FDA Perspective on Outcome Measures, Study Designs, and Statistical Approaches for Long-Term Efficacy Trials for Psychiatric Drugs

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Alternatives to Typical Randomized Withdrawal Study

- Effexor XR/GAD—6 mo parallel group/pbo
- Abilify/Schizophrenia
  - Started with stable but still symptomatic pts on another drug; randomized to Abilify or pbo
  - Looked at time to full relapse
- Risperdal/Schizophrenia
  - Randomized w/d, but haloperidol controlled
  - Showed superiority to haloperidol
- Non-inferiority design in schizophrenia maintenance trials
  - Cannot resolve this particular issue today; would need more data and separate discussion
- Recent approval of Wellbutrin XL for Seasonal Affective Disorder as example of true prophylaxis trial as opposed to maintenance trial

Flexible Definitions of Response as Approach to Facilitating these Trials

- Definition of “responder”
  - Usually defined in terms of reaching and staying below threshold value on some scale (e.g., HAMD)
  - One view is that need to be less rigid in definition, e.g., allow brief excursions above this, and even dosage adjustments—without declaring pt no longer a responder
  - May fit better with practice, and facilitate conduct of these studies

Flexible Definitions of Relapse as Approach to Facilitating these Trials

- Definition of “relapse”
  - Usually defined in terms of going above some threshold value on some scale (e.g., HAMD), needing dose change or another medication, etc
  - One view is that need to be less rigid in definition, e.g., allow brief excursions above this, and even dosage adjustments—without declaring pt as having relapsed
  - As with response, may fit better with practice, and facilitate conduct of these studies

Addressing Dose Response in Maintenance Trials

- The dose needed for acute treatment may not be the same as that needed for maintenance
- Maintenance trials could be done as multiple fixed-dose trials to better understand dose response

Need to Broaden Outcomes Beyond Symptomatic Improvement

- Functional measures: could look at maintenance of improved function in addition to increased time to relapse
- Possibly look at reduced mortality as endpoint of maintenance trial
  - Would need to be large simple trial
  - Possible approach would be to compare aggressive strategy to followup and focus on maximizing time on maintenance medication vs usual standard of care (i.e., expect that pts will stop medication; but find them and try to get them back on same med, or switch to another that is better tolerated); the difference between treatment arms would be the additional efforts made in following pts and engaging them in program)

How Long Should Antidepressant Drugs be Continued to Prevent Relapse in Clinical trials?

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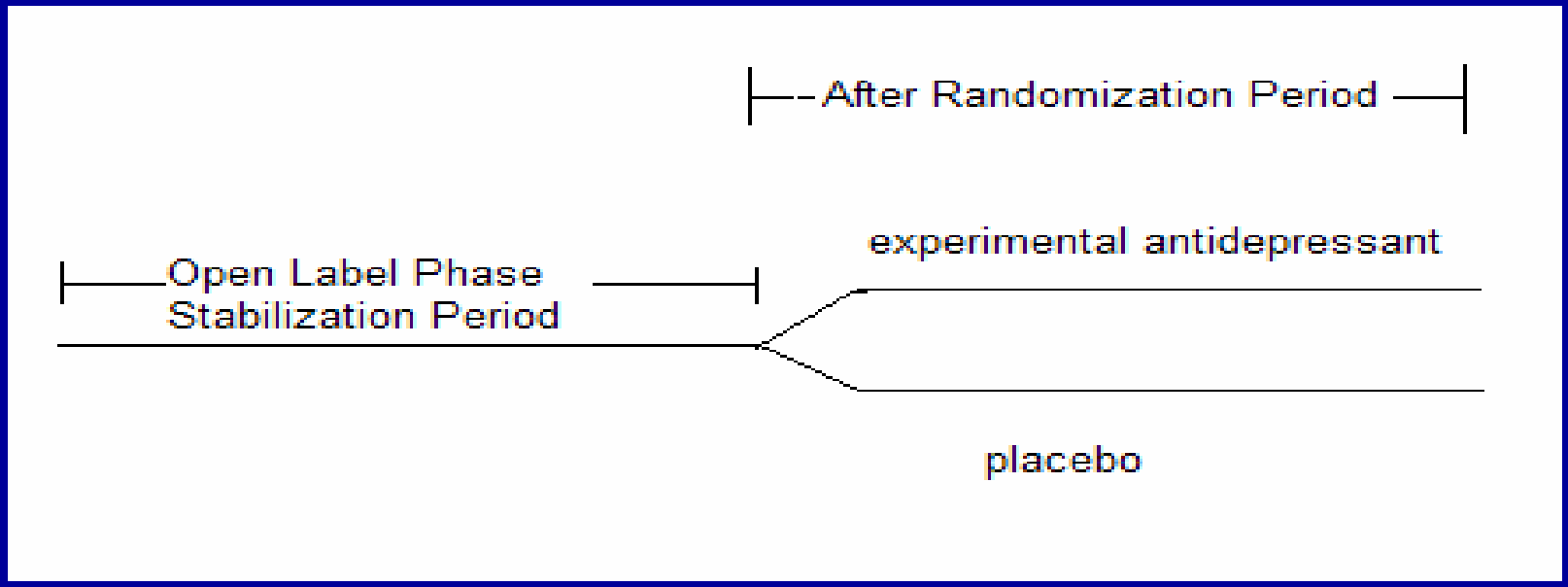
Background

