PET on the Mind: Radiopharmaceuticals for Brain Imaging

Elizabeth Rayes, PharmD, ANP
Brigham & Women's Hospital, Radiopharmacy

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DISCLOSURES

I have no conflicts of interest or financial relationships to disclose.

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LEARNING OBJECTIVES

- Describe Beta-Amyloid and it's role in Alzheimer's
- Discuss the use of F-18 Beta-Amyloid imaging agents
- Evaluate clinical trials on the use of tau & microglial radiotracers

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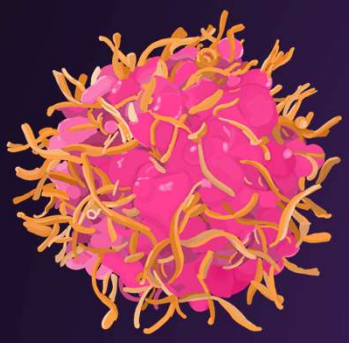
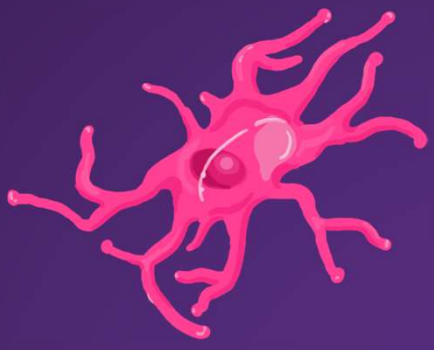
Pathology



Amyloid Beta

Tau



Microglia

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Amyloid Beta

- Derives from amyloid beta precursor protein
- Cleaved by beta-secretase & gamma secretase
- Ab 1-42 is main pathogenic peptide
- Neurotoxicity thought to mostly be caused by oligomers

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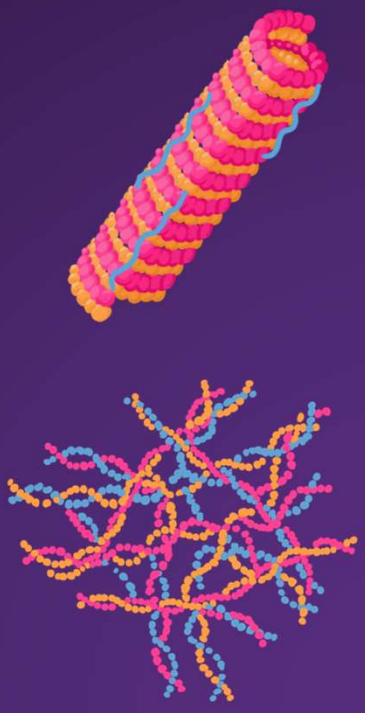
Tau Protein

- Tau promotes the assembly and stabilization of microtubules
- Hyperphosphorylation causes formation into neurofibrillary tangles → causes neurotoxicity
- Spatiotemporal distribution follows a predictable pattern
- Commonly present in a variety of neurodegenerative diseases



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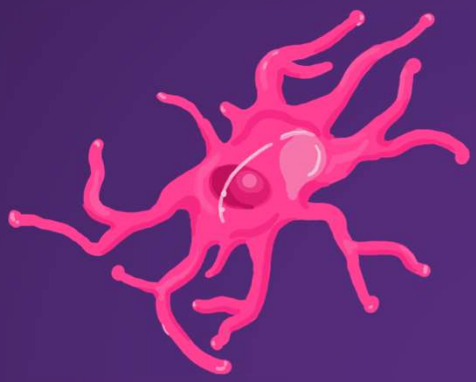
Microglia

- Engulf and clear debris → help to clear AB peptides
- Proliferate, activate and concentrate around amyloid plaques
- Express the majority of risk genes for Alzheimer's Disease
- Activated microglia can be neurotoxic



