

Thiamine for Parkinson's disease — promising signals, weak evidence, no RCT yet

As of April 2026, the clinical evidence that thiamine (vitamin B1) treats Parkinson's disease (PD) remains preliminary and uncontrolled. The only published human data are ~63 patients across three open-label, single-arm case series (Costantini group, Italy) plus a 5-patient US case series (Luong/Nguyen), with dramatic-appearing UPDRS reductions but no blinding, no placebo, and no independent replication. The long-anticipated benfotiamine-for-PD RCT linked to Thomas Jefferson / Dr. Daniel Kremens **does not appear to exist in ClinicalTrials.gov or PubMed** — the NIH-funded BenfoTeam trial (NCT06223360) is a 406-patient Phase 2A/2B in **early Alzheimer's, not PD**, [\(nih +3\)](#) and explicitly excludes PD. [\(Uci +2\)](#) The mechanistic rationale — KGDHC reduction in the PD substantia nigra, CSF free-thiamine decrement, α -synuclein glycation theoretically addressable by transketolase induction — is biologically coherent but insufficient to explain the ~55% UPDRS-III reductions Costantini reported. A scientifically sophisticated reader should treat high-dose thiamine (HDT) for PD as a **reasonably safe, physiologically plausible, but unproven adjunct**, [\(Michael J. Fox Foundation\)](#) pending a properly powered randomized controlled trial that is planned by the HDT Foundation but remains unfunded.

1. Clinical evidence: what exists and what doesn't

The Costantini open-label series — the entire foundational dataset

The late Antonio Costantini (neurologist, Villa Immacolata, Viterbo, Italy; died May 2020 of COVID-19 after a post-stroke recovery) [\(Highdosethiamine\)](#) built the HDT-PD hypothesis from four publications:

#	Citation	N	Design	Dose / route	Duration	Outcome
1	Costantini, Pala, Compagnoni, Colangeli. BMJ Case Rep 2013 (PMID 23986125)	3 drug-naïve PD	Case series, open-label	100 mg thiamine HCl IM 2×/wk (Mon/Thu) + low-dose other B-vitamins	15 days to reassessment	UPDRS-III improved 31.3-77.3% per patient; total UPDRS 31-71%
2	Costantini, Pala, Grossi et al. J Altern Complement Med 2015;21:740 (PMID 26505466)	50 PD (33M/17F, mean age 70.4, duration 7.3 y)	Observational open-label single-arm pilot	100 mg IM 2×/wk	95-831 d (mean 291)	Total UPDRS I-IV 38.55 → 18.16 (p=2.4×10 ⁻¹⁴); UPDRS-III 22.0 → 9.9 (p=3.1×10 ⁻²²); FSS 53.0 → 23.6 (p<0.0001)
3	Costantini & Fancellu. Neural Regen Res 2016;11:406 (PMID 27127471)	10 PD (multicentre)	Open-label	100 mg IM 2×/wk; levodopa increases allowed from mo 2	2 mo	UPDRS-III 21.6 → 11.8 (p<10 ⁻⁵); mean 59.6% relative reduction — confounded by concomitant levodopa up-titration to mean 515 mg/d
4	Costantini & Fancellu. Gerontol Geriatr Stud 2018;4(1):389 (non-indexed Crimson)	Narrative	"Overdose effects" commentary	—	—	Dose titration rules; IM contraindicated on anticoagulants; estimates 100 mg IM/wk ≈ 14 g oral/wk (≈ 2 g/d oral); 2×

#	Citation	N	Design	Dose / route	Duration	Outcome
						IM/wk ≈ ~4 g/d oral

An independent US group — **Luong & Nguyen, J Neurol Res 2012;2:211** — reported (PubMed) 5 male PD patients (ages 65–82) on 100–200 mg IM thiamine **daily** (different regimen), with narrative "dramatic" improvement in gait, tremor, sialorrhea within days. (b1parkinsons +2) No UPDRS data. **This and the Costantini series are the entirety of peer-reviewed human PD-specific evidence for thiamine**, along with a recent 2-patient case report of oral benfotiamine + methylcobalamin (Medical Research Archives) (Mann & Baratta, Med Res Arch 2025;13(5), low-tier fee-based journal). (Medical Research Archives) (Medical Research Archives)

