Tau PET: from binding to clinical meaning.

FICTIONAL SCENARIO | A hypothetical review question, informed by published evidence.

01 THE SCIENTIFIC QUESTION

A fictional team proposes one tau-PET endpoint across Alzheimer's disease (AD) and progressive supranuclear palsy (PSP), adding monoamine oxidase B (MAO-B) PET to study decline. **Does each tracer measure the relevant pathology, and can it track clinical change?**

3R	4R	3R + 4R
Pick's disease	**PSP / CBD**	**AD / CTE**
Florzolotau: emerging evidence [3]	PI-2620 / florzolotau: research use [2]	AD: strongest evidence. CTE specificity uncertain. [2,8]

Figure 1. Selected tauopathies. Repeat class alone does not establish tracer binding. [1-3]

02 ASSUMPTIONS TO EXAMINE

Tau is not one target. Adult brain tau has six major isoforms; 3R and 4R indicate microtubule-binding repeats. Filament fold also matters. PET does not resolve individual isoforms. Florzolotau has single-case PET-to-autopsy evidence in Pick's disease; broader validation is needed. Corticobasal syndrome does not uniquely identify CBD. [1-3]
Off-target binding means binding outside the intended target. THK5351 has a substantial MAO-B component. This is tracer-specific: one human flortaucipir study found no significant uptake difference with MAO-B inhibitor use. Choroid-plexus or meningeal signal can affect nearby estimates. [2,4,5]
Collinearity means correlated predictors. Tau-PET and MAO-B-PET may share spatial or disease-related variation without cross-binding. Strong correlation can destabilize their separate regression coefficients; covariate adjustment does not automatically isolate a pure tau signal.

03 IMPLICATIONS FOR INTERPRETATION

PET measures a pathology-related signal, not cognition directly. In AD, longitudinal tau measures relate to cognitive change. In a 2026 PI-2620 study of 23 people with PSP, PET change did not correlate with clinical progression. Neither result establishes a universal individual monitoring tool. [6,7]

04 RECOMMENDED NEXT STEPS

Specify pathology, tracer, regions and reference assumptions. Pair repeat PET with relevant memory, language, executive, motor or daily-function measures. Examine precision and predictor stability; distinguish cross-sectional association, validated prediction and within-person change.

A tracer-pathology match comes before a claim about clinical meaning.

SELECTED EVIDENCE | Sources support principles, not the fictional scenarios.

[1] Shi et al. Tau filament classification (2021)
[2] EANM/SNMMI tau PET recommendations (2026)
[3] Florzolotau / Pick's disease (2025)
[4] Ng et al. THK5351 / MAO-B (2017)
[5] Hansen et al. Flortaucipir / MAO-B (2018)
[6] Longitudinal tau and cognition in AD (2019)
[7] Gnorich et al. PI-2620 in PSP (2026)
[8] Flortaucipir / CTE neuropathology (2023)