Controversies
March 24, 2016

Martin M. Katz: Onset of antidepressant action

Donald F. Klein's correction of his response to Martin M. Katz's reply to Carlos Morra's comment

Dr. Morey and I both had trouble with Marty's response to my reply to Carlos Morra's comment in that the tables were insufficiently labeled. The section following is a copy of the tables and Marty's description.

"Below are the 2X2 Tables for the active drugs, the placebo and the chi square results.

The rows are number of "early improvements" (>20%), the columns are number of recovered (>50%) at outcome."

I mistakenly thought that analysis of "Depressed mood-retardation" would be to the point. I did not realize that analysis of Hamilton score would be better in terms of comparability with placebo group. Below the Hamilton scale is used. The first two lines supplied by Marty immediately above the table were deleted as simply confusing.

I. Active Drugs

Assuming that row one is the predication of greater than 20%

Hamilton Rating Scale

	>50%	≤ 50%	
>20%	15	2	PPV= 15/(15+2) = 0.88
≤20%	8	25	NPV= 25/(25+8) = 0.758
			Recovery rate = 0.46

17 were predicted to do well but 27 did - a marked under prediction

Conversely, if Row 1 is ≤20%, the column labels must be reversed to preserve the positive correlation

	≤50%	> 50%	
≤20%	15	2	PPV= 25/(25+8) = 0.76
>20%	8	25	NPV = 15/(15+2) = 0.88
			Recovery rate 27/50 = 0.54

The difference in PPV and NPV Recovery Rate are enough to indicate that Marty's directions are ambiguous, as Dr. Morey also found.

Note that 33 are predicted to do well but only 27 did, an over prediction. 27/33 = 0.82

This approximates Marty's statement that, "It was further demonstrated in these studies that this amount of 'early improvement', i.e., >20% increase, was clinically significant in that it could predict that 70% of patients showing this early improvement would go on to respond at 6 or 8 weeks to the experimental treatment".

So the second table is probably the correct one. However, it is unclear to me how this over-prediction means that it is clinically significant. Further, there is no contrast with placebo either in the paper by Katz MM, Berman N, Bowden CL,

Frazer A. or here.

II. Placebo Treatment Group

	Hamilton Rating Scale		
EI Recovered			
No	Yes		
3	10	13	chi-square=0.102
1	5	6	p<0.75
4	15	19	

Taken literally, this seems to indicate that 15/19 recovered on placebo. Dr. Morey puzzles over this, "The Katz et al. (2004) article indicates a 30% response rate for placebo (presumably 6 of 20 patients), yet the 2x2 table in Dr. Katz's response indicates that 15 of 19 patients recovered. Again, it appears that rows and columns were switched, and doing a transposition provides the reported results, suggesting 6 patients responding to placebo over the course of the trial." This seems reasonable - Col 2 should be 1 and 5. To preserve the chi-square the Table looks like: So 6/19 recovered

	≤50%	> 50%	
20%	10	5	Recovery rate 6/19 = 0.32
>20%	3	1	

Contrasting the recovery rates of active drug and placebo we find:

	Drug	Placebo	
Recover	27	6	33
Nrec	23	13	36

50 19

Contrasting the two recovery rates, chi-square = 2.77, far from significant. This casts doubt on any "finding" that Marty proposes.

Other major problems remain. This table is referred to as active drug = 50. This combines the 24 in the Paroxetine study with the 26 in the DMI study. No justification is given for this. Since Paroxetine was picked as a serotonergic agent and DMI as a noradrenergic agent, the combination is really strange. This table is not what we asked for, which was the individual studies.

I thank Marty for providing the placebo data as used in the calculations by Dr. Morey. That this non-significant 6 week contrast is held to justify a much shorter trial escapes me.

Donald F. Klein
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