The way through this intersection starts with you.

Patients with schizophrenia face a host of challenges. From the perplexing nature of their illness to the social stigma that surrounds it, these patients are also 2 to 4 times more likely to be at risk for developing diabetes.*

Diabetes and atypical antipsychotics.

To alert mental health professionals and their patients, the U.S. Food and Drug Administration (FDA) recently issued letters to all manufacturers of atypical antipsychotic medications advising them to add warning information on hyperglycemia and diabetes to their prescribing information.

Another counseling opportunity.

When counseling your patients, discuss the diabetes risks that may be related to their illness. Ideally, this increased attention to the symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment — and allow you to focus on treating the core symptoms of your patients’ mental illness.

Getting the resources you need.

We agree with the FDA that every patient prescribed any atypical antipsychotic should be screened for risk factors and monitored for symptoms of diabetes. To help you help your patients, Eli Lilly and Company is providing resources to help you screen your patients, including the American Diabetes Association’s Diabetes Risk Test. To access the ADA Risk Test, go to the ADA Web site: www.diabetes.org/info/risk/risktest.jsp.

For other health-related information, please call 1-800-Lilly-Rx, or contact your Eli Lilly and Company sales representative.


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Lilly Answers That Matter.
The Good Life: Meeting the physical needs of those with mental illness

- Glasgow's global health clinic
- Physical health checks for those with SMI

PLUS
- One session treatment for phobia
- Reviews

The Official Journal of

MHNA
Mental Health Nurses Association

AMICUS
the union
Health checks for those with SMI

Are patients with severe mental illness getting appropriate physical healthcare? How regularly are they receiving a physical check-up and how often do they get involved in some form of physical exercise? In this study, by Rishi Rahka and Mark McKeown a patient is considered to be suffering from a severe mental illness (SMI) if they either have a diagnosis of schizophrenia, bipolar affective disorder, severe depression or a form of psychotic illness where more than one admission to hospital or secondary care was required and for which they are still receiving anti-psychotic medication or mood stabilisers or anti-depressants. In many cases a combination of these types of medication are being utilised for general efficacy in their condition. This article represents an audit, supported by valid data which has arisen from feedback received from an unfinished project that is being carried out in eight different mental health trust sites across the country. It looks at the levels of physical health checks and physical activity in people suffering from SMI.

Full title: Health promotion for people with severe mental illness: are well-being support programmes the way forward? Rishi Rahka is an RMN who is currently working as a nurse advisor for the Well-Being Support Programme, a project that is being sponsored by Eli Lilly. He is based at Scarborough House Assertive Outreach Team, Birmingham and Solihull Mental Health Trust. Mark McKeown is also a nurse advisor on the same programme. He is working in Coventry Mental Health Trust.
Date: 02/11/2004 10:51:50 PM  
From: CN=Gregory T Brophy/OU=AM/O=LLY  
Subject: Preparation for After Action Review  
Attachments: After Action Review Process.ppt

Bert, here are some of my initial thoughts on the questions posed by David Kinard. Michele, attached are the key questions for the Review meeting on Friday from 10-12 - thanks for filling in for me on this. Robin, I would also like you to feed your thoughts into Michele on these questions.

To a great extent, how these questions are addressed depends on if the group looks at the broad question of ADA influence - from when we first got involved with this (my recommendation), vs. how we ran the drill once we knew the outcome was negative (i.e. we should have had greater influence early on before it was a done deal). So if people take the broader approach, here are some of my preliminary thoughts (for slide 4/5):

**Supposed to happen**: ADA was to come out with a recommendation similar to FDA's conclusion - comparable risk across atypicals

**What happened**: Differential risk, limited evaluation of the data, deck stacked against us even before the meeting began, railroaded process

**Why did it happen**: We underestimated the players, didn't really understand role & approach competition would take, under appreciated ADA backlash to other Lilly actions with it, inadequately influenced key players on decision, thought science and data would win - under appreciated the influence of weight gain on the action (perhaps too busy defending against it), FDA presentation was not as strong as it could have been to influence group (particularly the response to the weight gain question), our "full court press" action in the last few days was good, but came at a point too late to fundamentally influence the outcome.
Antipsychotic Drugs Raise Obesity, Diabetes and Heart Disease Risks:

Joint Panel Urges Increased Screening, Monitoring of Side Effects

(Alexandria, VA) – People who take antipsychotic drugs for the treatment of a variety of mental illnesses may be at increased risk for obesity, diabetes and high cholesterol – all of which can lead to heart disease. Because of this, a joint panel of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity has issued a consensus statement asking doctors to carefully screen and monitor patients on these medications for signs of rapid weight gain or other problems that could lead to diabetes, obesity and heart disease and refer them to specialists if necessary.

