What do the “Zyprexa (&other) Documents” say about industry sponsored CME?

RANZCP Congress 2009

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A/Prof Glen Spielmans, Metropolitan State University, Minnesota, USA.

Speakers Note 25 May 2009

By way of introduction, when I gave this talk today at our college's annual congress, I said this was not a talk I liked giving. My interests as a child psychiatrist are in quite different areas such as developmental psychology, interviewing skills with families, parenting programs and parent-child therapies. Talking about internal drug company documents is a long way from that.

However I said it was a talk I felt compelled to give to inform my colleagues of important information that had become available quite widely on the internet but was not well known to psychiatrists.

I stated that in no way was this talk meant to be taken personally, that industry people I'd met over the years had always been in my experience fine people. But rather the problem was the systems that put people in situations that ultimately lead to harmful outcomes for patients. The problem was as much the medical professions' as industry (on further thought probably collusion by the profession is the worse aspect as industry marketeers are in a way only doing their job of maximising sales). It is the systems - the relationship between Pharma and Medicine - which need to change (for which there is a rising mainstream chorus).

At a personal level I described how I had joined Healthy Skepticism 25 years ago when working as an intern with Peter Mansfield, the founder of HS at the Royal Adelaide Hospital. We had both done medical electives in South Asia and he told me of dumping of medications banned in the west, due to toxic side-effects, upon developing world doctors and patients. Despite that, for 20 years my awareness with these issues could be described as "intellectual insight" only, not producing much behavioural change.

It was only in the last 5 years that my sense of these issues moved to "emotional insight" over the GSK study 329 issue where adolescent suicidality/homicidality data was obscurred on paroxetine and I realised how some teenagers I'd prescribed this to in the 1990s had had this adverse reaction which I had been unprepared for even though the company knew. Also I had issues with the "TADS study" (my issues are in a paper on this on HS website).

Finally I became aware of gross overmedication and overdiagnosis of bipolar disorder, mainly in the USA, where very young children, many toddlers, were heavily medicated. It was through researching this phenomenon that I came across the "Zyprexa documents" and more latterly the Seroquel and J&J-Risperdal documents.

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Disclosure – Peter Parry

- Member of Healthy Skepticism
  - www.healthyskepticism.org

- No recent pharmaceutical company income to declare
  - Gave 2 or 3 talks on child psychiatry in mid 1990s at sponsored GP meetings payments of approx $200 per time
  - Occasionally fill out a postal/phone survey

Disclosure – Glen Spielmans

- Holds <$10,000 US in mutual fund (Vanguard Health Care) that invests nearly exclusively in drug companies

Pharma & Medicine both have vital roles to play…BUT - burgeoning academic literature on deficits of current system

- Outcomes from sponsored trials differ from independent trials.
  - Selective publication.
  - Ghost writing.
- Undue influence through CME
  - Influence of advertising & gifts.
  - Influence of sponsored CME/conferences.

Result is obscuring of fullest available knowledge in direction of overstating benefits and understating harms.

A rising chorus

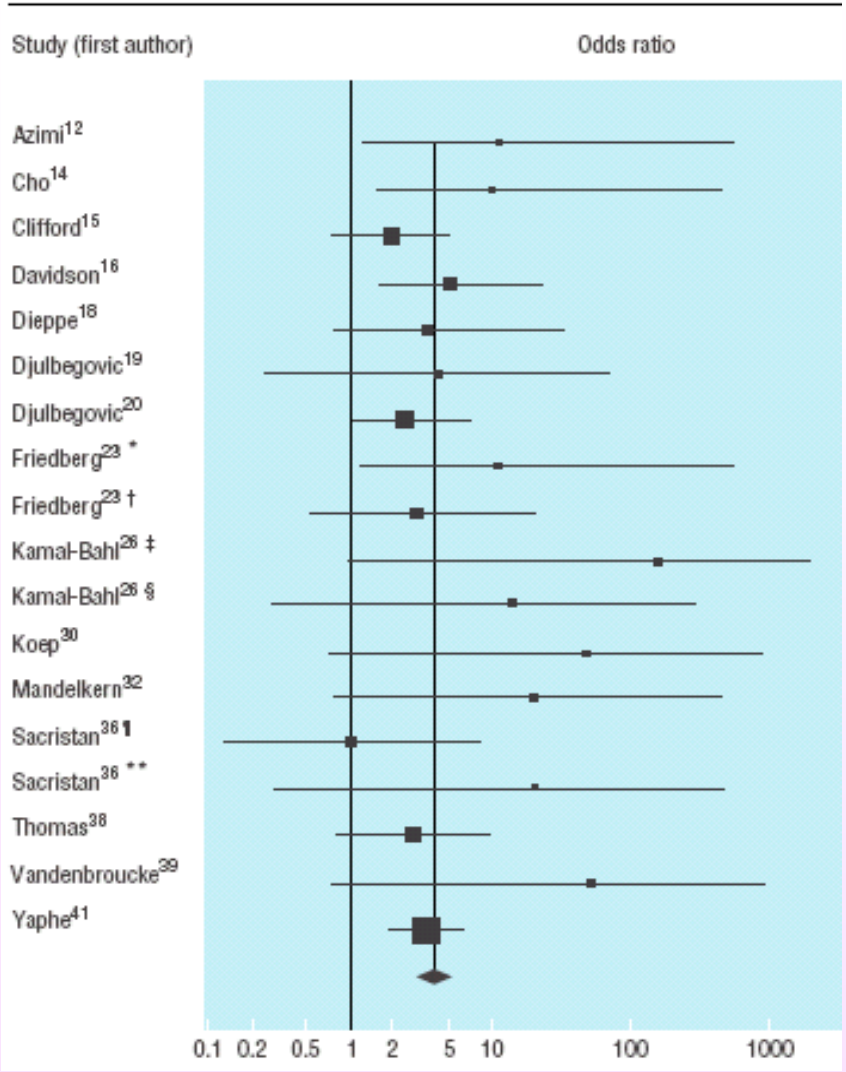
- *Lancet* editorial: Apr 2002: **"How tainted has medicine become?"**
  - **" Heavily, and damagingly so"**
- *BMJ* Aug 2008: **"Sponsorship of medical education".**
  - 3 article feature (Moynihan, Fletcher, Gould) included RANZCP 2009 sponsorship issue and resignation of convenor and other committee members.
- *JAMA* Sep 2008: Relman A. **"Industry support of medical education".**
  - **"Industry likes to call this education but it is not. It is marketing."**
- *PLoS Medicine* Nov 2008: Chan A-W. **"Bias, spin and misreporting: Time for full access to trial protocols and results."**
  - "**favorable results were often highlighted while unfavorable data were suppressed**; definitions of primary outcomes were changed; and methods of statistical analysis were modified without explanation in the journal article."

Critiques of pharma influence in clinical trial process through selective statistical methods.

- Pocock et al, *N Engl J Med.* 1987; 317:426-32
- Chan, *PLoS Med* 2008, 5(11): e230
- Jureidini et al, *Int J Risk Saf Med* 2008; 20(1-2):73-81
- Jureidini et al, *BMJ* 2004;328:879-83
- Svensson et al, *Psychother Psychosom.* 2004;73(1):10-6.
- Gøtzsche, *BMJ* 2006; Jul 29;333(7561):231-234
- Garcia-Berthou et al, *BMC Med Res Methodol* 2004; May 28;4:13
- Sackett, *CMAJ* 200;1 Oct 30;165(9):1226-37
- Sterne et al. *BMJ* 2001;322:226-231
- Gigerenzer et al. *Psychol Sci Pub Int.* Vol 8- 2:53-96
- Whittington et al. *Lancet* 2004; 363: 1341-1345.
- Angell, *JAMA.* 2008;300(9):1069-1071
- Sismondo, *Soc. Sci. & Med.* 2008;66:1909-1914

- **etc. etc. etc.** – the Sismondo paper in particular has several dozen references of similar papers.

Pharmaceutical Sponsorship and Outcome
Lexchin et al BMJ 2003



OR = **4.05** (95% CI 2.98 – 5.51) - indicating industry funding related to more positive outcome for pharmaco's drug (v placebo or comparator).

Critiques of influence of sales reps and CME.

- Several studies find doctors are influenced in direction of sponsors' drug by CME and also influenced by sales reps:
  - Spingarn et al .*Acad Med* 1996;71(1):86-8.
  - Kreyenbuhl et al. *Psychiatr Serv.* 2007;58(7):983-90.
  - Huang et al. *Acad Psychiatry* 2005;29(5):500-1.
  - Orlowski & Wateska, *Chest* 1992;102(1):270-3.
  - Bowman et al. *J Contin Educ Health Prof* 1988;8(1):13-20.
  - Steinman et al. *Ann Intern Med* 2006;145:284-93.
  - Wazana, *JAMA* 2000;283:373-80.
  - Grande et al. *Arch Intern Med.* 2009;169(9):887-893

- In contrast one study looked for association between exposure to meetings sponsored by drug companies and the frequency of prescribing but did not detect any:
  - Peay & Peay *Soc Sci Med* 1988;26(12):1183-9.

“I’m Not Influenced by Gifts”

- Psychiatry trainees who received *more gifts* from industry reported their prescribing habits as *less influenced* by gifts.
  - “the number of promotional items received was positively correlated with the belief that discussions with representatives have no impact on prescribing behaviour (r, = 0.24, p < 0.04).”
- Trainees as a group became more sceptical (?confident that they could resist influence) with increased seniority.

Hodges, Canadian Medical Association Journal, Sep 1995

“Educational” Vacations

- Cleveland Clinic physicians
  - Received full paid lavish “educational” junkets to luxury resorts, involving a new antibiotic medication
  - 19/20 MDs who attended junkets said such a trip would not or was unlikely to influence their practices
  - Prescriptions for the new drug skyrocketed disproportionately at the hospital shortly after the “educational” seminar

Orlowski & Wateska. The effects of pharmaceutical firms enticements on physician prescribing patterns. There’s no such thing as a free lunch. *Chest* July 1992

“There’s no such thing as a free lunch”

Orlowski & Wateska, Chest July 1992

Drug A usage showed a very significant change following the course invitations and the symposium (Fig 1). The usage of drug A had been an average of 81 ± 44 units per month for the 22 months before the

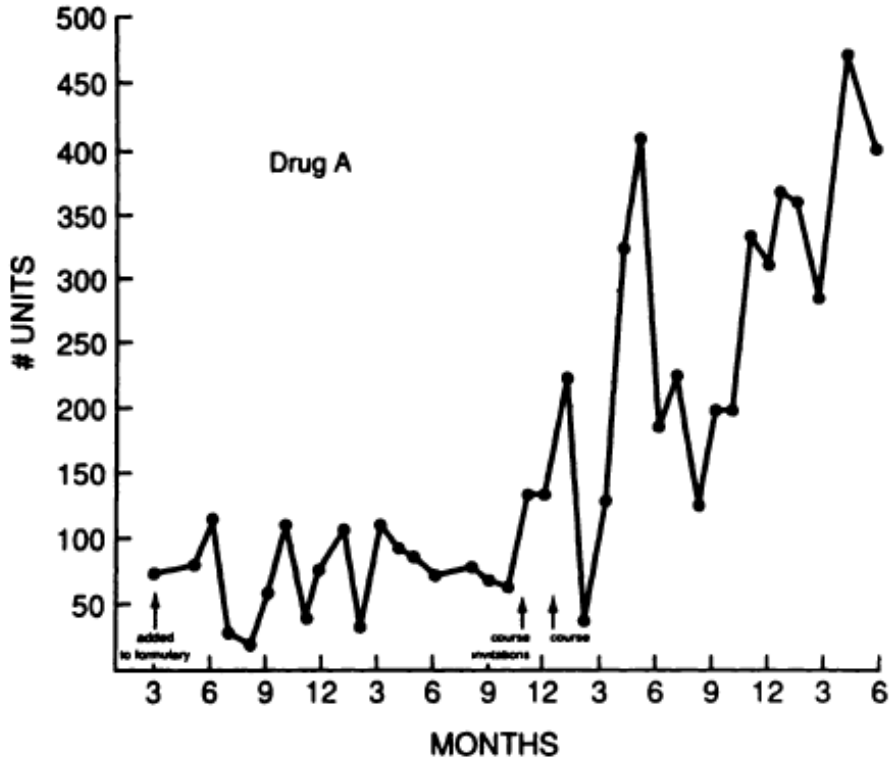


FIGURE 1. The number of dispensed units of drug A over 39 months of hospital use. Arrows indicate when drug was added to the hospital formulary, when course invitations arrived, and when symposium took place.

More Relationships = Less Bias?

- Dr Lawrence Ginsberg, Texas physician
  - His clinic prescribed psychiatric drugs to nearly 2000 foster children from 2002-2008
  - Has consulted for nearly 20 drug firms
  - **"If a physician talks to all the companies and prescribes for all the companies, then no company has an edge."**

Ramshaw, E. Some Texas foster kids' doctors have ties to drug firms. Dallas Morning News 17 Aug 2008

Media articles by prominent psychiatrists/physicians

- Marcia Angell: ***Drug Companies & Doctors: A Story of Corruption.*** The New York Review of Books, January 15, 2009.
    - former editor NEJM.
    - Angell M. *The Truth About the Drug Companies: How They Deceive Us and What to Do About It.* New York, NY: Random House; 2004.
- Daniel Carlat: ***Dr Drug Rep.*** The New York Times, November 25, 2007.
    - psychiatrist, former KOL re venlafaxine.
    - set up his own independent CME and online journal www.thecarlatreport.com

Law courts examining the problem.

- Several class actions and state prosecutions against (among others)
  - Eli-Lilly (Zyprexa),
  - Astra-Zeneca (Seroquel)
  - Janssen/Johnson & Johnson (Risperdal).
- Settlements to $Bs
- Alleged
  - selective drug trial processes,
  - off-label promotion,
  - withholding/understating risk of ADEs .

Zyprexa sales v settlements

- $40 billion in sales 1996 – 2009

- ~ $2.7 billion in court settlements
  - Includes “largest criminal fine in history”
    - $515 million for off-label marketing for dementia, Jan 2009.

What are the "Zyprexa Documents"

- Class action court case v Eli-Lilly re alleged
  - with-holding of ADEs data (wght gain and diabetes)
  - off-label marketing (dementia and subsyndromal mood swings).
- Lawyer (Gottstein) public health physician (Egilman) journalist (Berenson) in Dec 2006 made public **358 files** www.furiousseasons.com (Dawdy) www.boocompany.com/zyprexakills (anon.)
  - internal memos,
  - Powerpoints
  - marketing strategies…
- Judge (Weinstein) ordered cannot be removed from internet and has since stated they belong in public domain.

Several articles in New York Times and other mainstream media but little in the academic literature

- BMJ news report.
  - Dyer. BMJ 2007;334:171 (27 January)
- Healy & LeNoury. *Intl. J. Risk & Safety in Medicine* 2007
- Spielmans, G. - "The Promotion of Olanzapine in Primary Care: An Examination of Internal Industry Documents". *Social Science & Medicine* (in press)

Methodology for this presentation

- All 358 files independently viewed by Spielmans and Parry.
- Focus on 117 files relating to marketing of Zyprexa which involved training of sales reps, marketing strategies and CME.
- Thus this is “data-mining” for issues of concern.
- Eli-Lilly argued in court that the documents needed to be understood in context.
- For full context one has to read each file in full – the ZY number gives reference.

What do the Zyprexa documents reveal?

1. Marketing for NCEs (New Clinical Entities) and off-label indications.
2. Sophistication of pharmacos in interacting with and "influencing" its "customers".

   = physicians, pharmacists, hospitals/govt, allied health, patient advocacy groups.
3. Damage control
   - use of "spin", delaying tactics re Adverse Drug Events, esp weight gain and diabetes.

Other Zyprexa documents?

email (from case in Alaska - not in the 358 docs) from current CEO:

Eli-Lilly CEO

John Lechleiter

(paid $13 million in 2008)

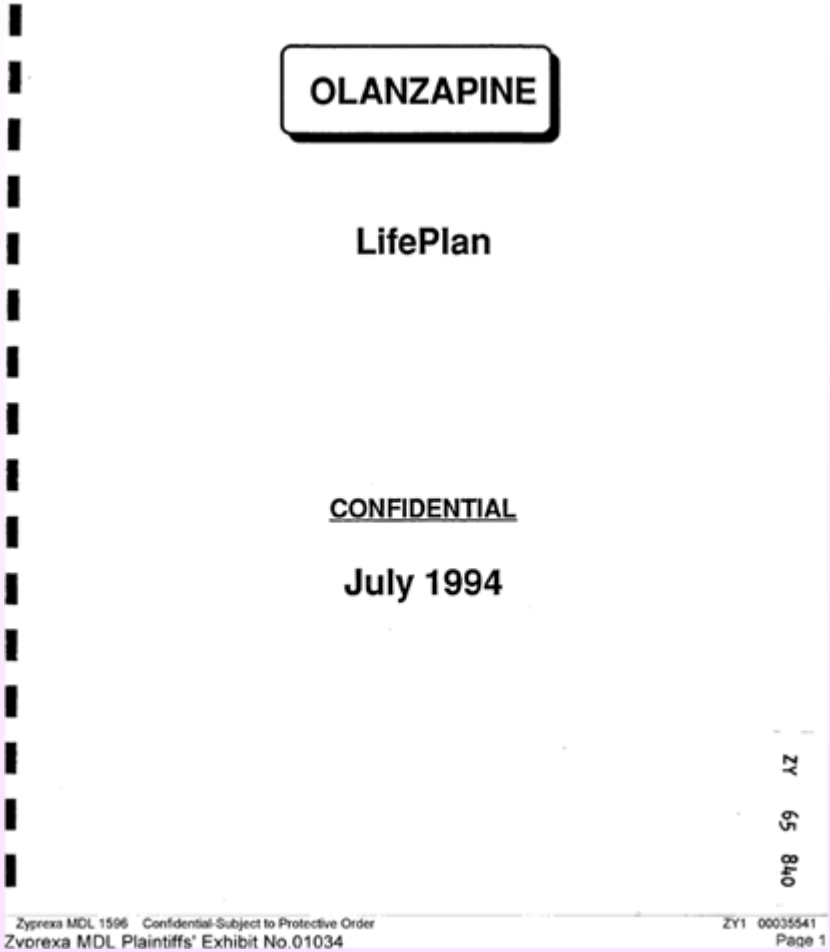
- 'The fact we are now talking to child psychs and peds and others about Strattera means that we must seize the opportunity to expand our work with Zyprexa in this same child-adolescent population'

Berenson in NY Times Mar 2008

1. Marketing and Creating New Markets

- The “life-plan” for Zyprexa changes as “Year-X” (expiration of Prozac patent in 2001) approaches.

