


Alan Breier
11/24/99 02:12 PM

To: Gerhard Mayr/AM/LLY@Lilly, Gino Santini/AM/LLY@Lilly, Lorenzo Tallarigo/EMA/LLY@Lilly, Albertus VanDenBergh/EMA/LLY@Lilly
cc: Alan Breier/AM/LLY@Lilly, John C Lechleiter/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Gary D Tollefson/AM/LLY@Lilly
Subject: Olanzapine-associated Weight Changes (OWC)

John asked me to overview the topic of olanzapine-associated weight changes (OWC). I want to emphasize to you that OWC has been and continues to be a top priority for the Zyprexa Product Team. Although it is a significant issue for us, perhaps our only/major clinical Achilles heel, and our competitors have robustly focused on it (reminiscent of anxiety and ) , the fact is Zyprexa offers the best combination of efficacy, safety and ease of use of any available treatment for psychosis and acute mania. The most critical immediate issue is to keep the focus where it belongs - superior treatment and outcome - an arena where we have no peer. What follows is a high level review. Please contact me for more information and your thoughts/recommendations.

Market Research

- OWC is seen as a greater issue for less severely ill patients; e.g. more impactful to bipolar patients than schizophrenics
- Females more concerned than males (**Fact:** weight changes are equal among males and females)
- OWC is not an age-related issue (although weight gain in the elderly is often viewed favorably)
- Cosmetic concerns is a far greater issue than long-term health implications
- "Outliers" are the main concern for physicians; 20 lb increase is viewed as threshold for concern (**Fact:** two-thirds of olanzapine-treated patients gain less than 20 lbs)
- Olanzapine is viewed to have more associated weight gain than risperidone, seroquel, and traditional neuroleptics (**Fact:** the order of weight gain among antipsychotics is: Clozapine>olanzapine>seroquel>risperidone> traditional neuroleptics)
- In US, when patients are switched because of weight gain, they tend to be switched to risperidone
- The plateauing of weight gain is not appreciated (**Fact:** weight gain plateaus after 6 to 9 months of treatment)
- Physicians view EPS as something they can address with dose adjustment but not OWC (**Fact:** OWC is not dose dependent)
- Physicians want more data
- Blanket detailing will be damaging since many physicians do not see OWC as an issue

Scientific Data

- All antipsychotic drugs and mood stabilizers are associated with weight gain; mechanism is not known
- Mean weight change associated with olanzapine at 36 months of treatment is 6.73 kg
- OWC plateaus between 6 to 9 months
- 22% of patients lose weight; another 22% gain less than 5kgs
- Low baseline weight, good clinical response and increase in appetite predict OWC
- As noted above, doses between 5mg and 20mg do not predict OWC
- When olanzapine is stopped, weight change returns to baseline levels
- Behavioral interventions (exercise and diet considerations) work to reduce weight gain even in the severely ill schizophrenic patient
- Prozac does not prevent OWC

Actions To Date

- In June 1999, a full OWC package compiled by Roland including verbatims, slide set, speaker notes, OWC facts, sent to major affiliates
- More market research under way, quantify SOM impact
- Two publications under review at American Journal of Psychiatry
- Numerous presentations at congresses, scientific venues, medical letter
- Two cross-functional action teams formed: one scientific which is addressing the mechanism of OWC and effective treatments (Steering Committee: S. Paul, R. DiMarchi, G. Tollefson, C. Fibiger, J. Caro, G. Probst); the other marketing (organized by Roland) which is focusing on immediate issues. strategy

ZY 2196 658

- Axid intervention study started (preliminary data suggests H-2 blockers may attenuate OWC; N=150, LPV December 2000, interim analysis summer 2000)
- Approximately seven IIT intervention studies funded (examining behavioral and pharmacological interventions)

ZY 2196 659

Robert B Vanlier
11/30/99 06:26 PM

To: Alan Breier/AM/LLY@Lilly, Frank Bymaster/AM/LLY@Lilly, Paula M
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Mitchell/EMA/LLY@Lilly

cc:
Subject: Interim body weights in 6-Mo PLGA Study

I thought you might find the attached graphs interesting. This is only through 76 days (less than half way). Although the effect is not statistically significant by Dunnetts at each time point, the visual trend seems compelling. Standard deviations are around 10% of the absolute body weights.