The consensus statement, published in the February issue of Diabetes Care, outlines guidelines for doctors treating people with a class of drugs known as second-generation antipsychotics (SGAs). These drugs, the use of which has soared in recent years, are used to treat a variety of mental illnesses, including: schizophrenia spectrum disorders; bipolar disorder; dementia; psychotic depression; autism and developmental disorders; and, to a lesser extent, delirium; aggressive behavior; personality disorders; and posttraumatic stress disorder.

The panel also concluded that the SGAs differ in their risk profiles and that some SGAs, such as clozapine and olanzapine, while effective treatment options, raise a greater risk of weight gain, diabetes and lipid disorders than others. The statement notes that “...Even for those medications associated with an increased risk of metabolic side effects, the benefits to specific patients could outweigh the potential risks.” Thus, while risks reviewed in this study should influence choice of medication, the need to balance benefits and a wide range of risks underscores the importance of tailoring treatments to individual patients.
Summary of the After Action Review of Zyprexa and ADA (held 2/13/04)

- Close contact was not maintained with the presenters or the writing panel of the consensus panel. **Solution:** a systematic well orchestrated approach is needed with similar events that are likely to happen in the future in order to ensure that the information available is accurate and free of interpretation bias.

- Crisis atmosphere on the Zyprexa leadership team during 2-3 weeks around the publication of the ADA consensus. **Solution:** A hand railed team with defined leadership, headcount and clear accountability needs to be created to address similar events. A team has been assembled led by Bert VandenBergh.
22 January 2004

Richard Kahn, PhD
Chief Medical and Scientific Officer
American Diabetes Association
1701 N. Beauregard St.
Alexandria, VA  22311

RE: Consensus Development Conference on
Antipsychotic Drugs and Obesity and Diabetes

Dear Dr. Kahn,

Eli Lilly and Company commends the American Diabetes Association for its initiative in addressing issues concerning metabolic adverse events in patients using atypical antipsychotics. As the sponsor that initially brought these issues to the attention of the ADA, Lilly appreciated the opportunity to partner with ADA, APA, AACE, NAASO, and other sponsors in presenting data at the Consensus Development Conference.

We have reviewed the Consensus Statement forwarded to us by the ADA and commend the working group for bringing focus to the critical issue of increased rates of diabetes in patients with serious mental illness. However, we have significant concerns regarding the conclusion that there are differential rates of treatment-emergent diabetes among second-generation antipsychotics (SGAs). We disagree with the following conclusion as stated on page 600:

“Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone are associated with little or no significant weight gain and no diabetes or dyslipidemia, although they have not been used as extensively as the other agents” (pg. 600).
Why this matters...

The data showed that everyone interviewed, which included not only psychiatrists, PCPs, and nurses, but also Lilly sales directors, DMs, sales reps and Marketing staff, exhibited language that was devoid of emotion around the side effects of Zyprexa. This represents an "emotional gap" that must be bridged before many MDs will feel more in control when treating patients on Zyprexa. Furthermore, if we can communicate to the MD on an emotional level and help them address the psychological impact of weight gain for the patient, we will most likely make significant strides towards resolving this issue in their minds.