Why the effect sizes should be treated skeptically

The pooled Costantini cohort (~63 PD patients) shows a ~55% **mean UPDRS-III reduction** within 1–3 months. (Academia.edu) (Liebert Pub) That magnitude **exceeds levodopa's typical effect and is larger than any disease-modifier tested in RCTs** (CoQ10, creatine, isradipine, inosine, exenatide, all <30% or null). If real, HDT would be the most effective PD symptomatic treatment ever reported. Several features argue against taking the effect size at face value:

- **Open-label, unblinded raters** throughout; same clinicians (AC, RF) administered treatment and rated UPDRS. (B1parkinsons) Videotaped exams were used but independent blinded re-rating was not documented. (scienceofparkinsons) PD is highly placebo-responsive (Michael J. Fox Foundation) — Fregni et al. (Eur Neurol 2006, cited by Costantini himself) showed objective motor placebo effects in PD of ~15–30%.
- **Ritual effects** of twice-weekly IM injection by attentive staff induce strong therapeutic-relationship non-specific effects.
- **Co-interventions:** low-dose B-complex co-administered; (B1parkinsons) (PubMed Central) levodopa increased during follow-up in the 2016 study. (PubMed Central) (ResearchGate)
- **Paired t-test p-values of 10^{-22}** reflect tight within-subject baseline/follow-up covariance in an uncontrolled design, not effect-versus-placebo.
- **Selection bias:** patients self-referred to a known HDT clinic with high expectations; drop-outs and non-responders are poorly characterized.
- **No biomarker/imaging corroboration** (no DaT-SPECT, no α -synuclein, no CSF TDP measured in responders vs. non-responders).

Replication status — essentially nil

- **No independent randomized, controlled replication exists as of April 2026.**
- The **HDT Foundation / b1parkinsons.org** (patient-led, continuing Costantini's work with Marco Colangeli, [B1parkinsons](#) Daphne Bryan, Sergio Pièche) [B1parkinsons](#) has designed a 4-arm (oral/IM × active/placebo) triple-masked RCT targeting >260 patients, [B1parkinsons](#) budgeted near €1 M, and is fundraising via GoFundMe [Highdosedthiamine](#) [B1parkinsons](#) — **not yet funded, not registered on ClinicalTrials.gov**. A retrospective dose-factors study at Ospedale Policlinico San Martino (Genoa, with Fancellu) is preparatory. [Highdosedthiamine](#) [Highdosedthiamine](#)
- The **McFarthing et al. 2024 PD pipeline review** (*J Parkinson's Dis* 14:899) listing 136 active PD drug trials on ClinicalTrials.gov as of January 2024 [PubMed Central](#) did not include any thiamine or benfotiamine PD trial. [PubMed Central](#) [PubMed](#)
- **Mainstream positions:** [ResearchGate](#) The Michael J. Fox Foundation states "the scientific evidence is insufficient to recommend thiamine for Parkinson's."
[Michael J. Fox Foundation](#) The Science of Parkinson's (Simon Stott, Cure Parkinson's) has declined to endorse thiamine without a controlled trial. [Science of Parkinson's](#)
[scienceofparkinsons](#) No AAN, MDS, EAN, or NICE guideline includes thiamine.
- The only adjacent high-quality evidence — **Bager et al. 2021 Aliment Pharmacol Ther**, a crossover RCT of 600–1800 mg/d oral thiamine showing reduced fatigue in IBD — is frequently invoked as proof-of-principle but does not address PD.
[Hormones Matter](#)

The "BENFO-PD / Kremens Jefferson" benfotiamine-PD trial likely does not exist as described

Extensive searching of ClinicalTrials.gov, PubMed, NIH RePORTER, Jefferson press releases, and the Kremens publication record finds **no registered benfotiamine-in-PD trial led by Daniel Kremens or Thomas Jefferson University**. Kremens is an active Jefferson movement-disorders neurologist [Atmrd](#) who speaks publicly about the PD pipeline [CGTLive®](#) (tavapadon, ND0612, CVN424, bemandaneprocel, stem-cell therapies) [Neurology Live](#) [Neurology Live](#) but not about a benfotiamine-PD trial he leads. [CGTLive®](#) The most likely source of this impression is **conflation with the BenfoTeam Alzheimer's trial:**

