

6 Mar 00

To: gadde001
cc:

Subject FW: Figure and Flow Chart
t

Kishore,

Attached are your figures. Please review and return comments to me before Wednesday 8 March at noon so that I can get changes back to before close of business on Wednesday.

Regarding manuscript.

Couple of comments:

1. Glaxo Wellcome Inc - no comma
2. Duke Medical Center - vs centre - both are used in the paper, also Behaviour, favourably - the editor at JAMA will catch these if you don't
3. Abstract - Context - Delete "SR"; change "help" to "facilitate"
Context Catecholamines have been implicated in modulating hunger and feeding behaviors and facilitating energy expenditure. Bupropion, a drug which enhances norepinephrine and dopamine in the central nervous system, may FACILITATE weight loss in obese patients.
4. Introduction - Suggest breaking into two paragraphs. I am faxing over the following article: Hauptman et al. Orlistat in the long-term treatment of obesity in primary care settings. Arch Fam Med 2000; 9: 160-167. Briefly, orlistat is well tolerated over 2 years except for the GI effects. This may provide some fair balance to the sentence stating that sibutramine is contraindicated with comorbid conditions.

INTRODUCTION

Approximately 97 million adults in the United States are estimated to be overweight or obese, with an alarming increase of this epidemic in the recent years (Fiegel et al, 1998, Mokdad et al, 1999). Both conditions carry an increase in the prevalence of many comorbid illnesses (Must et al, 1999) including type 2 diabetes, coronary heart disease, hypertension, gallbladder disease, and osteoarthritis, with an increased risk of mortality from all causes (Calle et al, 1999; Allison et al, 1999). Significant reduction of obesity-related illnesses and risk factors can occur with a modest (< 10%) weight reduction (Goldstein, 1992). Although diet, exercise, behaviour therapy and pharmacotherapy can be effective, many obese patients fail to achieve significant benefit from any given treatment modality and long-term outcome with most non-surgical treatments is often unsatisfactory (NIH tech assess, 1993). As is the case with other treatments, discontinuation of pharmacotherapy often leads to loss of the achieved weight loss benefit; hence, long-term treatment is necessary in most cases to maintain health benefits (National Task Force, 1996). Following withdrawal from the market of fenfluramine and dexfenfluramine in 1997, there has been a growing need for alternative weight management medications. Of the two currently available pharmacological interventions for long-term

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use, orlistat and sibutramine, the latter is contraindicated for use in patients with co-morbid illnesses such as hypertension and cardiovascular disease, which are commonly associated with obesity.

In search of additional strategies for weight management in the clinically obese, we conducted this preliminary investigation examining the efficacy and tolerability of sustained release bupropion (bupropion SR) in obesity. Bupropion SR is commercially available for treatment of depression (Wellbutrin SR[®]) and as a smoking cessation aid (Zyban[®]). The clinical benefits associated with bupropion SR treatment of these two conditions are believed to be related to the drug's effects on catecholaminergic systems (Richelson, 1994). The idea for the current investigation originated from a series of clinical observations (by Dr. Gadde) obese patients attending a university diet and fitness center. When these patients were treated for mild depression with bupropion SR, it was observed that they had a greater degree of success in losing weight. To our knowledge, the current investigation is the first randomized, placebo-controlled comparison of bupropion SR in obesity.

5. Methods - Suggest changing "habit" to "pattern"

Diet

Throughout the study, all subjects were instructed to follow a 1,600 kcal/day diet. They were also instructed to record their food intake in a diary, which was provided to them. At the beginning of the study, dietary instructions including the procedures for diary entries were given by a certified dietitian. The diet emphasized a balance of all food groups and daily intake of 8 glasses of water. The diet diaries were reviewed at each visit with the subjects and appropriate guidance was provided. The intent of the relatively loose structure of the diet program was to create a realistic eating PATTERN, which is likely to be sustainable upon discontinuation of the study treatment.

