Long-term Efficacy Trials: Industry Perspective

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Common Methodological Issues in Establishing Long-Term Efficacy for Psychotropic Drugs

- Broad consensus that currently available regulatory/developmental guidelines for establishing acute phase efficacy of psychotropic agents are generally acceptable
- Overwhelming agreement that based on their use for extended periods of time, long-term safety and efficacy data must be available
- Regulatory guidelines for psychotropic drugs used in long-term treatment are broadly similar and ignore disease specific issues

Time-line for Availability of Long-Term Efficacy Data

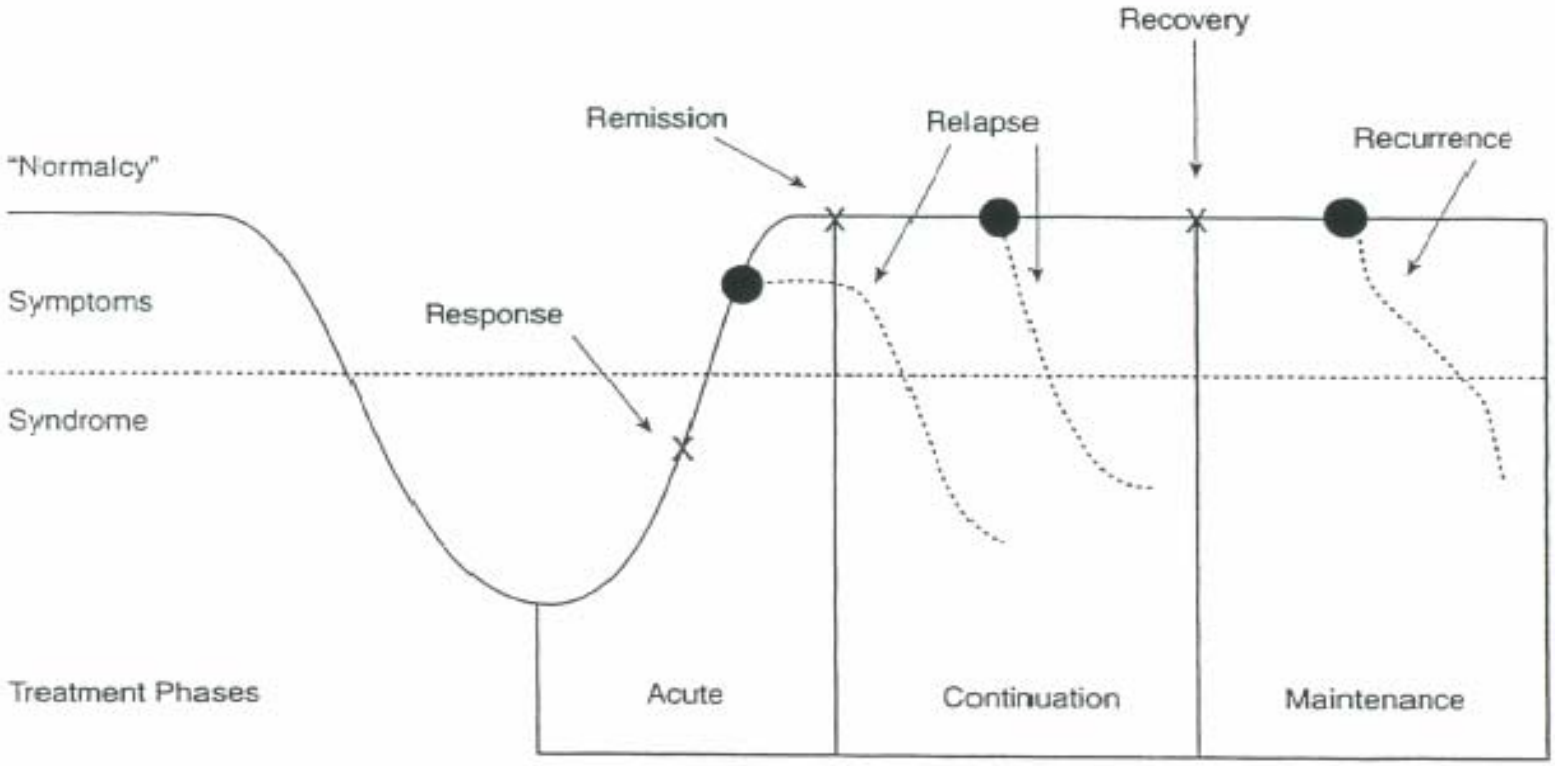
- Ideally at time of submission
- Unfortunately, this would delay submission by 2 or more years
  - Long-term efficacy trials can be started only after effective, well-tolerated dose-range established in Phase 2B/ Phase 3
  - Short-term pivotal efficacy trials require 4 to 8 weeks of treatment, while long-term efficacy trials (eg, randomized withdrawal) need ≥ 1 year of treatment