ZY100035541 Olanzapine Lifeplan


OLANZAPINE

LifePlan

CONFIDENTIAL

July 1994

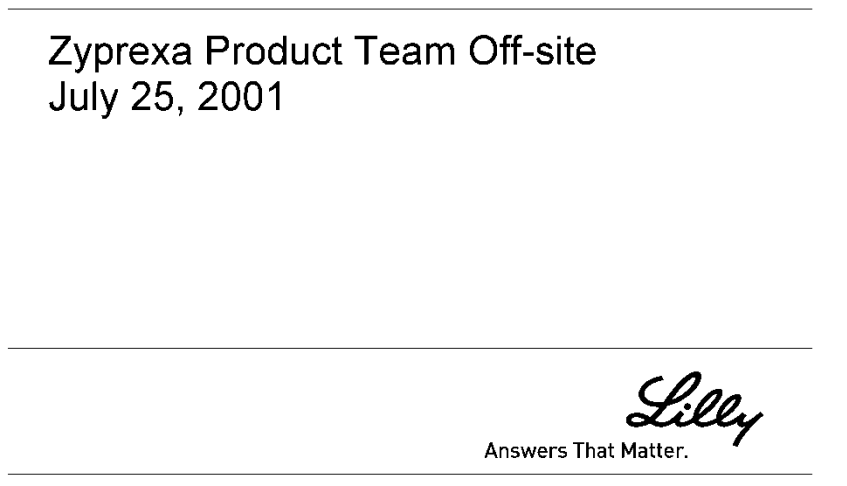
ZY 65 840

Zyprexa MDL 1596 Confidential-Subject to Protective Order ZY1 00035541
Zyprexa MDL Plaintiffs' Exhibit No.01034 Page 1

1994:

- The "Safer Clozapine"
- Market is Schizophrenia.
- No mention of bipolar or dementia.

ZY201548768 Betting the Farm



- Prozac patent due to expire August 2001.

ZY201548768 Betting the Farm

Straight Talk - What's at Stake

The company is betting the farm on Zyprexa … the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve *world class commercialization of Zyprexa*

If we succeed, Zyprexa will be the most successful pharmaceutical product ever … we will have made history

Disease State Prioritization

HIGHEST PRIORITY

A

A significant market opportunity exists for Zyprexa and we will invest/act to take a leadership position.

- Bipolar Disorder
- Dementia with Psychosis
- Depression w/ Psychotic Features
- Dysthymia
- PD with Treatment Associated Psychosis
- Schizoaffective
- Schizophrenia

- Unipolar Depression

SECOND PRIORITY

B

Need to move accurately to determine the market opportunity for Zyprexa.

We will aggressively invest to gain a competitive advantage and/or blunt competitors.

- Substance Related Disorders
- Anxiety Disorders
- Borderline / Schizotypal Personality Disorders

- Aggression
- Anorexia
- *Delirium with Psychotic Features*
- Psychotic Disorders of Low Prevalence
- Schizophreniform

THIRD PRIORITY

C

No investment of Lilly human resources.

We will accept/find investigator initiated proposals.

- Involuntary Movement Disorders?
- Autistic Disorder
- Attention Deficit Disorder
- Bulimia / Binge Eating Disorder
- Dementia Without Psychosis
- Pain Disorder
- PMS
- Sexual Dysfunction
- Somatoform Disorder
- Vestibular Disorders

- Nausea and Vomiting
- Other Personality Disorders

FOURTH PRIORITY

D

No investment of Lilly Human or Financial Resources.

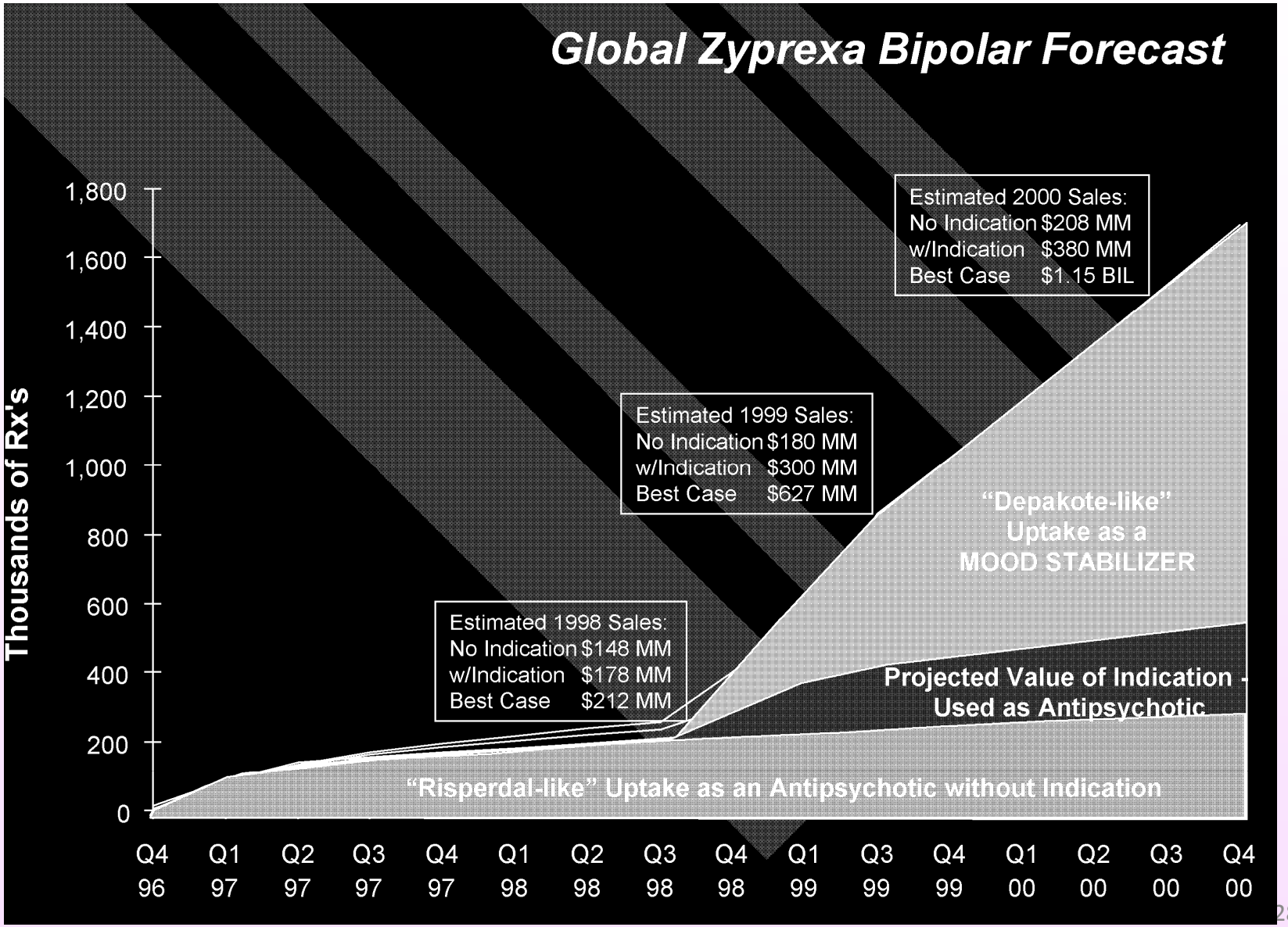
- Hypertension
- Epilepsy
- Trauma/Ischema
- Incontinence
- Sleep Disorders
- ALS/MS
- Irritable Bowel Syndrome
- Asthma
- BPH
- Dissociative Disorders
- Cessation & Withdrawal from Nicotine
- Tic Disorders
- Dermatitis
- Postpartum Psychosis
- Function Bowel Disease

Prioritize disease states opportunities to pursue new indications based on prevalence of the disorder, unmet medical need, and probability of technical success (market opportunity).

Strategic Intent:

Zyprexa will be the world's number one neuroscience pharmaceutical in history.

ZY200270343 Zyprexa Product Team summary 1997



Bipolar Vision of Product Evolution

To be a leader in the bipolar market, Zyprexa will need to be viewed as *true mood stabilizer*.
A *true mood stabilizer* will work in acute manic episodes without inducing depression, acute bipolar depression without inducing mania, and protect the patient from future episodes of mania or depression.

ZY200270343 Zyprexa Product Team summary 1997

STRENGTHS

- Efficacy in manic & psychotic symptoms of an acute manic or mixed episode
- Efficacy in rapid cycling bipolar patients
- Efficacy in depressive symptoms in patients with non-affective psychosis
- Excellent safety profile - toxicity, drug interactions)
- QD dosing & no titration for most patients
- Only antipsychotic w/ an indication for bipolar

WEAKNESSES

- Weight gain
- Higher cost (esp. vs. Lithium/Depakote)
- Only acute mania data/indication @ launch. Lack of maintenance or depression data
- No injectable form available at launch
- Lack of comparative data (lithium, haloperidol, Depakote)

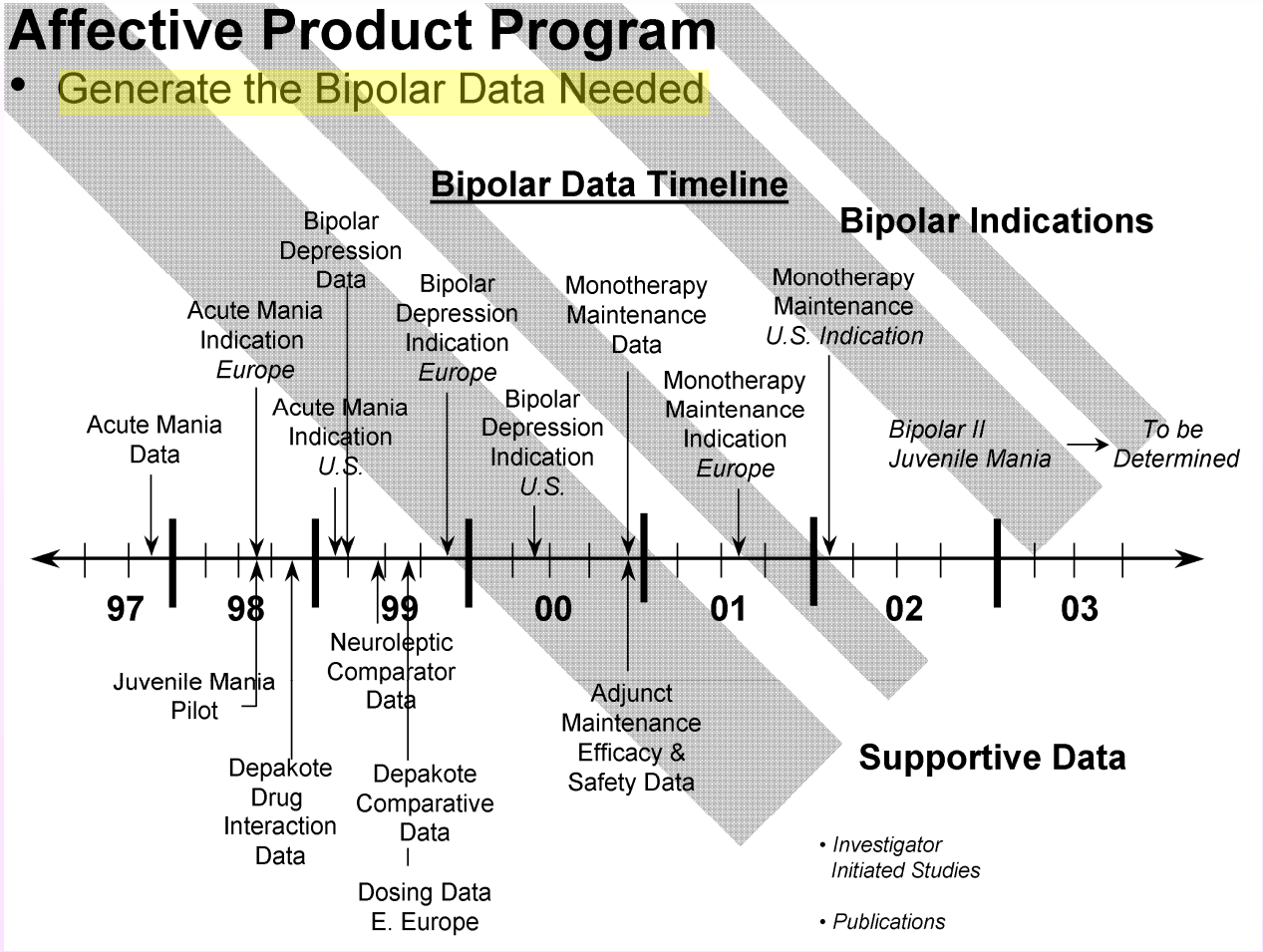
OPPORTUNITIES

- Unsatisfied market - Huge potential for increase in sales/value to Zyprexa & Lilly
- Chance to further boost the brand
- Capitalize on the success in treating psychosis
- Leverage psychosis sales w/ a 2nd indication and proven efficacy in an mood disorder.
- 1st antipsychotic to bipolar market - opportunity to further blunt the competition
- Change the bipolar treatment paridigm
- ROC

THREATS

- New atypicals riding Zyprexa coat tails.
- Not currently perceived as a mood stabilizer or a candidate for first-line treatment of bipolar disorder
- Increased number of competitors - anticonvulsants & atypicals
- Increased price competition restrictive formularies

ZY200270343 Zyprexa Product Team summary 1997



Summary

- We should take significant organizational pride in Zyprexa's success to date
- However, as the environment becomes increasingly competitive we must continue to work hard and together
- Zyprexa is a profound corporate opportunity
- Bipolar is an opportunity equal to our top NCE's. Can we launch and grow it properly in the face of redacted
- Alignment, communication, and effective implementation are essential

ZY100041262 PCP (primary care physician, ie GP) opportunity

PCP Opportunity/Decision
May 7, 1999

Setting the Stage:

- Antipsychotics and mood stabilizers are focusing on the psychiatrist market.
- Limited number of psychiatrists and patients that see psychiatrists.
- WLF opportunity (if upheld) changes the "rules of the game."
- Zyprexa is a very special molecule.
- Zyprexa's patent expires in 2011.

Zyprexa's Clinical Profile (PCP Opportunities?):

- Thought: Schizophrenia, Elderly, "Thought Continuum"
- Mood: Bipolar, Refractory Depression
- Behavior: Elderly, Impulse Control, Gambling, Drugs
- Medical: Stuttering, Nausea, etc…

ZY100041262 PCP opportunity

Next Steps:

- Alert US Ops Team of this potential investment item for 3 year plan – DONE
- Assign summer intern to project – DONE
- Solicit commitment from small, committed, entrepreneurial Swat team..
- -
- -
- -
- -

6 921

→ worthwhile to look at

→ Must have bipolar indication to explore

→ Purse targeted market research option (Pilot)

Heads up:

Narrow scope:

→ Define WLF options, Size, satisfaction

Benchmark →

→ Antidepressant market

- Greater paradigm shift...
- Expensive proposition...

→ Key ?

- Is there a patient flow ?

→ Zyprexa is safe and effective ←

→ Create a market...

ZY200083405 PCP vision

Zyprexa PCP Vision

Expand our market by redefining how primary care physicians identify, diagnose and treat complicated mood disorders (i.e. Bipolar Disorder)

ZY200083405 PCP vision

Our challenge

- PCPs have not been trained to recognize this patient…some afraid of the "B" word
- PCPs have traditionally not treated this patient
  - Lack of comfort with the disease state
  - Lack of comfort with the meds due primarily to safety concerns

….We can change their paradigm

ZY100040886 Primary Care Physician strategy

ZY 7119 493

Zyprexa Primary Care Patient Profiles

ZYPREXA Olanzapine

UPDATE

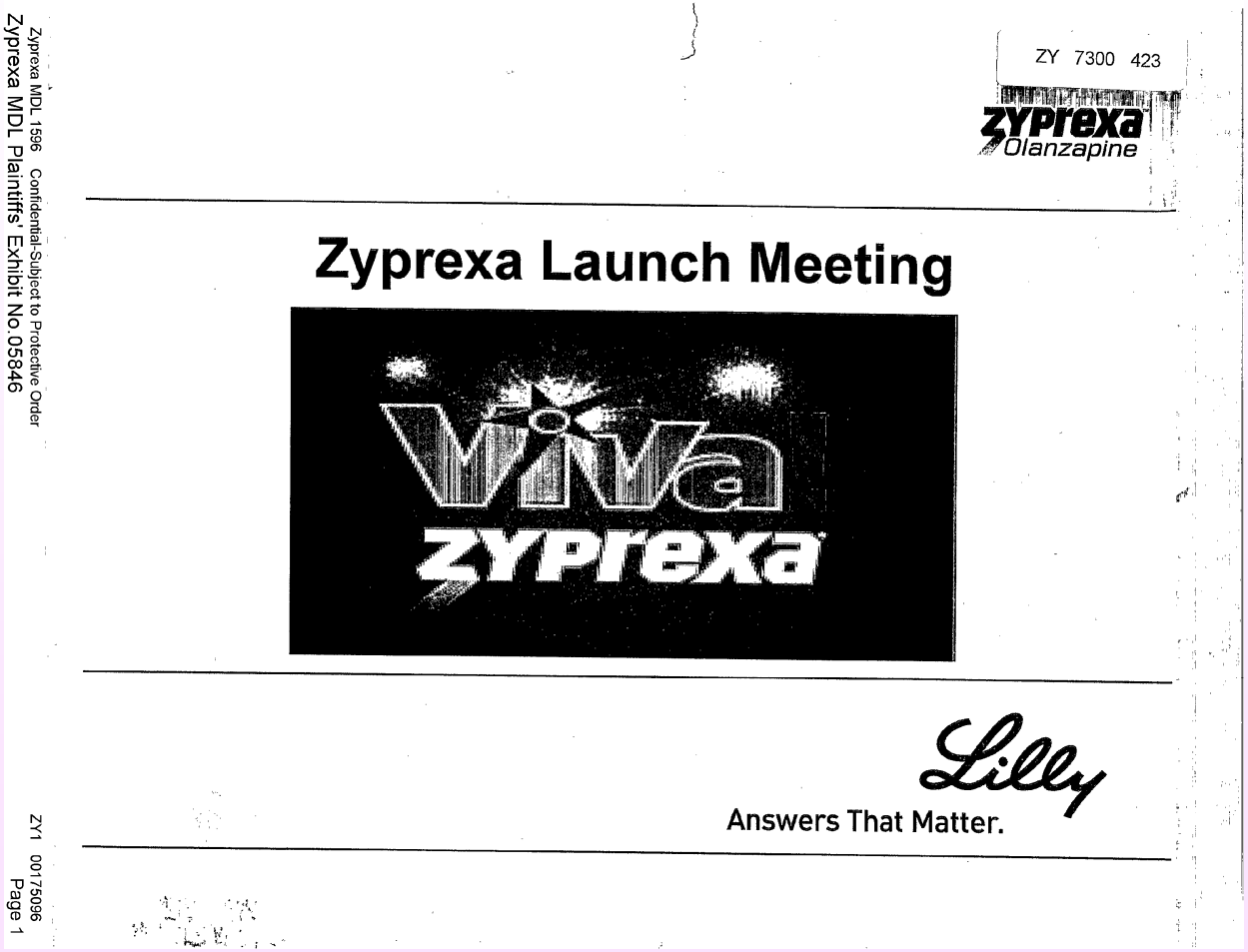
Martha-older agitated patient, focus is on behavior

David-younger patient, higher functioning, focus is on mood

Christine-early twenties, schizophrenia "lite", focus on thought.

include concept of comorbidity, multiple symptom domains in single patient ("real world")

ZY 100175096
Viva Zyprexa



ZY 7300 423

ZYPREXA Olanzapine

Zyprexa Launch Meeting

Lilly

Answers That Matter.

