LONG-TERM EFFS MANYS
FINAL STATS BS
DISCUSSED 1/20/00.

RETURN TO : Bruce J. Kinon, M.D.

Bruce Basson
01/21/2000 01:25 PM

To: Julie Gilmore, Bruce Kinon
Subject: Additional Wt. Gain Results

Here are some of the additional results arising out of our discussion yesterday. We should probably come to a consensus
over what we would like to include in the manuscript.

Bruce

Table 1. Distribution of Patients Endpoint BMI vs. Baseline BMI

The proportions at baseline are artificially chosen to be 33%:34%:33%. At endpoint, the same cut-points prod distribution of 20%:28%:52%. For patients in the lower third of BBMI, 50% are still low
at endpoint, and 85% are lower to middle at endpoint. Only 15% have moved all the way into the upper third. [BTW, I'm not sure 'tertile' is a word -- I think we should just say 'third'.]

	Ending BMI			
Baseline BMI	<=23.6	>23.6-27.6	>27.6	Total
<=23.6	94 50.27	65 34.76	28 14.97	187 33.10
>23.6-27.6	16 8.33	76 39.58	100 52.08	192 33.98
>27.6	1 0.54	19 10.22	166 89.25	186 32.92
Total	111 19.65	160 28.32	294 52.04	565 100.00

Frequency Missing = 8

Table 2. Proportion of Patients Gaining more than 7% of Body Weight

The median body weight at baseline is 75.3 kg. With a median weight gain of 5.9 kg (7.8%), just over 50% of should have gained 7% or more of their body mass, and this is confirmed in the following table (52%). The pro is lower for patients with BBMI > 27.6 (p = <0.001).

	Gained > 7%		
BBMI	No	Yes	Total
<=23.6	74 39.57	113 60.43	187 33.10
>23.6-27.6	79 41.15	113 58.85	192 33.98

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>27.6	116	70	186
	62.37	37.63	32.92
Total	269	296	565
	47.61	52.39	100.00

Frequency Missing = 8

Finally, some p-values to go along with the Prevalence rates that we report at baseline and endpoint.

Table 3. Tests of Agreement Between Baseline/Endpoint Prevalence Rates

	Prevalence Baseline	Endpoint	P-value
Hi Glucose	7%	10%	0.006
Hi Chol	22%	24%	0.333
Hi DiaBP	25%	23%	0.440

So in summary, for glucose, we have a rise in overall prevalence for the population, but no significant tie betw of high glucose and weight change, and vice versa for cholesterol and diaBP (i.e. no significant rise in overall pr but a significant relationship between incidence and weight gain.)

We will have to think about what this means, perhaps. To me, this begins to separate the glucose phenomenon from that which is occurring around the other two parameters.

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The Journal of Clinical Psychiatry
COMMENTS TO THE AUTHOR (S)

Manuscript #: 5262

Author (s): Kinon et al.

Title: Long -term olanzapine treatment on weight change and weight related healthfactors in schizophrenia

Reviewer#: 1

This is a paper that looks at the long term data on olanzapine's effect on weight gain and related issues in patients with psychotic disorders. It focuses on an olanzapine-treated data set, but does not compare these data to a control group. This is a clear weakness of this paper. It seems apparent that the authors have access to control data for patients taking haloperidol. The olanzapine data were not referenced to a conventionally treated cohort, but instead only obliquely compared to general non-psychotic and highly heterogeneous population data set. It thus fails to address the central question: Does a drug like olanzapine that is known to induce substantial increases in weight also cause more diabetes, glucose intolerance, and other weight gain related clinical phenomena - compared to reference compounds?

The absence of a satisfactory control population makes it impossible to accept the null hypothesis as the authors have suggested. In addition, the statistics referenced are of questionable pertinence. For example, Harrison's online (1998-2000 last modified 1/21/00) quotes the prevalence of diabetes in the general population based on fasting hyperglycemia as 1-2%. This reference contrasts the referenced prevalence of diabetes by the authors of 7.8%. If the reported prevalence of 7.4% in olanzapine treated subjects is accurate, then this would suggest a relative risk for diabetes of 3.7:1 in olanzapine treated subjects!