Best regards,

______________________________
Tom Reck
Market Research Associate
Zyprexa - U.S.
w) 317.655.8983
treck@lilly.com
Lingustic Market Research Objectives

• Understand the perceptions of weight gain internally and externally
  – Lilly Marketing
  – Lilly Medical
  – Lilly Sales Force
  – Called on Physicians and health care professionals

• Understand weight gain from a medical versus emotional standpoint

• Understand how weight gain and weight gain related health concerns play on the emotions of both MDs and patients in relation to Zyprexa
  – Pt demands to be taken off of Zyprexa b/c they don't want to be fat
  – MD takes pt off Zyprexa due to pt appearance and potential health related issues

• Understand what language Lilly can implement to help communicate with health care professionals regarding the weight gain issue.
  – Communication with MDs, Treatment Teams and potentially patients.

• Understand the marketing mix implications to most effectively communicate our message.
  – What can we do outside of the sales force.
Critical Observations on this new information

This data is an enhancement to and consistent with our previous message

Remember, handle this objection, like weight gain, in the context of overall efficacy.

- This is all about tone. We must handle the objection in a confident and forthcoming manner, but must only answer the question to the depth required.
  - Do not bypass the objection handle it when it happens.
  - Tailor the response to situation, probe, get back to joint discovery
Situational Analysis:
Where we were vs. Where we are going

From
- Weight gain is manageable
- Weight gain is predictable
- Weight gain is not the only predictor of diabetes
- Diabetes risk is a class effect with comparable rates across all products
- Diabetes is mainly a patient population issue
- Handling diabetes and weight gain as an objection

To
- Lilly understands the challenges physicians face in treating this population
- Lilly acknowledges weight gain challenges and potential consequences
- Lilly is providing me with options to address weight gain in some of my patients
- External entities provide me with the facts related to diabetes
- Lilly is providing help regarding how to assess, counsel, and refer patients at risk for diabetes
Big opportunity for the brand: Weight gain

Weight Gain

Perceived as very prevalent
Sometimes significant

Results

Patients denied Zyprexa
Unhappy customers (Declining Doctors)

Loss of $ Root of Problem

Issue cannot be “fixed”, must be managed
Relationship issue with the brand.
Our goal and focus is on creating a market with Donna. The competition wins if we are distracted into talking about diabetes. So, stand strong against their ploys and answer the AOC concisely and with confidence!
Handling the Diabetes AOC:

This is a highly competitive driven issue. Therefore, we will NOT proactively address the diabetes concern, but rather only when it arises from an MD.

If it does, please do the following:

1. Cushion/Clarify the AOC
2. Handle by providing the verbatim
3. Check for agreement, if not satisfied then utilize the sell sheet
4. Restate the verbatim while utilizing the diabetes sell sheet
5. Check for agreement and get back to Donna!
Handling AOC - Other Risk Factors

For customers who ask about Diabetes as it relates to risk factors such as weight, please provide the following verbatim:

1. While there is a relationship between weight (or specifically obesity) and diabetes, it is not exact and constitutes one of many risk factors for diabetes. For example, another is hyperprolactinemia (Inside cover, “A number of factors…” section 4)

2. Even among the patients that had substantial weight gain with Zyprexa, over 96% had no glycemic abnormalities at all. (Inside cover, “Weight gain…” section 2)

Remember correct tone is critical, Confident and informative! Our customers just want the facts and reassurance
I am concerned about weight gain.

**Cushion:** Thanks for letting me know your concern.

**Clarify:** Is this something you have seen in your patients or heard about?

**Address AOC:** Zyprexa may cause an increase in appetite that can lead to weight gain. The increase in appetite can be manageable, and diet and behavioral modifications can help. Many describe this as carb-craving so discussing this up front with your patients is helpful. You can suggest that patients drink diet soda instead of regular soda, or cut back on the amount of carbohydrates they eat. Some patients adopt a “1-plate rule” when they sit down for dinner. Increasing daily activity may also help manage weight.

**Check for Agreement** How do you manage weight gain that results from other medications? If the physician has further questions, offer to have a medical letter sent to them.