Zyprexa MDL 1596 Confidential-Subject to Protective Order
Zyprexa MDL Plaintiffs' Exhibit No.05846

ZY1 00175096
Page 1

ZY 100175096 Viva Zyprexa Incentives to sales reps

ZY 7300 461

ZYPREXA Primary Care Q4 Incentives

Objective: To launch / grow Zyprexa in the Primary Care market

Duration: 2 months - December 2000 v. October 2000

Metrics: Zyprexa TRx change for Targeted list

- Zyprexa TRx growth 1-5, earn add'l **$200**
- Zyprexa TRx growth 6-10, earn add'l **$500**
- Zyprexa TRx growth 11-15, earn add'l **$800**
- Zyprexa TRx growth 16+, earn add'l **$1,200**

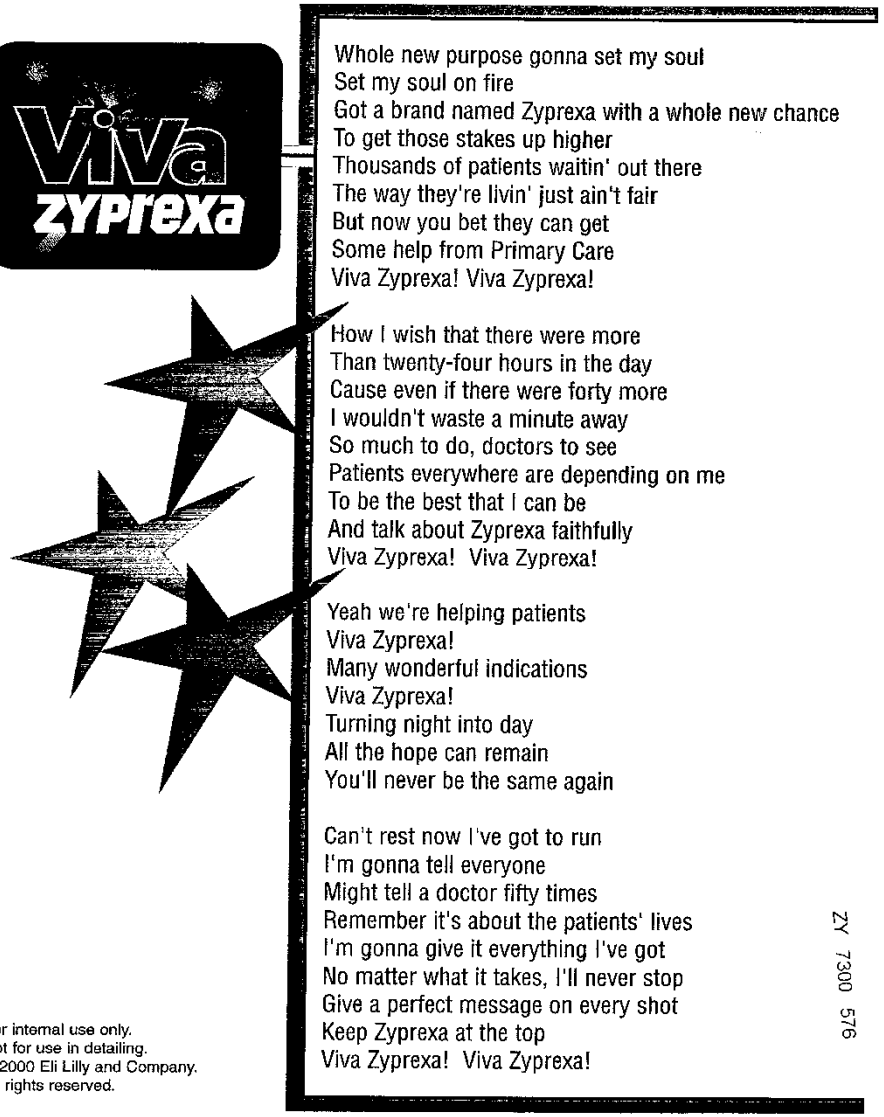
Kicker: Top 3 performers* / region receive **20** AwardPerQs

Incentives: Zyprexa incentives are **additive** to existing Q4 incentives

*Note: * Nominated by Sales Directors based on performance, leadership + implementation*

ZY 100175096 Viva Zyprexa

To the tune of "Viva Las Vegas"



ZY100520636 Primary care implementation guide June 2001

Overview

12 months ago, Lilly had not yet made the decision to launch ZYPREXA in primary care.

8 months ago, we met in Orlando for a very successful—and memorable—launch meeting.

Just over 3 months ago in Dallas, we reviewed the positive impact we've had on patients, families, doctors, and Lilly's bottom line.

"Viva ZYPREXA!" is more than a signature; it's a battle cry to make sure that every day we bring energy and passion to our customers, who are still getting acquainted with this incredible molecule. At the June 2001 district meetings, you will have the opportunity to take that energy to the next level. We have evolved the sales aid and message flow to better meet the needs of customers—identifying the right patient and linking that patient with the right safety and efficacy data. We are launching a powerful new reprint that highlights the efficacy of ZYPREXA in the treatment of mood and depressive symptoms. And we've just completed a 3-part "Lunch & Learn" CD that offers a new and effective way to tell a patient-focused ZYPREXA story.

ZY100040668 PCP strategy manual

Key message:

ZYPREXA is a safe psychotropic with proven efficacy in treating mental illness and reducing symptoms of mood, thought, and behavioral disturbances.

Sales Call:

Doctor, you know your patients better than any other clinician. Your patients rely on you to help them manage their mental health, and some may present with one or more of the following symptoms: agitation, elevated mood, aggressiveness, disorientation, and suspiciousness. What happens when they don't respond to "ordinary" treatment? Referrals can be expensive, difficult to schedule, or rejected by the patient.

I would like to share information with you about ZYPREXA, a versatile psychotropic agent indicated for bipolar mania and schizophrenia that may help these patients and their families. Let's meet one of these patients.

(Patient profile #1):

Martha is a widow you've known and treated for several years. As she's aged, she's become more complicated to manage—clinically, and at home. These are comments you hear from her family (read testimonials from profile). *Your main goal of treatment is to treat her illness and reduce her behavioral disturbances. Do you see patients like Martha?*

(Patient profile #2):

David is highly functional, and in good general physical health. He's been a patient of yours for a few years, and has been having trouble lately. His history includes treatment with several different antidepressants, but his current symptoms are not being well

ZY200061996 Sales Guide "Donna" June 2002

Patient Profile #1: Donna

Market Research Key Learning

Safety in this class of medications is extremely important to primary care physicians. EPS is consistently cited as their foremost concern. However, this is a great place to educate physicians on the negative impact prolactin may have on a patient because many primary care physicians are not familiar with the effects of prolactin elevation.

Thought Leader Feedback

The dose that has been found to be most effective for Donna in clinical trials is 10-15mg. Many primary care physicians may not be comfortable starting a patient at this dose (primarily due to drowsiness). But they need to understand they can titrate the patient up to the target dose while maintaining an excellent safety profile.

Understanding Needs

❶ Donna is a single mom in her mid-30s, appearing in your office in drab clothing and seeming somewhat ill at ease. Her chief complaint is, "I feel so anxious and irritable lately." Today, she says she's been sleeping more than usual and has trouble concentrating at work and at home. However, several appointments earlier, she was talkative, elated, and reported little need for sleep. You have treated her with various medications including antidepressants with little success.

Satisfying Needs

Feature-Benefit-Benefit

❷ You will be able to assure Donna that ZYPREXA is safe and that it will help to relieve the symptoms she is struggling with. First, extrapyramidal side effects are comparable to placebo; what that means to a patient like Donna is that she doesn't have to be as concerned with developing debilitating motor side effects as seen with other typical antipsychotics. The incidence of prolactin elevation is significantly lower than Risperdal®—in fact 100 fold lower in one study, which is pretty dramatic. So for Donna, side effects like sexual dysfunction, amenorrhea, galactorrhea, and increased risk of osteoporosis, which may be associated with prolactin elevation, may be avoided. Finally, ZYPREXA is pregnancy category C.

ZY200061996 Sales Guide "Donna" June 2002

Satisfying Needs

Feature-Benefit-Benefit

❸ ZYPREXA can help you help Donna to improve her symptoms of mood, anxiety, and disrupted sleep patterns. In fact, when looking at depressive symptoms associated with bipolar mania, ZYPREXA has shown significant improvement. So a patient like Donna may have less anxiety, less irritability, and may be able to sleep better with ZYPREXA.

❹ This effect may occur quickly—as early as day 2. Getting Donna's symptoms under control quickly will help you maintain the trust Donna has had with you as her family physician for years.

Check for Impact

How can the reliability of ZYPREXA'S efficacy and safety help you help a patient like Donna? What advantages do you see over other agents you may currently be using?

❺ Appropriate dosing for a patient like Donna is critical. Unlike other meds, dosing ZYPREXA is simple. You may start her at 5 mg once a day, with or without food. If her symptoms persist after one week, it is important to increase the dose to 10-mg—and you can feel comfortable doing so with ZYPREXA's safety profile.

Create Action

Cash in your chips

Doctor, today you agreed that ZYPREXA's reliability can help you to meet your therapeutic needs for your patients with complicated mood symptoms because… (recap the doctor's statements in regards to ZYPREXA's efficacy).

Action Statement

Based on your confidence in ZYPREXA's efficacy and safety, will you try ZYPREXA in a patient like Donna?

Proposal

Would you prefer 5-mg samples or performance scripts for this patient? Also available:

- Patient Education
- Diagnostic tools for future patients
- Patient DVD to help identify more patients

Summary

I will provide you _____(resource preferred by customer). I would like you to get a patient like Donna started today. I will be back in a week to follow up.

ZY100041630
“2001 from “Year X to Year X-ceptional”

our timing is impeccable.

This is Year X for
Eli Lilly, and the conventional wisdom is that companies just don't "bounce back" from losing patent protection from their biggest product.

I personally challenge each of you drive toward a goal that will help turn Year X into Year X-ceptional.

ZY100041630
2001 from “Year X to Year X-ceptional”

During the first half of 2001, we on the Brand team have focused on two key points of emphasis:

peer-to-peer activity and competitive differentiation.

Regarding peer-to-peer,

we've just completed the second of two speaker training programs and have unleashed more than 130 psychs and PCP's

who are chomping at the bit to help you sell Zyprexa.

ZY100041630
2001 from “Year X to Year X-ceptional”

We don't fear competitors--
frankly, we welcome them because they're going to help grow our market.

In marketing jargon, they are Category Builders.

More noise means more attention on mood, thought and behavioral disturbances,
and more acceptance by our customers.

The market will expand and we will be in a position to make the most of it.

When you compare Zyprexa to Risperdal, Geodon, Seroquel, Depakote, Haldol, you name it--
we've got a great story to tell and our friends at Pfizer, Janssen and elsewhere are going to help us tell it.

ZY100041630
2001 from “Year X to Year X-ceptional”

For Zyprexa,

weight gain is the ultimate topic to handle with skill.

Take this opportunity to tell the truth, to fight fire with facts and to put this manageable side effect in perspective.

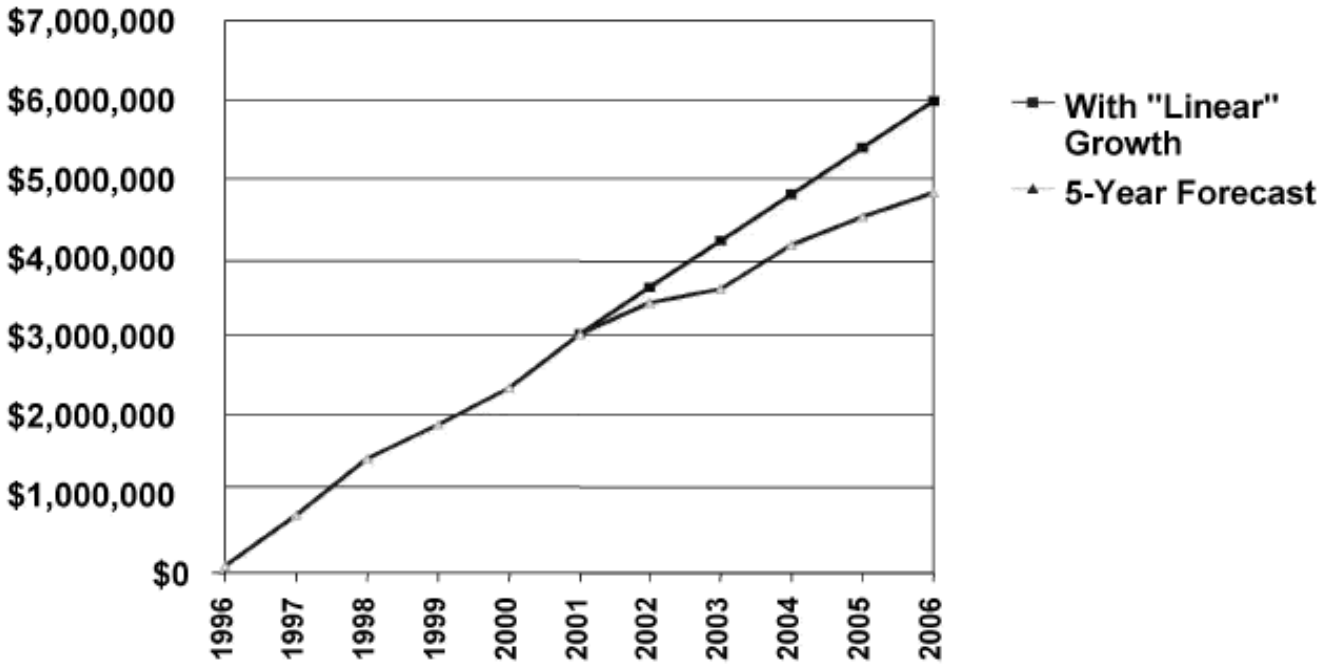
Keep it simple,

so that you don't overwhelm the doctor with data.

ZY200227498 Global value committee rv of Zyprexa Aug 2002 Strategic intent

Strategic Intent

$6 billion by 2006…..delivering linear growth!!



npany Confidential

Average growth per year from 1997-2001 = $589 million

4

2. Studying & Influencing Customers

- Sophisticated market research is applied to "customers"
  - mainly psychiatrists and primary care physicians
    - also pharmacists, nurses, allied health, health maintenance organisations, public health authorities, patient advocacy groups etc.
- Segmentation – type casting of physicians and tailoring information to personality styles to maximise sales.

Cross-Brand Segmentation: Selling Through Advanced Customer Knowledge

Lilly

Answers That Matter.

ZY200083203 Neuroscience segmentation for sales

Why conduct a Neuroscience Segmentation?

Previous Success With Segmentation

edacted

Neuroscience Segmentation will…

Prioritize customers based on growth potential

&

Better understand customers so we can tailor our approach

…So we can be the Neuroscience Industry Leader, know our customers better, and Sell MORE!!!!

ZY200083203 Neuroscience segmentation for sales

How Did We Segment Our Customers?

Who:

- Child Psychiatrists, Psychiatrists, and Primary Care Physicians

Redacted

What:

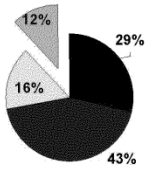
- ***Behavior:*** So we can identify which customers are most valuable
- ***Attitudes:*** So we can tailor our approach to each segment
- ***Marketing Preferences:*** So we can customize our marketing tools

Redacted

State of the art analytics combines the two methodologies together to identify all MDs into a segment

ZY200083203 Neuroscience segmentation for sales

High Flyer General Profile



Who are they?

Earliest adopters of new medications & new uses of medications

Mainly general or family practice

How do they approach treating patients?

