Study Group. (2013) *Mov Disord*. 28:380-3.