Bob

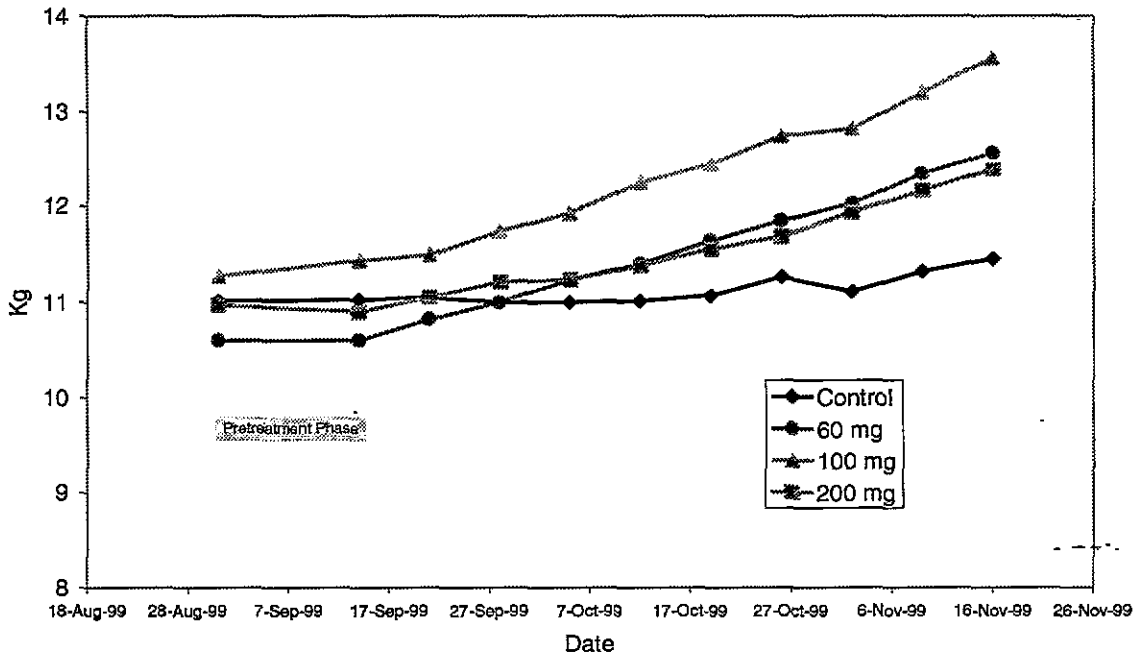


Body weights Curves.do

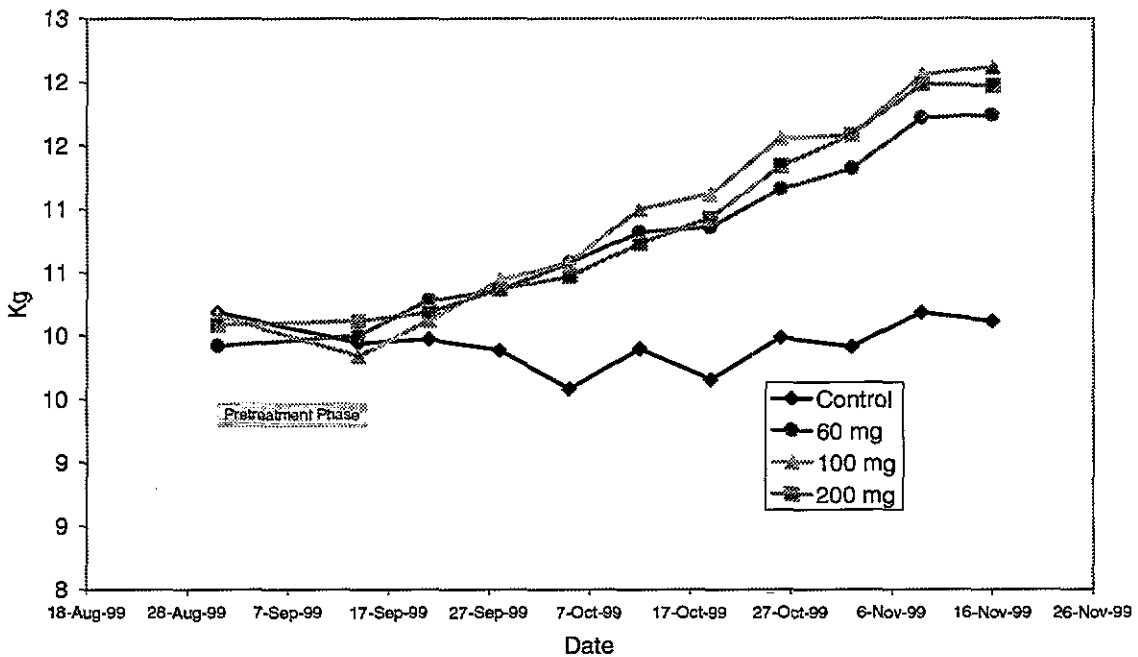
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Body weights for Dogs Receiving Biweekly Injections of Olanzapine PLGA Microspheres. Study D01499

Mean Body Weight in Males



Mean Body Weight in Females



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