Multi-national clinical trial outcomes in international studies of bipolar disorder

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Cross-cultural Communication
An Example of Different Meanings of the Same Gesture

UK & USA = O.K.

JAPAN = MONEY

RUSSIA = ZERO

BRAZIL = INSULT
The example of Mania: Current definition (DSM-5)

- A distinct period of abnormally and persistently elevated, expansive or irritable mood, and abnormally and persistently increased activity or energy\(^a\) for ≥1 week and ≥3 of the following symptoms
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep
  - More talkative than usual or pressure to keep talking
  - Flight of ideas or subjective experience that thoughts are racing
  - Distractibility
  - Increase in goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences
- Marked impairment
- Not attributable to substances or medical conditions

Impact of geographical/cultural variations on trial outcome

3-week, double-blind, placebo and active controlled randomized multinational study on 438 adults with bipolar I disorder (most recent manic or mixed episode)

MRS ≥ 14
2-10 day wash-out

Ziprasidone 80-160 mg/d N= 178

Placebo N=88

Haloperidol 8-30 mg/d N=171

3 countries, 33 centers

9 India 9 Russia 15 USA

Vieta et al, IJNP 2011
Impact of geographical/cultural variations on trial outcome: Response to placebo

Vieta et al, IJNP 2011
Impact of geographical/cultural variations on trial outcome: Response to placebo

<table>
<thead>
<tr>
<th></th>
<th>India</th>
<th>Russia</th>
<th>US</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0</td>
<td>0</td>
<td>1 (4.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Day 4</td>
<td>3 (8.3)</td>
<td>0</td>
<td>3 (12.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Day 7</td>
<td>5 (13.9)</td>
<td>0</td>
<td>3 (8.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Week 2</td>
<td>5 (13.9)</td>
<td>3 (10.7)</td>
<td>7 (29.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Week 3</td>
<td>7 (19.4)</td>
<td>4 (14.2)</td>
<td>7 (29.2)</td>
<td>0.42</td>
</tr>
</tbody>
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Vieta et al, IJNP 2011
Impact of geographical/cultural variations on trial outcome: Discontinuations

- Arm with more discontinuations:
  - India: Placebo
  - Russia: Placebo
  - US: Haloperidol

Figure 1. Kaplan-Meier Curves for Discontinuations Over Time by Country and Treatment

Vieta et al, IJNP 2011
Impact of geographical/cultural variations on trial outcome: Change in Mania scores

Figure 2. Change in MRS Score at Week 3 Following Treatment With Ziprasidone or Haloperidol by Country

- **India**: -19.1
- **Russia**: -13.6
- **US**: -13.2

Baseline MRS scores were higher in India (34.4) than in Russia (28.0) or the United States (23.8)

Vieta et al, IJNP 2011
Impact of geographical/cultural variations on trial outcome: Baseline differences

**Table 2. Patient Demographics and Drug Dosage**

<table>
<thead>
<tr>
<th></th>
<th>India</th>
<th>Russia</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients, n</strong></td>
<td>179</td>
<td>139</td>
<td>119</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>74</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>69</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>Placebo</td>
<td>36</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td><strong>Mean baseline weight, kg</strong></td>
<td>57.1</td>
<td>73.9</td>
<td>82.4</td>
</tr>
<tr>
<td><strong>Mean dosage (week 3), mg/d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>128.4</td>
<td>121.8</td>
<td>126.5</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>20.7</td>
<td>15.2</td>
<td>15.3</td>
</tr>
</tbody>
</table>
YMRS Scoring
Optimizing Reliability

Sources of ratings error include variability in:

– Available information
– Cultural biases
– Diagnostic or Training biases
– Interpretative biases by raters
– The interviewer and the interviewee
  • Manic patients can change quickly
  • Some interviewers can elicit more information than others
YMRS Items

1. Elevated Mood
2. Increased motor activity-energy
3. Sexual interest
4. Sleep
5. Irritability
6. Speech (Rate and Amount)
7. Language-Thought Disorder
8. Content
9. Disruptive-Aggressive Behaviors
10. Appearance
11. Insight
Figure 2. YMRS Item Shifts: Moderate or Worse at Baseline to Mild/No Symptoms at Week 3

On YMRS items with a score range of 0-4, a score of 0 represents no symptoms; 1=mild; 2=moderate; 3=marked; 4=severe.

On YMRS items with a score range of 0-8, a score of 0 represents no symptoms; 2=mild; 4=moderate; 6=marked; 8=severe.

***P<.001.

Vieta et al, ENP, in press
Matters for debate

• Baseline geographical/cultural differences
• Symptoms are expressed differently across cultures
• Validity of tools and questionnaires in different languages
• Rater training (in their own language!)
• Centralized ratings
• Biomarkers