- **NCT06223360 "BenfoTeam"** — NIA R01AG076634; coordinated by ADCS at UC San Diego; [ALZFORUM](#) PIs Howard Feldman, José Luchsinger, Gary Gibson (Burke/Weill Cornell); [ALZFORUM](#) **406 participants, 50 US sites, 18-month seamless Phase 2A/2B, adaptive 600 vs 1200 mg/d benfotiamine vs placebo;** [Emory +3](#) primary outcomes ADAS-Cog13 and CDR-SB; [ALZFORUM](#) [CenterWatch](#) secondary plasma biomarkers of

amyloid/tau/AGE. (CenterWatch +3) Registered January 2024; enrolling through 2025-2026; (Emory) results not expected before ~2027-2028. (ALZFORUM) **The exclusion criteria explicitly bar PD** (CenterWatch) ("significant neurodegenerative diseases other than AD, including Parkinson's disease"). (Uci) (Ucbraid) This is not a PD trial. (CenterWatch)

- The precursor **Gibson & Luchsinger 2020 Phase 2A** (NCT02292238; n=70 MCI/mild AD; 600 mg/d × 12 mo) (ALZFORUM) showed **ADAS-Cog decline 43% lower** than placebo (PubMed Central) (Medical Research Archives) (near-sig, p=0.125), **CDR worsening 77% lower (p=0.034)**, (Medical Research Archives...) significant AGE reduction (ALZFORUM) (Emory) (p=0.044), (PubMed Central) (PubMed) and a 161-fold blood thiamine rise (HealthUnlocked) — safe, (HealthUnlocked) signal of efficacy in AD. (HealthUnlocked) (medrxiv)

If a Kremens/Jefferson benfotiamine-PD protocol is in planning stages, it is either unregistered, investigator-initiated early-phase (possibly funded via the Parkinson Study Group or a foundation), or confused in the source material. **Any user claim of "BENFO-PD results expected 2024-2026" should be treated as incorrect** unless a specific NCT number surfaces. The closest contemporary registered activity in benfotiamine for PD is the b1parkinsons.org-listed aspiration to test benfotiamine absorption/efficacy in PD, which is not a registered trial. (B1parkinsons) (B1parkinsons)

Preclinical benfotiamine work in PD models (all since 2023)

Two 2024 rodent studies establish preclinical PD evidence (ALZFORUM) — both from non-independent, thiamine-advocate-adjacent labs:

- **Bashir et al., Eur J Pharmacol 2024;962:176234** (ALZFORUM) — intranasal MPTP rats, oral benfotiamine 100 and 200 mg/kg × 42 d; dose-dependent motor recovery and midbrain dopamine restoration. (ScienceDirect +2)
- **Wang, Han et al., PLOS One 2024;19:e0307012** — subacute MPTP C57BL/6 mice, benfotiamine improved pole/hang tests, partially restored TH+ neurons in SNpc/striatum; (nih) mechanism via **Nrf2 nuclear translocation**, HO-1/GCLM/NQO1 upregulation, ↑GSH/SOD, ↓MDA. RNA-seq effects distinct from NLRP3 inhibitor MCC950. (PubMed +3)

Notably, **no α-synuclein-based PD model (PFF, SNCA-AAV, Thy1-aSyn) has been tested with benfotiamine or thiamine** — a striking gap given the α-syn glycation hypothesis. Earlier precedents include Tapias et al. 2018 Hum Mol Genet (benfotiamine neuroprotective in tauopathy mice via Nrf2/ARE), (Medical Research Archives) (PubMed) Klivenyi/Beal et al. 2004 J Neurochem (E3-deficient DLD+/- mice more vulnerable to MPTP), and Yamashita et al. 1993 (intrastratial TPP induced up to 1400% dopamine release, pharmacologic not cofactor effect). (ResearchGate)

Critical mechanistic appraisal

The standard rationale — replacing TPP cofactor for KGDHC/PDH in PD substantia nigra — is probably wrong. The substantia nigra KGDHC deficit (Mizuno 1994 Ann Neurol; PubMed Gibson 2003 Neurochem Int) almost certainly reflects **oxidative inactivation of the enzyme protein** (Springer) (Jeitner/Gibson 2005 J Neurochem: KGDHC sensitive to 4-HNE, peroxynitrite, HOCl), not cofactor limitation. Flooding the system with extra thiamine cannot regenerate an oxidatively-damaged enzyme.

