MCI White Paper

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MCI Consensus (1)

- Stage of disease prior to a clinical diagnosis of dementia.
- Complaints of cognitive change unaccompanied by significant functional change, although some complex activities may be affected.
- Cognitive performance worse than age matched controls.
- Numerous terms used to define this entity.
- Overwhelming epidemiologic data indicating higher rate of conversion to dementia than non-MCI subjects.

MCI Consensus (2)

- Autopsy data confirms AD changes in patients who die during MCI stage.
- MCI is heterogeneous; subtypes include AD, vascular, mixed, rare dementia sub-types
- Ambiguities in diagnosis; regulatory feedback suggests studies should be confined to a single MCI sub-type at a time
- Differences in progression rate by APOE genotype suggest may be different or heterogeneous disease mechanisms
- Progression as measured by Biomarkers not established.
- Regulatory acceptance of MCI label based on delay to diagnosis paradigm unlikely
- None of the delay to diagnosis studies reported to date have demonstrated significant difference in conversion rates.

Delay to Diagnosis of MCI Paradigm

It is unclear how mild cognitive impairment would be diagnosed by the community physician, and whether such patients would be the same and respond similarly to those in clinical trials

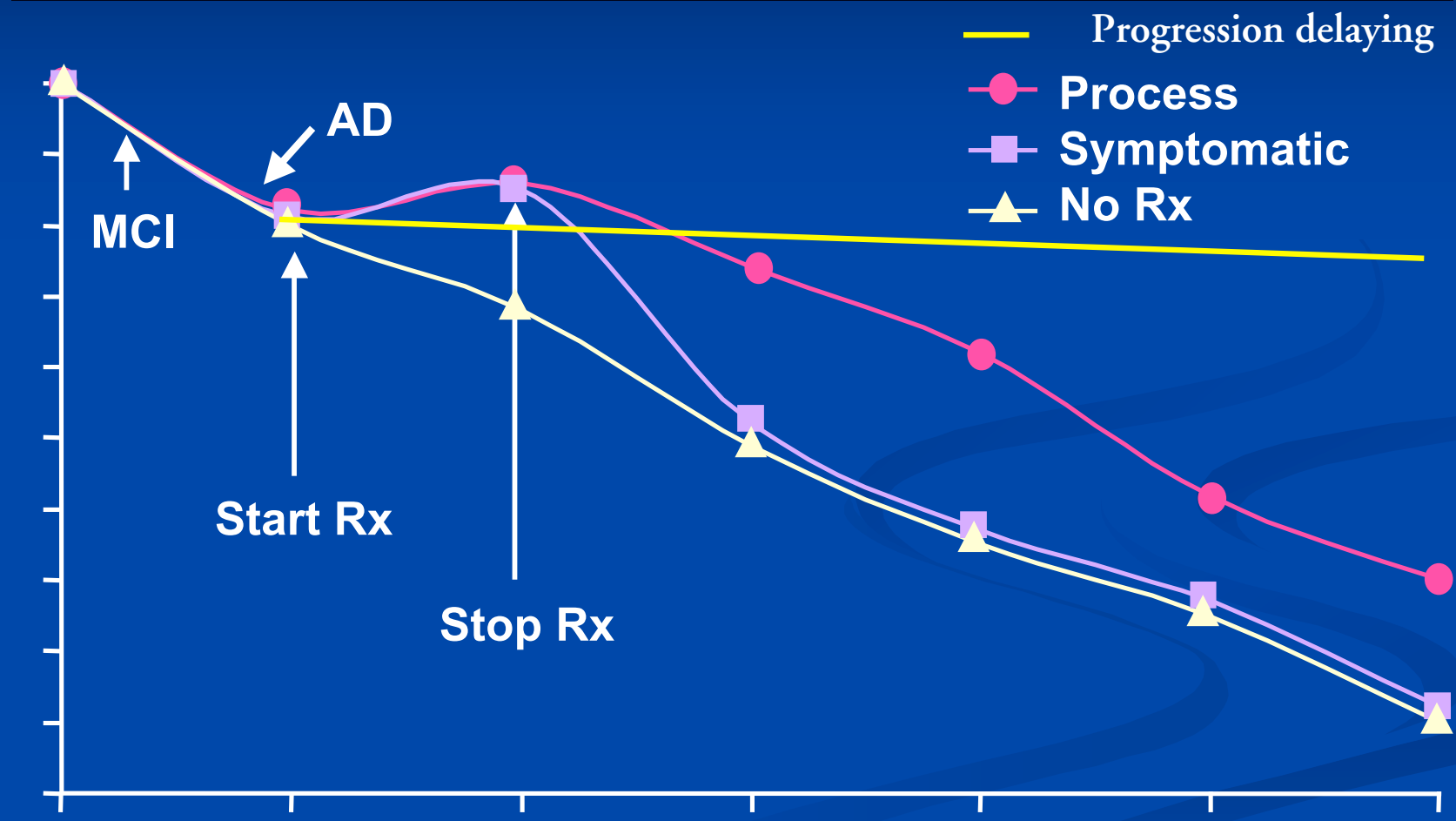
- MCI criteria in clinical trials contain subjective features, that depending on interpretation give widely varying conversion rates (where are the cutoffs in cognitive testing, how much dysfunction in ADLs is allowed?)
- Likely to be very low conversion rates in first year in clinical trials as truly borderline patients will be excluded
- Conversion criteria from MCI to Dementia are not well defined in the community and may differ between clinical trials

MCI Consensus (3)

Delay to Diagnosis Studies

- Six 3/4 year trials performed with fairly similar selection criteria, outcome measures
- Minor differences in selection criteria (eg, NYU Paragraph Recall cut-off scores) affects rates of conversion
- Considerable disagreement between caregiver, investigator and adjudication board diagnosis of dementia.
- High attrition; some evidence of higher intolerance to cholinergic agents
- **General agreement that these studies are unlikely to demonstrate benefit in patients with MCI.**

Theoretical Trajectories of Treatment Interventions on the Course of AD



Study Designs for MCI/ Mild AD Trials for the Future

- Double-Blind, Placebo-Controlled, 6-month
- Long-term, parallel group studies may be better to demonstrate efficacy/safety
- Selection criteria to reflect mild AD
- Analyses determining both time to failure* and longitudinal change in outcome measures** recommended
  - *AD; Nursing Home Placement; MMSE < 10; loss of two ADLs; Death
  - **Cognition; Global function; ADLs; Behavior
- Biomarkers suggested
  - Structural MRI
  - PET-FDG
  - Amyloid PET
  - CSF-A_,Tau

Biomarker Caveats

- MRI- Cholinesterase inhibitor study supports increased brain volume
- MRI- Vaccination -- Clinical improvement but reduced brain volume

Ideal Features for Long Term MCI or Mild AD Trials

- Trial length - long enough to show change
- Assessments - appropriate to disease stage, sensitive to change
- Study design - ideal is double-blind, placebo-controlled
- Biomarkers
  1. Measure change secondary to disease progression, structural MRI, CSF-Tau
  2. Measure parameter related to drug mechanisms, A_ lowering compound – amyloid PET etc.

MCI – Study Design

1) Double-Blind, Placebo-Controlled
2) 3 Year duration
3) Primary assessment
   a) *Cognitive battery sensitive to MCI changes*
   b) *ADCS-ADL*
4) Secondary assessment
   a) *Behavioral tests, eg, Behave AD, NPI, Cornell Depression Rating Scale*
   b) *CIBIC+*
   c) *Structural MRI*