Heterogeneity in Disease Course in Psychiatric Illnesses

- Need for long-term data, and consequently study design vary by disease course
  - ***Schizophrenia*—chronic; may not return to baseline; irregular exacerbations**
  - ***Bipolar disorder*—recurrent disorder with manic and depression phases, highly variable in timing & duration**
  - ***Anxiety disorders*—shorter treatment often is adequate**

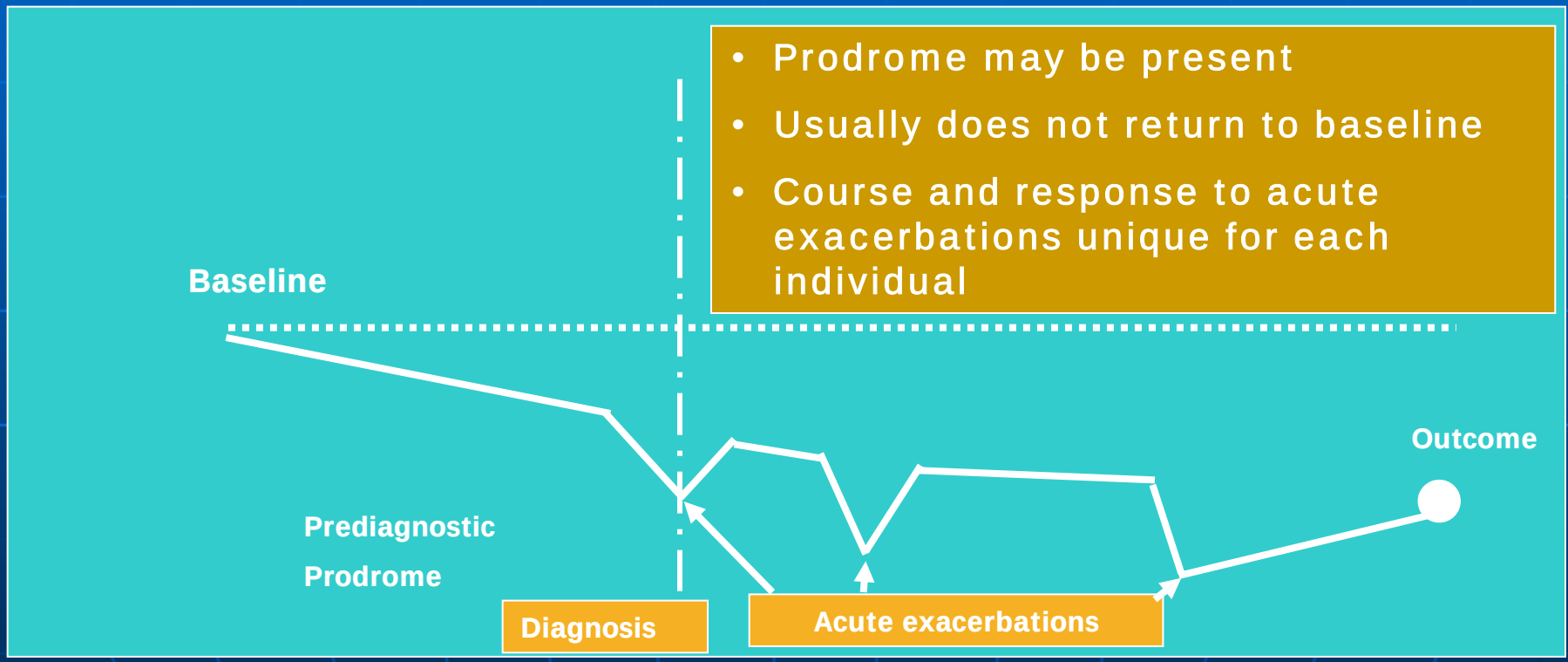
- Most current terminology relating to treatment phases is based on depression research:
  - **Response -- Relapse**
  - **Maintenance of effect -- Recurrence**
  - **Remission -- Prophylaxis**
  - **Recovery**

Generalized Course for Depression



- Broadly similar course for most persons with disorder
- Frequently returns to baseline

Variable Course of Schizophrenia



Conclusion: Different study designs are needed to address differences in diseases and treatment needs.