**Get back to Selling**
Doubt is our product since it is the best means of competing with the "body of fact" that exists in the mind of the general public. It is also the means of establishing a controversy. Within the business we recognize that a controversy exists. However, with the general public the consensus is that cigarettes are in some way harmful to the health. If we are successful in establishing a controversy at the public level, then there is an opportunity to put across the real facts about smoking and health. Doubt is also the limit of our "product". Unfortunately,
Doubt is also the limit of our product. Unfortunately, we cannot take a position directly opposing the anti-cigarette forces and say that cigarettes are a contributor to good health. No information that we have supports such a claim.
Answers

** Medicines. ** Discovering breakthrough treatments. Confronting many of the most challenging diseases facing humanity.

** Information. ** Openly sharing the knowledge you need. Helping you make the best health care decisions possible.

** Medicine and information. ** The answers you’re looking for.

We’re celebrating 125 years of lifesaving innovation.  www.lilly.com
When asked a question about weight gain, Dr. Tollefson’s response misleadingly turned an adverse event into a therapeutic benefit. He states, “So we went back and analyzed our data and saw that the vast majority of weight gain reported initially as an adverse event, in fact, was weight gain occurring in patients who had baseline before starting treatment, had been below their ideal body weight. So we really look at this, with the majority of patients, as being part of a therapeutic recovery rather than an adverse event. And that data, I think, is fairly compelling, because it was included in our labeling. (Emphasis added)”

The information on weight gain was indeed included in the approved labeling, but as an adverse event, not a therapeutic benefit. Since the product was approved at the time of this teleconference, Dr. Tollefson knew or should have known what information the approved labeling contained and in what section it appeared. His statements were therefore, false and misleading.
13% of patients had diabetes in the landmark CATIE schizophrenia study at baseline—4 times more common than in the general population.¹

Be aware.
Screen and monitor your patients.
Make a difference.
41% of all patients had the metabolic syndrome at baseline in the landmark CATIE schizophrenia study.²

Be aware.
Screen and monitor your patients.
Make a difference.

# Lab Chemistry: Change from Baseline to Ave of 2 Highest Values

<table>
<thead>
<tr>
<th></th>
<th>O (n=336)</th>
<th>QT (n=337)</th>
<th>R (n=341)</th>
<th>P (n=261)</th>
<th>Z (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.E.)</td>
<td>15.0 (2.8)</td>
<td>6.8 (2.5)</td>
<td>6.7 (2.0)</td>
<td>5.2 (2.0)</td>
<td>2.3 (3.9)</td>
</tr>
<tr>
<td>Median Exposure-adj. Mean</td>
<td>7.0</td>
<td>4.3</td>
<td>5.5</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>13.7 (2.5)</td>
<td>7.5 (2.5)</td>
<td>6.6 (2.5)</td>
<td>5.4 (2.8)</td>
<td>2.9 (3.4)</td>
</tr>
<tr>
<td><strong>Hemoglobin A1C (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.E.)</td>
<td>0.41 (0.09)</td>
<td>0.05 (0.05)</td>
<td>0.08 (0.04)</td>
<td>0.10 (0.06)</td>
<td>-0.10 (0.14)</td>
</tr>
<tr>
<td>Median Exposure-adj. Mean</td>
<td>0.20</td>
<td>0.10</td>
<td>0.07 (0.08)</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>0.40 (0.07)</td>
<td>0.04 (0.08)</td>
<td>0.09 (0.09)</td>
<td>0.11(0.09)</td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.E.)</td>
<td>9.7 (2.1)</td>
<td>5.3 (2.1)</td>
<td>-2.1 (1.9)</td>
<td>0.5 (2.3)</td>
<td>-9.2 (5.2)</td>
</tr>
<tr>
<td>Median Exposure-adj. Mean</td>
<td>8.5</td>
<td>3.5</td>
<td>-3.0</td>
<td>0.5</td>
<td>-1.0</td>
</tr>
<tr>
<td></td>
<td>9.4 (2.4)</td>
<td>6.6 (2.4)</td>
<td>-1.3 (2.4)</td>
<td>1.5 (2.7)</td>
<td>-8.2 (3.2)</td>
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<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.E.)</td>
<td>42.9 (8.4)</td>
<td>19.2 (10.6)</td>
<td>-2.6 (6.3)</td>
<td>8.3 (11.5)</td>
<td>-18.1 (9.4)</td>
</tr>
<tr>
<td>Median Exposure-adj. Mean</td>
<td>33.5</td>
<td>17.5</td>
<td>3.0</td>
<td>2.0</td>
<td>-7.0</td>
</tr>
<tr>
<td></td>
<td>40.5 (8.9)</td>
<td>21.2 (9.2)</td>
<td>-2.4 (9.1)</td>
<td>9.2 (10.1)</td>
<td>-16.5 (12.2)</td>
</tr>
<tr>
<td><strong>Prolactin (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.E.)</td>
<td>-6.1 (1.2)</td>
<td>-9.3 (1.4)</td>
<td>15.4 (1.5)</td>
<td>0.4 (1.7)</td>
<td>-4.5 (1.6)</td>
</tr>
<tr>
<td>Median Exposure-adj. Mean</td>
<td>-0.9</td>
<td>-2.7</td>
<td>9.2</td>
<td>1.4</td>
<td>-24</td>
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<tr>
<td></td>
<td>-8.1 (1.4)</td>
<td>-10.6 (1.4)</td>
<td>13.8 (1.4)</td>
<td>-1.2 (1.6)</td>
<td>-5.6 (1.9)</td>
</tr>
</tbody>
</table>
Schizophrenia and diabetes 2003: an expert consensus meeting
EDITED BY T. G. DINAN

