

# FDA Perspective on Disease Modification in Schizophrenia

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# Goals and Expectations

- Develop treatments that provide clinically meaningful benefits (patients' Expectations)
- Primary Endpoints must be clinically meaningful
- Capture how patients Feel, Function, Survive
- Disease modifying treatments must impact how patients feel, function, or survive
- Must it impact the biological process as well?

# Challenges in Schizophrenia

- What are the pathophysiological processes?
- Is it a progressive disease or illness? Course, trajectory, rate? Heterogeneous clinical courses and probably heterogeneous underlying pathophysiology, at different phases of illness
- Progression in everyone or subgroups? Identify patients & groups who will deteriorate.
- Which aspects of D/O and DZ are progressive? Positive Sx, Negative Sx, Cognitive impairment (specific), general deterioration of functioning or specific functional impairments?
- When to study progression? How long to study?
- What type of study designs?

# Definitions of Disease Modification

- Gold Standard: Improves all aspects of the disease/disorder (Biological, Clinical symptoms, Functioning)
- Targets fundamental pathogenic mechanisms; ideally at the initiating processes & events (right place, right time)
- Cummings (AD): Affect the underlying pathophysiology of the disease and have a beneficial outcome on the Course of AD
- For CNS DZ: Neuroprotective, Neurorestorative treatments
- Sampo – only patient-centered: delay disability in AD, independent of the biological mechanism

# European Task Force (AD) Definition

- DzMod Rx: has a long-lasting effect on disability ( $\geq 18$  months)
- Implies only effect on clinical progression
- But, symptomatic treatment (donepezil) can delay progression (donepezil) without affecting disease process
- Call it Disease *Course* Modification?
- Is this enough? It's a substantial clinical benefit.
- But do we call it disease modification?

# Other Proposed Definitions

- Based on clinical benefits – changing course
- Slowing disease progression
- Delay in reaching predefined disease milestones (conversion from MCI to AD; prodromal/APS to Schizophrenia)
- Reduction in progression of a biomarker: halting neurodegeneration or neuropathology (neuritic plaque), amyloid, cortical atrophy, hippocampal atrophy, metabolism-PET)

## Rheumatoid Arthritis: Disease-modifying Antirheumatic Drugs (DMARD)

- Labels (I&U) anti-TNF agents: “Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- Indications & Usage doesn't include the term 'disease modifying' but...
- DM Concepts, Definitions, Labeling language (Indications, Clinical Studies sections) will differ by disease

# Why these Claims are Possible in RA

- Established that the disease is progressive
- Understanding of some of the disease process
- Established connections among inflammation, joint destruction, clinical symptoms and real-world functioning (how patients feel and function; survival of joints)
- Developed validated clinical, laboratory, radiologic endpoints
- Subgroup/Enrichment: patients who failed other DMARD (methotrexate).



# RA Endpoints

- American College of Rheumatology (ACR) score: composite of clinical and biomarkers
- Clinically meaningful elements: symptoms, signs, inflammatory markers, radiologic, functional disability
- Responder analysis (clinically meaningful)

# Components of ACR Response

## Definition

- Number of Tender Joint
- Number of Swollen Joints
- Physician Global Assessment
- Pain
- Disability Index
- Erythrocyte sedimentation rate
- C-Reactive Protein

# Radiographic Response

## Structural Joint Damage

- Total Sharp score
- Erosion score
- Joint Space Narrowing score

# Physical Function Response

- Disability Index of the Health Assessment Questionnaire (HAQ-DI)

# Multiple Sclerosis

- Established disease progression
- Understand some of the pathophysiology: inflammatory/immune; white matter destruction
- Subgroup/Enrichment/Indication: Relapsing MS, specific disability scale score, some failed on interferon
- Clinically meaningful endpoints (symptoms, function, MRI findings)
- Primary endpoint: Time to onset of sustained increase in disability. Defined event. Survival analysis. Endpoint at 2 Years
- Kurtz Expanded Disability Status Scale (EDSS)