Long-term Efficacy: What Questions Does the Industry Need to Answer?

- Patient: Will the drug that I responded to continue to work long-term?
- Physician:
  - Will the drug that the patient responded to continue to work long-term?
  - What happens if the medication is discontinued?
  - How long must the medication be taken?

Long-term Efficacy: What Questions Does the Industry Need to Answer?

- Regulatory Agencies: Demonstrate that maintenance of the response achieved requires continued use of the drug.
- Society: Is the benefit of the drug reflected in decreased morbidity/mortality, improved QoL, and overall reduced cost of disease?

Potential Long-Term Efficacy Claims

- Prevention of relapse within the index episode
- Maintenance of effect
- Long-term efficacy
- Prevention of recurrence of new episodes
- Effect on disease progression, reduction of intensity, frequency and duration of new episodes

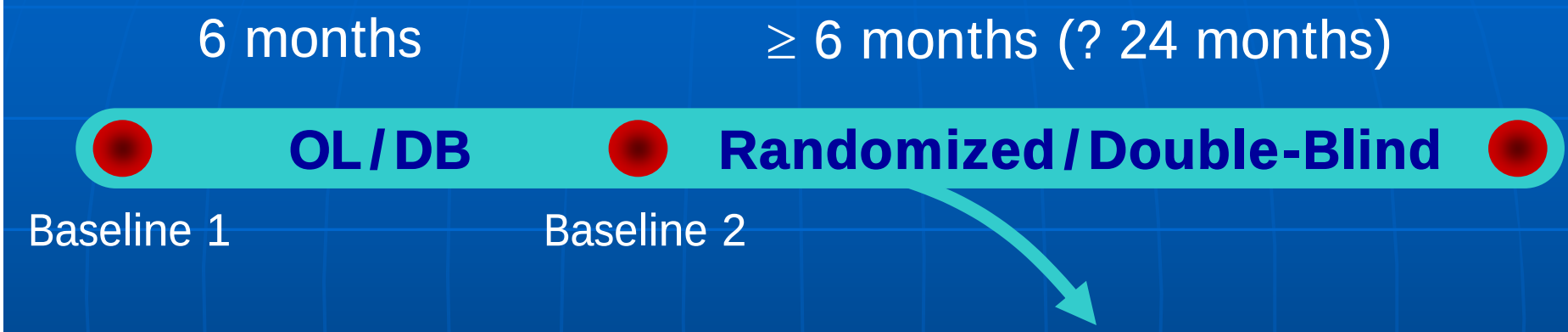
Treatment Phases in Psychiatric Illnesses

- **Acute phase or short-term treatment**
  - Control of symptoms/attainment of acceptable level of response (4-6 weeks of treatment)
- **Continuation treatment**
  - Consolidates response attained/conversion of partial to full remission/prevention of relapse (stable remission for 4 – 6 months)
  - Depressive episode following recovery is considered to represent a new episode of illness, i.e. recurrence
  - Relapse represents an exacerbation of the index episode
- **Maintenance treatment**
  - Recommended for responders who have evidence for an increased risk of recurrence, i.e., patients experiencing multiple episodes in the last few years

Current Treatment/Regulatory Guidelines

- **Acute phase/short-term treatment**
  - General satisfaction with guidelines 4 – 8 week trials
  - High translatability of label for clinical practice/prescribers
- **Continuation/Long-term treatment**
  - Relapse prevention i.e. time to failure: the only labeling approved by FDA; not a specific claim for CHMP.
  - Well founded statistical basis; however, relevance for prescribers questionable for long-term treatment
  - Maintenance of effect: continuation of response obtained in short-term treatment over an extended period of time
    - High translatability for findings for patients/prescribers
    - Statistical analysis/basis need consideration; development of alternatives paradigms need consideration

Relapse Prevention Design



Relapse Prevention Design: Study Phases

Study Period	Design	Treatment Duration	Objective
Stabilization	Open Label/Double Blind	6 months	Selection of stable patients
Randomised Treatment Period	Double Blind	12 months	Relapse determination (time to relapse, incidence)