Highest comfort treating neuroscience diseases among PCPs

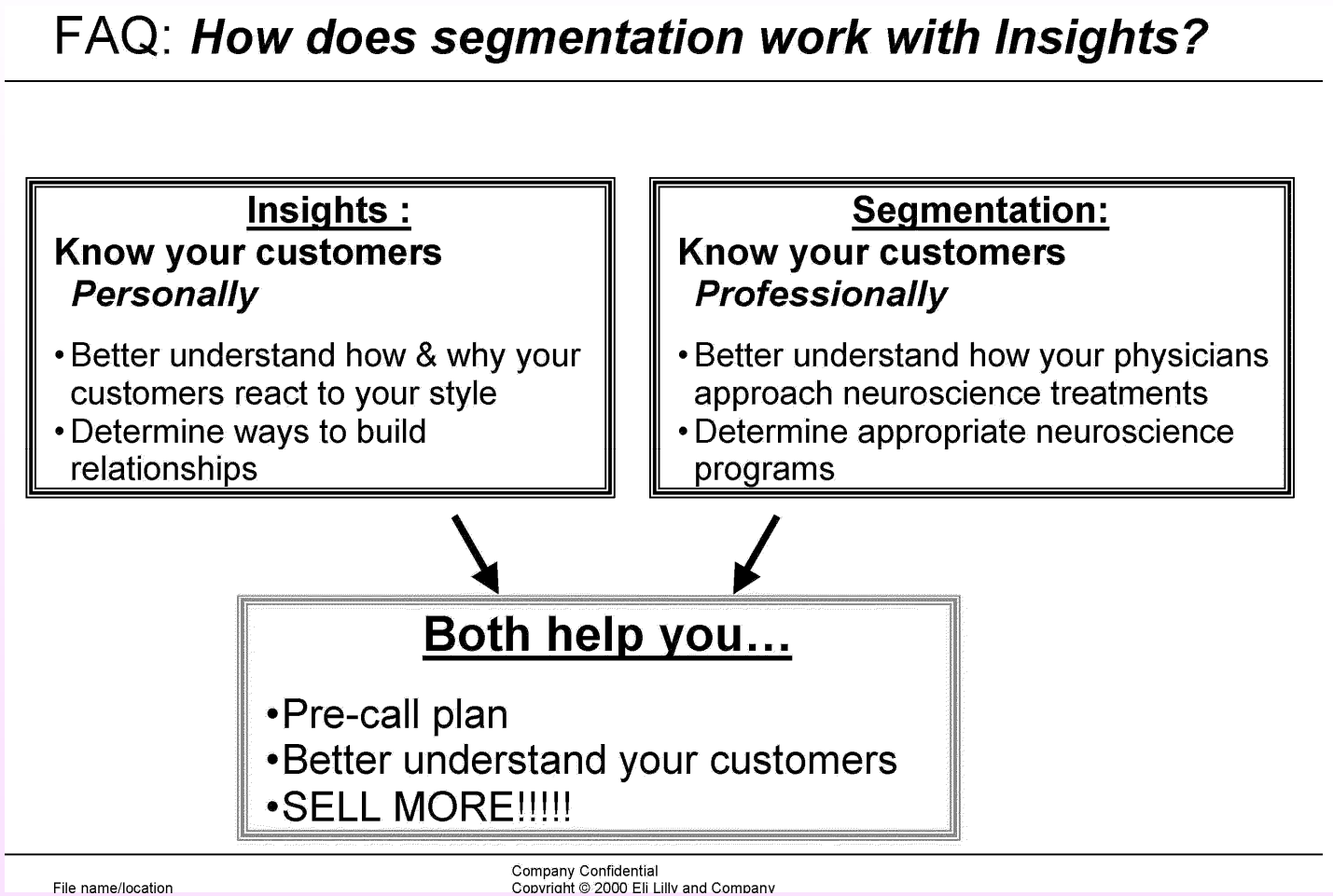
- Not bound by the label
- Willing to push the dose of medications they are comfortable with
- Willing to use adjunctive therapy
- Typically they are treating symptoms rather than a diagnosis

What do they like from a pharmaceutical company?

Keep them connected with the up to date information

- Prefer to learn from a psychiatrists about new information
- Interventions tailored to their interests
- Not adverse to frequent calls if new info is offered

ZY200083203 Neuroscience segmentation for sales



ZY200085380 Segmentation sales practice

The Importance of Neuroscience Segmentation

"I don't mind using higher doses or trying something new if it gets the job done. My patients have serious problems that require the latest medical developments so I don't have time for a sales rep who comes in with outdated information."

Dr. Cruise

- Have you met someone like Dr. Cruise?
- How would you describe him to a new representative?
- How might an early understanding of his segment type help build a stronger relationship?
- What could happen if you came unprepared for this type of doctor?

We'll talk more about Dr. Cruise later.

ZY100174816 Keyplayer Playbook Aug 2002

Key Player Playbook

Following is a summary of Zyprexa's Key Players.

Physician Segments*	Health Care Professionals	Payer Segments	Other
Rule Bound	ER Doctor (I)	Public Payer (I,R,LTC)	Thought Leaders (I,R,LTC,PCP)
High Flyer	Institutional Pharmacist (I)	Institutional Payer (I,LTC)	Advocacy (I,R,LTC,PCP)
Skeptical Experimenters	Ward Nurse (I)	Private Payer (R,PCP)	Bipolar Patient and Family (R,PCP)
Selective Majority	Psychiatric Residents (I)		
Systematic Conservatives	CMHC Treatment Team (R)		
	Retail Pharmacist (R,PCP)		

Notes

* All Psych segments practice in Institution (I), Retail (R), and LTC; All PCP segments practice in PCP office.

Tier 1: Critical to "holding on" in '03 and pretty well resourced

Tier 2: Critical in '03 meeting growth targets and under / marginally resourced

Tier 3: Important in '03 and critical beyond '03 to continue to meet growth targets and under / marginally resourced

Key Player profiles for physicians are provided below since they these doctors work across all settings. Zyprexa is focusing its marketing plan on High Flyers and Rule Bounds, who in the Psychiatric market provide the first and second highest volume of prescriptions. High Flyers will aggressively treat mental illness (off-label, high dose) and Rule Bounds are most likely to be loyal to a brand.

ZY100174816 Keyplayer Playbook

High Flyers: Priority Doctor Segment Due to Volume but Likely to Try Competitive Entrants
This key player is Zyprexa's top customer, due to the Psych's volume and early adoption. Of chief concern is this key player's tendency to try new products (notably Aripiprazole, Geodon IM, or Risperdal Depot). To prepare for new entrants in the AP / MS class, Zyprexa needs to partner with new Lilly neuroscience products to enhance our relationships with these key customers, especially through programming. High Flyers have the highest detail responsiveness and second highest DTP responsiveness.

Significant programs, and funding, will be targeted toward this key player, as well as the Rule Bounds.

	Zyprexa Strategic Opportunity
Prescriber Information	• Psych: 16% of population accounts for 31% of Zyprexa Rx (highest volume) • PCP: 12% of population accounts for 22% of Zyprexa Rx (2nd highest volume significantly behind Selective Majority)
Zyprexa Strategic Importance	• Most critical segment for Zyprexa and all NS brands due to Psych volume and adoption • High expertise / influence among peers • Push the envelope with indications and doses (note: Zyprexa only promoted per label)
Zyprexa Marketing Goal	• Turn to Lilly for new ways to treat my patients • Partner with new NS Brands or High Flyer will seek out newer competitors to Zyprexa
	Key Player Mindset and Action
Statement Defining Key Player	• I eagerly seek out new ways to treat my patients (first to adopt new medicines)
Motivation, Attitudes, Beliefs	• Actively seek new info that will allow them to treat more patients, and treat them better – Psychiatrists: Trying to get a patient to 100% and like to have treatment options; this means tailoring a medication cocktail by using the MOA of the drugs. – PCPs: Stepping out of comfort zone to treat a disease they don't often see • Seek deep understanding of *how* drugs work; make decisions based on MOA • Willing to try new medicines early because "they still have patients that are not yet 100%"
Behavior	• Not bound by rules, guidelines or system; proactively take action to get patient better • Treat based on symptoms, not formal diagnosis • Will push the envelope with off label doses and indications (based on MOA)
	Marketing Preferences
Marketing Preferences	Psychs • Detail responsiveness: Highest • DTP responsiveness: Moderate (2nd highest) • P2P responsiveness: Low to Moderate • Like pharmaceutical company sponsored programs and tools in "fun" environments. PCPs • Detail responsiveness: Highest • I-Physician Net responsiveness: Highest • P2P responsiveness: Highest
Do's	• Group interaction and patient focus • Reps as source of latest information • Key segment to learn from via CFF's and RCFF's • CME with "new" content • Patient ed / starter packs to reinforce importance of patient satisfaction • Forum / club to reinforce NS leadership in social way • Advisory Boards • Consultant web-site • Partner PCP with Psych
Don'ts	• Present well known data as if it's true or gloss over fair balance
	How We Want Them to Think and Act
Marketing Objectives	• High Flyer Psychiatrists believe that Zyprexa offers dependable control that enables a therapeutic alliance to increase patient capture and retention at the appropriate dose. • High Flyer Psychiatrists to believe that Zyprexa has the most dependable control with a known and manageable side effect profile that isn't dose dependant • Increase High Flyer Psychiatrist's perceptions of Zyprexa as a collaborative, committed leader in order to maintain current level of loyalty
Programs (promotional and non-promotional)	• Shown later

Plan based on $104.9M soft targets. Buy-ups to be discussed at BC III.

ZY100174816 Keyplayer Playbook

Don'ts	• Present well known data as if it's true or gloss over fair balance
	How We Want Them to Think and Act
Marketing Objectives	• High Flyer Psychiatrists believe that Zyprexa offers dependable control that enables a therapeutic alliance to increase patient capture and retention at the appropriate dose. • High Flyer Psychiatrists to believe that Zyprexa has the most dependable control with a known and manageable side effect profile that isn't dose dependant • Increase High Flyer Psychiatrist's perceptions of Zyprexa as a collaborative, committed leader in order to maintain current level of loyalty

ZY100507583 email re exec summary diabetes and “our high flyers” Mar 2002

Cassandra Mehlman

03/19/2002 02:17 PM

To: Thomas L Reck/AM/LLY@Lilly
cc:
Subject: Re: Executive Summary for Diabetes MR

Great summary. I agree with all your conclusions except that in my view, for most segments, the DMT message DOES conflict with the comparable rates message. Although the DMT message did build equity, most physicians said that we would in fact "admit" "own up" etc. to diabetes. Kathy and I spoke today, and agree that the DMT message played out the best with High Flyers and High Flyers are the group most likely to hear this message in an SCC or RCM anyway. Our thoughts are to kill the message except for in DTP forums...where our High Flyers are attending. We feel the DMT message is probably too risky to our label and sends the message that we own diabetes otherwise. Please let me know your thoughts.

Cassie Mehlman
Zyprexa Brand Team
Marketplace Management

ZY100174816 Keyplayer Playbook

Skeptical Experimenter: Psych Only

This key player is Zyprexa's third top physician customer (psych only), due to their high volume and their credibility among their peers. By nature, they are inherently distrustful of marketing and use their personal experiences to guide how they will continue to treat patients. Since Skeptical Experimenters are experts in the populations they treat, they are very knowledgeable about the MOA of medications and use them to tailor medications to their patients. They are

	How We Want Them to Think and Act
Marketing Objectives	• The MOs for the High Flyer should be utilized
Programs (promotional and non-promotional)	Programs not specifically planned for this physician segment (most similar to High Flyer needs with a higher degree of skepticism for marketing programs) **Let them demonstrate their expertise** • Advisory Boards • Round Table / P2P (but not with Rule Bounds) • Key segment to learn from via CFF's and RCFF's • Consultants website where they can post non-anonymous feedback to Lilly and colleagues and engage in chats/debates about patients and treatments • Preceptorships **Let them tinker** • Experience trials /Clinical trial involvement / Research Grants • Symposia, CME with "new" content, Telesessions, Audio Conference • Audio conferences/Telesessions; Enduring materials from previous events; Office forms/Script pads; Symposia

ZY200455949 selling to skeptical experimenters email Feb 2003

Indy SPEED: How can we "up our game" in selling to our Skeptical Experimenters??????

TIPS ON SEGMENTATION: Skeptical Experimenter
Tools:
1. Tollefson reprint - it's industry sponsored but it supports the NIMH study (NOT industry sponsored) from last year!!! More "proof".....

2. Tollefson reprint - only atypical thus far to have shown comparable efficacy to Clozaril - Risperdal vs. Clozaril study did not show comparable

4. Use new detail pieces as "new data"..... "Can I get your thoughts on this new data based on your clinical experience?"

Strategy:
1. Not worried about indication/label - TALK BROAD SX EFFICACY!!!
2. Get them to talk about their experience! THEY ARE IN CONTROL OF PATIENT TREATMENT!
3. Don't tell them what their experience is or has been!
4. Get their agreement to try Zyp in a new way.....
5. "Will you get your own experience by using Zyp in a pt. like the one we've discussed today"?
   "Will you try Zyp and see for yourself.....
6. DON'T be too defensive if they disagree!! Tone is especially important!!! Acknowledge their concerns!!!
7. Progressive team selling especially important with these customers!!! Chip away little at a time!!!
8. Who do they respect? Like? Schedule roundtable lunch/dinner with that person ASAP!!
9. Use them as case presenters at small, round table venues

hope this helps!! Cindy

ZY100174816 Keyplayer Playbook

Institution Key Player: Psychiatric Residents

This key player may play an integral role in starting therapy in acute settings today. More importantly, as future practitioners, they will drive significant value for all of Zyprexa's formulations in the years to come. Future prescribing patterns of residents and their perception of Lilly is strongly influenced by residency directors and other thought leaders who teach and direct them during their residency. Influencing Residents, who are typically eager to learn, can be driven through specifically targeted marketing programs.

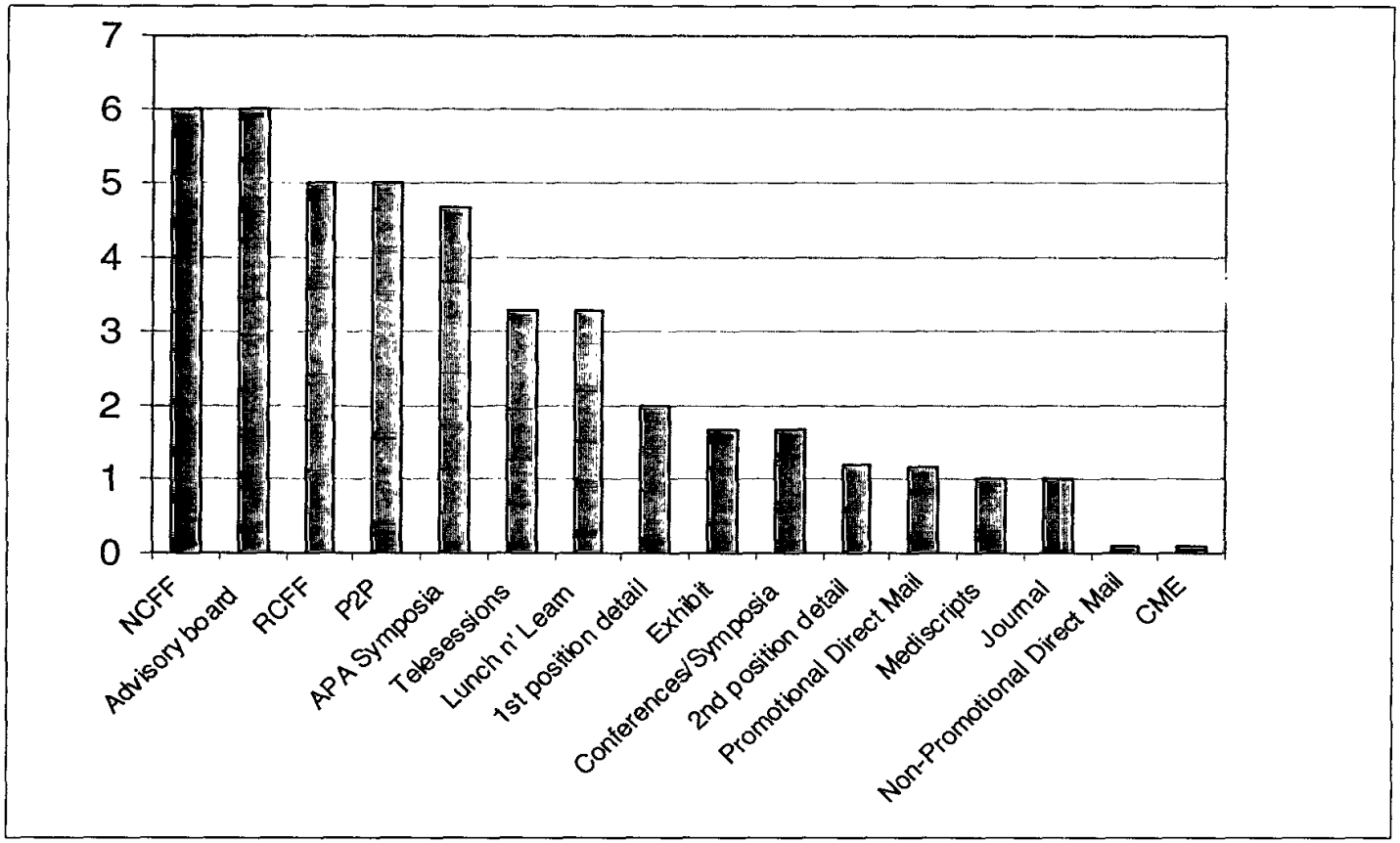
~$0.5 million funding is available for this key player, whose value is truly greater in the longer-term; Zyprexa will seek opportunities to collaborate within Lilly's Neuroscience Portfolio

	Zyprexa Strategic Opportunity
Zyprexa Strategic Importance	• Current prescribers in teaching hospitals, VA's and State Hospitals • Future thought leaders and prescribers
Zyprexa Marketing Goal	• Psychiatric Residents turn to Lilly/Zyprexa to learn new ways to treat their patients
	Key Player Mindset and Action
Statement Defining Key Player	• I practice in a conservative manner, according to how I was taught. Teach me more.
Motivation, Attitudes, Beliefs	• Motivated by new information and the desire to learn yet are skeptical of drug companies and product information • They want a deep understanding of how drugs work to ameliorate the symptoms patients experience
Behavior	• Often bound by the rules of their programs and the institutions in which they practice • They often moonlight in order to make extra money and therefore have the ability to drive a significant portion of the capture opportunities
	Marketing Preferences
Marketing Preferences	• They are driven by applying new information into their own practice • Like pharmaceutical company sponsored programs and tools that are not product specific, ranging from CME programs to patient education materials. • They like to receive new information in "fun" environments
Do's	• Partner for educational purposes • Demonstrate long-term mindset for relationship building • Demonstrate patient focus via patient ed and starter kits • Reps as one source of information • Patient ed / starter packs to reinforce importance of patient satisfaction • Forum / club to reinforce NS leadership in social way • Advisory Boards • High reliance on PDA technology
Don'ts	•
	How We Want Them to Think and Act
Marketing Objectives	• Psychiatric Residents believe that by capturing and retaining patients at the appropriate dose, Zyprexa offers dependable control that enables a therapeutic alliance • ER Docs are aware of novel treatment options and recognize that for an agitated patient, Zyprexa IM provides the best opportunity to provide dependable control • Psychiatric Residents believe Lilly / Zyprexa is a collaborative, committed leader who proactively confronts Zyprexa side effects and provides solutions
Programs (promotional and non-promotional)	• **Build Relationship** via kick-off program, Life Skills Workshop, Emory Program • **Partner for Educational Purposes** via disease state / Zyprexa modules, forum sponsorship, AADPRT sponsorship • **Build Awareness for RAIM Launch via:** ▪ **Sales:** Detail pieces, premium items, etc. ▪ **P2P:** Grand Rounds, Lunch and Learns, Independent Scientific Exchange, etc. ▪ **DTP:** Associations, Symposia, CME, Psych-Link, Dexel Telesessions, Journal Ads ▪ Emory Resident Program, etc. ▪ **Web:** Zyprexa.com ▪ **Media:** General, Trade and Business

ZY100174816 Keyplayer Playbook

- A customer exposure is the relative value of a marketing / consulting intervention in delivering your branded / message / consulting feedback; messages with high value tend to take place in live settings (e.g. peer to peer programming); relative values are determined by industry and class norms collected by HCI/Neilsen.

