

Alternative Therapies for ATTR

What your mother never told you

John Berk, MD

Amyloidosis Center
Boston University Medical Center

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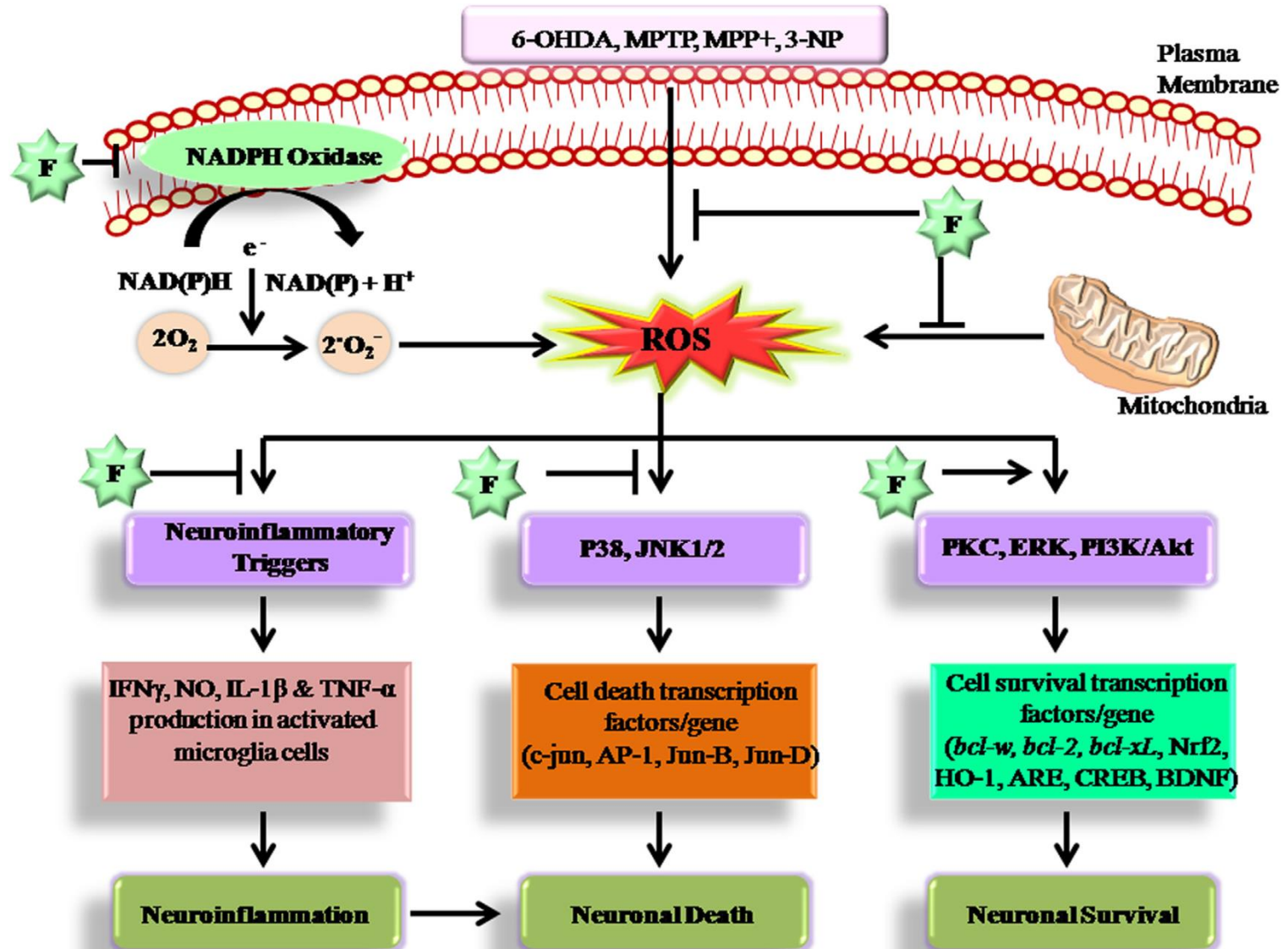
Neurodegenerative Disease