Relapse Prevention Design: Study Phases by Disease

Disease	Stabilization Period	Randomised Treatment Period
Depression/Schizophrenia (Symptomatic Patients)	Acute treatment 6 weeks Stabilization 6 months	Depression 6 - 12 months
Depression/Schizophrenia/stable patients	Historical documentation Cross titration and stabilization/6 months	6 - 12 months
Bipolar Disorder/Frequently Relapsing	Stabilization 4-6 months	18 - 24 months
Schizophrenia suicidality	None	18 - 24 months

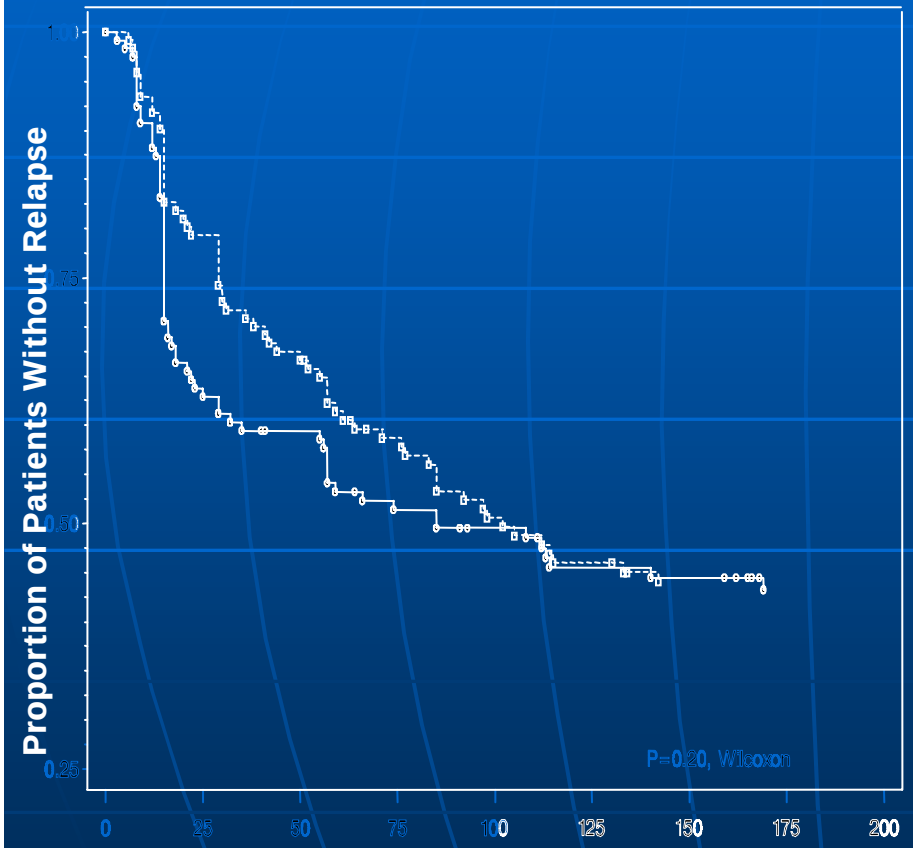
Relapse Prevention Design

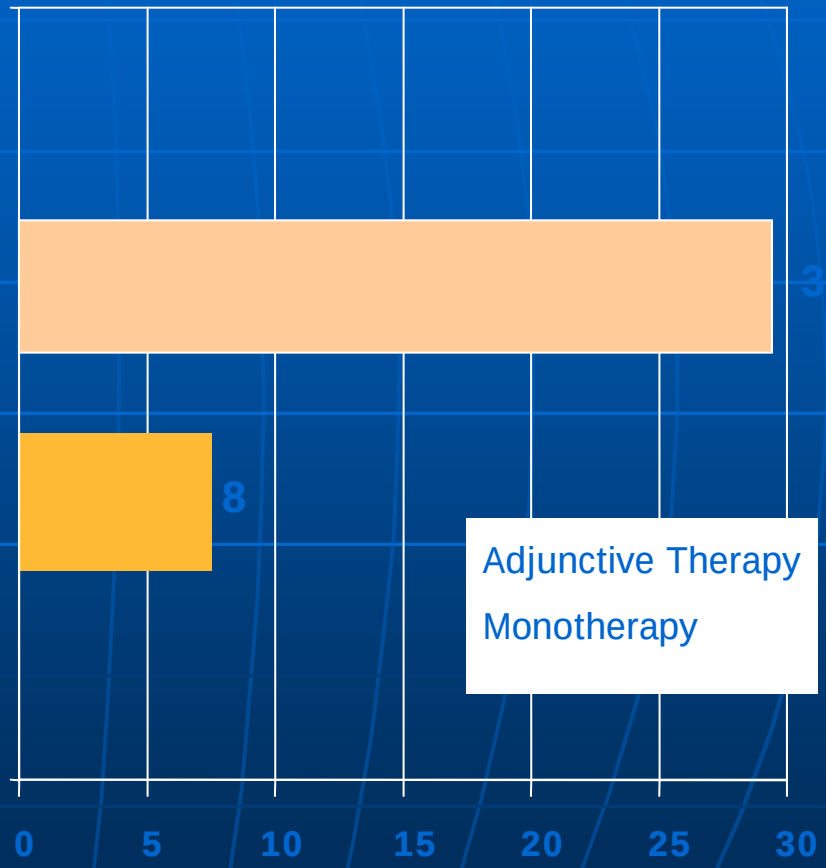
- Randomized treatment
  - Definition of relapse (diagnosis specific)
    - Combination of hard and soft criteria
    - Short-lived event in chronic illnesses
    - Need for confirmation of relapse
  - Use of independent monitoring boards Outcomes
  - Incidence versus time to relapse
  - Alternative outcomes
    - Number of “days well”
      - Diagnosis specific
      - Investigator versus patient/informant reported
    - Frequency, severity and duration of symptom fluctuations
      - Cyclical disorders

Issues with Relapse Prevention Design

- **Randomized Withdrawal (RW) Design broadly accepted as a design to evaluate ability of treatment to prevent relapse in index episode**
  - Stabilization requirement excessive
  - Placebo switch of responders considered unethical
  - Single episode of worsening given excessive weight
  - Effect of abrupt withdrawal
  - Patients may deteriorate but not meet relapse criteria: study would be still considered positive
  - Most frequently asked question, i.e., “will continuing medication that induced benefit (e.g., remission) maintain this benefit for long-term use”, is not answered by the RPT design
  - Maintenance of effect trials would answer this question

Relapse Prevention Design





Maintenance of Effect Design: Key Features

- Design combines acute short-term efficacy assessment with long-term efficacy in subsets of patients
- Study has short- and long-term endpoints for symptom control and maintenance of effect