# MS Biomarkers

- Described MRI biomarker findings in label: Clinical Studies section (14)
- Proportion of patients with newly enlarging T2-hyperintensive lesions
- Proportion of patients with Gd-enhancing lesions
- Previously established as Clinically Meaningful – symptoms, signs, disability

# Alzheimer's Disease

- Understand some of the disease process
- Progressive Illness/disease; but when do study it? In which subgroup(s), for how long?
- Much progression has occurred before clinical diagnosis
- Which endpoints
- Role of amyloid
- Does clearing amyloid alone work: vaccine results
- Creates number of challenges in study design

# Focus on MCI and Familial AD

- Subgroups, Enrichment
- Amnestic MCI plus Amyloid abnormality
- May highly predict conversion of MCI to AD
- (~ 80% predictive value?)
- Industry may aim for this level of prediction in order to conduct studies



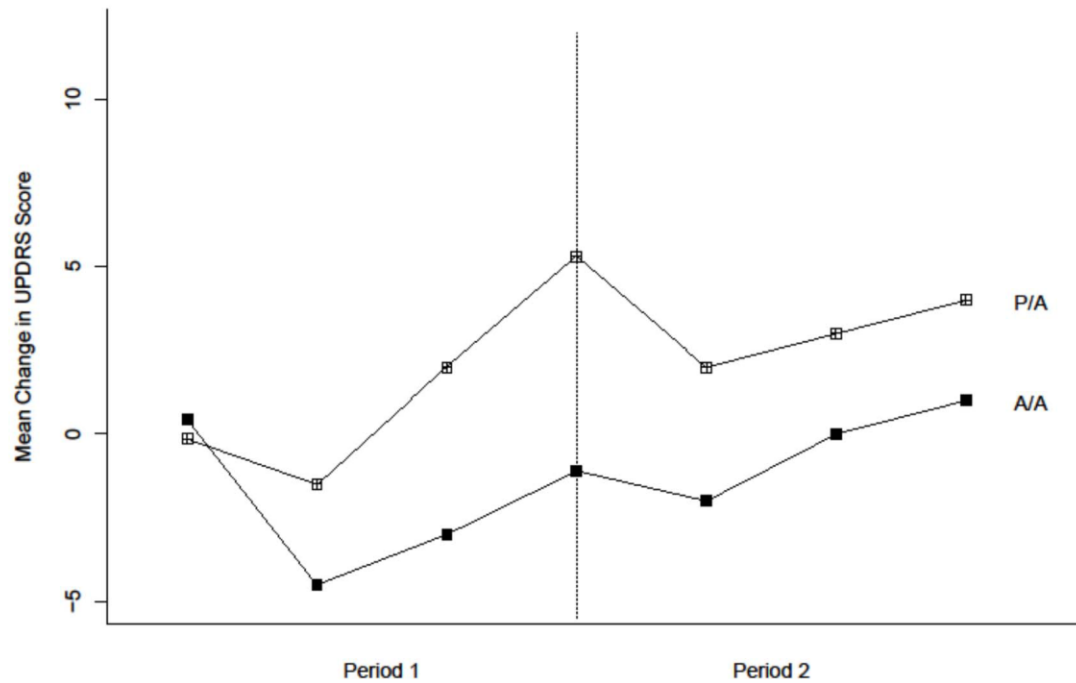
# Parkinson Disease Trials

- Problem separating effects on symptoms from from potential disease-modifying effects
- MAOB inhibitor
- The drug may provide both symptomatic benefit and disease modification
- Specific study designs (Two-period): Delayed start, randomized staggered withdrawal