Olanzapine and Hyperglycemia

Frequently Asked Questions

- Does olanzapine cause diabetes?
- Does olanzapine cause elevations in glucose levels?
- Should I monitor glucose levels in my olanzapine-treated patients?
- Should I initiate olanzapine in patients with risk factors for diabetes or who have diabetes?
- What should I do if my patient's glucose levels are elevated during olanzapine treatment?
  - Should I discontinue olanzapine?
  - Is there a blood glucose level that should prompt stopping olanzapine?
  - What other steps should I consider?

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Cindy Coe Taylor
05/07/99 05:23 PM

To: Bruce Basson, Bruce Kinon cc: Virginia Stauffer
Subject: Weight change manuscript draft

Hi Bruce and Bruce,

I'm happy to report that the weight change manuscript is coming along nicely. I have separated out the two manuscripts (although I haven't done any work on the second long-term labs manuscript) and I think that it flows much better now. I also reworked the discussion to reflect the focus that marketing stressed at the meeting last week. I am at a point where I would like your thorough review of the manuscript (feel free to make changes directly in the document and/or query me with whatever method works best for you). Additionally, I need your help with writing the "limitations" paragraph of the discussion and possibly adding more on clinical relevance if you feel this is necessary. Please keep in mind that we are already over the 5,000 word limit for this journal and some "pruning" may need to be done. Also, I incorporated the information on discontinuing patients in the discussion section-let me know if you think that we need supporting data in the results section. I will stay out of the document during the beginning of next week so that you can review it. Please let me know when you have finished. Then, hopefully, we can meet our deadline to get it in to internal review by the end of next week.

Thanks,
Cindy

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RETURN TO : Bruce J. Kinon, M.D.

WT GAIN

Bruce Basson
02/16/99 05:45 PM

To: Bruce Kinon
Subject: Weight Gain

Bruce, we should probably meet again soon to discuss the latest weight gain results. Give me a day or two to get them together.

I think I figured out what was odd about the Risperidone data w.r.t appetite: 72% of the reduced appetite people on Risperidone dropped out (N = 18-->5, compared to N = 18-->12 for olanzapine).

I have the Barnes and Simpson-Angus data, and so far it hasn't been having all that much impact. However, there are a few things I want to tighten up in the modeling, so let me wait on talking about that.

Keep in mind that with regard to the Barnes and Simpson-Angus ratings that BPRS Response correlates highly with both of these variables AND that the Barnes and Simpson-Angus responses themselves are positively correlated. Basically this makes it very difficult to say which factor is having the effect.

It would be a good idea to TRY to throw all these factors into a model together at some point, to get an idea of relative predictive strengths. Without that, how will we say which of the significant factors is most signficant? I see running factors in pairs and threes only, because otherwise these models will almost surely start running into convergence problems. That process by itself could take a week.

I'm having a bit of trouble envisioning what to do with the Glucose and Cholesterol data. You have the graphs which show a certain rise in both over 3 years for Olanzapine (HGAJ). Here is a table:

Year	Mean Baseline Glucose	Mean Change in Glucose	Mean Baseline Cholesterol	Mean Change in Cholesterol
0	5.42	0.00	5.32	0.00
1	5.41	0.31	5.32	0.06
2	5.49	0.56	5.34	0.04
3	5.51	0.81	5.32	0.11

The problem is, we are seeing a creeping sort of rise, without the same plateauing that we see with weight. What I'm wondering is, a) is this relevant? i.e. does this happen generally to the population with aging? b) what can we compare ourselves to? A baseline analysis will indicate that glucose and cholesterol go up steadily over three years, even if by only small amounts. I think I'm going to try narrower bins = 6 months and see what happens.

I've also been looking at risk ratios to see if drop-outs are affecting things: the proportion of patients above/below 7.8si (=140 mg/dl) at baseline vs. the proportion who were high subsequently. Any ideas on this?

Something to think about for the future: I'd like to submit these analyses both to the Monday morning meeting and to SPROM. I think it's important enough to get plenty of peer review.

Anyway, I'll try to schedule something on Thursday if you are around. See you,

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