- Level of therapeutic response pre-defined for patients at short-term endpoint
- Long-term endpoint assesses proportion of patients still meeting pre-defined response criteria, preferably in comparison to an active control

Maintenance of Effect Design

Baseline 1
- Acute treatment
- Control:
  - Placebo
  - Active comparator

Baseline 2
- Continue all patients on current medication
- Benefit definition applied

Maintenance of Effect Design

- Outcome
  - Percent of patients at week 52 maintaining benefit seen at 6 week endpoint
    - Compare to active control (non-inferiority – CPMP)
    - Mean change from week 6 to week 52 in responders (statistical issues)
    - Lack of use of rescue medication
  - Area under the curve
    - Number of days well or in remission
      - MDD, anxiety disorders
      - Schizophrenia, BPD
      - Substance abuse disorders
    - Investigator versus patient reported outcomes

Maintenance of Effect Design

- Provides useful information to clinicians and patients on benefit of continuing treatment
- Shorter duration and easier to conduct
- Less of an issue for IRBs/ECs, clinicians and caregivers

Long-Term Efficacy Trials

- **Double-blind, long-term treatment studies are an alternative approach**
  - Differs from typical extension study
  - Assesses long-term effectiveness
  - Analyses based on all randomized patients
- Predefined response criterion (e.g. 30% HDRS reduction) to be met at long-term endpoint (e.g. 1 year)
  - Short-term endpoint e.g. 4 – 6 weeks assessed as usual e.g. mean change HAM-D, PANSS, etc.
  - Allows patients not doing well to receive rescue/add-on treatment
  - Analysis allows separate assessment of patients meeting long-term efficacy criteria as mono-therapy, number of patients needing intervention, number of patients meeting success criteria after intervention, number of patients meeting failure criteria, cost effectiveness

Additional Designs

- Prevention of recurrence
  - Recurrence: “a reemergence of symptoms [new episode] after a time of no or minimal symptoms”
- Adjunctive treatment designs
  - Treatment as usual ± test drug