Methods - JAMA may want you to describe your scale in a Figure or Table, rather than Appendix.

A scale was developed (by Dr. Gadde, copyright, 1999) to assess diet compliance. The best compliance was given a score of 5 and the worst compliance was rated 0 on a scale of 0-5. The description of the diet compliance rating scale provided in Appendix 1.

Methods - BDI scores are not discussed in results. I know this is for Paper #2, but do you think the reviewers will ask for it? Similarly, vital signs are provided for 8 week portion of the study, but not the continuation. Similarly, SF-36 and lipids are listed in Methods but no results are given.

Initial 8-week Study

All 50 subjects were included, with the last observation carried forward, in analyses of the primary outcome measures: 1) percentage weight loss compared with initial weight; 2) actual weight loss in kilograms; 3) percentage of subjects who achieved weight loss of 5% or more; 4) frequency of adverse events. Secondary outcome measures included diet compliance, heart rate, blood pressure, lipids, Ham-D, BDI, CGI and SF-36 quality of life scale.

Results - First sentence is a little confusing, suggest clarifying who the 18 subjects were and then going into the description.
Continuation phase

A total of 18 subjects (16 BUPROPION SR; 2 PLACEBO) who had met the responder criteria qualified and entered the double-blind 16-week continuation phase (figure 1). Of the 14 subjects who qualified from the bupropion SR group at the end of the initial 8-week study, 13 entered the continuation phase while one subject was satisfied with the weight loss and chose not to enter the continuation phase. All three responders to bupropion SR in the crossover study entered the continuation phase, thus bringing the total number of subjects receiving bupropion SR in the continuation phase to 16. Two subjects qualified from the placebo group at the end of the initial 8-week study and none qualified from the crossover study, thus leaving a total of 2 subjects receiving placebo in the continuation phase. Fourteen of the 16 subjects receiving bupropion SR and both subjects receiving placebo completed a total of 24 weeks treatment. Of the two subjects who prematurely discontinued treatment in the bupropion SR group, one subject withdrew at week 12 citing dissatisfaction with achieved weight loss (3.6%), and another subject withdrew at week 16, after achieving an 11.1% weight loss, citing a family crisis.

Results - I agree that improvement in vital signs appears to be correlated with weight loss. I think this should be mentioned in the discussion. But, you may want to "save" this for the follow-up paper.

Vital Signs

At week 24, significant decreases were noted in heart rate (74.6 ± 8.0 to 70.1 ± 3.8 ; $p=0.0003$) and blood pressure - both systolic (129.0 ± 18.7 to 115.4 ± 8.2 ; $p=0.0001$) and diastolic (83.2 ± 7.7 to 78.6 ± 7.8 ; $p=0.003$) - in the bupropion SR treated subjects. (In the discussion, mention that this correlates with weight loss?)

Results - Suggest you move the first sentence to Methods. One usually does not add references to the Results.

Weight loss may result in decrease in bone density in women (Dr. Drezner to provide reference), thus increasing osteoporosis risk. Hence, we examined bone density at baseline and week 24. The density of lumbar vertebrae was examined using a total body DEXA. There was no significant change in bone density during 24-week treatment with bupropion SR (Paired t-test).

Discussion

Suggest changing last sentence:

The efficacy of bupropion SR in the early phase of treatment was impressive with 8-week completers achieving a mean weight loss of 6.2% (SD 3.4%). Because only the subjects who had achieved at least 4 kg or =5% weight loss in the first 8 weeks were eligible to enter the continuation phase, the 12.9% (SD 5.6%) weight loss achieved by the bupropion SR patients completing 24 weeks may be an overestimate of the true effect. A comparison between the BUPROPION SR and the placebo in the continuation phase would not be appropriate because only two subjects received placebo in this phase. Both subjects on placebo achieved a WEIGHT LOSS OF APPROXIMATELY 10% at week 24.