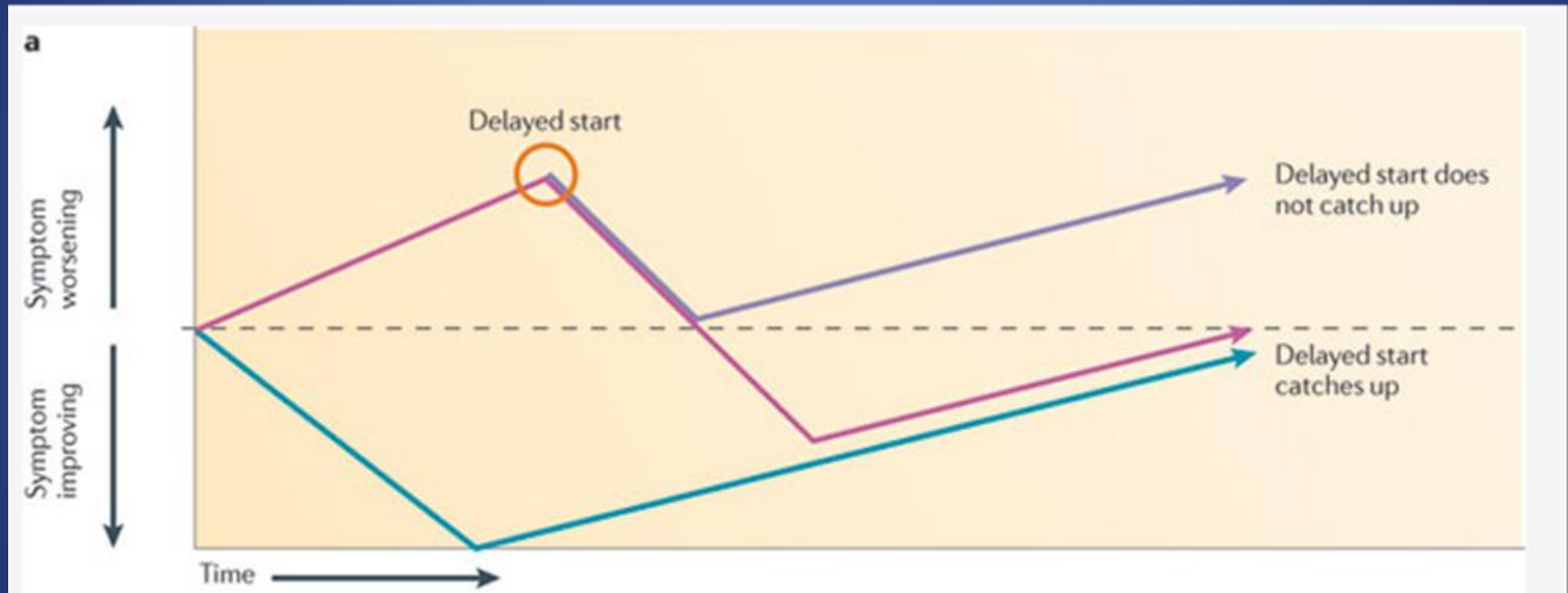
# Delayed Start Design (Leber 1996,)

- Subjects randomized to 1) active treatment followed by active treatment (A/A), or 2) placebo followed by active treatment (P/A)
- Period 1: Estimation of Total treatment effect ( $\alpha_T = \alpha_D + \alpha_S$ )
- Period 2: Estimation of symptomatic ( $\alpha_S$ ) and disease-modifying ( $\alpha_D$ ) components