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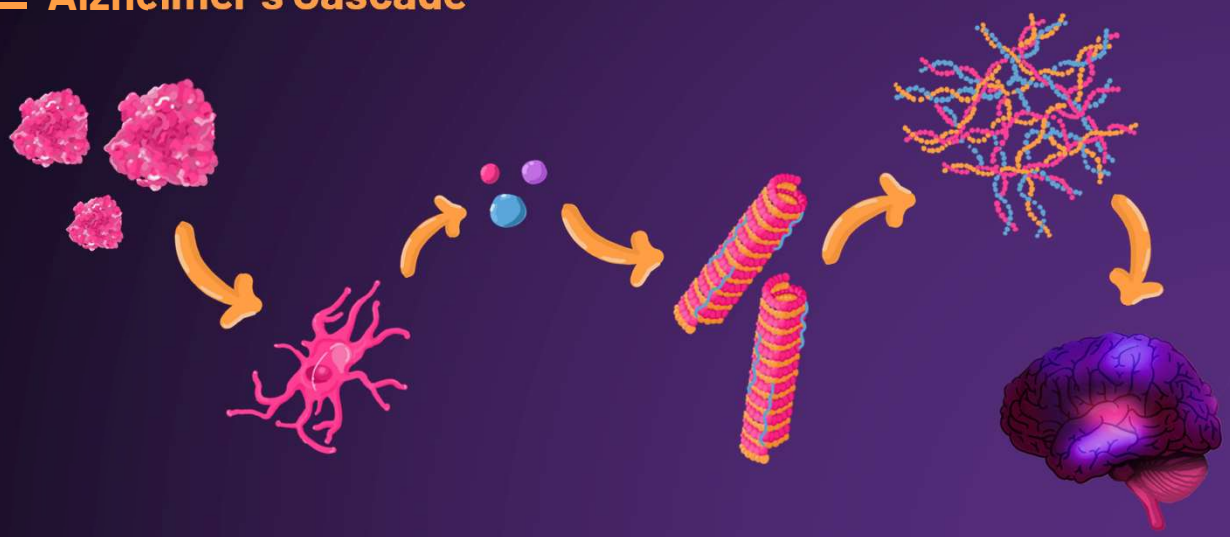
Alzheimer's Cascade



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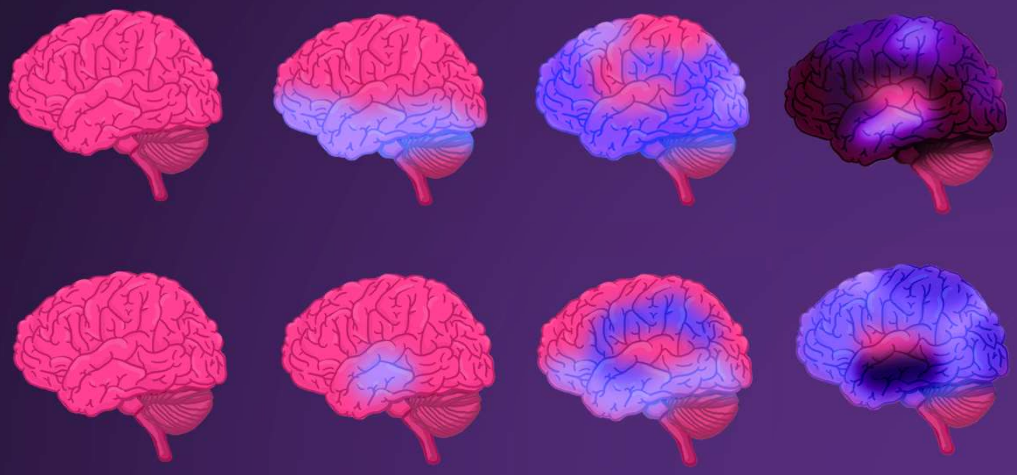
Brain Progression

Amyloid Plaques

Neurofibrillary Tangles



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55,000,000

People have dementia worldwide.