Suggest changing "active drug" to "bupropion SR"

The robust effect of bupropion SR treatment in the first 8 weeks might have been influenced by a greater number of early terminations and poorer compliance with diet in the placebo group. A shortcoming of this study is that the diet prescribed was not individualized. However, the difference between the BUPROPION SR and placebo groups in their diet compliance was

notable. A possible explanation is that bupropion SR might have exerted beneficial effects in the form of decreasing appetite and food craving, and perhaps enhancing motivation. This study was designed to capture the weight loss efficacy of bupropion SR in a setting similar to a primary care office. As such, the ancillary interventions such as diet and behaviour therapy were minimal. Failure of 19 of the 50 enrolled subjects to complete the first 8 weeks and the minimal response in the placebo group may be a reflection of the chosen design. An explanation for the higher discontinuation rate in the placebo group, for all reasons and particularly due to dissatisfaction with treatment is that the BUPROPION SR may have provided a more satisfactory benefit for the subjects.

Suggest changing "superiority" to "effectiveness"

Results of the crossover study, although of a very small sample, showed a trend for bupropion SR's EFFECTIVENESS over placebo. When the subjects who failed to respond to placebo were switched to bupropion SR, some of them responded to the drug.

Suggest the following changes: clarifying patients at risk, deleting about Web based pharmacies. It may be a real issue, but will the users of Web based pharmacies be reading JAMA? Also, you state earlier that the study was designed to mimic a primary care practice, with respect to diet management. In this paragraph, you imply that the use of bupropion may not be appropriate in primary care practices.

ORIGINAL:

Bupropion SR was generally well-tolerated in this study with dry mouth being the only adverse effect, statistically different from the placebo treatment, in the initial 8-week comparison. Two subjects developed a skin rash during the course of treatment. Adverse effects were mild in the 16-week continuation phase. The safety and tolerability data from this study must be interpreted with caution because of the small sample size of this cohort. Clinicians should be aware of the seizure risk associated with bupropion SR in depression and smoking cessation trials. The incidence of seizures with bupropion SR is approximately 1 in 1,000 which is comparable to the seizure risk associated with other antidepressants (Dunner et al, 1998). At the maximum dose of 400 mg/day used in the present study, the seizure risk with bupropion SR is estimated at 4 in 1,000 (ref: Product information brochure). People with histories of bulimia, anorexia, and seizures may be at the greatest risk for developing seizures with bupropion SR treatment; hence, its use is contraindicated in those with a history of any of the three conditions. In this study, considerable time and effort were put in to identifying and excluding such high-risk subjects. Because such an extensive assessment may not occur in general clinical settings, the seizure potential discussed above remains the primary concern with use of this drug in weight management. As more and more patients are obtaining prescription medications via the Web-based pharmacies, it is of concern that a person with anorexia or bulimia, for whom use of bupropion SR is not considered safe, might obtain it by providing incorrect information to the Web-pharmacy. Given the high prevalence of binge-eating pattern in obese patients, it is imperative to rule out associated purging behaviour and/or laxative abuse if this medication is considered as a weight management tool.

REVISED:

Bupropion SR was generally well-tolerated in this study with dry mouth being the only adverse effect, statistically different from the placebo treatment, in the initial 8-week comparison. Two subjects developed a skin rash during

the course of treatment. Adverse effects were mild in the 16-week continuation phase. The safety and tolerability data from this study must be interpreted with caution because of the small sample size of this cohort. Clinicians should be aware of the seizure risk associated with bupropion SR in depression and smoking cessation trials. The incidence of seizures with bupropion SR is approximately 1 in 1,000 which is comparable to the seizure risk associated with other antidepressants (Dunner et al, 1998). At the maximum dose of 400 mg/day used in the present study, the seizure risk with bupropion SR is estimated at 4 in 1,000 (ref: Product information brochure). BUPROPION SR IS CONTRAINDICATED IN PATIENTS WITH histories of bulimia, anorexia, OR seizures BECAUSE THEY may be at the greatest risk for developing seizures with bupropion SR. Given the high prevalence of binge-eating pattern in obese patients, it is imperative to rule out associated purging behaviour and/or laxative abuse if BUPROPION SR is considered as a weight management tool.