- Alzheimer's Disease (AD)
- Parkinson's Disease (PD)
- Amyotrophic Lateral Sclerosis (ALS)
- Multiple Sclerosis (MS)

Mechanisms of disease

- Inflammation/oxidative stress
- Cell death

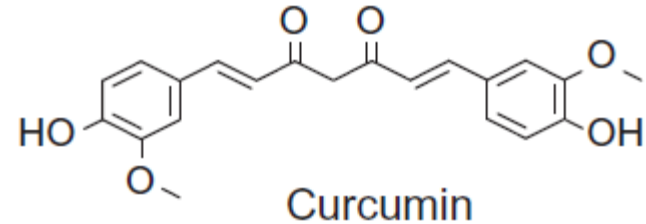
Neurodegenerative Disease



Polyphenolic Nutraceuticals

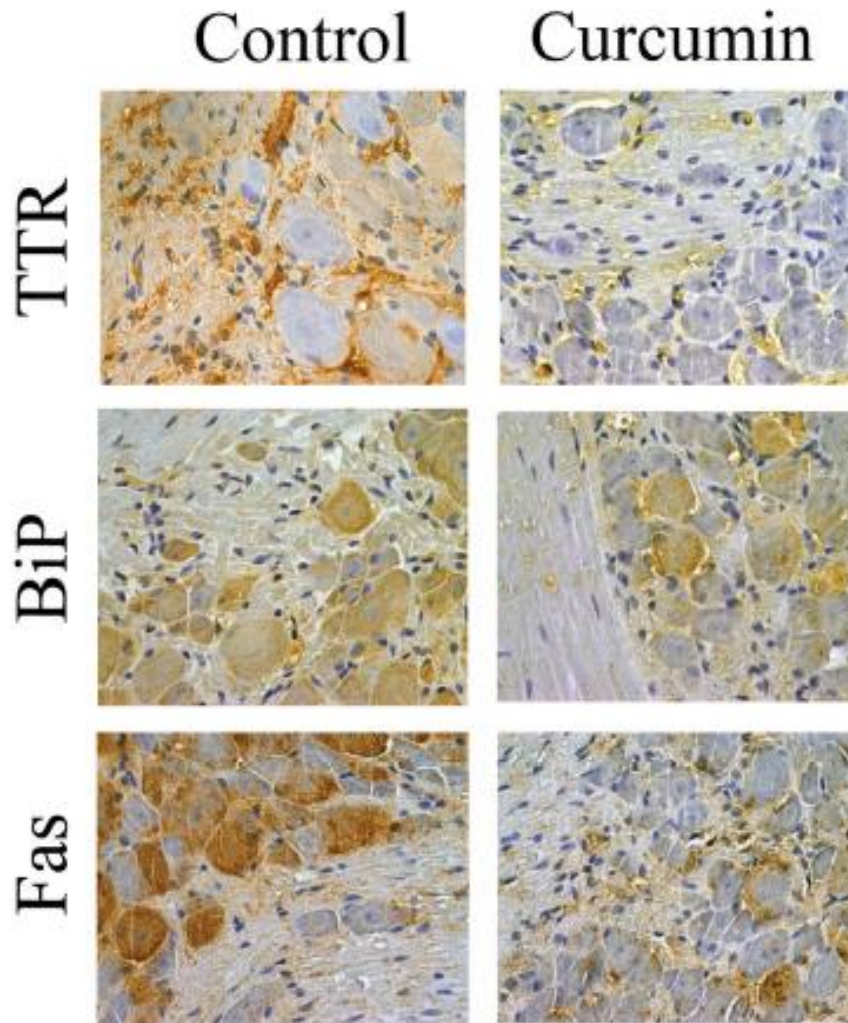
- Flavonoids
 - Vegetables, fruits, grains, bark , stems, teas, wine
- Effects on AD pathology
 - Limit oxidative injury
 - Inhibit A β fibril/aggregation, destabilize formed A β
 - Inhibit killer cell activation
 - Increase cell survival signaling
- Curcumin (active spice of Tumeric)
- Epigallocatechin gallate (EGCG)
- Resveratrol