Relative Value of Exposures



- Exposure requirements for physicians were calculated by accounting for the number of opportunities a doctor has to make a medicine change (new/start/switch); institutional physicians make more changes that private practice physicians, for example.

ZY100174816 Keyplayer Playbook
planning the scientific data

Deep Dive on High Impact Marketing Programs

Marketing – Medical Alignment

Project Rosetta Stone has driven massive improvements in Marketing-Medical Alignment

The primary deliverable of the Scientific Data Disclosure on Non-Registration Trial (SDD/NRT) Strategy Project was a global three-year clinical trial and data dissemination plan focused around messages supporting Zyprexa's brand promise for schizophrenia and bipolar disorder. The Zyprexa Product Team and the U.S. Affiliate Medical and Marketing Teams jointly drove the initiative. The primary benefit of this integrative planning process will be in aligning medical and health outcomes efforts to brand strategy, targeting efforts where there are demonstrated gaps in our ability to use science to support the brand promise, and maximizing the use of medical and health outcomes resources.

The project had several distinct components. First, eight message categories were developed from the Brand Promise and a ninth message was added to address payer concerns; sub-message categories were developed as shown below. A scientific inventory examined the support in the published data for the various elements of the brand promise. This information was used to evaluate the areas where the support from published data was strong, moderate, and weak. After the scientific inventory was performed, all information on trials and disclosure events from the ZPT and affiliates was collected, mapped to message categories, and assembled into a database. For each of the nine message categories, a 'Current State Map" was developed, showing the database locks, planned publication timelines, and data disclosure events. These current state maps provided an accurate perspective on the global plans around each message area. The database was evaluated for gaps in both trials and data disclosures. As gaps were identified, detailed recommendations for trials, data mines, and disclosures were developed. Planned trials and disclosure events were assigned as 'prioritized' or 'non-prioritized.' This information was critical to determining which clinical trials to fund in 2003 and will be critical to developing a data dissemination plan for implementation (to be developed in August 2002).

ZY100174816 Keyplayer Playbook
planning the scientific data

Below are the manuscripts planned: (These Manuscripts are all also included in the publication plan under development.)

Study Code	Topic	Message Area Supported	Physician Segment
HGIY	Agitation/dose escalation	Count on it to Control	Rule Bounds
HGHQ-Extension	v. valproate	Wide Range Effectiveness	Rule Bounds
HGIA	Zydis data	Dependability in Multiple Formulations	Rule Bounds
HGHR	Olanzapine improves TD	Wide Range of Effectiveness	Both
HGJB	v. Seroquel	**********	**********
HGJT	v. Risperidone/Acute Mania	Count on it to Control	Both

There are several manuscripts planned for the upcoming year. In general these are also well aligned with strategy. HGJB was initially placed in the high priority bucket. However, the first cut of this data suggests that the study offers stronger support for "enduring efficacy and relapse less" and "realize and individual's potential" than it does for "wide range of effectiveness." The dissemination plan is being reviewed in light of this.

Investigator Initiated Trials, Relationship Building, and External Authorship

Given our current business needs, it is important that funds spent on IIT's predominantly support the brand strategy. The review process should consider whether they are on strategy, as well as looking at whether they fill current gaps in our scientific data.

If resource constraints do place limits on expenditures for IIT's, another way we can use Medical Liaisons to support the development of relationships is through increased efforts to cultivate external authors to either develop publications from our existing data, or collaborate with Lilly authors on existing projects.

Scientific Messaging Effectiveness

A major goal for the year 2003 is to examine how scientific messaging influences our customers' perceptions. We traditionally expend considerable effort in studying our promotional messages. It is the intent of this project to get the same level of understanding about the impacts of our scientific messaging processes. In order to get an effective understanding, it will be important whenever possible study differences among our physician segments in response to scientific messaging.

Some of the questions to be examined in this process include:

- Which journals do our customers read?
- What kinds of articles do they read?
- When reading a publication of a clinical trial, what sections do they actually read?
- What is the difference in perception when the data comes from an external versus Lilly-sponsored source?
- What are the impacts of using external authors?
- Are messages more effective when they are explicitly and affirmatively stated; do some physicians ignore these and draw their own conclusions from the data.
- What kinds of data are more persuasive? Which scales do our prescribing customers respect?
- Which messages can be effectively conveyed with case reports?
- How can slides be made to more effectively convey messages?
- How effective are our DTP events, symposia, and CME programs?

ZY200540696 email re “want patient to stay on Zyprexa long term”
Oct 2002

To: CN=Mauricio F Tohen/OU=AM/O=LLY@Lilly
CC: CN=Giedra M Campbell/OU=AM/O=LLY@Lilly; CN=John C Saunders/OU=EM
CN=Richard C Risser/OU=AM/O=LLY@Lilly
Date: 10/16/2002 11:38:37 AM
From: CN=Doug Williamson/OU=AM/O=LLY
Subject: Re: Clinical Summary update

But, surely we want patients to stay on OLZ long-term, so the reversibility of the event is not an advantage?

Doug Williamson MD, MRCPsych
Zyprexa Bipolar Team
317 433-2486
redacted
Assistant: Jean Krauss
(+1) (317) 651-4180

Mauricio F Tohen

10/16/2002 09:49 AM

To: Giedra M Campbell/AM/LLY@Lilly
cc: Doug Williamson/AM/LLY@Lilly, John C Saunders/EMA/LLY@Lilly, Richard C
Subject: Re: Clinical Summary update

I would like to include the FU glycemia issue because it points towards the reversibility of the event

ZY200540696 email re "want patient to stay on Zyprexa long term" Oct 2002

Hi John--

It was good to talk to you this morning (afternoon!) and hammer out some of the clinical summary issues. Below is a summary of specific issues/areas that I would still like you and the othe reviewers to review (though I would also encourage another complete review from anyone who has the time!), and then after that, under a line, are excerpts from previous e-mails, with ANSWERS to questions that we discussed today, so that other reviewers can see what we covered.

I am also attaching the latest version in case anyone needs it, but if you have already printed yesterday's version to look at, yesterday's should be fine, although there have been some more recent text corrections as detailed below (plus the table numbering has been updated).

Please re-review efficacy key findings (Section 2.1)

Please review the conclusions of each of the efficacy sections: 2.3.5, 2.4.5, and 2.5.5. In particular, please verify that the sentences about FU seem okay, given the less robust results of that study in the protocol-defined analyses.

Please review overall conclusions of efficacy section (2.7).

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 reasons for discontinuation in both treatment groups were lack of efficacy, adverse events, and patient decision. Placebo-treated patients were statistically significantly more likely to discontinue due to lack of efficacy than were olanzapine-treated patients. There were no other statistically significant treatment group differences for individual reasons for discontinuation.

ZY201558654 “Competitive literature review” May 2002

- **Authors’ Conclusions**: Schizophrenia patients who received atypicals were more likely to have diabetes than those who received typicals, and the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone. The authors also state that the results are strongly suggestive of a causal relationship.
- **Brief Overview of the Method**: VA administrative claims database identified 38,632 outpatients with schizophrenia who were treated with antipsychotics over a 4-month period in 1999. The proportion of patients diagnosed with diabetes mellitus (DM) was compared between patients who received typicals and those who received atypicals, and again between patients who received typicals versus those who received a specific atypical antipsychotic (clozapine, olanzapine, quetiapine, and risperidone), adjusted and unadjusted for age (5 age groups).
- **Major Shortcomings:**

1. **No cause-effect relationship**. Although the authors claim that the results strongly suggest a causal relationship, the findings merely point to a correlational association between the prescription of atypical antipsychotics and the diagnosis of DM. It does not demonstrate that atypical antipsychotics **cause** an increase in the odds of being diagnosed with DM. It is highly likely that schizophrenia patients who are treated with atypical antipsychotics are different from those who are treated with typical antipsychotics on a host of characteristics, including risk factors for DM, such as family history of DM, ethnic background, weight, physical activity, hypertension, low HDL/high TG, and a history of impaired glucose intolerance. None of these risk factors was addressed in this study.
2. **Olanzapine vs. risperidone.** The study findings need to be interpreted in their correct context, which is that compared with typical antipsychotics, risperidone prescriptions were significantly associated with increased odds for DM on 2 of 5 age groups, while olanzapine prescriptions were significantly associated with increased odds for DM on 3 of 5 age groups. There is a difference on only **1 of 5** age groups (on the age group 40-49). Furthermore, the odds of having a diagnosis of

- Lilly reviews numerous studies by independent researchers and competitors re hypergylcaemia, diabetes and hyperlipidaemia.
- Are “reviewed” in (hyper)critical manner with an apparent pre-conception that Zyprexa can’t cause these problems.
- **?a source of meaningful peer-review if all pharmacos made them public!**

ZY100023162 letter from MD to Eli-Lilly executive

12-3

Nov 20, 1997

Dear Dr Tolfson:

Thank you for sending me the Zyprexa slide kit for use in lecturing and teaching. I understand a new kit will be shortly available with more complete information. Kindly send me a set of the new slides as soon as possible. A local Lilly rep has asked me to do several presentations, and I would like to make the best and closest effort.

Thank you!

cordially

ZY100174816 Keyplayer Playbook thought leaders and consultants

Thought Leaders

Cross Brand Key Players: Thought Leaders

The Zyprexa Guild and Executive level Thought Leaders are well respected and acknowledged by their peers, other experts and key audiences as leaders and influence the thinking and the treatment practices of their peers at a national, regional or local level. Guild and Executive Thought leaders are experts in the disease and the diagnosis of the disease. They are typically in the academic setting (professors/researchers) and treat a minimal number of patients, if any. The Guild and the Executive Thought Leaders usually serve on the academic advisory boards, providing feedback to the Zyprexa Product and Brand Team.

The Consultants currently have greater clinical experience and are primarily responsible for continuing to shape and to define Zyprexa as extraordinary in moving lives forward in the bipolar and the schizophrenia marketplace. The Consultant Thought Leaders are the core advocates between the Guild and those at the regional and local levels, and are on our demand realization advisory boards. These clinicians are a critical component of successful DTP interventions and stimulate the physicians at both the regional and the local level.

Discussion from the August 17, 2000 Weight Gain and Hyperglycemia Steering Committee

Hosted by Alan Breier and Norma Ascroft

Attendees:

Dan Casey, MD
Don Goff, MD
David Allison, PhD
David Henderson, MD
John Newcomer, MD
Jogin Thakore, PhD

Internal Attendees

Norma Ascroft, PharmD
Charles Beasley, MD
Chris Bomba
Alan Breier, MD
Jamie Dananberg, MD
Peter Feldman, PhD
Mike Griffeth
Suni Keeling
John Krueger
Mark Milliken, PharmD
Vin Rampey, PhD
JR Richards
Surajah Roychowdhury, PhD
Simean Taylor, MD, PhD
Anna Thornton, PharmD
Skip Vignati, MD

ZY100175630 expert panel with Lilly wght gain and diabetes steering committee Aug 2000

Reactions to what each of the consultants have seen today?

Allison

- Weight gain is a marketing and health issue, separate from glucose. This issue will not kill the drug but is more of a marketing issue. The glucose story is dangerous and could be quite damaging to the product and needs to be addressed quickly. The competitive environment is brutal.
- For the current analysis of Lilly's hyperglycemia database, Lilly needs to take a look at the statistical analysis and make it a stronger story.
- For hyperglycemia, a large study is fine but the smaller clinical and nonclinical studies are equally important to publish quickly and get information out there; from a regulatory and legal point of view, sponsors need to prepare for worst case scenario – the Lilly has on hand with clinical or preclinical data, the better.

- Zyprexa team is tracking in the right direction with weight gain by showing that the patient or health care profession can treat/ manage the weight gain; intervention studies are a good approach.
- Overall with both issues, be honest and put out good information that is driven by science.
- How much danger will Zeldox be? Zeldox may prove not be as effective but may definitely have the ability alter the olanzapine message and creates perception(s).
- Continue to explore interesting aspects of weight gain with this drug such as the "disinhibition" CNS theory that possibly effects peoples eating habits (see discussion under weight gain below)

Goff

- Emphasize in your message that not all patients gain weight. It seems the Zyprexa team has been managing this relatively well so far. The Competition is always hard to manage. Having options is the key. Be able to recommend to treating physicians at what point will you recommend treatment or interventions; provide treatment options; admit that there may be certain amount of weight gain and patients will have to way out options with their clinicians.
- An algorithm approach to provide to clinicians? Be very cautious of this approach. This is often done with weight intervention in "normals" and is *not* successful. It is difficult to be able to exactly predict the sensitivity and specificity of candidates to follow a laid out plan or algorithm.

ZY100175630 thought leaders with Lilly wght gain and diabetes steering committee Aug 2000

Thakore

- (His) Experience already shows that schizophrenia patients already gain greater amount of visceral fat –increases risk already of DM, CA, etc; so don't do algorithms ("if this, then that") but put everything into perspective with scientific sharing of data. Algorithms are complicated and competitors can take advantage of this – turn them the wrong way.

Casey

- On the right track to search and provide answers to clinicians whom are definitely looking for answers for both issues. There are other signals that Lilly needs to be paying attention to now such as *lipids* that should be addressed early versus playing the defense mode like we are now for hyperglycemia. For example, (he) has heard rumors that some clinicians are recommending patients sign an ICD before olanzapine therapy due to the health risks.
- Overall, there are health risks in this patient population. A sponsor can really impact this area and put this issue of weight control and glycemic control, along with healthier living and increased education, (e.g., smoking sessation, lipid monitoring, hypertension management, prolactin and bone density) into perspective. This builds credibility
- Lilly can deflect the issues as not only olanzapine-related. This is most likely a class issue. Comment by group: have to manage this carefully that we do not blame the disease.

ZY100174816 Keyplayer Playbook

public and private health beauraucrats

Access in 2002 – Success with Public and Private Payers

To date, Lilly USA has been very successful in keeping access to Zyprexa across payers and providers. Zyprexa is available on all 50 State Medicaid formularies and the majority of managed care organizations. Zyprexa is beginning to encounter formulary restrictions from those payers who have fixed budgets, primarily VA/DoD, DSH/PHS and State Contract Entities. These entities are usually given a fixed budget for a given period of time, which is often independent of patient volume for that given period of time. To manage their budget, they limit access to expensive medications. Managed Medicaid plans looked at restricting access to Zyprexa due to low patient capitation rates, but to date no plans have moved against Zyprexa.

Zyprexa Marketing Goal	• Maintain Equal Status to all atypicals and Unrestricted Access to all prescribers
	Key Player Mindset and Action
Statement Defining Key Player	• I manage to my budget, provide adequate care and keep as many constituents as content as possible
Motivation, Attitudes, Beliefs	• Drug utilization is out of control because of sales rep promotion and DTC advertising • Decreasing state revenues means states are forced to make a choice between providing excellent care to a few patients or adequate care to many patients • Legislatures and Regulators manage the "issue at hand" and are highly influenced by current public opinion as well as lobbyists, consultants and advocacy organizations

	How We Want Them to Think and Act
Marketing Objectives	• Legislators, regulators, decision-makers, P&T members and thought leaders to believe that all atypicals and mood stabilizers should be available • Decision makers believe that equal status is at a minimum cost neutral and provides better patient outcomes and that unrestricted access allows for appropriate treatment of the mentally ill. • Believe that weight gain does occur with Zyprexa but it is manageable and diabetes/hyperglycemia occurs at comparable rates to other atypical antipsychotics

ZY201358723 private negotiations w regulators "better influence outcome" undated

Zyprexa regulatory briefing

We anticipate differential labeling (re: risk for hyperglycemia, treatment emergent diabetes and related metabolic issues) with our next submission; redacted
redacted

- Expect label change in the Precaution section at a minimum, more likely as a warning
- Even FDA attempts to "class-label" could take 6-12 months to implement with other products
- Analyst community has indicated that this could be a trigger for Lilly disinvestment

There is substantial risk in opening the Zyprexa label to a public Advisory Committee discussion; that risk is not new and has been previously communicated internally. redacte
redacted
redacted Based on launch plans and sales forecasts in the U.S., as well as portfolio management decisions in other key affiliates, the redacted may no longer justify the risk to the Zyprexa label.