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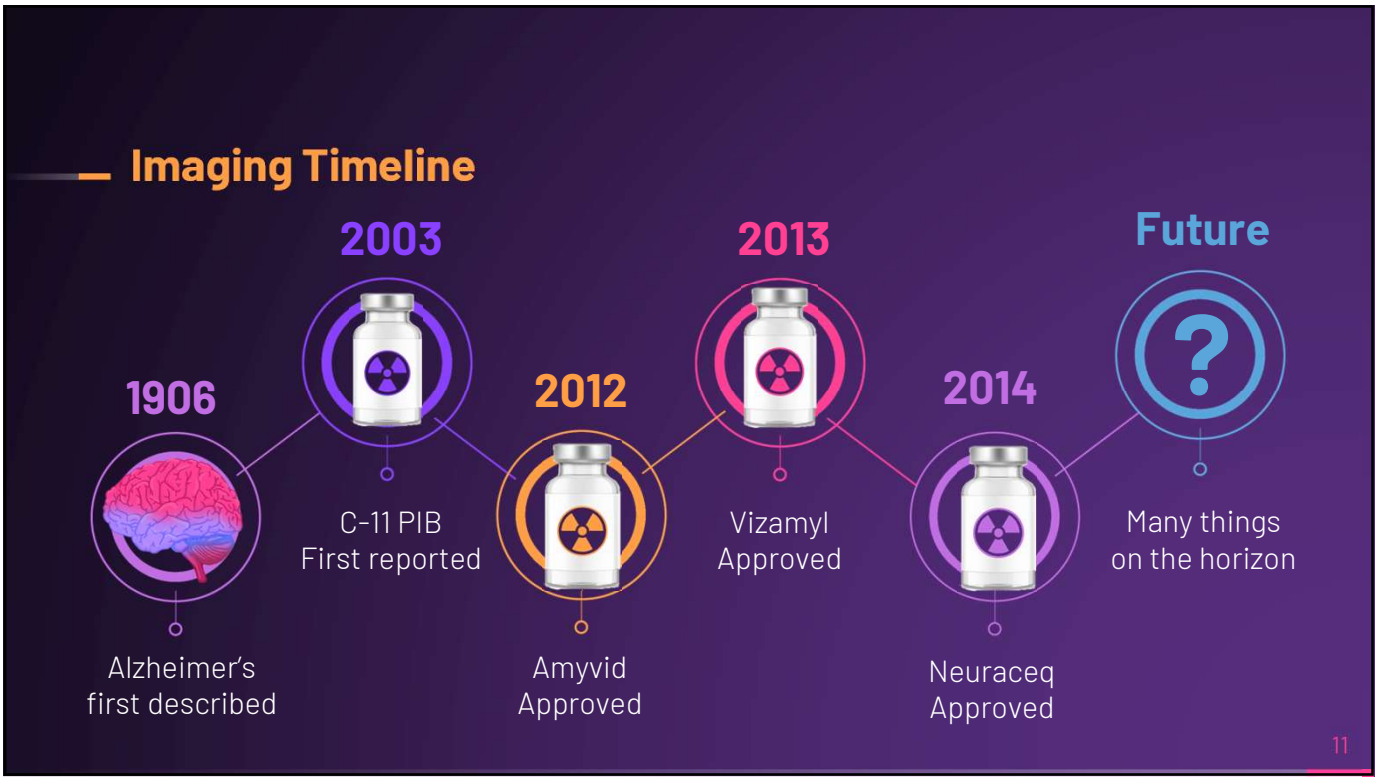
Imaging Timeline
1906
Alzheimer's first described
2003
C-11 PIB First reported
2012
Amyvid Approved
2013
Vizamyl Approved
2014
Neuraceq Approved
Future
Many things on the horizon
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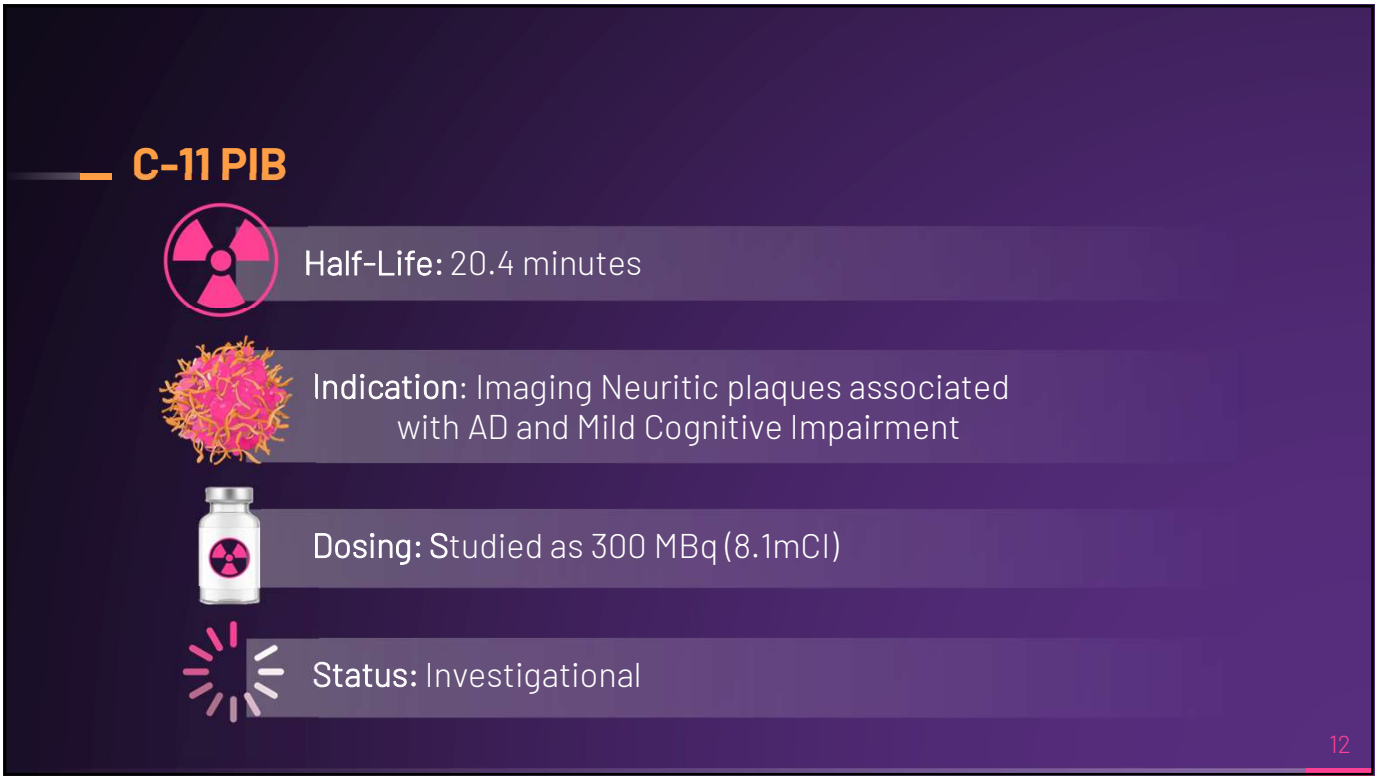
C-11 PIB
Half-Life: 20.4 minutes
Indication: Imaging Neuritic plaques associated with AD and Mild Cognitive Impairment
Dosing: Studied as 300 MBq (8.1mCI)
Status: Investigational
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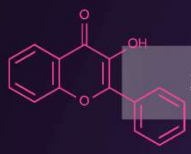
C-11 PIB