Curcumin



- Natural polyphenol (diarylheptanoid)
- Inhibits A β aggregation/breaks up A β fibrils
- Blocks toxicity of A β fragments on brain cells
- Competes T4 binding to TTR
- Promotes clearance of TTR aggregates
- Inhibits steps of ATTR fibril formation
- Crosses blood brain barrier

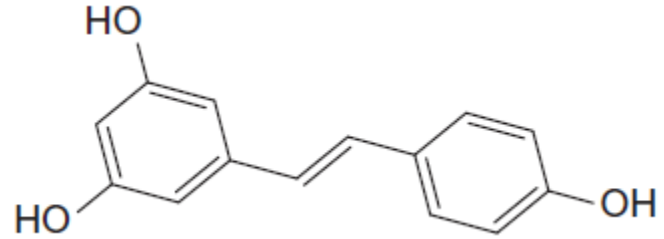
Curcumin decreases ATTR and injury signals in mouse nerves



COMMENTS

- Prefibrillar aggregates
- 6 weeks curcumin in drinking water
- Poor bioavailability
- Unachievable levels
- Does not recapitulate human disease

Resveratrol

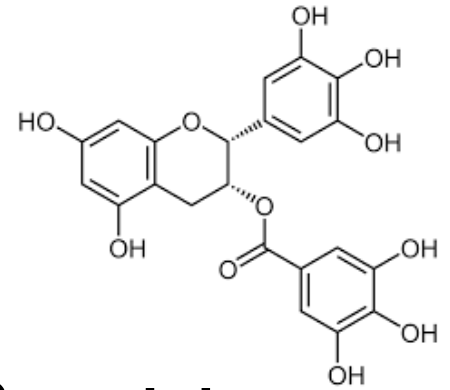


- Damaged grapevines, pines, peanuts
- Stabilizes TTR tetramer conformation (T4 pocket)
- Promotes aggregation of potentially toxic TTR monomers

Comment:

- Insufficient data in humans
- Poor bioavailability
- Effective dose undefined

EGCG



- Inhibits neurodegeneration in ALS
- Protects rat brain neurons from A β toxicity
- Activates cell survival (PI3K/Akt) pathway
- Stabilizes TTR tetramers
 - Different mechanism than diflunisal
- Inhibits ATTR amyloid fibril formation
- Promotes breakdown of amyloid deposits
 - Early amyloid aggregates
 - Mature/fixed amyloid deposits

EGCG

ATTR

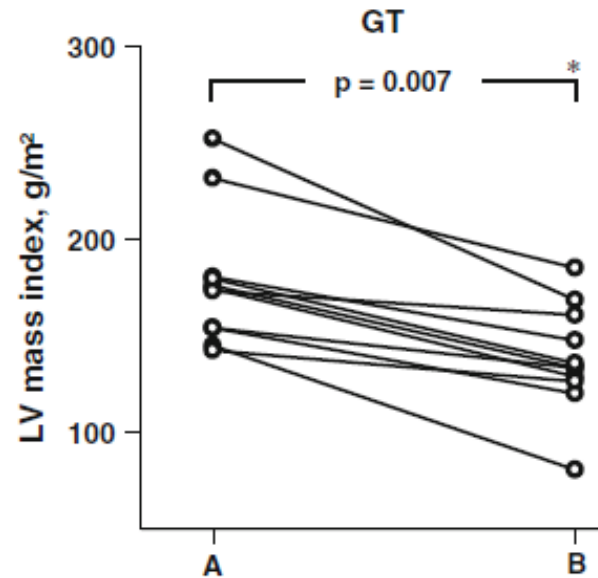
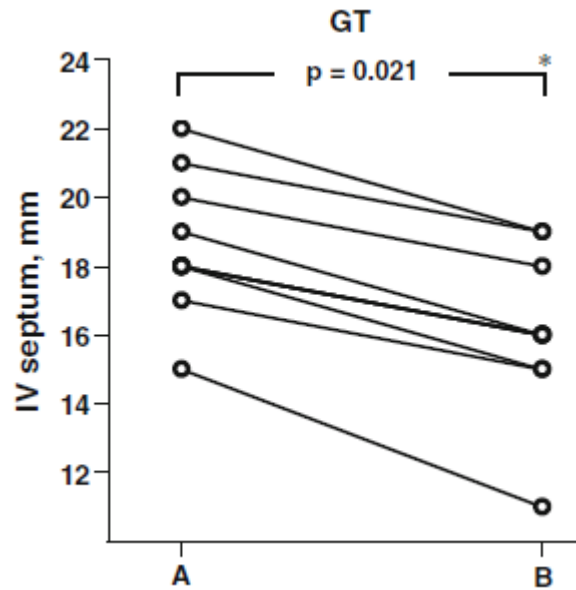
- 14 ATTR cardiomyopathy patients
- EGCG 500-700 mg/day x 12 months
- Findings
 - Echo: no change in LV wall thickness
 - Cardiac MRI: 12.5% decrease LV mass