### Delayed Start Design



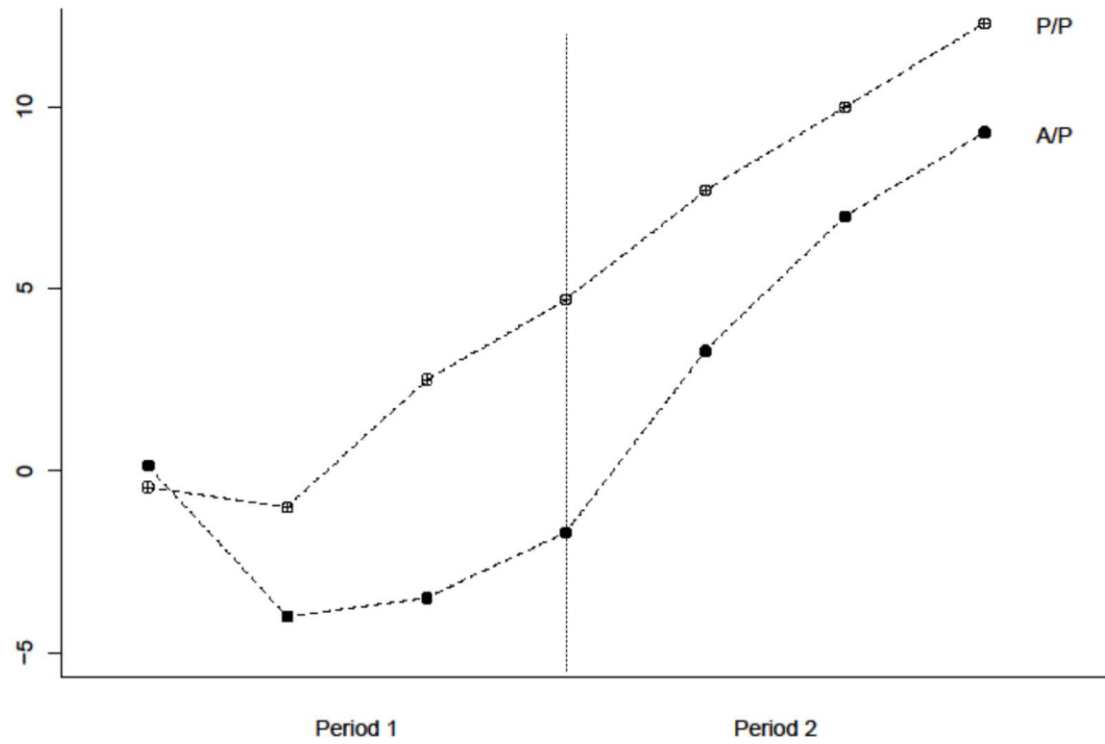
# Meissner et al (2011)



# Withdrawal Design (Leber 1996)

- Subjects randomized to active treatment followed by placebo (A/P) vs. placebo followed by placebo (P/P)
- Period 1: Estimation of Total treatment effect ( $\alpha_T = \alpha_D + \alpha_S$ )
- Period 2: Estimation of symptomatic ( $\alpha_S$ ) and disease-modifying ( $\alpha_D$ ) components

## Withdrawal Design



# Single-period (parallel) vs. 2-period study

- 1-Period. Comparing Slopes. Difficult to determine whether the treatment effect is symptomatic, disease-modifying, or both. Must separate the short-term beneficial effects on symptoms and DZ-mod effects.
- Problem with simple comparison of slopes: Magnitude of the symptomatic effect may depend on factors that change over time (true disease state, measured disease state, age, drug exposure)
- Absence of valid markers of underlying disease progression
- Reliance on clinical measures of outcome

# 2-Period Designs

- 2-period can possibly distinguish between symptomatic and disease-modifying effects when there are no available direct measures of underlying disease progression.
- Challenges in Knowing: natural history, when to intervene, how long to study each phase
- Problems: Model assumptions, lack of blinding in Period-2 (DS), dropouts, missing data, interpretation, statistical analysis, estimating treatment effects, feasibility, implementation, recruitment



# Potential Subgrouping or Enrichment

- Subtypes based on clinical, cognitive, functional courses of illness
- Prodromal, Attenuated Psychosis Syndrome, prodromal + positive family history, first episode
- Biological features: neurodegeneration, circuitry, imaging findings, neurophysiology, genetic subgroups (VCFS), immune or inflammatory dysregulation,

# Claims & Description of Findings

- Will always depend on scientific progress and evidence established in trials
- Clinically meaningful treatment effects can always be described in labeling, somehow
- Treatment of X, treatment of subtype X, treatment of feature Y associated with X, delayed onset of X, reduced risk of X