Structure: Derived from Thioflavin T

Critical Organ: Bladder Wall

Imaging Protocol: 40-70 minutes post injection

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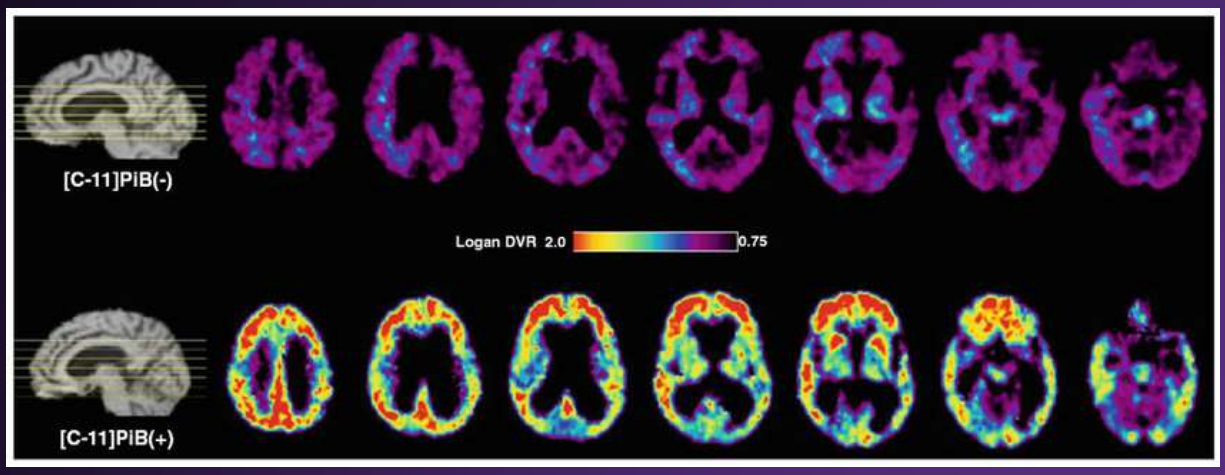
C-11 PIB Images



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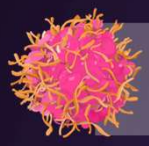
Amyvid (F-18 Florbetapir)



Indication: Estimate B-Amyloid neuritic plaque density in those being evaluated for AD

Dosing: 370 MBq (10mCI) --- Max 10mL
Strengths: 50 or 100 mL multidose vial
500-1900 MBq/mL (13.5-51 mCi/mL) at EOS
Appearance: Clear, Colorless solution

Status: Approved in 2012

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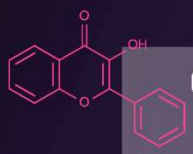
Amyvid (F-18 Florbetapir)



Components: 0.1 to 19 mcg Florbetapir, 4.5mg sodium ascorbate, 0.1mL dehydrated alcohol in 0.9% NaCl
pH: 5.5 to 8.0

Critical Organ: Gallbladder Wall

Imaging Protocol: 10 minute images starting at 30-50 minutes post injection

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Amyvid (F-18 Florbetapir)