The only reproducibly reported thiamine abnormality in idiopathic PD is **low CSF free thiamine** (Medical Research Archives) (ResearchGate) (Jiménez-Jiménez et al., Neurosci Lett 1999; n=24 PD vs 40 controls) (Medical Research Archives) — and even there, **TPP (the active cofactor) was normal.** (PubMed) Plasma thiamine is **normal in PD** (PubMed Central) (PubMed Central) (Gold et al., Metab Brain Dis 1998) — contrasting with AD. (scienceofparkinsons) (Semantic Scholar) The Bettendorff/Mastrogiacomio 1996 postmortem series found reduced brain TDP in AD and frontotemporal dementia but **no clear PD-specific brain TDP deficit.** Håglin 2020 found low plasma thiamine only in male PD-MCI, not globally. (Medical Research Archives...)

If benfotiamine works in PD, a more plausible mechanism is **Nrf2-mediated antioxidant activation** (PubMed) (PubMed Central) (Wang 2024, (PubMed Central) (PLOS) Tapias 2018) (PLOS) (nih) and/or **transketolase-mediated reduction of methylglyoxal → reduced α-synuclein glycation.** α-Syn glycation is pathogenic (Vicente Miranda et al., Brain 2017, Outeiro lab: MGO-glycated α-syn promotes oligomerization and worsens mouse nigrostriatal degeneration; (Oxford Academic) Chegão 2022 npj Parkinson's Dis), (PubMed) and glyoxalase-1 overexpression is protective. (PubMed Central) However, **no published study has demonstrated that benfotiamine reduces α-syn glycation or aggregation in any PD model,** and the only clinical benfotiamine-AGE data in humans (Alkhalaf et al., 12 weeks in non-diabetic vascular patients) showed **no change in plasma/urinary AGEs** (ResearchGate) — raising doubt about in-vivo target engagement at achievable doses.

The gulf between the **modest mechanism** (incremental antioxidant/anti-glycation effect in non-deficient brains) and the **~55% UPDRS-III reduction** reported by Costantini is itself a red flag for placebo and bias.

2. Practical: forms, doses, and pharmacology

Feature	Thiamine HCl	Benfotiamine	Sulbutiamine	TTFD / Fursultiamine
Class	Water-soluble quaternary thiazolium salt	S-acyl thioester prodrug (amphiphilic, not truly lipid-soluble — has	Isobutyryl-thiamine disulfide (truly lipophilic; ring-opened	Thiamine tetrahydrofurfu disulfide (lipophilic; ring-