The position of the Zyprexa Product Team is that private negotiations (in advance of a submission) provide the opportunity to better influence the outcome, and that the timing of any outcome should be considered in the context of corporate performance (e.g. manufacturing issues, new product launches, etc.)

redacted

ZY100174816 Keyplayer Playbook

Spending to maintain access can best be explained through a military analogy. To support access in Medicaid, Lilly has to be active in the State or Maneuver. Maneuvering means retaining a public relations firm and contract lobbyist as well as supporting advocacy. If Medicaid begins to move against the pharmaceutical industry, or flares up, Lilly goes in and a skirmish ensures. A skirmish may mean generating specific state data, mobilizing advocacy, and engaging the PR firm and contract lobbyist all to bring pressure on the state to not enact the formulary change. A battle ensues if the State is highly motivated to restrict access to medications and has the ability and will to see the restrictions put in place, a la Florida. The primary Lilly organization that works to keep access in Medicaid is the SGA organization. Lilly is active in 31 states in 2002. More states in 2003 are expected to try and limit access to pharmaceuticals in Medicaid.

	Maneuvers	Skirmish	Battle	Total
3 States			$500,000	$1,500,000
20 States		$350,000		$7,000,000
8 States	$200,000			$1,600,000

Strategies for an APA conference

- The Zyprexa documents dealt with how sales reps should handle:
  - psychiatrists
  - espionage from sales reps of other pharmacos
- At the 2002 and 2003 APA meetings.

ZY201220087 APA 2002 preparation

Zyprexa APA Executive Summary

APA is a:
1) celebration of science
2) competitive jungle
3) sensory overload
4) test of individual and collective will and stamina

APA is all of the above and more, and this year's meeting will be both stimulating and intense. Lilly is the undisputed neuroscience leader, and make no mistake – competitors are gunning for us, particularly Zyprexa. Their envy is understandable – Zyprexa sells more than Risperdal, Seroquel and Geodon combined. And, in addition to market leadership in schizophrenia, we've set our sights on becoming the foundation of treatment for all phases of bipolar disorder.

ZY201220087 APA 2002 preparation

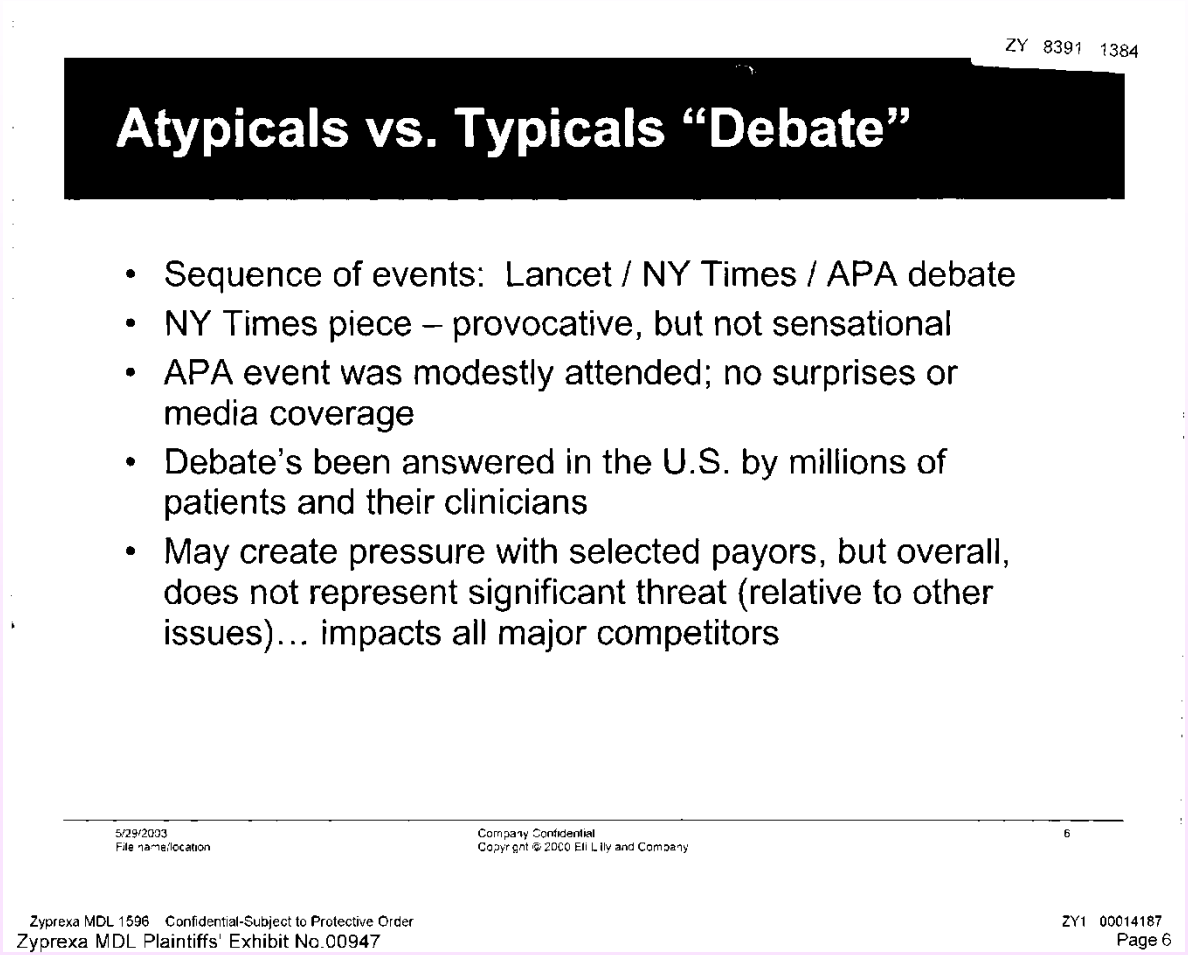
APA 2002 will showcase many exciting aspects of the Zyprexa brand, but two "debuts" stand out: 1) We will share the results of HGGY, which demonstrates Zyprexa's role in bipolar depression, a significant step in our bipolar foundation strategy; and 2) the public launch of the Zyprexa Brand Promise, the result of the most comprehensive market research initiative in the brand's history. Customers will learn how Zyprexa offers dependable control, which leads to a more productive therapeutic alliance, and ultimately, helps patients move their lives forward and realize their individual potential. Additional highlights will be shared in poster presentations, CME symposia or in press releases to the media; this information is contained in your APA binder.

What to expect – and how to respond

Competitors will attempt to commoditize efficacy and create concerns about Zyprexa (issues associated with weight gain, diabetes, etc.). Lilly sales representatives will wear buttons that say, "Ask me about Efficacy," and attendees will carry Lilly bags reading "Make Efficacy Matter." The point of these is to remind customers (and us!) that there are significant efficacy differences among therapeutic options, and discussions about extremely rare adverse events should not occur without a linked discussion of efficacy and patient outcomes.

While you are working the booth, attending scientific sessions or entertaining customers, rest assured that behind the scenes will be a very active network monitoring poster sessions, symposia and booth activity, with a focus on developing swift, effective answers to issues that arise.

ZY100014182 APA 2003 review dealing with atypicals v typicals debate



ZY 8391 1384

Atypicals vs. Typicals "Debate"

- Sequence of events: Lancet / NY Times / APA debate
- NY Times piece – provocative, but not sensational
- APA event was modestly attended; no surprises or media coverage
- Debate's been answered in the U.S. by millions of patients and their clinicians
- May create pressure with selected payors, but overall, does not represent significant threat (relative to other issues)… impacts all major competitors

5/29/2003
File name/location

Company Confidential
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6

Zyprexa MDL 1596 Confidential-Subject to Protective Order
Zyprexa MDL Plaintiffs' Exhibit No.00947

ZY1 00014187
Page 6

3. Managing ADEs - Weight Gain and Hyperglycaemia/Diabetes

- The Zyprexa documents show a progression from
  - denial
  - Zyprexa ADEs = all other atypicals "class effect"
  - reluctant "ownership"
    - weight gain and to lesser extent diabetes higher in Zyprexa,
    - "empathic" management of the issues.
- By 2005 "Zyprexa may not be for everyone."
- Many slides culled here, see longer versions @ www.healthyskepticism.org

ZY100426128 US schizophrenia advisory panel review HGAJ study with advisor comments **December 1995**

Weight: Weight gain with olanzapine over the six week acute phase averaged about 1.88 kg. Weight gain appears to be the most consistent nontherapeutic physical finding across olanzapine clinical trials. Treatment-emergent type II diabetes was rare. The mechanism behind the weight gain is unknown, but a decrease in satiety may be involved. [Note: For all patients treated with olanzapine for any amount of time, forty percent gained ≥7% body weight. Patients who remained on olanzapine for 12 months gained an average of 24 lbs at the end of the 12 months. The data on factors associated with weight gain is currently being analyzed.]

Several advisors commented on the association of olanzapine with weight gain and encouraged Lilly to subject the data to a full analysis. Clinically significant weight gain is a risk factor for other conditions such as increased blood pressure, increased cholesterol, and type II diabetes. The advisors also noted that Lilly has an opportunity to develop strategies to help manage the weight gain.

ZY100074131 FDA warning letter **November 1996**

5. 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.

These promotional labeling pieces and the teleconference are considered to be false and misleading and in violation of the Act. DDMAC requests the following actions:

1. Immediately discontinue the use of all promotional labeling pieces, and cancel all advertisements containing any of the false and/or misleading statements discussed above.

ZY100040198 verbatims for doctors re weight gain

ZY 2153 860

Weight Gain Management

- **Be prepared for the issue and related concerns**
  - No "Flinch Factor"

European Planners Meeting

Weight Gain Management

- **Acknowledgement of the class side effect**
  - **In HGAJ, at 1 year (N=349)**
    - **a minority of patients gained >10kg (28%)**
      ---> most gain between 10-15 kg
    - **16% of patients LOST weight**
    - **Over 56% of patients gained ≤10 kg!**

ZY100040198 verbatims for doctors re weight gain

ZY 2153 873

Weight Gain Management

- **How should the MD manage this "class" side effect?**
  - **There have been no clinical trials conducted to examine weight gain to date, but anecdotally:**
    - » **Tried changes in diet/exercise?**
      - **Weight gain is class phenomenon - with atypical compounds patient is able to function again and lead a healthier more active lifestyle**
    - » **Co-prescribe a treatment to control weight?**
    - » **Last option should be alternative therapy**

ZY100040198 verbatims for doctors re weight gain

ZY 2153 875

Weight Gain Management

- **Don't introduce the issue!!!**
  - **Maintain focus on main message. Primary objective is to effectively control all symptoms of psychoses and reintegrate the patient.**

European Planners Meeting

ZY100379985 ADEs report from early placebo controlled trials **1997 or later** (large font in document)

prolactin (*see* PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (*see* ANIMAL TOXICOLOGY), careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

In the olanzapine clinical trial database, as of September 30, 1999, olanzapine-treated patients (N=4234) who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Random glucose levels ≥ 160 mg/dL but < 200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 2% of patients. Of these patients, the random elevated glucose levels were found to be transient in 44% of them while they continued to receive olanzapine. Random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 1% of patients. Of these patients, the random elevated glucose levels were found to be transient in 26% of them while they continued to receive olanzapine.

ECG Changes--Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of

ZY100094522 internal Lilly email Dec1998 re hyperglycaemia and diabetes

Bruce Kinon
12/01/98 12:42 AM

To: Peter Clark/AP/LLY@Lilly
cc: Jack E Jordan/AM/LLY@Lilly, Jeffrey T Ramsey/AM/LLY@Lilly, John R Richards/AM/LLY@Lilly, Robert P Schmid/AM/LLY@Lilly
Subject: Re: Wishing/Goldstein articles

Dear Peter,

Thank you for advising me of the response to the hyperglycemia issue. I do have concerns regarding making any connections between olanzapine-induced weight gain and hyperglycemia. Therefore, in my opinion, I would not include your following statement:

"Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes."

ZY201016928/9

letter re high rate diabetes **Nov 1999**

VCBH Ventura County
Behavioral Health Department

NOV 23 199

A Division of the Ventura County Health Care Agency

Pierre Durrand, DPA
Health Care Agency Director

November 17, 1999

John Hayes, MD
US Medical Director
Eli Lilly and Co.
Indianapolis, Indiana, 46285

Dear Dr. Hayes:

This is to inform you that we have contacted our local drug representative for Zyprexa in our county as well as the regional supervisor to let them know that we have had eight patients out of possibly thirty five patients on Zyprexa show up with high blood sugars. Two patients had to be hospitalized due to out of control diabetes and the other six, who were not diabetics prior to taking Zyprexa, ended up with blood sugars higher than 120 fasting.

We treat the monolingual Hispanic population who is already at risk for diabetes and have come to realize that Zyprexa tends to throw many of them into a hyperglucose estate. Most of the eight patients were taken off the Zyprexa with normal return to their blood sugars except for the two whose blood sugars went up to 500+ and these were controlled after discontinuing the Zyprexa.

I believe it is Lilly's responsibility to look into this delicate matter in lieu of the many reports that are coming out showing the danger of Zyprexa with weight gain and hyperglycemia. I think that it would make sense for Lilly to investigate and report on these findings rather than turn the other way and send literature on how all antipsychotics increase the probability of hyperglycemia. In this particular instance it is a very

A Division of the Ventura County Health Care Agency

Pierre Durrand, DPA
Health Care Agency Director

distinct group that is watched closely with baseline blood sugars and the buck should not be passed that easily.

Right now, we have stopped using Zyprexa in our region since our Hispanic population is very high and we cannot run the risk of having these folks end up with high blood sugars. We have a staff of approximately thirty psychiatrists in the county and all are aware of this situation. Our count y serves a population of nearly 5,000 mental health patients.

Please, take this situation into consideration. I guess what we are asking is a report from Lilly in regards to Zyprexa and its potential for high blood sugar, regardless what the general antipsychotic statistics are. We certainly have never seen this with Haldol, Navane, Risperdal , and others to this extend.

If you need to reach me, please do so at your earliest convenience or our Quality Assurance, doctor of pharmacology, Dr. Patti Yoshida (805) 652-6187. We would be glad to help as much as we can. We have certainly used Zyprexa in the past with other groups to our satisfaction.

Sincerely,

Albert Marrero, M.D.

Albert Marrero, MD
Staff Psychiatrist
(bilingual)

ZY100382455 form letter for ?doctors re hypergly/diabetes aprox

late 1999

CONCLUSION

Given the multiple factors which can destabilize glycemic control and the prevalence of diabetes especially among schizophrenics, definitive conclusions regarding the relationship between Zyprexa and hyperglycemia cannot be drawn at this time.

We hope this information is responsive to your specific request. If you have any further questions, please contact us at 1-800-545-5979.

Very truly yours,

ELI LILLY AND COMPANY

Guy C. Ruble, Pharm.D.
Medical Information Administrator
U.S.M.D. Medical Information Services

Bruce J. Kinon, M.D.
Senior Clinical Research Physician
U.S. Medical Operations

ZY100592565 Olanzapine core safety & efficacy beliefs summary undated.
Notes EL trials not designed to spec test re diabetes

Diabetes

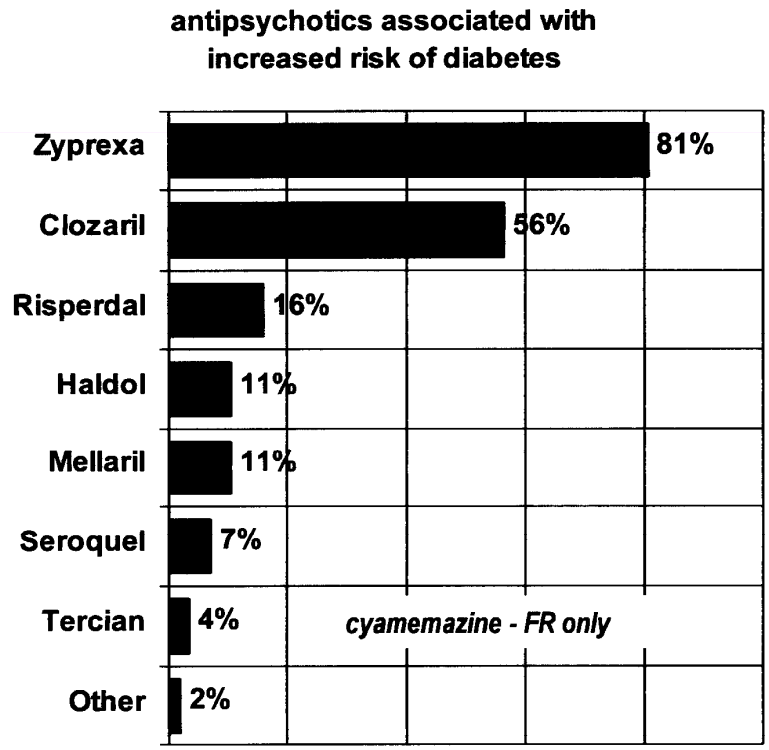
1) In an analysis of our clinical trial databases, the strongest predictor for treatment-emergent diabetes was the patient's baseline risk factors for diabetes.
2) Patients with schizophrenia-spectrum disorders, bipolar disorder, and major depressive disorder are at greater risk of diabetes than the general public.
3) Being overweight (and hence weight gain) is associated with an increased risk for diabetes. Over time, our hypothesis is that this same association holds for patients who become overweight while taking Olanzapine. However, many factors other than being overweight also influence diabetes risk (including genetic predisposition, diet, exercise, and comorbid conditions). Diabetes frequently affects individuals who are not overweight and most people who are overweight do not develop diabetes. In a retrospective analysis of our clinical trial data (including double-blind treatment of 6-52 weeks), we did not identify a significant association between treatment-emergent weight gain and diabetes for patients taking Olanzapine. A potential reason for this is that most of our studies were not designed (especially given the relatively short duration of these studies) to study a link between Olanzapine therapy and Diabetes. This issue requires additional research. Based on our data and our review of the published data on this subject, we believe that:

   a. Currently available study results do not consistently support differences in the risk of diabetes in patients treated with Olanzapine compared with other atypical agents.
   b. A causal link between Olanzapine therapy and Diabetes has not been established.