s53 Introduction
T. G. Dinan

s55 Diagnosis, epidemiology and pathogenesis of diabetes mellitus: an update for psychiatrists
R. I. G. Holt

s64 Diabetes mellitus and schizophrenia: historical perspective
D. Kohen

s67 Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia
C. Bushe and R. Holt

s72 Stress and the genesis of diabetes mellitus in schizophrenia
T. G. Dinan

s76 Metabolic disturbance in first-episode schizophrenia
J. H. Thakore

s80 Antipsychotics and diabetes: review of non-prospective data
P. M. Haddad

s87 Association between atypical antipsychotic agents and type 2 diabetes: review of prospective clinical data
C. Bushe and B. Leonard

s94 Retrospective analysis of risk factors in patients with treatment-emergent diabetes during clinical trials of antipsychotic medications
P. Cavazzoni, N. Mukhopadhyay, C. Carlson, A. Breier and J. Buse

s102 Diet, diabetes and schizophrenia: review and hypothesis
M. Peet

s106 Diabetes and its prevention: pragmatic solutions for people with schizophrenia
S. Gough and R. Peveler

s112 'Schizophrenia and Diabetes 2003' Expert Consensus Meeting, Dublin, 3-4 October 2003: consensus summary
Expert group
Diabetes in Asylum History

Maudsley 1897
Kooy 1919, HG
Raphael & Parsons 1921 HG
Drury & Farron-Ridge 1921 HG
Lorenz 1922 HG (Catatonia)
Barrett & Serre 1924 HG
Henry & Magnan 1925 HG
Kasanin 1926 HG

2-4 fold increase in risk
Antipsychotics and Glucose

Courvoisier et al 1953 Glycemia
Giacobini & Lassenius 1954 Glycemia
Merivale & Hunter 1954 Glycemia
Charatan & Bartlett 1955 Glycemia
Hiles 1956 DM & Glycemia
Winkelmayer 1962 DM
Keskiner 1973 DM – 25%
US
1.2% 18-44
6.3% 45-64

Isle of Ely
4.5% undx diabetes
16.7% GTT

Australia
7.4% diabetes
16.4% GTT or HG

Japan & Sngpre
5 – 9% diabetes
10-18% GTT
North Wales Asylum

No. Patients – 3,170  No. Diabetics - ?
No. Psychoses - 1,041  No. Diabetics - ?
No. Mood Dis - 695  No. Diabetics – ?
Other - 1,434  No. Diabetics - ?
North Wales Asylum

No. Patients – 3,170  No. Diabetics - 64
No. Psychoses - 1,041  No. Diabetics - 20
No. Mood Dis - 695  No. Diabetics - 12
Other - 1,434  No. Diabetics - 28
North Wales Asylum

No. Patients – 3,170  No. Diabetics - 128
No. Psychoses - 1,041  No. Diabetics - 40
No. Mood Dis - 695  No. Diabetics – 24
Other - 1,434  No. Diabetics - 56
North Wales Asylum