Feature	Thiamine HCl	Benfotiamine	Sulbutiamine	TTFD / Fursultiamine
		charged phosphate) (MDPI)	dimer) (ChemicalBook)	opened) (Wikipedia)
Oral bioavailability vs HCl	Reference	~5× plasma Cmax, ~3.6× AUC (Loew 1996); (ScienceDirect) (PubMed) 1147% plasma, 196% erythrocyte TDP (Xie 2014) (Wiley Online Library)	Higher than HCl; ↑ plasma thiamine, TMP, TDP, and ThTP in rat brain (Bettendorff)	~300% AUC vs thiamine nitrate ~50× blood and ~2× brain thiamine in animals (Grokopedia)
BBB / brain penetration	Crosses via SLC19A2/3 (saturable) + passive diffusion at supraphysiologic plasma	Controversial / primarily peripheral. (B1parkinsons) Volvert 2008 (BMC Pharmacol) — mice, 100 mg/kg × 14 d: no rise in brain thiamine/TDP. (Springer +2) Pan 2010 + Xie 2014 see modest rise in free thiamine, not TDP (ScienceDirect +2)	Best brain penetration of the class. ↑ thiamine, TMP, TDP, ThTP in hippocampus/PFC (Wikipedia)	Good; [¹¹ C]TTFD PET in humans (Watanabe 2021 confirms brain uptake; bypasses THTR entirely (ScienceDirect)
Typical clinical dose	Supplement 1.5-100 mg/d; Wernicke's 500 mg IV TID × 3-5 d; Costantini PD: 100 mg IM 2×/wk OR 2-4 g/d oral (HealthUnlocked)	Diabetic neuropathy 300-600 mg/d; AD 600 mg/d × 12 mo (Gibson 2020); (clinicaltrials) BenfoTeam 600 or 1200 mg/d (Emory +3)	400-600 mg/d (max 800 mg/d short-term) (Medindia)	Rx 25-100 mg/d (Japan); (PubMed) supplements 50-300 mg/d
Unique mechanism	Cofactor replenishment; non-cofactor signaling via ThTP/AThTP	Transketolase induction → shunts triose-P away from AGE, hexosamine, PKC, NF-κB (1mg +3) (Hammes 2003 Nat Med); (PubMed) (Nature) Nrf2 activation (PubMed)	Central cholinergic + glutamatergic potentiation; modulates D1 receptor density	Intracellular reduction by GSH/thioredoxin bypasses transporter dysfunction; (Patsnap Synapse)

Feature	Thiamine HCl	Benfotiamine	Sulbutiamine	TTFD / Fursultiamine
				hepcidin antagonist
PD clinical evidence	Strongest but uncontrolled (Costantini n=63, Luong n=5); Protocol: 100 mg IM Mon+Thu, OR oral 2 g/d (lighter/early) to 4 g/d (heavier/longer-duration), divided BID pre-breakfast + pre-lunch, water only	No PD RCTs; (B1parkinsons) 2 case reports (Medical Research Archives) (Mann 2025); (Medical Research Archives) positive MPTP rodent data (ALZFORUM +3)	No PD trials	No PD trials; off label use via Lonsdale/Overt tradition
Safety	Oral: no UL; rare IV anaphylaxis (~1:250 000, Wrenn 1989: 0.093% major/1070 IV doses); (PubMed) Costantini 4 g/d × 2+ y well tolerated; over-dose signal = jitteriness → reduce	Safe to 1200 mg/d (Sheng 2021 SAD/MAD); Gibson 2020 safe at 600 mg/d × 12 mo; no serious AEs (ALZFORUM +2)	Well tolerated 2 mo; (WebMD) caution in bipolar disorder (Douzenis 2006 mania); FDA Dietary Supplement Ingredient Advisory List Dec 2019 ; DoD prohibited (OPSS)	Sulfur body odc "paradoxical reactions" at initiation (anecdotal); caution in sulfur hypersensitivity

Specific protocol details

Costantini HDT protocol (confirmed):

- **IM:** 100 mg thiamine HCl Monday + Thursday, continued indefinitely;

(PubMed Central +2) fixed weekdays for adherence (PubMed Central)

- **Oral equivalent** (per Costantini 2018): 100 mg IM/wk \approx 14 g oral/wk, i.e. **\sim 2 g/d for lighter recent-onset patients; \sim 3 g/d mid-range; \sim 4 g/d for patients $>$ 90 kg or longer-duration**; (Crimson Publishers) (B1parkinsons) divided BID before breakfast and before lunch; water only (not juice — citric acid destabilizes thiamine); (HealthUnlocked) low-dose B-complex co-administered
- Oral preferred over IM for patients on anticoagulants (B1parkinsons) (hematoma risk); (B1parkinsons) titrate by symptom response — "jitteriness, insomnia, tachycardia" signals over-dose \rightarrow pause 1 week, restart at half-dose (B1parkinsons +2)
- Standard PD medications (levodopa, MAO-B inhibitors) continued unchanged at baseline; (B1parkinsons +3) expect possible need to **down-titrate levodopa** weeks-months later if patient becomes over-responsive (dyskinesias); Costantini reports thiamine may enhance levodopa efficacy (B1parkinsons +3)
- **No documented PK/PD interaction with levodopa, carbidopa, entacapone, rasagiline, selegiline, or amantadine**
- Monitor **B12 every 6–12 months** (particularly if on metformin) — b1parkinsons.org recommends this. Magnesium 375 mg ER twice weekly is suggested but should not be combined in pill-for-pill with thiamine to avoid Mg overload (Highdosedthiamine)