Storage: 25C (77F) – Excursions permitted from 15-30C (59 to 86F)
Pearls: Amyvid must NOT be diluted

Clinical trials: 3 single arm studies
-Healthy patients, Terminal patients & port-mortem
-92% sensitivity (95% CI 80 – 100%)
-100% specificity (95% CI: 78-100%)

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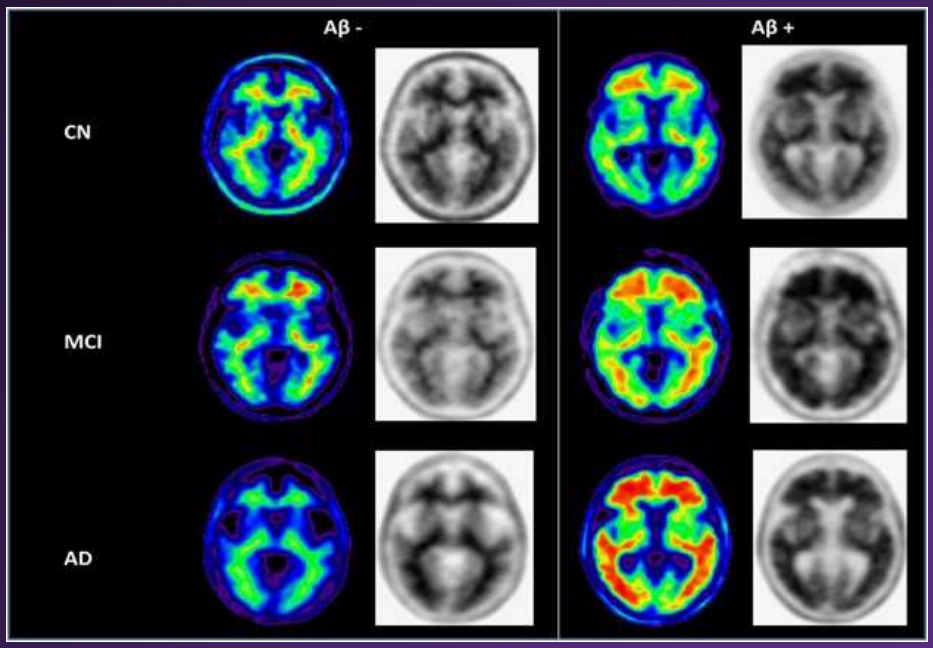
Amyvid (F-18 Florbetapir) Images



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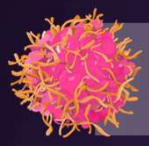
Vizamyl (F18 Flutemetamol)



Indication: Estimate B-Amyloid neuritic plaque density in those being evaluated for AD

Dosing: 185 MBq (5mCI) with 40 s --- Max 10mL
Strengths: 10 or 30 mL multidose vial
150 MBq/mL (4.05 mCi/mL) at EOS
Appearance: Clear/Colorless to slightly yellow solution

Status: Approved in 2013

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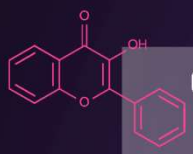
Vizamyl (F18 Flutemetamol)



Components: up to 2mcg flutemetamol, 20 microliters ethanol, 9mg sodium chloride and 4.98 mg polysorbate 80 in 0.014 M phosphate buffer
pH: 6.0 to 8.5

Critical Organ: Gallbladder Wall

Imaging Protocol: 20 minute images starting at 90 minutes post injection

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Vizamyl (F18 Flutemetamol)

Side effects: Flushing, headache, increased blood pressure, nausea and dizziness

Storage: 2 to 30C (36 to 86F)
Pearls: Vizamyl must NOT be diluted

Clinical Trials: Two clinical trials
-Range of cognitive function and post-mortem
- Median sensitivity: 8 – 9 (Range 81, 86-93)
-Median Specificity: 8 (Range 44, 60-92)