No. Patients – 3,170  Diabetics – 5
Psychoses - 1,041  Diabetics – 0
Mood Disorders - 695  Diabetics – 2
Other - 1,434  Diabetics – 3

No. with pre-existing diabetes – 2 (0.06%)
1994 – 2006

Schizophrenia
Delusional Disorder
Acute and Transient Psychoses
Non-specific Non-Organic Psychosis
Bipolar Disorder
Manic Episodes
  \[ N = 395 \]

Hospital Database
Pharmacy Database
General Practitioners
Diabetes & F Codes

1996-2006

1031 Individuals

F00-99  368 ***
F10-19  204
F20-29  45
F30-39  230
F40-69  284

413 now dead –
Prevalence 617/200K = 0.3%
SMI - 66
Prevalence of Diabetes in Serious Mental Illness

![Graph showing the prevalence of diabetes in serious mental illness over years. The y-axis represents cases per 100, and the x-axis represents years: Yr 0, Yr 3, Yr 5, Yr 7, Yr 9, Yr 11, Yr 13, Yr 15. The prevalence increases significantly from Yr 7 onwards, reaching a peak at Yr 15.]
Obesity is being presented as the next massive threat to health - our children may even die before us due to the terrible danger of being fat. Celebrity chef Jamie Oliver has taken to dressing up in a fat suit to make the point.

A couple of years back, a NEJM study was reported on a US news website: 'Obesity could shorten the average lifespan of an entire generation - today’s children are facing an obesity epidemic that could be the most serious in history.

Dr Malcolm Kendrick exposes sloppy science, medical myths and unhealthy assumptions in healthcare

Obesity is no casus belly

Obesity is being presented as the next massive threat to health - our children may even die before us due to the terrible danger of being fat. Celebrity chef Jamie Oliver has taken to dressing up in a fat suit to make the point.

A couple of years back, a NEJM study was reported on a US news website: 'Obesity could shorten the average lifespan of an entire generation - today’s children are facing an obesity epidemic that could be the most serious in history.

Obesity is a massive tsunami headed toward the United States,' says pediatric endocrinologist David Ludwig, director of the obesity program at Children's Hospital in Boston and one of the study’s authors.

From what I have read in the UK medical and lay press, most people seem to be broadly in agreement with this last statement. However, it must be borne in mind that while Americans are more aware of the dangers of obesity, the UK public is just beginning to wake up to the problem.

Here is one of my favourites, an Italian study of 62,000 men and women aged 20 to 69. In young men, there was no relationship at all between weight and overall mortality; in young women, the lowest mortality rate was at a BMI of 27; in older men, the lowest mortality rate was BMI 29; and in older women, the lowest mortality was BMI 32.

The authors’ conclusion: ‘These uncommon high values of BMI carry the lowest risk for death among men and women.’

There is extremely strong evidence that eating disorders are on the increase, and that a BMI of less than 18 massively increases the risk of premature death.

Last year, the Eating Disorders Association (EDA) answered more than 18,000 calls to its adult helpline. The EDA estimates that nearly 18% of anorexics calling its helpline will die, and many others will develop long-term health problems like osteoporosis.
Odds ratio of MI as a function of fasting blood glucose

Fasting glucose (mmol/L) quartile

- 1st Quartile
- 2nd Quartile
- 3rd Quartile
- 4th Quartile

<81mg/dL  81–94mg/dL  94–114mg/dL  >114mg/dL

Carotid intima-media thickness as a function of FPG

• The ADA “Table 2” is somewhat misleading because makes the drugs look linear in their side effects with its use of plusses and minuses. It should list Clozaril & Zyprexa first with 22 lbs weight gain in 14 months, then Seroquel & Risperdal second (7 lbs.), and then Abilify and Geodon (2.2 lbs).

  o “The efficacy ‘improvement’ of Zyprexa, even if it existed, would not justify its much higher weight gain.”

  o “Even if Zyprexa was a bit better, which is not shown, as a doctor, you err on the side of caution—you should start with a treatment that has low side effects and work your way up if you don’t get the benefits you want—but don’t risk the weight gain first”.

• Lilly is “burning credibility” by denying the metabolic side effects of Zyprexa through semantics.