AL

- 59 patients with AL amyloid cardiomyopathy
- EGCG 600-800 mg/day + AL amyloid treatments
- Findings
 - 11 patients -- > 2 mm septal wall decrease
 - 6 months (range, 3-10)

EGCG

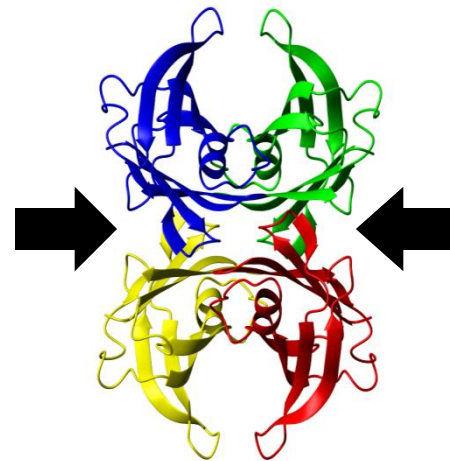
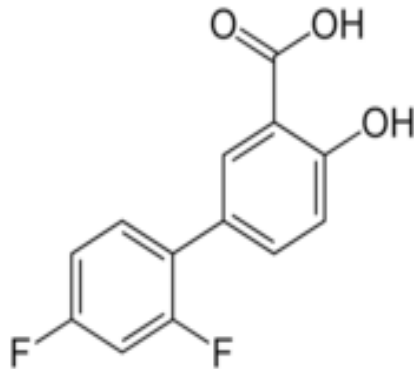
AL Amyloid Cardiomyopathy



