

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

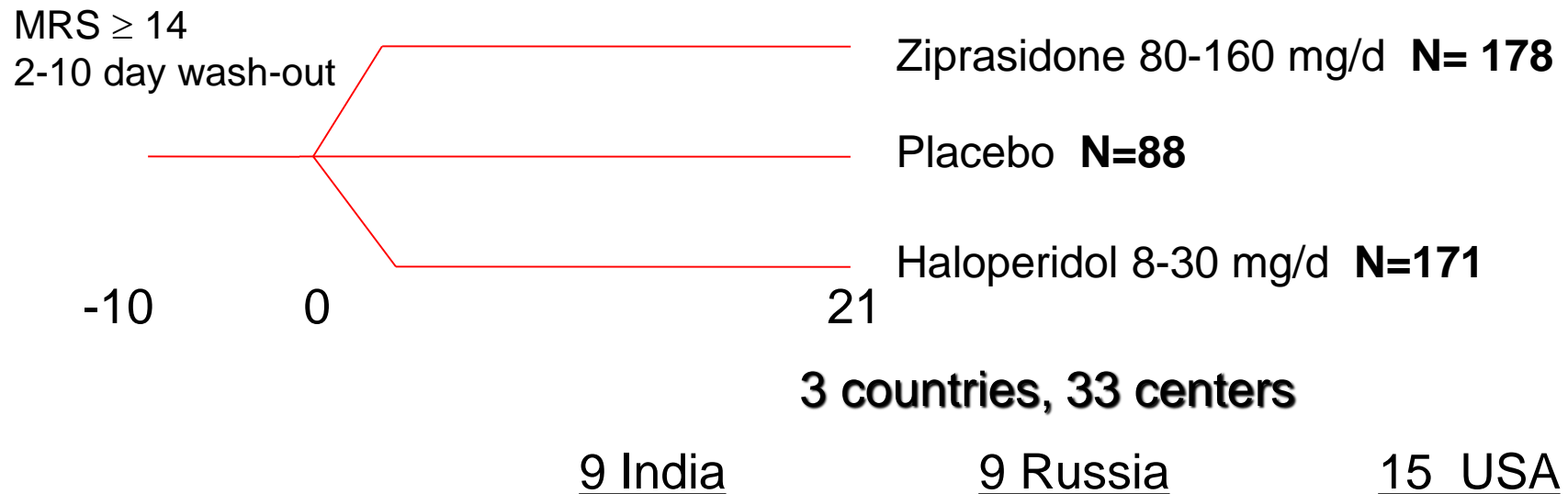
BRAZIL = INSULT

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

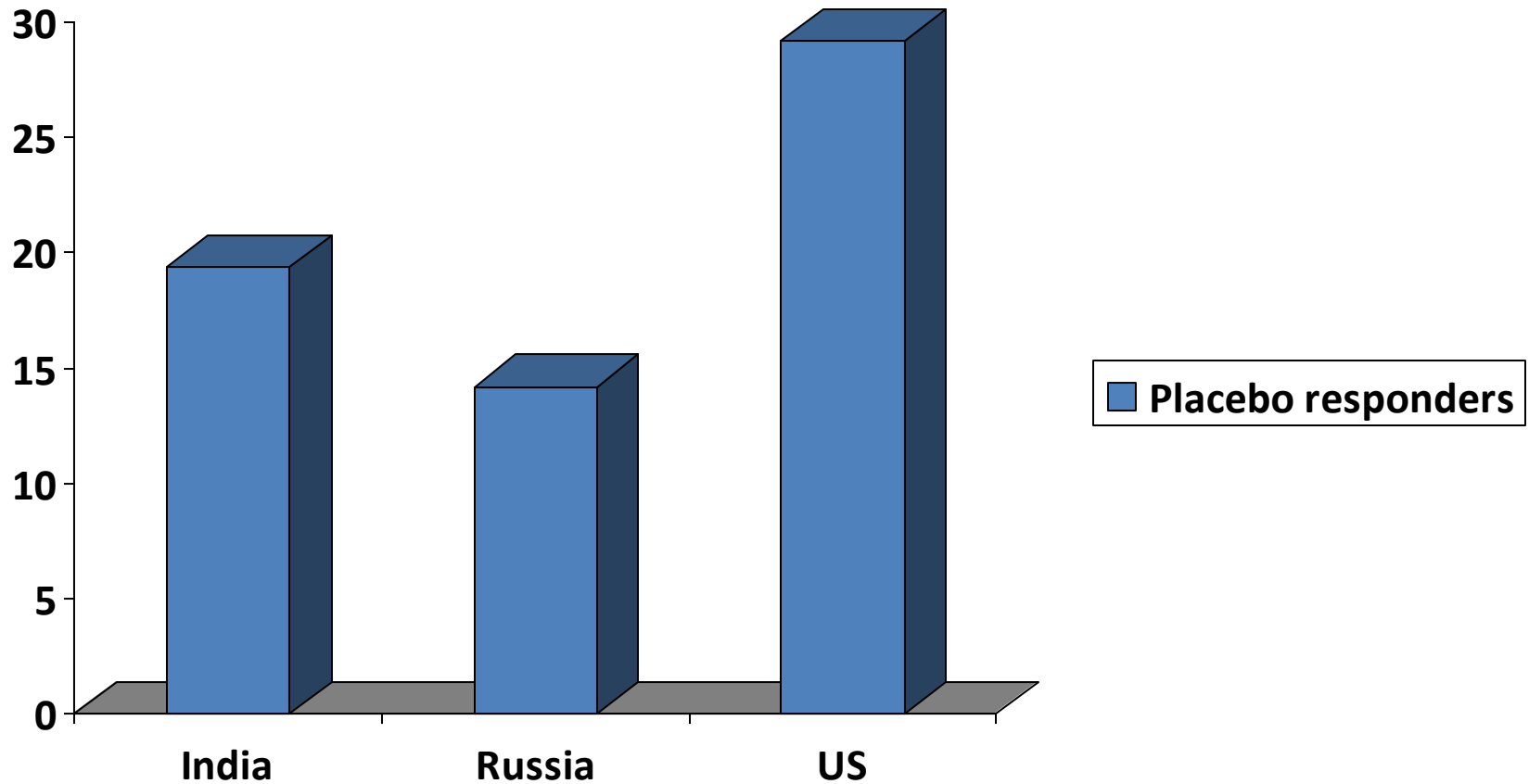
- A distinct period of abnormally and persistently elevated, expansive or irritable mood, **and abnormally and persistently increased activity or energy^a** for ≥ 1 week and ≥ 3 of the following symptoms
 - Inflated self-esteem or grandiosity
 - Decreased need for sleep
 - More talkative than usual or 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)