• Many practitioners are aware of the different metabolic profile of Zyprexa, and many would prefer straight answers from the company.

  o “Lilly is playing a language game with the FDA pronouncements. Because the FDA class warning is about diabetes, Lilly can claim that there is no direct link with diabetes—which is true in one sense. But there is a direct link with weight gain, visceral fat, insulin sensitivity, and thus diabetes, stroke, and myocardial infarction. So while Lilly is technically correct, this is whitewash. They are, however, doing an outstanding job of politicizing and language games.”
Dec 2006 - $1.2 billion in plaintiffs’ settlements & more unsettled

Pennsylvania, Louisiana, West Virginia, Alaska, New Mexico, Mississippi
Montana – “all funds spent by Montana or its citizens on Zyprexa since its launch in 1996, treble damages and attorneys' fees”.

+ 20 States
Causality isn't established

Scientifically, causation is never "established" except as the best (most consistent) theoretical explanation for an empirical association.

Has anyone in industry or law ever read anything about causation?
Diabetes is a disease which often shows itself in families in which insanity prevails.

Henry Maudsley

The Pathology of Mind
### Background Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td>Compound Synthesized</td>
</tr>
<tr>
<td>1983</td>
<td>Project Team Formed</td>
</tr>
<tr>
<td>1984</td>
<td>First Human Dose</td>
</tr>
<tr>
<td>1985</td>
<td>First Efficacy Dose</td>
</tr>
<tr>
<td>1986</td>
<td>Development Initiated in Japan</td>
</tr>
<tr>
<td>1987</td>
<td>Registration Phase GPAC Review</td>
</tr>
<tr>
<td>1988</td>
<td>Patent Issued</td>
</tr>
<tr>
<td>1989</td>
<td>Product Decision</td>
</tr>
<tr>
<td>1990</td>
<td>HWT Team Formation</td>
</tr>
<tr>
<td>1991</td>
<td></td>
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**GDT/dle**

**July 20, 1995**
<table>
<thead>
<tr>
<th>Objective</th>
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<td>Emerging market registration</td>
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<td>- Mania</td>
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<td>- Psychosis in Alzheimer’s</td>
<td>U.S.</td>
<td>Lieberman, et al, Kahn</td>
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<td>Expand the package insert wording</td>
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<td>- Relapse prevention</td>
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<tr>
<td>- Refractory</td>
<td>U.S.</td>
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<tr>
<td>Commercialization -</td>
<td>multistate</td>
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<tr>
<td>Local opinion leader involvement - templates</td>
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</table>
All,

Attached you will find the executive summary from our recent linguistic research study. Please let me know if you would like the final PowerPoint presentation.

Why this matters...

The data showed that everyone interviewed, which included not only psychiatrists, PCPs, and nurses, but also Lilly sales directors, DMs, sales reps and Marketing staff, exhibited language that was devoid of emotion around the side effects of Zyprexa. This represents an "emotional gap" that must be bridged before many MDs will feel more in control when treating patients on Zyprexa. Furthermore, if we can communicate to the MD on an emotional level and help them address the psychological impact of weight gain for the patient, we will most likely make significant strides towards resolving this issue in their minds.

Best regards,

Tom Reck
Market Research Associate
Zyprexa - U.S.
w) 317.655.8983
treck@lilly.com
Section 3.2.1.1: John, here is how I rewrote the HGHL disposition section to try to soften the "only 66 completers" language. New or revised text is shown in green:

Table WS.2.2 (Section 2.3.2) summarizes patient disposition and reasons patients discontinued from the double-blind maintenance period. Three hundred sixty-one patients began double-blind treatment (225 olanzapine, 136 placebo). Patients who experienced recurrence were discontinued from the double-blind maintenance period (and entered into the open-label rescue period), but “recurrence” was not formally captured as a reason for discontinuation for these patients. At the end of the double-blind maintenance period, 66 patients had completed all 12 months of treatment without recurrence of a manic, mixed, or depressive episode or discontinuing for any other reason. A statistically significantly greater percentage of olanzapine-treated patients completed double-blind treatment compared with placebo-treated patients (23.6% vs. 9.6%). The most common