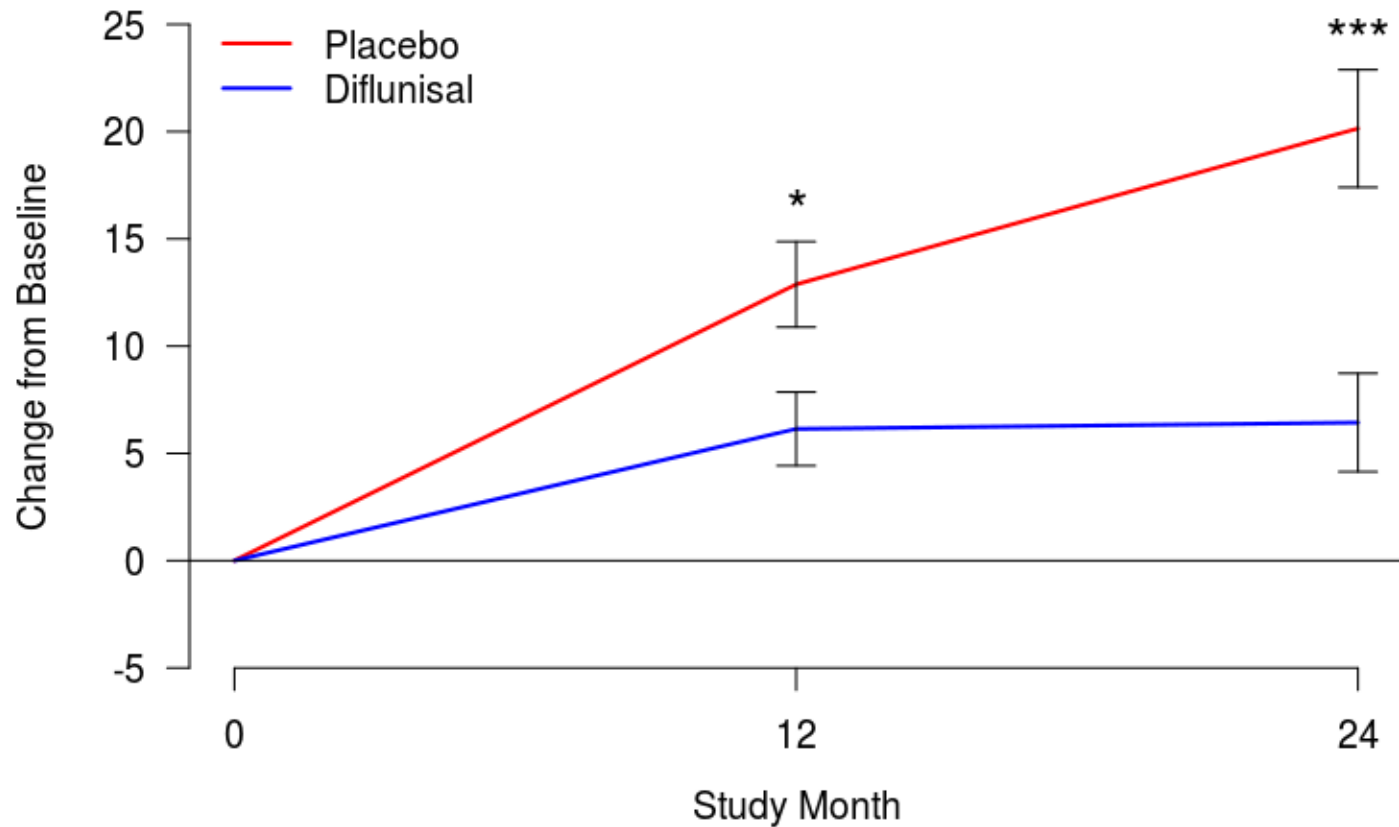


Diflunisal IND 68092

- 2',4'-difluorophenyl salicylate derivative
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High serum concentrations and low toxicity