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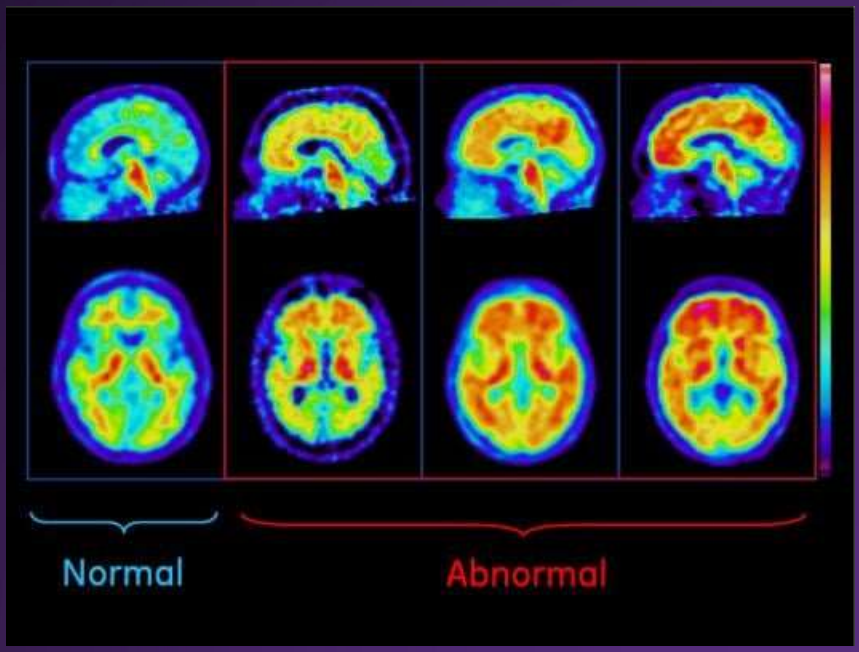
Vizamyl (F18 Flutemetamol) Images



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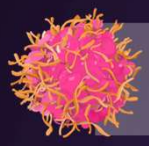
Neuraceq (F18 Florbetaben)



Indication: Estimate B-Amyloid neuritic plaque density in those being evaluated for AD

Dosing: 300 MBq (8.1mCI), 6sec/mL --- Max 10mL
Strengths: 30 mL multidose vial
50-5000 MBq/mL (1.4 to 135 mCi/mL) at EOS
Appearance: Clear, Colorless solution

Status: Approved in 2014

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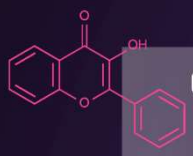
Neuraceq (F18 Florbetaben)



Components: 3 micrograms Florabetaben, 4.4mg ascorbic acid, 118mg ethanol, 200 mg macrogol 400, 28.8 mg sodium ascorbate
pH: 4.5 to 7.0

Critical Organ: Urinary Bladder Wall

Imaging Protocol: 15 -20 minute images starting at 45 to 130 minutes post injection

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Neuraceq (F18 Florbetaben)

Side effects: Injection site reaction, irritation & pain

Storage: 25C (77 F), Excursions allowed 2-42C (36-108F)
Pearls: Neuraceq must NOT be diluted

Clinical Trials: 3 single arm studies
-Range of cognitive function and post-mortem
-Median sensitivity: 98 – 96 (Range 96-98, 90-100)
-Median Specificity: 80 – 77 (Range 77-83, 47-80)

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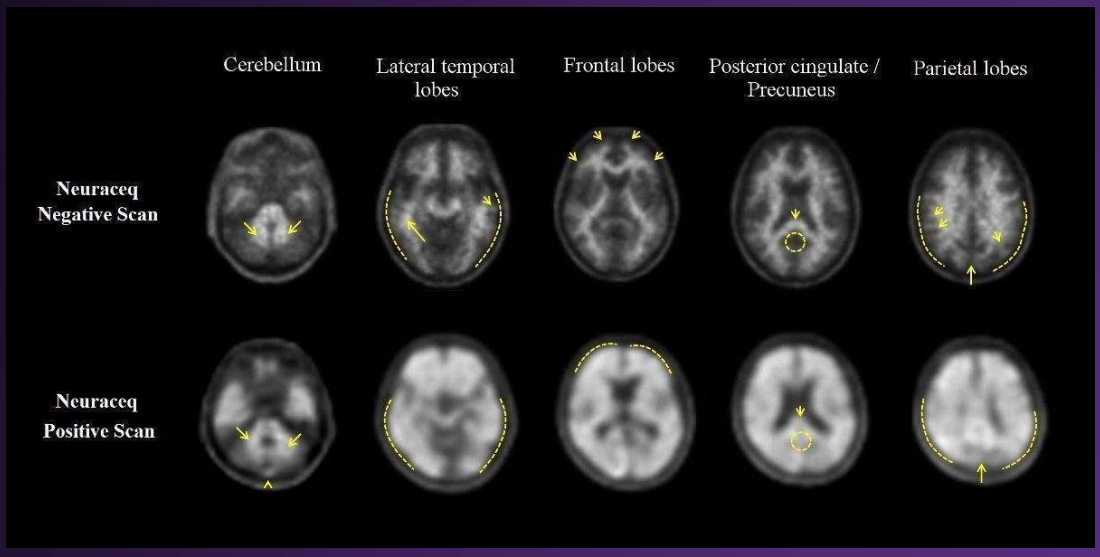
Neuraceq (F18 Florbetaben) Images