Also, is there no data re: body composition with sibutramine or orlistat - the other commercially available oral agents? I can appreciate that you want to cite previous articles published in JAMA, but given leptin is SC and not commercially available, is it a relevant comparison. Suggest deleting the sentence.

The loss in fat tissue accounted for 74% of the weight loss achieved with bupropion SR treatment at week 24. This finding compared favourably with body composition changes associated with loss of weight on a balanced diet (Jim Hill to provide reference?). It is notable that more than 95% of body mass decrease resulted from loss in fat mass during recombinant leptin treatment in a recently reported trial (Heymsfield et al, 1999). There was no change in bone density associated with weight loss achieved at week 24 with bupropion SR treatment. This finding may be of importance in light of the knowledge that women lose bone density with weight loss, thus increasing their osteoporosis risk (need reference from Dr. Drezner).

For years we have been stating that weight gain is not an issue with Wellbutrin or Zyban. The last two sentences imply that before you came along, it never occurred to anyone to consider weight loss studies with bupropion.

Original:

In 8-week pre-marketing trials of bupropion SR in depression, a weight loss of greater than 5 pounds occurred in 14% and 19% of patients treated with 300 mg/day and 400 mg/day, respectively, compared with 6% of patients treated with placebo (Product Information). In a review of pooled data from three controlled trials of 8 weeks duration with bupropion SR, the mean changes in weight for subjects treated for depression were 0.9 kg and 1.3 kg with 300 mg/day and 400 mg/day, respectively (Settle et al 1999). In short-term trials examining the efficacy of bupropion SR for smoking cessation, the patients in the bupropion SR group gained slightly less weight than the placebo group (Jorenby et al, 1999). The subjects who were treated with a nicotine patch also gained less weight than the placebo group in this trial. Over all, the differences between bupropion SR and placebo on the patients' body weight in depression and smoking cessation trials were relatively small and did not provide strong signals that the drug might have significant weight reducing effect in obese patients. Rather, it was a series of clinical observations that led to the hypothesis that this drug may have a clinically significant beneficial effect on weight in primarily obese patients seeking treatment for this reason.

REVISED:

In 8-week pre-marketing trials of bupropion SR in depression, a weight loss of greater than 5 pounds occurred in 14% and 19% of patients treated with 300 mg/day and 400 mg/day, respectively, compared with 6% of patients treated with placebo (Product Information). In a review of pooled data from three controlled trials of 8 weeks duration with bupropion SR, the mean changes in weight for subjects treated for depression were 0.9 kg and 1.3 kg with 300 mg/day and 400 mg/day, respectively (Settle et al 1999). In short-term trials examining the efficacy of bupropion SR for smoking cessation, the patients in the bupropion SR group gained slightly less weight than the placebo group (Jorenby et al, 1999). The subjects who were treated with a nicotine patch also gained less weight than the placebo group in this trial. ALTHOUGH the differences between bupropion SR and placebo on the patients' body weight in depression and smoking cessation trials were relatively small, THESE FINDINGS DO SUPPORT THAT BUPROPION SR MAY HAVE A BENEFICIAL EFFECT ON WEIGHT IN PRIMARILY OBESE PATIENTS.

CONCLUSION: Same comment as above re: primary care clinics.

Original:

In summary, the findings of this study provide the preliminary evidence that bupropion SR may help some obese patients. Further studies with larger sample sizes with inclusion of both genders are needed to confirm these preliminary observations. Also warranted are studies to examine the possible mechanisms by which bupropion SR might affect weight, e.g., effects on energy expenditure, thermogenesis, and direct and/or indirect effects on adipose tissue. The small sample size of the study does not permit us to make any definite conclusions regarding the safety of bupropion SR in obese subjects. Moreover, the special and time-consuming attention, paid in this study to screen for risky subjects, may not be feasible in the busy offices of primary care due to practical difficulties such as time constraints. As such, these data should not be extrapolated to general clinical settings until further safety and efficacy data are gathered in large-sample studies.