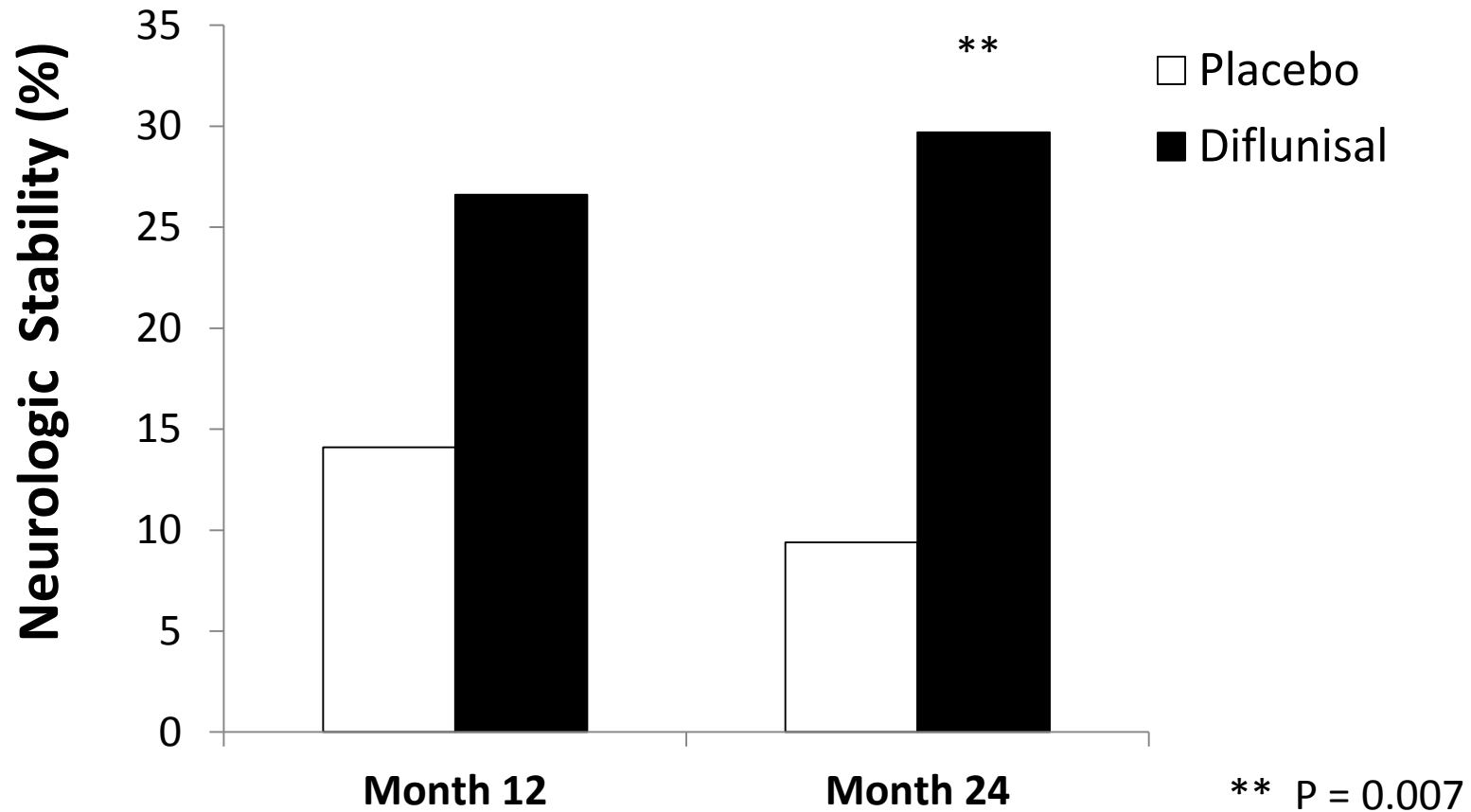


ANCOVA: NIS+7



ANCOVA significance at: * - 0.05 level, ** - 0.01 level, *** - 0.001 level

No Worsening in 30% taking Diflunisal for 2 YRS





Conclusions

- Diflunisal inhibits neurologic progression and preserves quality of life in patients with ATTR-FAP
- Effective across gender, mutations, and severity of disease at entry
- Provides a rare example of repurposing old drugs for new indications

Doxycycline/TUDCA

- Doxycycline 100 BID/TUDCA 250 mg TID x 12 m
- 20 Subjects (17 ATTRm, 2 ATTRwt, 1 Domino LT)

Months	N	Nerves	Heart
6	10		
12	7	Subst. stability	No progress
Discontinue	2		
Lost	1		

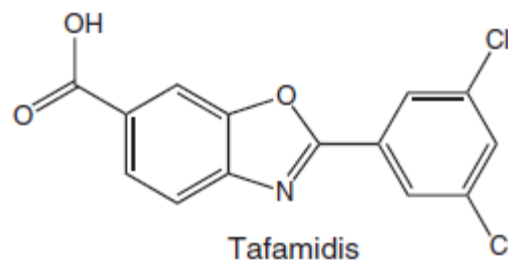
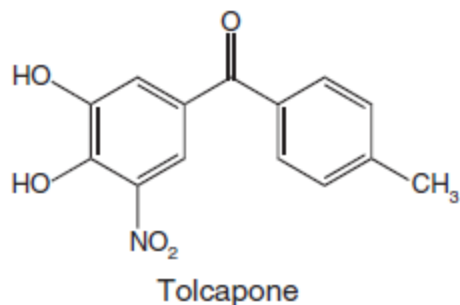
New TTR Tetramer Stabilizers