- Randomized Withdrawal Trial:
  - Patients who responded to the experimental treatment and were stabilized for some defined period of time are randomized to either continuing on the experimental treatment or switching to placebo.



Questions of Interest

- What is a suitable length of the stabilization period (SP, also known as open-label phase) in a randomized withdrawal trial?
  - Could different lengths of SP affect comparisons of long-term efficacy?
  - Could different lengths of the after-randomization period (ARP) affect comparisons of long-term efficacy?

Paper by Geddes et al. (Lancet 2003)

- Meta-analysis based on relapse rate (31 studies, 4410 patients); 4 groups were compared:

SP/ARP in months	Stabilization Period (SP)	After-Randomization Period (ARP)
1-2 /12	1-2 months	12 months
1-2 /18-36	1-2 months	18-36 months
4-6 /12	4-6 months	12 months
4-6 /18-36	4-6 months	18-36 months

- **Paper's Conclusion**: no suggestion of clear difference in efficacy between trials with shorter (1-2 months) SP and those with longer SP (4-6 months)

Paper by Geddes et al.

Event Rates by Treatment Groups:				
SP / ARP in months	No. of Trials	Anti-depressant (T)	Placebo (P)	Difference (P-T)
1-2 /12	6	93/583 (16%)	248/620 (40%)	24%
1-2 / 18-36	3	39/120 (33%)	71/116 (61%)	28%
4-6 / 12	5	182/1014 (18%)	341/986 (35%)	17%
4-6 /18-36	10	85/350 (24%)	222/353 (63%)	39%

My Meta-Analysis Results*

Type of Comparison	Odds Ratio Estimates (95% C.I.)	P-Value
1-2/all vs. 4-6 /all	0.29 (0.22, 0.37) v.s. 0.33 (0.28, 0.40)	0.35
1-2 /12 vs. 4-6 /12	0.28 (0.21, 0.37) v.s. 0.42 (0.34, 0.52)	0.025
1-2 /18-36 vs. 4-6 /18-36	0.30 (0.18, 0.52) v.s. 0.17 (0.12, 0.24)	0.09
* Based on fixed-effects model		

My Findings

- Depending on whether duration of after-randomization period was considered:
  - If not: No suggestion of significant difference in long-term efficacy when comparing shorter (1-2 months) with longer (4-6 months) stabilization periods.
  - If yes: Suggestion of different trends for comparisons between different lengths of stabilization periods.
- Whether patients were randomized sooner (shorter SP) or later (longer SP) could affect treatment comparisons in long-term efficacy.

My Further Exploration

- Given 12 months after-randomization period, when the stabilization period was
  - 1-2 months: statistically significant difference in relapse rates between treatment and placebo (p=0.001).
  - 4-6 months: no statistically significant difference (p=0.0932).
- Question: What does this imply?
  - Longer SP, less likely significant??

My Conjecture

- When the stabilization period is
  - 1-2 months: Patients may not really be stabilized.
    - More likely to relapse during a short ARP for patients randomized to the placebo group than to the treatment group.
  - 4-6 months: may be stabilized and treated if the treatment really works.
    - Chance of relapse during a short ARP can be similar between treatment groups.
- Implication: Relapses may occur sooner in trials with shorter SP, as compared to longer SP.

Importance of Duration of After-Randomization Period

- Concept:
  - If the treatment really works, patients, who stop the treatment after being treated for a sufficient period of time, should for a while perform as well as those who were also treated for the same period of time, but still continue the treatment.
  - If the after-randomization period is not long enough, the difference in relapse rates between the treatment and placebo may not be captured.

Summary of My Key Points

- SP needs to be long enough to make sure patients are really stabilized.
- If SP is long enough, ARP
  - needs to be long enough to effectively compare long-term treatment effects between groups.