Impact of geographical/cultural variations on trial outcome: Response to placebo



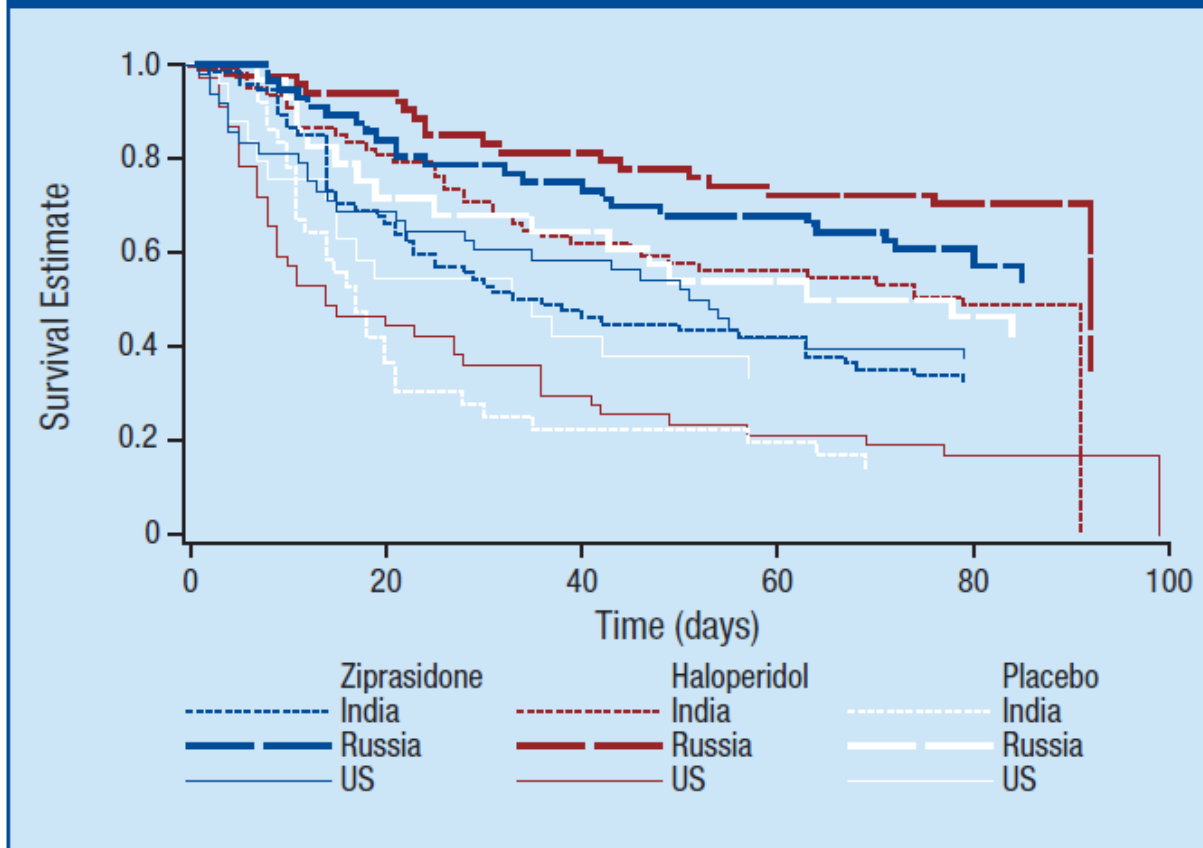
Impact of geographical/cultural variations on trial outcome: Response to placebo

Table 1. Placebo Responders by Country

Visit	India n (%)	Russia n (%)	US n (%)	<i>p</i> Value
Day 2	0	0	1 (4.2)	0.27
Day 4	3 (8.3)	0	3 (12.5)	0.17
Day 7	5 (13.9)	0	3 (8.8)	0.11
Week 2	5 (13.9)	3 (10.7)	7 (29.2)	0.23
Week 3	7 (19.4)	4 (14.2)	7 (29.2)	0.42