September 2000

Q2b

Those who associate increased risk of diabetes with specific agents mainly mention Zyprexa



Base: those who attribute increased risk of diabetes to specific antipsychotics (57)

- about 10% of the sample associate increased risk of diabetes with specific antipsychotics -
  - almost half this group are in the USA (23/57) … 11 in Canada
- most (of this small group) mention Zyprexa in this context - about half also Clozaril
- other agents mentioned by just 1 or 2 in each market

ZY100378053 email hyperglycaemia "threat for olanzapine" Sep 2000

Robert W Baker
10/09/2000 02:31 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Christopher C Bomba/AM/LLY@LILLY, Alan Breier/AM/LLY@Lilly, Thomas M Brodie/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, James B Gregory/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY, Bruce Kinon/AM/LLY@Lilly, Michael B Murray/AM/LLY@LILLY, John R Richards/AM/LLY@Lilly, Eugene R Thiem/AM/LLY@LILLY, Mauricio F Tohen/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly
cc:
Subject: meeting with endocrinologic consultants

FYI: The Lilly diabetes/encocrine group held an academic advisory board meeting this weekend in Atlanta. They kindly alotted two hours for discussion of olanzapine's potential hyperglycemia risks, and Charles Beasley, Chris Bomba, Patrizia Cavazzoni, Suni Keeling, and I attended. Unfortunately, this consultation reinforced my impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketting focus on the topic.

On the positive side, like other endocrinologists, they were not impressed with the Newcomer findings. They were however concerned by our spontaneous AE reports, and quite impressed by the magnitude of weight gain on olanzapine and implications for glucose. Much of their input for helpful steps came back to addressing weight gain. They also provided several suggestions for further analyses of existing data and suggestions for new studies. Citing methodological questions, at least the vocal members were not reassured adequately by our analyses, such as the finding that relative risk was not higher than comparative drugs. Disconcertingly, one member compared our approach to Warner-Lambert's reported argument that Rezulin did not cause more hepatic problems than other drugs in its class.

We (especially Chris and Suni) did successfully use this meeting to connect with a number of leading endocrinologists who are likely to be helpful moving forward.

Let me know if you have questions, and I invite comments from other Lilly attendees. thanks,

ZY100378070 emails re mtg with endocrinologic consultants Oct 2000

Robert W Baker
10/10/2000 10:19 AM

To: Charles M Beasley Jr/AM/LLY@Lilly
cc:
Subject: Re: meeting with endocrinologic consultants

Dear Charles -

thanks. Agree regarding weight gain and we've been shifting in the direction of more acknowledgeme and talking about potential interventions. At least within the mania group we're now testing a "sell she with recommendations including that for some patients risk-benefit ratio may favor another drug with l effect on weight. Probably won't be popular internally, but we are exploring it.

From diabetes standpoint, I'm tweaking medical slides to be more cautious in tone, will forward soon f your comment.

Thanks,

R
Charles M Beasley Jr

Charles M Beasley Jr
10/10/2000 10:00 AM

To: Robert W Baker/AM/LLY@Lilly
cc: Paul Berg/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly

Subject: Re: meeting with endocrinologic consultants

Agree but believe that the emphasis on marketing approach is to acknowledge weight gain and not underplay it while for diabetes to becautious until we are sure.
Charles

Some Lessons learned from Weight Gain & P450

Brush fires can turn into forest fires

Be forthcoming, don't just deny, address and own the issue

Don't just fight battle, pull back to positives

Give tools to the sales force to help tell MDs what to do

Be relentlessly consistent

- across marketing mix
- SF alignment and execution

Tailor objection handling by segment

Market Research on "message"

Very consistent takeaway of key message points -- comparable rates amongst relevant agents, common and complex issue where weight gain is only one factor, no demonstrated direct effect of Zyprexa

- Careful to take time to explain Kaplan-Meier curves well

This appears to be generally believable

Makes 'em think, but not all MDs change their basic premise

ZY 100175585 Diabetes situation analysis Dec 2000

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

ZY 100175585 Diabetes situation analysis Dec 2000

What are we going to do with the SF in January?

Option 1 -- keep existing piece

Positives

- Representative familiarity
- No additional error

Negatives

- FDA neuropharm (current + future)
- FDA DDMAC
- Problems with PBO data itself
- Pollyanna "just like Lilly usually does"

Option 2 -- use revised piece

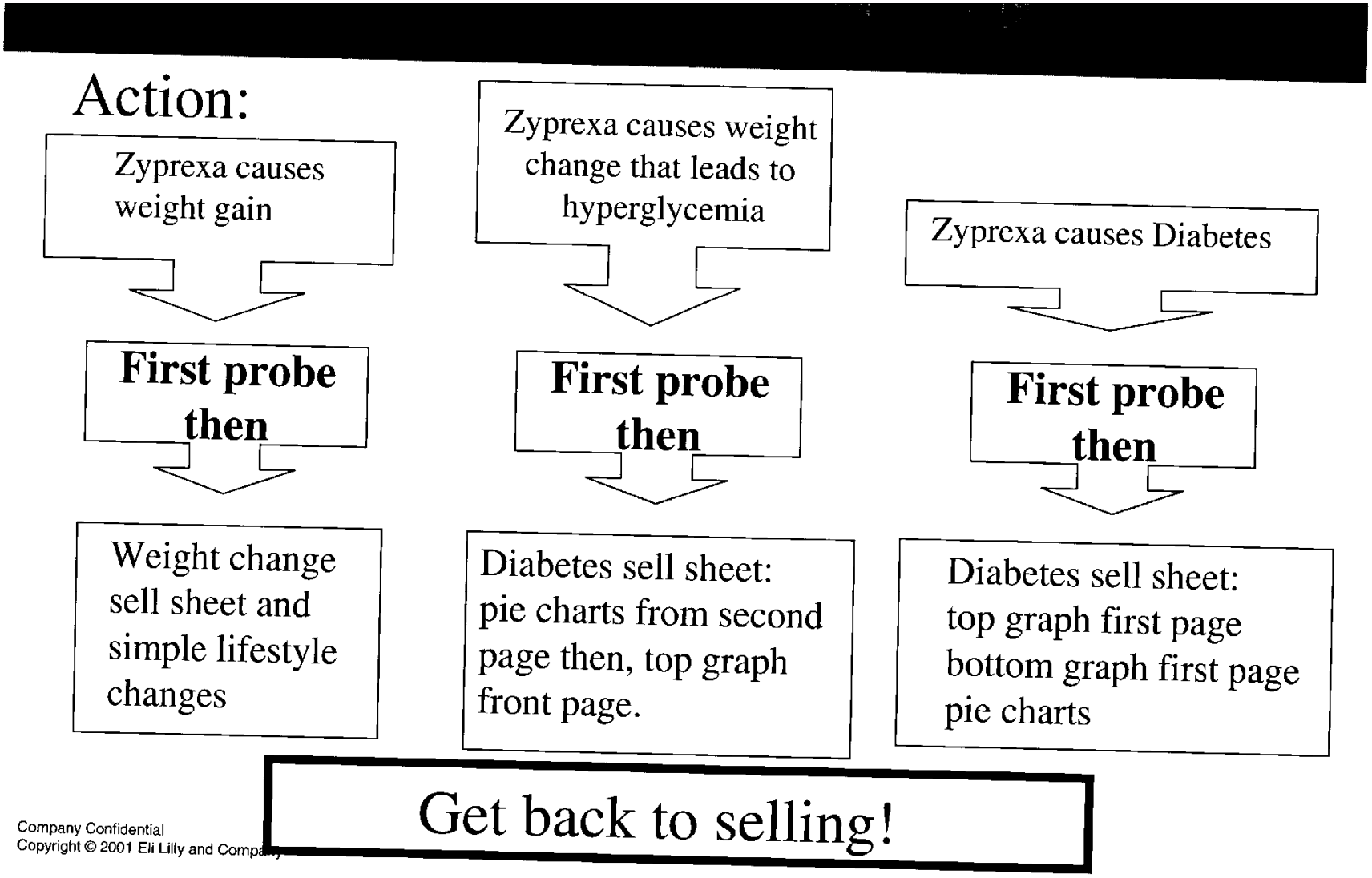
Positives

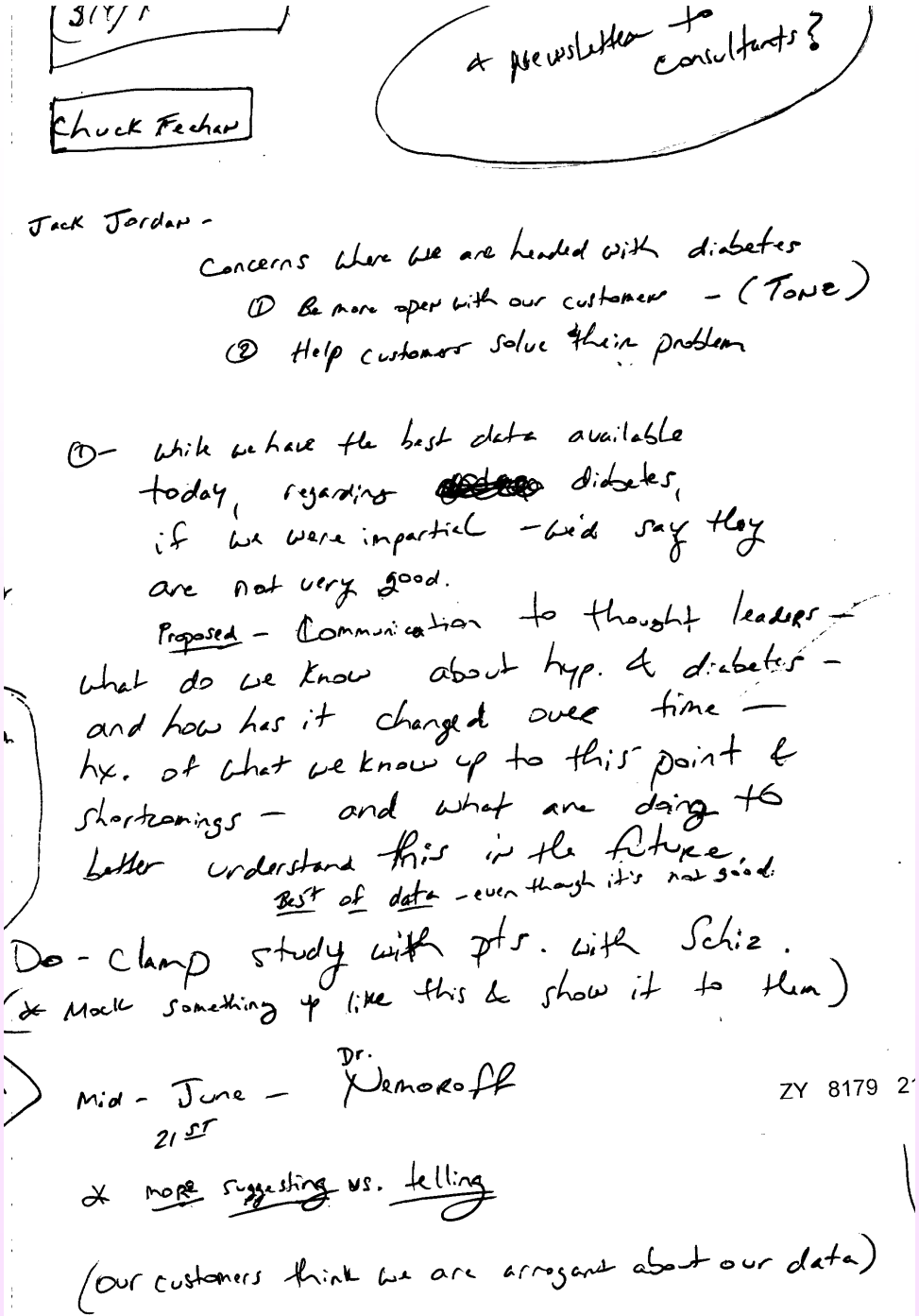
- Comparison to relevant agents
- Is more forthcoming
- Impactful with many MDs
- We believe it -- and outside experts

Negatives

- Does not (yet) clearly explain to all MDs the apparent contradiction
- It's a change and more complicated (training issue)
- May not match publication
- FDA (neuropharm + DDMAC)

ZY100504593 Handling hyperglycemia/diabetes Nov 2001





ZY100508680 jottings re diabetes data..."if we were impartial – we'd say they are not very good"

"our customers think we are arrogant about our data"

ZY200664695 Market research on handling diabetes to psychiatrists Mar 2002

Key Findings:

- Treating diabetes would cross a defined line in the minds of psychiatrists regarding standard of care
  - None are interested in treating it; some are legally bound by insurers not to treat medical illnesses
  - All indicated that they would refer such patients out as soon as they suspected a problem
- By directly addressing diabetes, Lilly is owning up to the issue in MDs' minds – this contradicts the intent of the Comparable Rates msg, despite the fact that MDs view DMT as an educational piece
- Providing objective education materials to physicians - like the DMT piece – is seen favorably
  - Sincere efforts by pharma co's to treat patients are perceived to be rare, but would build equity
  - Some MDs expressed that this piece must represent a bigger problem w/ Zyprexa and diabetes
- MDs see Lilly as the brutish aggressor due to our QTc campaign, not the underdog we'd like to be
  - MDs resent the amount of money and time Lilly spent on the QTc campaign; some seemed to feel sorry for Pfizer

ZY200399435 email re Prof Newcomer's presentation in UK re diabetes and atypicals Aug 2002

"if I were with J [Janssen], I'd be throwing some cash at this chap"

"class effect" (insofar as atypicals can be seen as a class, which they're not). It seems J were the company who offered to fund so they got the data and Csernansky agreed that he may have got the same result with zyprexa/quetiapine or (God forbid!) amisulpride. Major partisan message was that R is the only drug that has long-term RCT data and can be shown to reduce relapse. Also made point that John Geddes change his mind about atypicals (ie over BMJ paper) on the strength of these data.

Newcomer - Not quite a authoritative and, in fact, less to say on reflection, but this was the killer presentation of the evening as far as mopst of the audience was concerned. Basic presentation of the ArchGenPsych paper with some additions. Not obviously partisan but Z consistently implicated as a likely cause of type 2 diabetes or cardiac problems via weight gain. Lots of very complicated data, presented quite simply giving this black-and-white message. I think he said that there was no proven direct link between any atypical and endocrine problems but I doubt whether any member of the audience will have heard this. This was a very visceral presentation about the risks of weight gain and made a huge impact on me such that I though carefully before prescribing Z or Q over the next fortnight. The effect has worn off a bit now and I've spent some time thinking about what he actually said rather than the emotional impact of being implied that my prescibing of Z could seriously limit my patients' health/life (not said but implied). I know Newcomer has spoken to BAP but not sure where else. I think if I were with J, I'd be throwing some cash at this chap to get his message more widely know.

Without doubt, this was the most effective pharmaceutical meeting I have been to for some years.

ZY100737693 Letter re "10%" metabolic ADEs Sep2002

Holston Counseling Services

a division of Frontier Health

1570 WAVERLY ROA
KINGSPORT, TN 376
Phone: 423-224-13
Fax: 423-224-13

FYI - letter we received in med info
Kristine

September 5, 2002

Mark J. Bernauer, R.Ph. Medical Information Administrator
USND Medical Information Services
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285, USA

This is to acknowledge the receipt of your letter of August 26, 2002 which included information about blood glucose changes with Zyprexa. It just confirms the theory that there are lies, damn lies, and statistics. My personal experience with Zyprexa is that about 10% of our patients experience changes in cholesterol, triglycerides and blood glucose. This is why I have singled out Zyprexa for attention from our physicians and insisted that every patient have baseline blood glucose, cholesterol and triglycerides and that this be repeated three months after instituting Zyprexa, six months and at every six month intervals. We are not doing this for the other atypicals because our clinical experience shows that they are far less likely to produce changes in these three lab tests and, therefore, affect patients' lives, than your product.

Sincerely yours,

James M. Turnbull, M.D.
Senior Vice-President for Medical Services
Frontier Health, Inc.

ZY201381347 email re “neutralising issue” in Japan re hypergly/diabetes concerns Nov 2002

To: CN=Neil W Aubuchon/OU=AP/O=LLY@Lilly
CC: CN=Matthew R Pike/OU=AM/O=LLY@Lilly; CN=Michael E Bandick/OU=AM/O=LLY@Lilly
Date: 11/20/2002 10:51:14 AM
From: CN=Bin Gu/OU=AM/O=LLY
Subject: Re: Request

Neil,
Thanks for the good questions. Could I suggest we have a conference call to discuss this. I would suggest either this Thursday 6-7:00pm (Indy time)=Friday 8-9:00am (Japan time) or early next week . Please let us know your choice so I can arrange it. Thanks!

Also I forward Diabetes position paper (in case you haven't) for the discussion.

****
Gu,Bin
(317) 277-6483

Neil W Aubuchon
11/19/2002 07:14 PM

To: Bin Gu/AM/LLY@Lilly
cc: Matthew R Pike/AM/LLY@Lilly, Michael E Bandick/AM/LLY@Lilly
Subject: Re: Request

Bin,

Thanks for staying late and promptly answering our question. It is very helpful.