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Comparing the Agents

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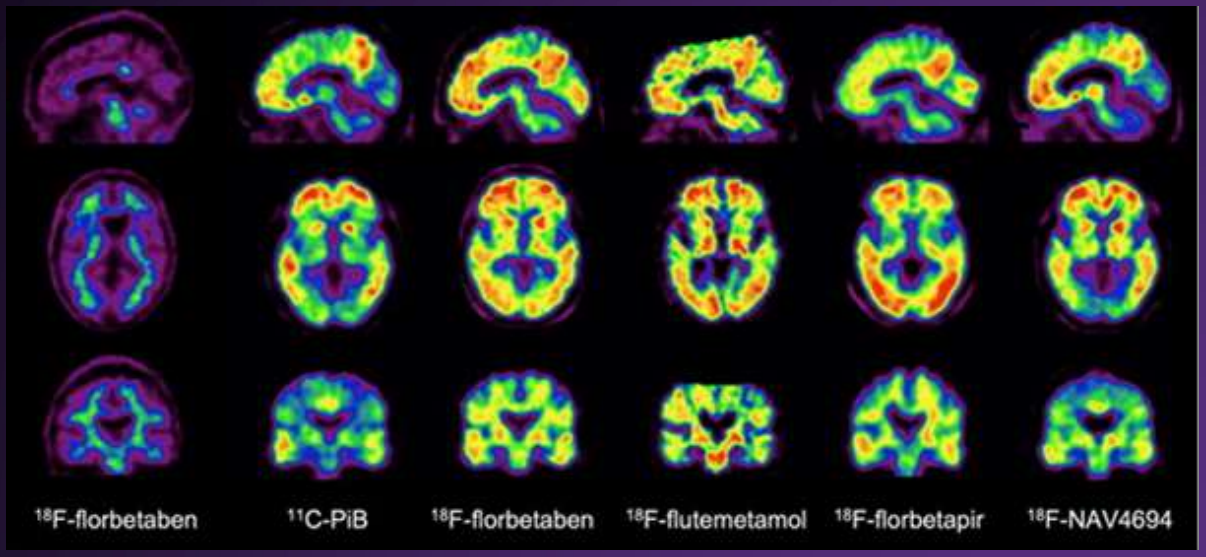

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Appropriate Use Criteria

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When to use a Beta-Amyloid Agent

- Confirmed cognitive impairment, AD is a possible diagnosis and the presence (or absence) of amyloid would effect diagnosis & treatment plan
- Patients should also meet one of the following:
  - Persistent or progressive unexplained mild cognitive impairment
  - Satisfy core clinical criteria for AD due to any cause concomitant with atypical course or mixed etiology
  - Progressive dementia and an atypical early age of onset (<65 years)

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Inappropriate uses for Beta-Amyloid

- Patients 65+ who meet standard AD definitions & tests
- Asymptomatic patients or no clinical confirmation of impairment
- To try & determine dementia severity
- Based solely on family history or risk factors for AD
- As a substitute for genetic testing for mutations that cause AD

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On the Horizon

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F18 NAV4694 (F18 Flutafuranol)

- Currently in Phase 3
- Beta-Amyloid Agent
- Low white matter & high cortical binding in Alzheimer's
- Comparable to C11-PIB

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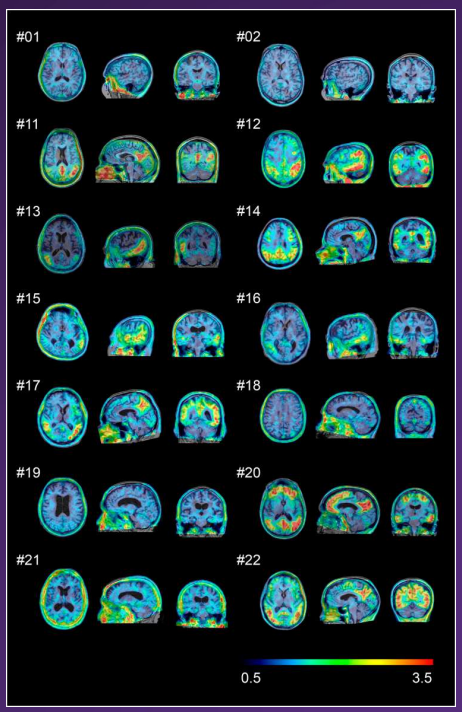
F18 PI-2620