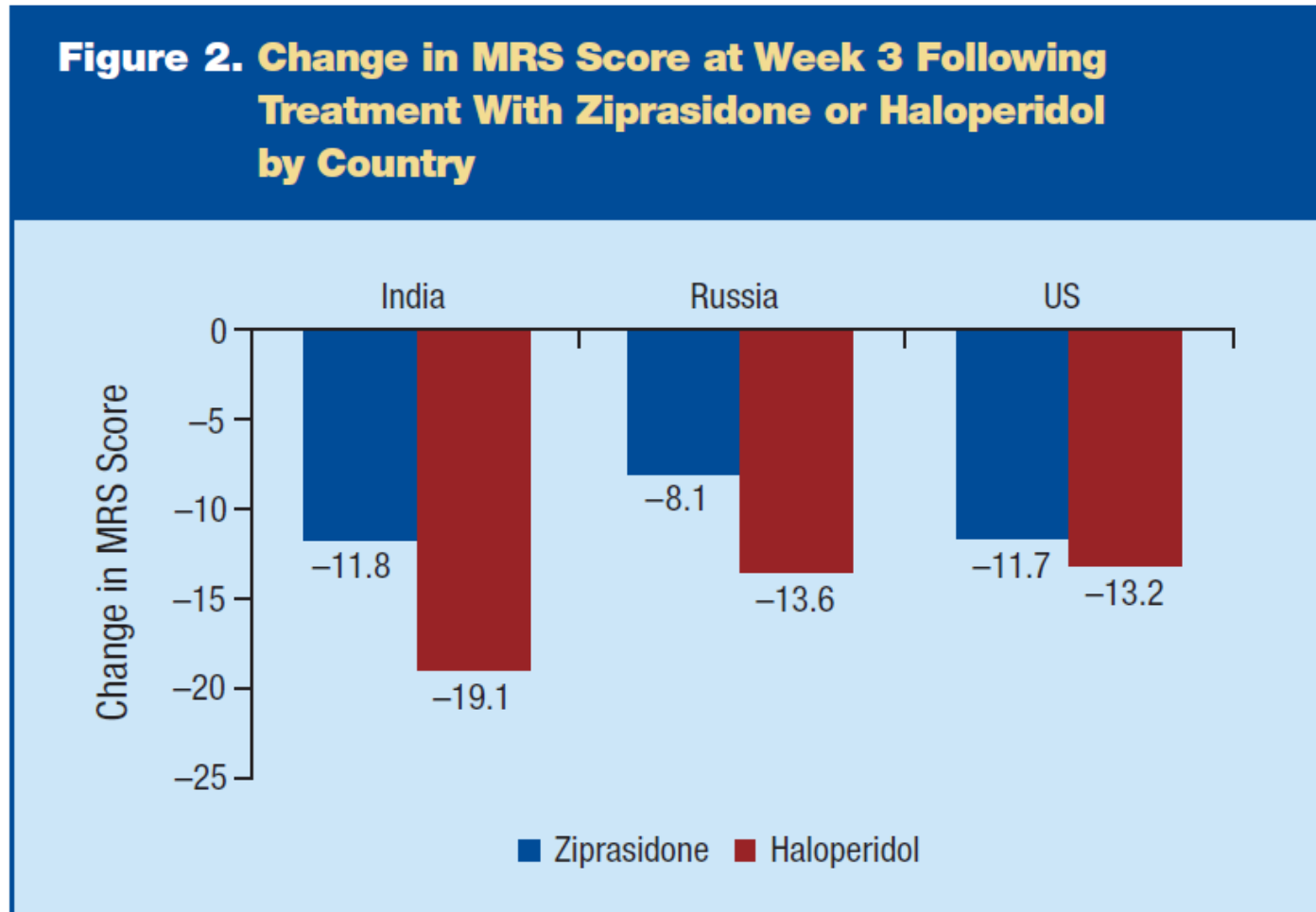
Impact of geographical/cultural variations on trial outcome: Discontinuations

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



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

Impact of geographical/cultural variations on trial outcome: Change in Mania scores



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

Impact of geographical/cultural variations on trial outcome: Baseline differences

Table 2. Patient Demographics and Drug Dosage			
	India	Russia	US
Number of patients, n	179	139	119
Ziprasidone	74	56	48
Haloperidol	69	55	47
Placebo	36	28	24
Mean baseline weight, kg	57.1	73.9	82.4
Mean dosage (week 3), mg/d			
Ziprasidone	128.4	121.8	126.5
Haloperidol	20.7	15.2	15.3