Tolcapone

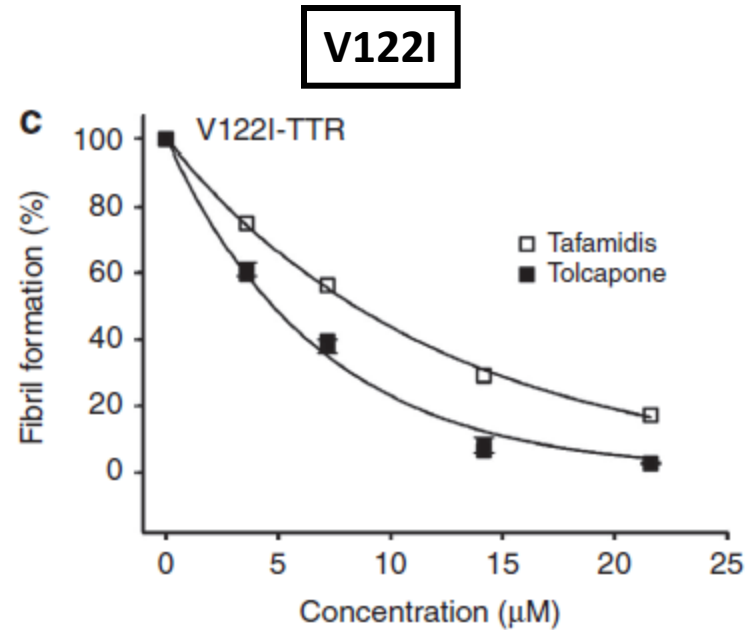
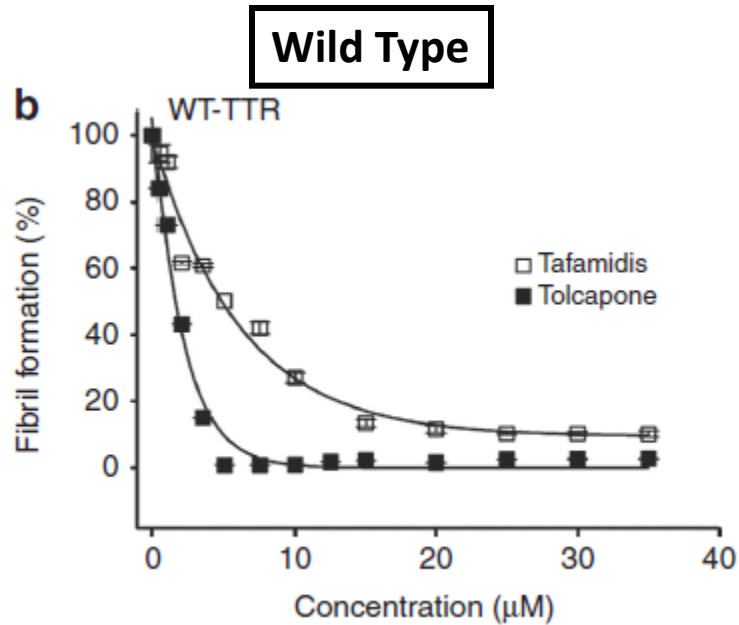
- Catechol-*O*-Methyltransferase (COMT) Inhibitor used in PD
- Crosses blood-brain-barrier
- Binds T4 docking site on TTR tetramers
- TTR tetramer stabilizing effect ~2X similar concentration

Tafamidis

- Short half life may require reformulation



Tolcapone inhibits WT & V122I ATTR



New TTR Tetramer Stabilizers

AG10

- Binds T2 docking site
- More selective binding of T4 than Tafamidis or Diflunisal
- No identified toxicities
- Potentially more mg potent than other TTR protein stabilizers