- Binds to both 3-repeat and 4-repeat tau isoforms
- Shows Tau deposition in AD subjects
- High-sensitivity, low off target binding
- May also be useful in other taupathies



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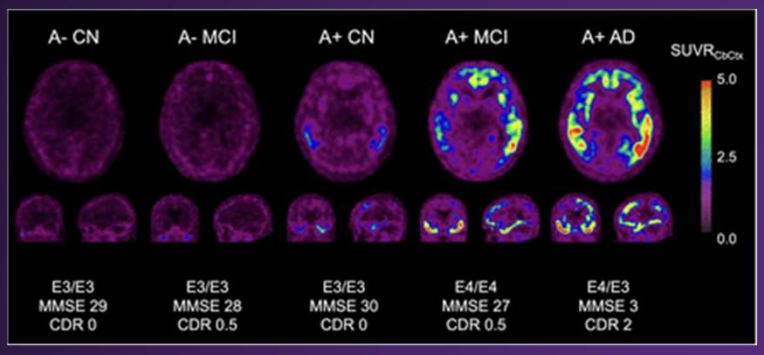
F18 MK6240

- Shown promise in distinguishing AD patients from non-AD patients
- Can detect lower tau levels than earlier tracers
- No defluorination or off-target signals to MAO-B have been observed



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F18 RO948

- High specificity for AD-tau type
- Potential diagnostic marker in differential diagnosis of AD
- Potentially useful in distinguishing AD from other neurodegenerative disorders
- Better Pharmacokinetics and metabolic properties, higher signal-background ratio than F18 flortaucipir

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F18 GTP1

- No measurable binding to MAO-B or evidence of defluorination
- A potential prognostic biomarker for AD
- Consistent with other Tau tracers

F18 PM PBB3

- Correlated well with cognitive changes
- Based off C11-PBB3, has higher metabolic stability and less off target signals
- Improved signal-background ratio

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F18 JNJ311/069

- Potential tau-specific tracer
- Shown moderate brain uptake, rapid brain washout and minor off-target specific binding
- PK profile similar to F18 Flortaucipir

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F18 PBR06

- Detects alterations in translocator protein 18 kDa (TSPO)
- May be useful in imaging microglia activation in the progression and treatment of AD
- Also potentially useful in other neurodegenerative diseases

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F18 DPA714

- Binds 18 kDA (TSPO), overexpressed in microglial activation
- Could be useful in detecting low levels of inflammation in the brain
- Potentially allow for shorter dynamic PET scans

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Which of the following best describes the role of Amyloid-Beta in Alzheimer's Disease?

A) Amyloid plaques are the main neurotoxic component involved in disease progression
B) Amyloid beta forms plaques that are a hallmark of AD pathology and may disrupt cell function
C) Amyloid beta 1-40 is the pathogenic form
D) There is a strong correlation between plaque burden and disease severity

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C) Amyloid beta 1-40 is the pathogenic form
D) There is a strong correlation between plaque burden and disease severity

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What is an appropriate use of Amyloid-Beta Imaging?

A) Imaging an asymptomatic patient with risk factors for AD
B) To determine a patient's dementia severity
C) When presence (or absence) of amyloid-beta plaques would be useful in determining a diagnosis and treatment plan
D) In a patient 65+ who meets standard AD definitions and tests

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D) In a patient 65+ who meets standard AD definitions and tests

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Which is NOT a way novel Tau & Microglial tracers may improve Alzheimer's diagnostics?

A) Selective tau imaging may help us to gather more information on AD neurobiology and its correlation with cognitive function
B) May be useful in imaging microglia activation in the progression and treatment of AD
C) Potentially useful in distinguishing Alzheimer's from other neurodegenerative disorders
D) Tau imaging shows promise to definitively diagnosis AD without the use of other diagnostics

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Which is NOT a way novel Tau & Microglial tracers may improve Alzheimer's diagnostics?

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B) May be useful in imaging microglia activation in the progression and treatment of AD
C) Potentially useful in distinguishing Alzheimer's from other neurodegenerative disorders
D) Tau imaging shows promise to definitively diagnosis AD without the use of other diagnostics

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Questions?

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Author links open overlay panelJorge A. Trejo-Lopez 1, 1, 2, 3, 4, 5, & AbstractThe key pathological hallmarks—extracellular plaques and intracellular neurofibrillary tangles (NFT)—described by Alois Alzheimer in his seminal 1907 article are still central to the postmortem diagnosis of Alzheimer's disease (AD). (2021, November 2). *Neuropathology of Alzheimer's disease*. Neurotherapeutics. https://www.sciencedirect.com/science/article/pii/S1878747923001617

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