YMRS Scoring

Optimizing Reliability

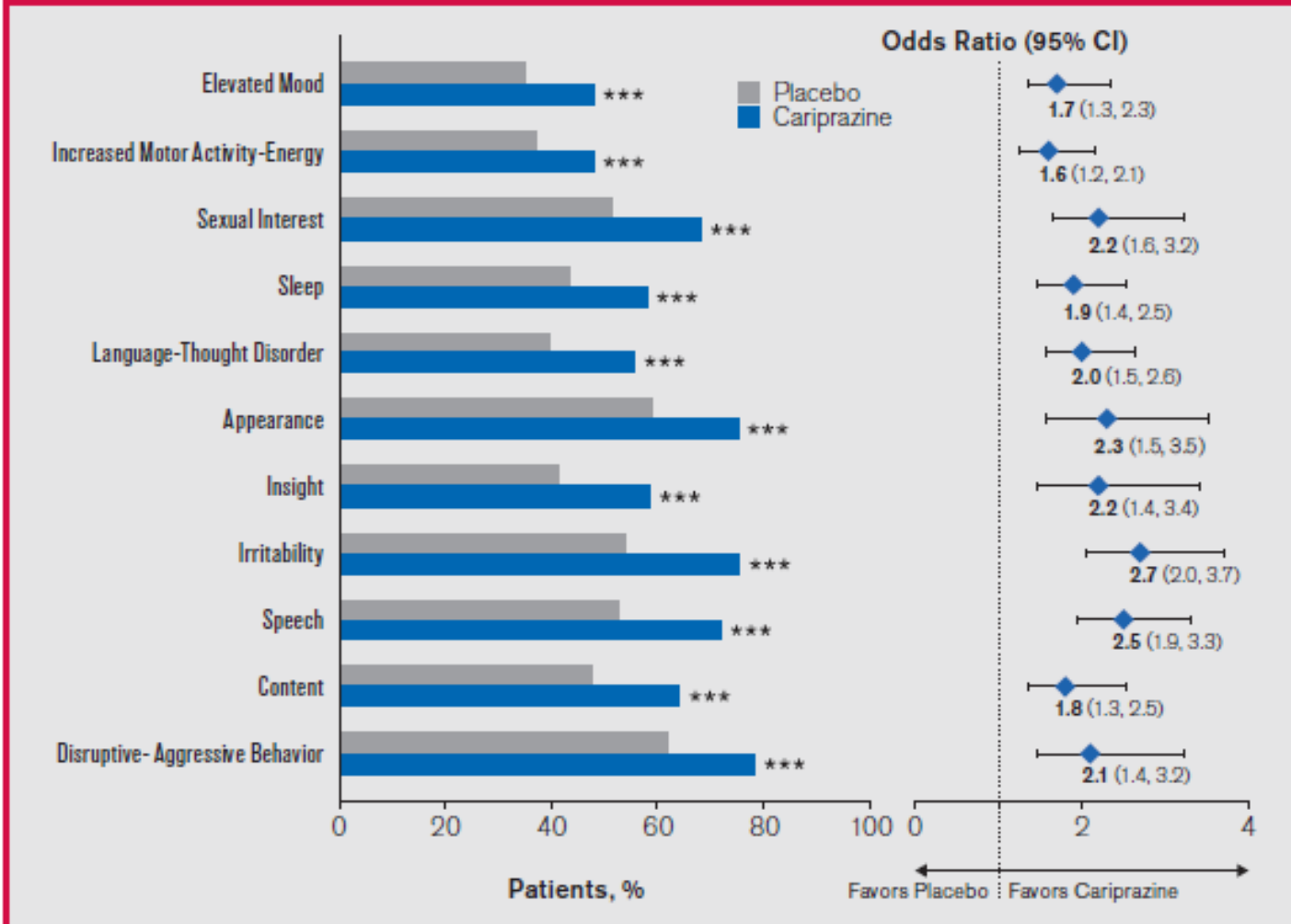
Sources of ratings error include variability in:

- 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.
 *** $P < .001$.

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