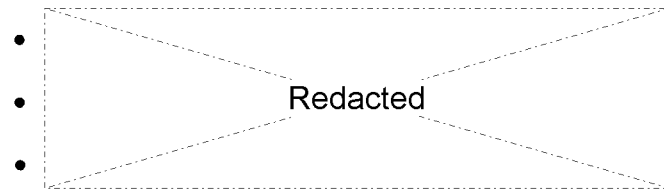



Questions from Jack Jordan Meeting:

- Insulin-resistance and hyperinsulinemia story
- Treating patients with psychiatric disorders who have diabetes – demonstrate it is manageable in this patient population



- Syndrome X
- Wellness guidelines and recommendations
- Bring lipid data to CV factors – tight story
- Diabetes and CV side ... working closing with  group
- Ketoacidosis – type 2 issue / vulnerability

ZY 7152 857

Insulin-resistance (IR) – Hyperinsulinemia

Positioning Statement

"IR (a decrease in IS) may be seen in some patients who gain weight irrespective of drug treatment"

What We Know

- The most up to date information is currently, and continuously, being integrated into the global medical letter.
- *Hyperglycemic Clamp Study*

A small decrease in insulin sensitivity (IS) was observed after 2 weeks of therapy with Olz and Risp which can mostly be attributed to weight gain. However, this study was not directly designed to look at insulin sensitivity. The primary objective of this study was to look at potential direct effect on insulin production by the pancreas. There was no evidence that Olz acutely (i.e. over 2 weeks) suppresses production of insulin by the pancreas in normal volunteers.

- *Euglycemic Clamp*

Results Q1, 2002

This is considered the 'gold standard' study to assess insulin receptor sensitivity and will answer questions about Olz potential effect on insulin receptor sensitivity.

What We Do Not Know

- Mechanism of action
- Long-term effects
- Whether this is a class effect or molecule specific
- Whether it is solely weight gain related or an independent mechanism

How We Will Fill the Knowledge Gap

- Euglycemic clamp study will help answer several of these questions

ZY 7152 858

Patients with Diabetes / Psychosis

Positioning Statement

- The presence or absence of diabetes should not exclude AP medication. Patients should be screened and treated according to ADA guidelines

What We Know

- The presence or absence of diabetes should not exclude AP medication
- Choice of AP should be based on an efficacy benefit and versus a side effect trade off
- There are well established guidelines

What We Do Not Know

- Limited long-term data
- Has not been study and it is unlikely that major studies will be conducted in this population

ZY 7152 859

Redacted

ZY 7152 860

Redacted

ZY 7152 861

Syndrome X

Obesity is a recognized as a risk factor for syndrome X. To study whether treatment with AP's is associated with an increased risk for syndrome X a multi-year prospective comparative study with several thousands of patients would be required. We are unlikely to run this study due to higher priorities at this time.

ZY 7152 862

Wellness Guidelines / Recommendation

Position

This is tactical execution and our experience is that this is best left in the affiliate's hands. Additionally, we have found that each affiliate prefers to develop their own material based on their local guidelines. We have shared various best practices with global affiliates over the last year.

Best Practice Material

- Using U.S. guidelines
- Reintegration.com
- Meaningful Day

ZY 7152 863

Lipid Data → CV

Positioning Statement

An increase in triglycerides and cholesterol can be seen with obesity and weight gain, irrespective of the causes of weight increase. This can be an increased risk factor for CV disease and should be treated in accordance with established guidelines.

What We Know

- Olz is associated with a moderate increase in triglycerides, and a small increase in cholesterol. The increases seem to be related to weight gain.
- Set guidelines are available for the general population, with no indication that guidelines should be different for patients with schizophrenia.

What We Do Not Know

- Mechanism of action
- Difference in AP's

How We Will Fill the Knowledge Gap

- Collect data from ongoing clinical studies
- Continue to analysis clinical trial data base to detect trends

ZY 7152 864

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ZY 7152 864.001

Ketoacidosis

Positioning Statement

Cases of DKA have been reported in association with olanzapine treatment, as well as with other atypical treatments. However, these reports are very rare (occurring in less than 0.01% of patients treated with olanzapine) and a direct causal relationship has not been established.

What We Know

- New Q&A is being prepared
- In the reports of DKA during olanzapine treatment, the patients presented with one or more risk factors for diabetes. These risk factors included family or personal history of diabetes, pancreatic disorders, alcoholism, obesity, weight gain preceding olanzapine treatment or during olanzapine treatment, and concomitant treatment with drugs that have been associated with glucose dysregulation [including conventional antipsychotics-phenothiazines (i.e. Thorazine, Mellaril, etc.), other atypicals, and drugs such as beta blockers and thiazide diuretics.]
- From the hyperglycemic clamp we know that there is no evidence that Olz acutely (ie over 2 weeks) suppresses production of insulin by the pancreas in normal volunteers.

What We Do Not Know

- Among reported cases of DKA, there are very rare reports of DKA in patients with no apparent risk, mechanism unclear.

How We Will Fill the Knowledge Gap

- No plan to do additional studies beyond the two clamp studies.