Revised:

In summary, the findings of this study provide the preliminary evidence that bupropion SR may FACILITATE WEIGHT LOSS IN some obese patients. Further studies with larger sample sizes with inclusion of both genders are needed to confirm these preliminary observations. The small sample size of the study does not permit us to make any definite conclusions regarding the safety of bupropion SR in obese PATIENTS. IT IS IMPERATIVE TO SCREEN PATIENTS WITH PURGING OR LAXATIVE-ABUSE BEHAVIORS. Also warranted are studies to examine the possible mechanisms by which bupropion SR might affect weight, e.g., effects on energy expenditure, thermogenesis, and direct and/or indirect effects on adipose tissue.

Table 2 - what is "intercurrent"

Let me know if you have any questions about my suggestions.

Tim

> -----Original Message-----

> From: Melissa Kennedy [SMTP:melissakennedy@prodigy.net]

DOJ005701

charts with one and two year data. This data needs to be summarized for the 2000 NAASO meeting. Also, the follow-up manuscript needs to be prepared and target journal needs to be discussed.

Regarding target journal, I was surprised to learn of the change to Lancet. I support the decision (given their rapid turnaround time and given submission of this manuscript has been delayed), although I think JAMA would have been very interested, given that they highlighted the APA data in their June issue.

Regardless, GW should have input into decisions like this. Given your grant is approx 140K, of which approx 130K has been paid, emphasizes that we partner in publishing decisions that consider both patient and brand issues. It is unlikely that additional support for other investigator-initiated projects will be embraced enthusiastically if there is no input from GW or if input from GW is not considered.

Thanks and I look forward to talking with you next week,

Tim

> -----Original Message-----

> From: Leadbetter, Robert A
> Sent: Friday, March 17, 2000 2:20 PM
> To: 'gadde001@mc.duke.edu'
> Cc: Metz, Alan; Kuhn, Timothy A
> Subject: Manuscript

>

> Kishore,

>

> I have tried to reach you today but without luck. We have had a chance to
> review your manuscript and are pleased with the latest version. However
> please contact me or Tim at your earliest convince and before you submit
> it. There are still some concerns that we think could compromise the
> success of getting it published. I look forward to talking to you.

>

> Bob

> Robert A. Leadbetter, M.D.
> Principal Clinical Research Physician, Psychiatry
> US Medical Affairs
> Glaxo Wellcome Inc
> ph: (919) 483-7152
> fax: (919) 483-0053
> email: ral73653@glaxowellcome.com

18 Mar 00

To: "Leadbetter, Robert A" <ral73653@GlaxoWellcome.com>, gadde001
cc: "Metz, Alan" <am31422@GlaxoWellcome.com>

Subject: RE: Manuscript
t:

Kishore,

One other point.

In the version of the manuscript that was faxed to Alan, the figure was changed. In your original, it listed "bupropion SR" and now the figure lists "bupropion"

Why was the "SR" removed?

Thanks

Tim

23 Mar 00

To: gadde001
cc: "Metz, Alan" <am31422@GlaxoWellcome.com>, "Kuhn, Timothy A" <tak8925@GlaxoWellcome.com>

