Should the randomized withdrawal design for relapse prevention studies in mood disorders be updated?

Co-chairs:
Atul Mahableshwarkar, MD / Gary Sachs, MD
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The Problem of Defining and Detecting Relapse in Maintenance Studies

• Ethical dilemmas and other practical obstacles
• Randomized withdrawal design
  • Associated with high success rate
  • Several recent studies have detected far fewer relapses than anticipated/needed for adequate statistical power
  • Does not address management of patients reaching remission on other treatments
• How can we study treatments that might be true maintenance therapies?
Randomized Withdrawal design: Multiple Phase/Multiple Issues

<table>
<thead>
<tr>
<th>Phase</th>
<th>Major Concerns</th>
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<tbody>
<tr>
<td>0</td>
<td>Sample size requirement. Recruitment process. Value proposition. Site selection/Training</td>
</tr>
<tr>
<td>1</td>
<td>Initial eligibility requirement (appropriate subjects). Allowable treatments, response criteria</td>
</tr>
<tr>
<td>2</td>
<td>Stability Criteria (enrichment). How long/how stable, Follow-up interval</td>
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<tr>
<td>3</td>
<td>Outcome criteria. Follow-up interval. Quality Assurance (internal validity). Generalizability</td>
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<tr>
<td>4</td>
<td>Necessity or contaminant. Recruitment tool. Leakage risk</td>
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Phase 0: Pre-op and Recruitment
- Acute Episode
- Stabilization
- Last Blinded Study Visit

Phase 1: Open treatment
- Baseline Visit

Phase 2: Open treatment Phase 2

Phase 3: Double-Blind Treatment
- Optional phase 4 Open Follow-up period
- Last study visit
- Outside treatment

Contact from referral or Media message: Consent
Relapse Design:
Lessons from STEP-BD and other naturalistic studies

MDI is characteristically a recurrent conditions

Euthymic Interval approaches 1 yr
Kraepelin, 1921
(N= 406)

Median Duration

Yrs

1st 2nd 3rd 4th 5th

Recurrence

1.5 1.7 1.8 2.8 4.3
Relationship Between Cycle Length and Episode Number

Adapted from Goodwin and Jamison
Expectable Course Untreated

If onset at age 16, given median rate of recurrence by age 30, EXPECT ≥ 10 episodes

Untreated Bipolar illness is incompatible with adult developmental tasks
Maintenance and continuation phase:
Adequate Controlled Clinical trials

<table>
<thead>
<tr>
<th>At least one Positive Trial</th>
<th>Only Negative or Failed Trials</th>
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<tbody>
<tr>
<td>Lithium $^{101}$</td>
<td>Imipramine $^{101}$</td>
</tr>
<tr>
<td>Valproate $^{88}$</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Lamotrigine $^{63, 102-103}$</td>
<td>Paliperidone</td>
</tr>
<tr>
<td>Olanzapine $^{32, 104-105}$</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole $^{106}$</td>
<td></td>
</tr>
<tr>
<td>Quetiapine $^{107}$</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone $^{108}$</td>
<td></td>
</tr>
<tr>
<td>Risperidone (Long acting Injectable)</td>
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* Statistical power $\geq 0.8$ to detect meaningful differences at $p<0.05$
(Sources: references listed above)
• Successful category A studies all used Randomized Withdrawal Design.
  – Randomized patients who had experienced a remission of acute phase symptoms during treatment with the study medication prior to randomization.
  – This methodological issue has important clinical implications.

• The data from these successful maintenance studies cannot support the practice of switching from acute phase treatments to a new maintenance treatment after resolution of an acute episode.

• The data do provide a persuasive argument against treatment disruption and support continued treatment with agents that were a part of a successful acute phase regimen.
Challenges with outcomes for longitudinal follow up of interventions for patients with Mood Disorders

- Ethical Concerns
  - Operational criteria for surrogate outcomes short of full episode criteria are required
- Is the STEP-BD concept of “Roughening” a reasonable surrogate for relapse?
- Prior evidence
  - Strong historical track record
  - Recent Trials less successful
- What do scale scores mean?
- Results from a multicenter RCT
STEP-BD Naturalistic Data

Mean episodes in year prior to entry
- 2.7 depressive
- 2.8 hypomaniac, manic, or mixed
- Defined “Recovered” consistent with DSM IV
  - Euthymic 8 consecutive weeks
  - (no more than 2 moderate symptoms)

STEP-BD observational data (with treatment)
58.4% Recovered” from index episode
- Euthymic periods in prior 2 years
  - Mean duration of longest period=133 days

Clinical status at study entry
- Depressed: 26%
- Recovered: 27%
- Subsyndromal: 19%
- Manic: 3%
- Hypomaniac: 4%
- Mixed: 9%

Course of illness after recovery

Median time to recurrence=45 weeks

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>2 years</th>
<th>Time to 25%</th>
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<tbody>
<tr>
<td>Episode of any type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>29%</td>
<td>49%</td>
<td>21 wks</td>
</tr>
<tr>
<td>Mood Elevation</td>
<td>22%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>6%</td>
<td>14%</td>
<td>85 wks</td>
</tr>
<tr>
<td>Hypomaniac</td>
<td>6%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3%</td>
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Higher bipolar relapse rate with residual symptoms

STEP—BD, Relapse study, Data as of 08/15/2001

Time to relapse

Survival Distribution Function

0.00
0.25
0.50
0.75
1.00

Time to event/censoring

0 50 100 150 200 250 300 350 400

Full Episode

Roughening
What is the meaning of a Rating Scale Score?

Total scores may not always indicate clinically significant severity.
Rule of Thumb: All MADRS Items

Ratings from 0 to 6

0..Absent

1.

2. Subjectively increased

3.

4. Definitely pathological and moderate

5.

6. Definitely pathological and severe
Patient A: MADRS above 20 and meets MDE criteria
Patient B: MADRS =18 does not meet MDE criteria
Does it matter how much medicine is in the capsule?

Standard Li Level better than low Li Level

Effect of abrupt change from standard to low serum levels of lithium: Reanalysis of double-blind lithium maintenance data

Effect carried by group with abrupt ↓ 50% Li dose

Perlis, RH; Sachs, GS; Lafer, B; Otto, MW; et al. AJP 59.7 (Jul 2002): 1155-9.