Safety of high-dose thiamine (reviewed across Wrenn 1989; McLaughlin 2019 n=8606 IV push doses, zero anaphylaxis; (ScienceDirect) Smithline 2012 BMC Clin Pharmacol single 1500 mg oral safe in healthy; Costantini \sim 2500 pts across diseases: (Beyond Health +2) 4 cutaneous allergies, no fatalities, no hepatotoxicity/renal toxicity signal): **high-dose thiamine HCl is remarkably safe**. The Institute of Medicine/NAS has declined to set an upper limit because of lack of documented toxicity. (PubMed Central) **The real controversy is not safety but efficacy.**

Benfotiamine vs HCl for PD — a key practical tension: benfotiamine is more convenient (oral, high peripheral bioavailability), (Nava Health +2) but **Volvert 2008's negative brain-penetration result means benfotiamine may not deliver the intracellular brain thiamine that Costantini's focal-transport-defect hypothesis requires.** (Medscape +3) The b1parkinsons.org group (successor to Costantini) explicitly states benfotiamine "cannot yet be recommended" as a substitute for HCl in PD, pending trial data. (B1parkinsons) Conversely, if the true mechanism is Nrf2-mediated antioxidant action (PLOS) (2024 MPTP studies) (PLOS) or peripheral transketolase \rightarrow AGE reduction \rightarrow reduced α -syn glycation, benfotiamine's peripheral loading might be sufficient or even preferable.

Sulbutiamine and TTFD — no PD-specific trial evidence; Bunik et al. 2021 reported in a CMT neuropathy pilot that single 200 mg sulbutiamine or 150 mg benfotiamine produced hand-grip and transketolase-activation responses comparable to 100 mg thiamine. (ResearchGate) (ResearchGate) Sulbutiamine has the best-documented brain TDP elevation in

rodents, [Wikipedia](#)) but concerns include FDA advisory listing, bipolar mania risk, and paucity of human CNS data. TTFD/fursultiamine is used in Lonsdale-tradition protocols (Elliot Overton / EONutrition) [EONUTRITION](#) for dysautonomia and CFS/POTS, with reported "paradoxical reactions" during initiation [Parkinson's News Today](#) — this is anecdotal and not in peer-reviewed PD literature.

Practical algorithm synthesized from the evidence

The most defensible practical approach, given what exists:

1. If pursuing HDT most faithfully to the published evidence, use **thiamine HCl IM 100 mg Mon/Thu, or oral 2-4 g/d divided BID** [PubMed Central +2](#) per Costantini; [Liebert Pub](#) [ResearchGate](#) treat it as unproven adjunct, not substitute for PD standard care. [PubMed](#) [Liebert Pub](#)
2. Benfotiamine (600 mg/d in two divided doses, [HealthUnlocked](#)) scalable to 1200 mg/d based on AD BenfoTeam tolerability) [nih](#) is a reasonable oral alternative for patients who cannot do IM or tolerate g-scale HCl, but understand it has **no PD clinical efficacy data** and its brain penetration is contested.
3. TTFD or sulbutiamine have weaker mechanistic fit for the Costantini "focal transporter defect" hypothesis and no PD data; reserve for specific contexts (e.g., suspected THTR dysfunction) with awareness of the sulbutiamine safety caveats.
4. Monitor UPDRS-II/III, B12, and PD medication requirements; down-titrate levodopa only if clinically indicated.
5. Inform patients honestly that this is an **open-label experiment**, not a proven therapy, [Michael J. Fox Foundation](#) and enroll in an RCT if available.

