Concepts Underlying Strategy of Development of New Chemical Entities for Mild Cognitive Impairment: Revisiting The Prevailing Consensus in 1999

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Strategy for the Development of a Program for Studying MCI

- Indication
  - Issues Surrounding MCI
- Investigational Agent
  - Pre-clinical and clinical data suggesting potential for an effect
- Operationalizing
  - Trial design needed to satisfy scientific and regulatory requirements for a “win”

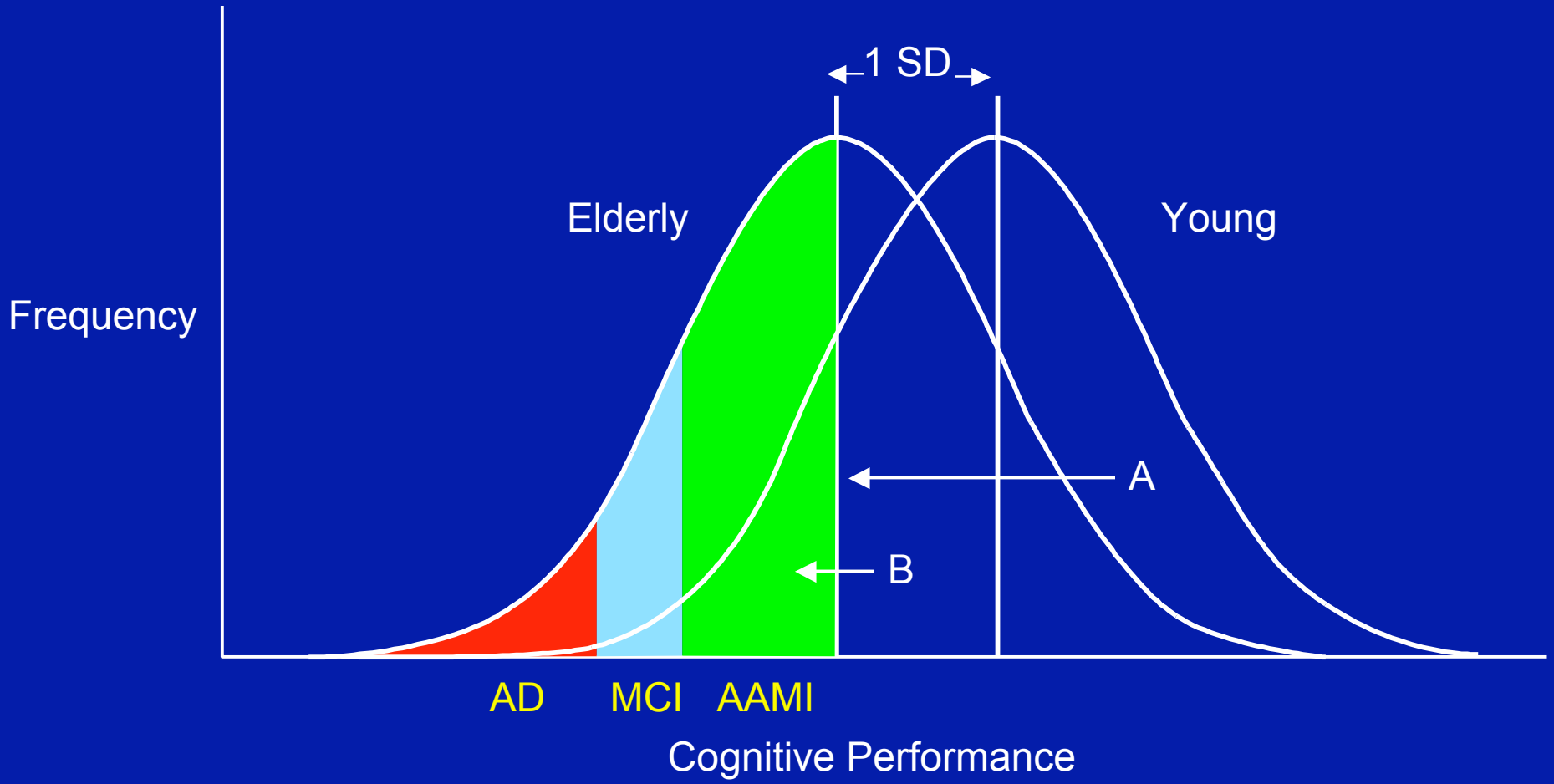
Issues Surrounding MCI as an Indication

- Is MCI
  - a new disease entity?
  - very early AD?
  - a heterogeneous syndrome with variable outcomes?
  - an approvable indication?
- Pathophysiology/ Neurochemical/ Neuropathological substrates
  - progression of neuropathological changes
  - Neurochemical changes
  - Maturation of the neuropathological substrates

Conceptualization of MCI

- Continuum in cognitive function from normal aging to AD
- AD develops for many years prior to symptoms sufficient for diagnosis
  - MCI is stage of progression between normal cognitive function and mild AD (MCI is very early AD)
- Cognitive and neuroimaging markers of early AD are generally present in MCI
- At autopsy, all MCI cases are reported to have AD neuropathology
- MCI phase can last 5 or more years
- Rate of conversion to AD is about 15% per year

Aging, AAMI, and AD



Adapted from Ferris and Kluger. *Aging, Neuropsychology and Cognition*, 1996.

Evidence Supporting the Indication of MCI

- Epidemiologic/ Clinical data confirm state of MCI
- Petersen et al. 1999 found conversion from MCI to AD at a rate of 12%/yr vs 1-2% in normals
- Ebly et al. 1995 (Canadian study) estimate prevalence of 16% over the age of 65; 5yr conversion rate at 50%
- Verret et al. 1999 report 3 yr conversion rate of 45% for patients with CDR 0.5

Likely Subtypes of MCI

- Prodromal stage of Alzheimer's disease (AD)
- Prodromal stage of vascular dementia (VaD)
- Prodromal stage of mixed VaD/AD
- Prodromal stage of other rare dementias
- Stable or reversible cognitive impairment (heterogeneous or unknown causes)

Trial Design Requirements to Satisfy Scientific and Regulatory Needs

- Scientific
  - Patients diagnosed as MCI are neither normal nor have AD
  - Conversion to AD is diagnosable by clinical criteria alone (not based on psychometric scores only)
  - Conversion supported by change data from a disease valid, biological marker (MRI)
- Regulatory
  - Validity of diagnosis
  - Validity and interpretability of outcome criteria
  - Adequacy of trial to provide “substantial” evidence of efficacy

Primary Efficacy Variables

- Time from baseline (number of days after randomization) to a clinical diagnosis of AD

- The composite standardized (Z) score of cognitive function created by using a battery of 10 cognitive tests

Long-term Trials in MCI

- At least 6 trials of two or more years of duration initiated
- FDA reviewed and agreed with delay to diagnosis design; CHMP reviewed 4 of the protocols
- Subsequently, both contested notion that above trials would lead to a MCI label
- Five MCI delay to diagnosis completed
- Four did not meet primary endpoints
- Future of MCI as an indication not certain in absence of scientific community consensus