Subject: FW: Kishore response

> Kishore,
>
> I regret it has been so difficult to reach you, however it is important we
> have an opportunity to be sure your manuscript is ready for publication
> prior to submission. I will attempt to respond via email, however please
> feel free to call me if our input is not clear.
>
> * On page 4, 2nd paragraph you note "The idea for the current
> investigation originated from a series of clinical observations.... that
> obese patients.. when Rxd with bupropion SR for mild depression, had a
> greater degree of weight loss." However, on page 17-18 you note the
> hypothesis re: weight loss was observed in "primarily obese patients
> seeking treatment for this reason." These two statements seem
> inconsistent.
> * GW did recognize the potential of bupropion SR to have weight
> reducing effects from the depression and smoking clinical trials which
> supported the idea of pursuing your study.
> * On page 15 you have a sentence about blood pressure effects. I
> think it is awkward, as it stands alone, and would suggest a brief
> elaboration noting the observed decrease and that this may be addressed in
> a future paper (?correct).
> * Page 15-16 paragraph. Your revision here was excellent. However I
> still think you should drop the reference to web-pharmacies as this is not
> something observed in your study and may be viewed as speculative. It
> risks compromising the manuscript's review.
> * Also I would advise dropping the 7th sentence in the page 15-16
> paragraph (In this study, considerable....) as it is dealt with in the
> Methods section, and your safety points are otherwise well presented in
> this paragraph. You are particularly correct to point out the high
> prevalence of binge-eating in obese patients and thus the imperative to
> R/O purging or laxative use.
>
> We look forward to your response and an opportunity to review further
> versions of the manuscript, as well as an expedient submission. I hope
> the obesity protocols you are currently participating in are going well.
>
> Bob
> Robert A. Leadbetter, M.D.
> Principal Clinical Research Physician, Psychiatry
> US Medical Affairs

DOJ005704

> Glaxo Wellcome Inc
> ph: (919) 483-7152
> fax: (919) 483-0053
> email: ral73653@glaxowellcome.com

>
>
>

> -----Original Message-----
> From: gadde001@mc.duke.edu [SMTP:gadde001@mc.duke.edu]
> Sent: Wednesday, March 22, 2000 2:43 PM
> To: Leadbetter, Robert A
> Subject:

>
>
>

> I have been extremely busy in the past week and hence not been able
> to return
> your phone calls. Can you send a detailed e-message?

27 Mar 00

To: gadde001
cc: "Metz, Alan" <am31422@GlaxoWellcome.com>, "Kuhn, Timothy A" <tak8925@GlaxoWellcome.com>

Subject: Manuscript
t:

Kishore,

I am assuming you received our comments on the manuscript and want to know if you have had an opportunity to incorporate them. When do you plan to submit the manuscript?

Bob
Robert A. Leadbetter, M.D.
> Principal Clinical Research Physician, Psychiatry
> US Medical Affairs
Glaxo Wellcome Inc
ph: (919) 483-7152
fax: (919) 483-0053
email: ral73653@glaxowellcome.com

29 Mar 00

To: gadde001
cc:

Subject: RE: your visit
t:

Kishore,

28 April, first thing in the morning.

1. How many subjects have completed 1 year follow-up (all assessments)
2. How many subjects have completed 2 year follow-up (all assessments)
3. 2000 NAASO abstract deadline is 1 July; will we be submitting 1yr vs 2yr vs both

4. What is the status of the manuscript? Have you spoken with Bob? I need to see the final version before it is submitted. I leave at noon on Friday and will not be back in the office until 13 April so I would like to see the final version before close of business tomorrow 30 March.

Thanks,

Tim

> -----Original Message-----

> From: gadde001@mc.duke.edu [SMTP:gadde001@mc.duke.edu]

> Sent: Tuesday, March 28, 2000 5:51 PM

> To: Kuhn, Timothy A

> Subject: your visit

>

>

>

> Can you pick of the one the following dates for your visit?

>

> April 21

> April 28

> May 1

> May 3

> May 5

25 Apr 00

To: gadde001

cc:

Subject: Lack of contact

t:

Kishore,

Would you please call me at your earliest convenience so we may arrange a time to get together. There are a number of issues I would like to discuss with you. How about lunch?

Bob

Robert A. Leadbetter, M.D.

> Principal Clinical Research Physician, Psychiatry

> US Medical Affairs

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DOJ005706