3. Form-by-form evidence and tradeoff summary

Thiamine HCl (parenteral/high-dose oral) carries the only direct PD clinical evidence (Costantini N≈63, Luong N=5), all open-label and susceptible to placebo. [PD Optimism](#) Its safety record is robust. [PubMed Central](#) [Academia.edu](#) Its mechanism for PD — overcoming a focal intracellular transport defect by supra-physiologic diffusion [PubMed Central](#) — is speculative and untested. [Semantic Scholar +2](#) Tradeoff: **best PD-specific evidence, but that evidence is methodologically weak; IM inconvenient, oral g-scale regimens require adherence.**

Benfotiamine carries no PD clinical efficacy data, [Medical Research Archives](#) [Elsevierpure](#) two supportive 2024 rodent MPTP studies, [ALZFORUM +4](#) and positive Phase 2A Alzheimer's signal (Gibson 2020: 77% lower CDR worsening, p=0.034, n=70). [Medical Research Archives...](#) Its peripheral PK is superior (~5× plasma thiamine vs HCl at equimolar dose), [ScienceDirect +4](#) but **brain penetration is contested (Volvert 2008 strongly negative),**

(Springer +2) and its transketolase-AGE mechanism is hyperglycemia-biased (Review of Ophthalmology) and may not engage in normoglycemic PD. Tradeoff: **best oral convenience and AGE/glycation mechanism; weakest direct PD evidence; brain delivery uncertain.**

Sulbutiamine has the best-documented brain TDP/ThTP elevation in rodents (Wikipedia) and central cholinergic/glutamatergic effects, (PubMed Central) (Google Patents) but no PD trials, FDA advisory listing, and bipolar safety concerns. (WebMD) Tradeoff: **strongest CNS penetration, weakest regulatory/safety footing, no PD data.**

TTFD / fursultiamine has human PET-confirmed brain uptake, (ScienceDirect) bypasses thiamine transporters, (PureBulk) and is used clinically in Japan (Alinamin-F). (Wikipedia) No PD trials; anecdotal use in dysautonomia. Tradeoff: **unique transporter-bypass for hypothetical THTR dysfunction, but evidence base is mostly practitioner-reported.**

Conclusion — what has changed, and what to watch

The narrative that high-dose thiamine dramatically reverses Parkinson's disease rests entirely on open-label reports from one Italian clinic and one small US series.

(Science of Parkinson's +2) **Every methodological weakness of preliminary nutraceutical research is present simultaneously:** no blinding, no placebo, raters = treaters, selection bias, co-interventions, absence of biomarker confirmation, and effect sizes too large for the proposed mechanism. The most honest framing is that the clinical signal is **hypothesis-generating**, (B1parkinsons) the safety signal is **reassuring** (Science of Parkinson's) (decades of data at g-scale oral and IM doses), and the scientific question remains **genuinely open.**

Two concrete things have changed in the 2020–2026 window that shift the rational posture slightly in thiamine's favor: (1) the **Gibson/Luchsinger 2020 Phase 2A benfotiamine-in-AD RCT** demonstrated a plausible neurodegeneration-slowing signal (PubMed Central) ($p=0.034$ on CDR) under proper blinding, (Medical Research Archives...) confirming that the general strategy can produce positive controlled-trial results in a related disease, (PubMed Central) (PubMed) and this has precipitated the 406-patient BenfoTeam confirmatory trial (Uhhospitals) (Uci) (NCT06223360, reading out ~2027–2028); (TrialsToday +3) (2) two 2024 MPTP-model rodent studies show that benfotiamine is neuroprotective (ALZFORUM) via **Nrf2 activation** (PLOS) (ALZFORUM) — a mechanism independent of classical cofactor replacement, (PubMed) providing a more plausible causal pathway than the "cofactor deficiency" story. (PubMed +2) Together these justify **ongoing interest in a properly-powered benfotiamine or thiamine-HCl PD RCT** (Medical Research Archives) — but do not justify the confident claims found in patient-advocacy materials.

What to watch: (a) whether the HDT Foundation's planned 260+ patient 4-arm PD RCT secures funding and registers on ClinicalTrials.gov; (HighdoseThiamine) (B1parkinsons) (b) whether BenfoTeam's 2027–2028 AD readout is positive and galvanizes a PD-specific trial;

(c) whether any α -synuclein-model preclinical benfotiamine study is published — this is the most glaring gap; (d) whether independent groups attempt to replicate Costantini's open-label findings with blinded raters. Until those things happen, thiamine-for-PD is best classified as **physiologically plausible, probably safe, and clinically unproven.**

ResearchGate

Science of Parkinson's