Let me ask you two follow-ups:

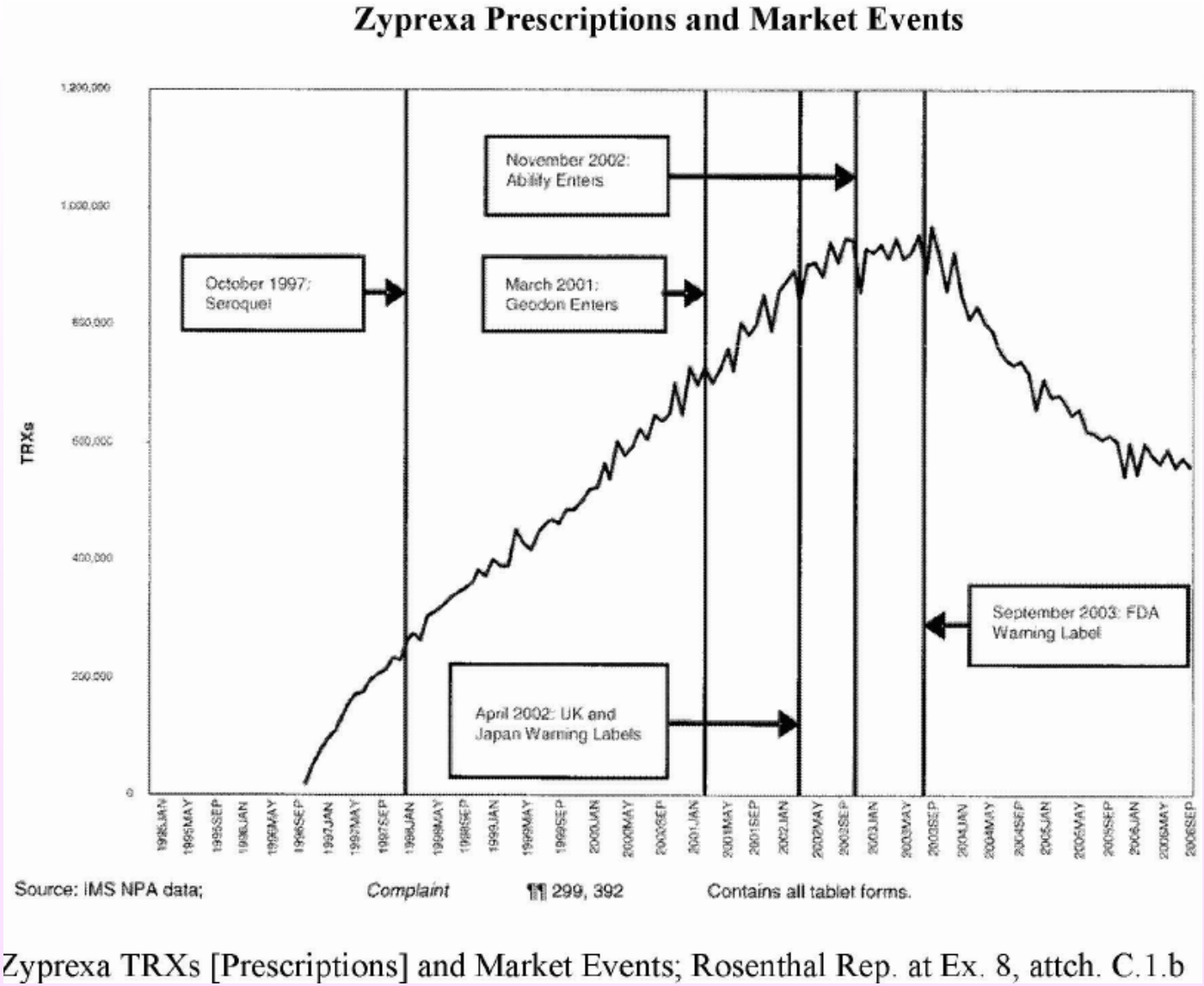
1) What is the strategy regarding diabetes? Are we trying to show through retrospective studies that it isn`t that big of a problem? I understand that we are trying to neutralize the issue, but how are we trying to do that?

2) If you could provide (even informally) the key results of the hyperglycemia/diabetes publications that have been submitted that would be

ZY100386523 regulatory activity timeline from 1985 to FDA decision 15 Sep 2003

09/15/03 -	20-592 and 21-086 – Received letter from FDA requesting inclusion of warning regarding hyperglycemia and diabetes in labeling

Judge Weinstein draft order in Zyprexa case July 2008, page 117
Perhaps why E-L so resistant to PI label change re diabetes/hypergly.



Zyprexa TRXs [Prescriptions] and Market Events; Rosenthal Rep. at Ex. 8, attch. C.1.b

ZY201238586 Issue management wght gain/diabetes
mid 2003

Problem Statement: United States

We have learned that diabetes and weight gain are inextricably linked!

As a result of concerns about weight gain and fear of diabetes, an increasing number of physicians are either avoiding Zyprexa in the acute phase or switching longer term. These actions are depriving patients of the benefits of Zyprexa.

We expect that a similar change may occur in Europe with the launch of Abilify/Geodon in 2004.

ZY200192865 Integrating wght gain into the brand promise

BRAND MATTERS – October 2003 Issue (11.13.03 version)

Full Stories:

INTEGRATING WEIGHT GAIN INTO THE BRAND PROMISE

The ZYPREXA brand has many positive attributes. For physicians, ZYPREXA means offering proven benefits in the treatment and management of acute bipolar mania and schizophrenia. It means offering a dependable medication with rapid and robust system control, the flexibility to treat a variety of symptoms of bipolar mania and schizophrenia, and a predictable safety profile. For many patients, ZYPREXA can mean the ability to reach their full potential.

The ZYPREXA brand also carries with it a reputation for causing fear of weight gain and diabetes in the mind of our customers. Physicians' perceptions of weight gain and increased risk of diabetes are often linked.

Physicians believe weight gain is the key issue for ZYPREXA, and, they think if you can address weight gain may reduce the risk of diabetes and other health-related consequences. They are looking for tools to address weight gain that will enable them to continue to use ZYPREXA due to its efficacy. According to Michael W. Magdycz, RPh, manager, ZYPREXA marketplace management, "it's time for a fundamental change."

Magdycz believes a major change in tone and approach is required (empathetic with conviction) to restore confidence in our ability to realistically help our physicians handle these concerns. Weight gain will no longer be handled as an objection. Instead, weight gain will be discussed up front, and integrated into the brand promise. The brand will soon begin to reflect this shift:

Where we were…

- Weight gain is manageable
- Weight gain is predictable
- Weight gain is not the only predictor of diabetes
- Comparable rates of incidence of diabetes across all products
- Diabetes is mainly a patient population issue
- Handling diabetes and weight gain as an objection

Where we are going…

- Lilly understands the challenges physicians face in treating this population
- Lilly acknowledges weight gain challenges
- Lilly is providing physicians with options to address weight gain in their patients
- Third parties provide physicians with the facts related to diabetes
- Lilly is providing help regarding how to assess, counsel, and refer patients at risk for diabetes

We will select tactics for each strategy that offer us best chance of success and execute the *%#&*! out of them

Lilly

Answers That Matter.

ZY201588969 letter to ADA protesting differential warnings on atypicals Jan 2004

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).

ZY200598805 emails re literature saying antipsychotics of equal efficacy Jan 2004

Date: 01/14/2004 12:55:32 PM
From: CN=Jerry D Clewell/OU=AM/O=LLY
Subject: Re: Annals of Pharmacotherapy Recent articles of interest 2004
Attachments: Liu cost comparison review OLZ vs RIS Ann Pharma 1-04.pdf; Sprague Selection of APDs Ann Pharm 2-04.pdf

Ginny et. al.
I too would like to offer a couple of observations from the Payer world relative to these studies and the environment.

It can not be understated that the Annals (as well as AJHP) are very widely read pharmacy journals that influence clinical pharmacists and their recommendations at the patient, and P&T Committee levels.

These reviews, especially in addition to this month's publication of the Consensus Guidelines for Schizophrenia (published in AJHP), can provide powerful arguments for P&T committee members to restrict access to olanzapine on the basis of (1) perceived parity or near parity in efficacy in light of (2) the perceived 2X cost differential between olzanzapine and risperidone.

1. **Selection of atypical antipsychotics for the management of schizophrenia- Denise Sprague**

   Payers have already expressed to me (just yesterday) that they view this information as confirming their interpretation of the data that there is very little clinical difference between olanzapine and risperidone. Never mind the author's comments that drug therapy should be individualized.

What can/should we do in reaction to these perceptions?

I believe this means that we have to step up all publication and communication efforts to educate decision makers and their consultants (Thought Leaders, PBM's, etc) on the long-term effectiveness (relapse prevention, and medication persistence) of olanzapine. We were specifically criticized yesterday by a large Medicaid payer consultant for not being able to provide more peer-reviewed publications supporting an argument for long-term effectiveness.

As a company, we all need to do a much better job of proactively listening to payers (and other customers) concerns, and proactively communicating important information such as adverse effect label changes without a tone of minimizing their importance (e.g. wt gain, diabetes, CVA). Payers and clinicians have clearly articulated that this is an area where Lilly has lost its scientific integrity and therefore exposed us to great scepticism when we need to communicate the positive benefits of our products.

Best Regards,

Jerry D. Clewell, Pharm.D., MBA BCPS
Sr. Neuroscience Outcomes Liaison
Eli Lilly and Company

ZY201588819 internal Lilly lit rv on comparative metab ADEs of atypicals undated but latest ref used 2003.

anonymous Lilly reviewer concludes Risp and Quet are more likely to have metab ADEs than current warnings, but also that Olz sits with Cloz as most likely agents to give metabolic ADEs

Atypical Antipsychotics & Metabolic Abnormalities[4]

ADA/APA Guidelines

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	--	--

Suggested Effects

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	+/-	D
Quetiapine	++	+/-	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	+	--

+ = increase effect; -- = no effect; **D** = discrepant results; * Newer drugs with limited data

ZY200581528 email: our "position (no differential between atypicals on diabetes) is making us look foolish"
Mar 2004

To: CN=Thomas A Hardy/OU=AM/O=LLY@Lilly; CN=Sara Kollack-Walker/OU=AM/O=LLY@Lilly
CC: CN=Robert W Baker/OU=AM/O=LLY@Lilly; CN=Michael Overdorf/OU=AM/O=LLY@Lilly
Date: 03/10/2004 04:26:25 PM
From: CN=Vicki Poole Hoffmann/OU=AM/O=LLY
Subject: Re: Revisions - BHM Editorial

Sara and Tom,

Not that you asked for my opinion, but here it is anyway.

I think we should delete most of the third paragraph and all of the fourth as they are defensive and attempt to show that there is no differential risk of DM among atypicals in spite of the differences in weight gain. Our advisors have told us that this position is making us look foolish. I like the beginning of the third paragraph ("Weight gain and dysfunction in glucose and lipid metabolism during antipsychotic drug therapy are clearly of concern. An increase in body weight has been linked to metabolic dysfunction (insulin resistance, hyperglycemia, dyslipidemia) and to an elevated risk for the development of diabetes and cardiovascular disease. However, the relationship among these metabolic parameters may be more complex, especially in patients who suffer with a serious mental disorder and who may already be at risk for metabolic adverse events.") but I think we should follow it with our belief that all patients should be monitored for weight gain and changes in metabolic parameters regardless of the antipsychotic chosen (a position consistent with the ADA Consensus Statement). We might make a comment that those promoting the notion that patients initiated on certain antipsychotics do not require monitoring are doing a disservice to patients.

I think we could also safely challenge the ADA recommendation that clinicians should consider switching antipsychotics in patients who gain > 5% of their initial body weight. This is not supported by the data, (most assessments of body weight change use a threshold of 7%) and it could be dangerous since patients may gain this much weight before they are psychiatrically stable. Switching at this point would be costly and may delay psychiatric recovery. Robert has commented to me several times that we know what to do for patients initiating therapy, regardless of drug choice, and even those with risk factors, (they should be monitored), what we do not know is what to do about patients who become obese. This may be something we want to work in.

Vicki

Strategy Overview

What's new

- More assertive recognition and acceptance that **Zyprexa may not be for everyone**
- The four quadrant model to facilitate the benefit/risk discussion

What's not

- We must continue providing meaningful resources through weight management and wellness solutions to our customers
- We will continue to analyze and report on new safety information regarding Zyprexa for affiliates

The Seroquel documents

- Seroquel (quetiapine): AstraZeneca's atypical antipsychotic
- Many issues raised in documents released through litigation process (Federal court in Florida)
  - Selective publication of clinical trial data and perhaps misleading analyses in journals/ presentations
- Available at blog: http://industry.bnet.com/pharma/10001228/e-mail-astrazeneca-knew-in-1997-that-seroquel-caused-weight-gain/

AZ Presentation in 2000

An Analysis Suggests SEROQUEL(R) Has Greater Efficacy Than Haloperidol

PR Newswire. New York: May 16, 2000. pg. 1

- Results from four trials: Seroquel has significantly higher response rate than Haldol
- Academic researcher on study said in accompanying press release:
  - "Almost 50 years later, however, many patients are still taking [typical antipsychotics], even though more effective treatments like SEROQUEL exist."
  - "I hope that our findings help physicians better understand the dramatic benefits of newer medications like SEROQUEL because, if they do, we may be able to help ensure patients receive these medications first."

AstraZeneca's Internal Analysis

*Based on same four studies presented in prior slide
*Finds advantages for Haldol, not Seroquel

The following table is an attempt to simplify the claims that could be obtained from these results. A ✓ is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or using LVCF. A ✗ marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel.

Table 1

Comparator	Category						
	Anxiety	Total BPRS	Factor I	Factor V	Hostility	Hostility Cluster	Mood Cluster
Placebo	✓	✓	✓	✓	✓	✓	✓
Haloperidol	-	✗	-	✗	-	✗	-
Chlorpromazine	-	-	-	-	-	-	-
Risperidone	✗	✗	✗	✗	-	✗	✗
Other typicals	-	✗	-	✗	-	✗	-

Omnibus MSJ Exhibit 2

Internal Data vs. Published Data

*AZ concerned with internal data showing Seroquel as inferior to Haldol in efficacy for schizophrenia (last slide) – how to handle this?

From: Tumas John JA
Sent: Thursday, March 23, 2000 10:05 AM
To: Goldstein Jeffrey JM; Murray Michael MF
Subject: FW: Meta Analyses
Importance: High

Jeff and Mike,

Here's the analyses that I got from Emma. I've also attached a message that I sent to her yesterday asking for clarification.

The data don't look good. In fact, I don't know how we can get a paper out of this.

My guess is that we all (including Schulz) saw the good stuff, ie the meta analyses of responder rates that showed we were superior to placebo **and** haloperidol, and then thought that further analyses would be supportive and that a paper was in order. What seems to be the case is that we were highlighting the only good stuff and that our own analysis support the "view out there" that we are less effective than haloperidol and our competitors.

Once you have a chance to digest this, let's get together (or telelconference) and discuss where to go from here. We need to do this quickly, because Schulz needs to get a draft ready for APA and he needs any additional analyses we can give him well before then.

Thanks,

John

Omnibus MSJ Exhibit 4

Omnibus MSJ Exhibit 13 “could put positive spin” on “cursed” study 15

INTERNAL MEMORANDUM

Date: 12-Feb-1997 03:40am EDT

Tel No: 01625 517679

To: See Below

From: Richard Lawrence

Subject: RE: US/Canada Investigator meeting and Study 15

I am not 100% comfortable with this data being made publically available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

Adopting the approach Don has outlined should minimise (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study

Athena, with Mark Sahl having left I am not certain who is replacing him. Whoever it is..... ought they speed a reserve press release through?

“cursed” Study 15

Study 15 Report (1996) Section 4.1 (p37 -52)

- 301 patients in full or partial remission of schizophrenia from 34 centers
- Results:
  - Significantly more psychotic relapse on Seroquel than Haldol
  - Some symptom measures favored Haldol

“cursed” Study 15

What was reported?

- "Treatment with quetiapine at higher doses relative to haloperidol appears to have a positive impact on important domains of cognitive performance that have been found to predict role function and community outcomes in patients with schizophrenia."
- "The potential cognitive benefits of quetiapine relative to haloperidol add to a growing list of benefits of treatment with quetiapine including: no dose related EPS, low level of overall side effects, high levels of patient satisfaction, and good tolerability."
- ***Seroquel's poor performance on psychotic relapse and symptom measure scores are not noted anywhere in the paper.***

- Velligan DI, Newcomer J, Pultz, J, Csernansky J, Hoff, AL et al. 2002. Does cognitive function improve with quetiapine relative to haloperidol? Schizophrenia Res;53:239-248

Omnibus MSJ Exhibit 6 slides for KOL speaker, email says have been "tweaked"

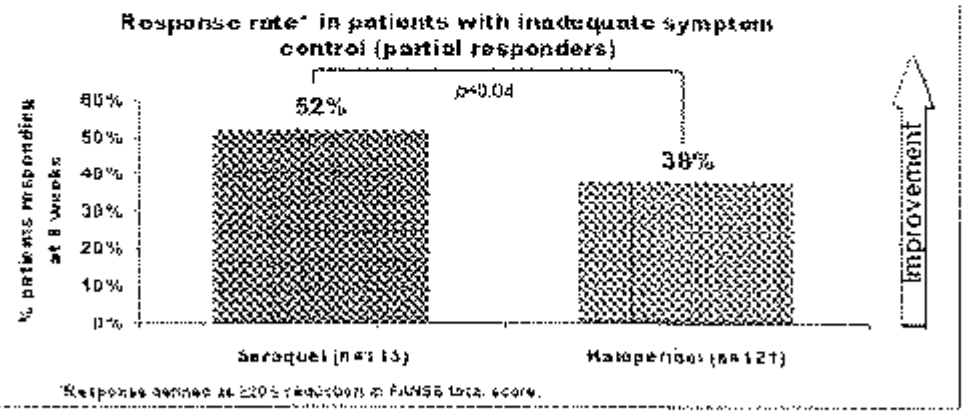
Initial target dose: 600 mg/day

Unsurpassed efficacy at the right dose

For acutely ill patients

Efficacy at least as effective as haloperidol

- Comparable reduction of positive and negative symptoms…with a significantly superior clinical response rate



*Response defined as ≥20% reduction in PANSS total score.

8-week, double-blind, randomised study of patients with partial or no response to 1 month of fluphenazine 20 mg/day.

Emsley RA et al. *Int Clin Psychopharmacol*. 2009;15:121-131.

3

Q. Well, let me ask, since you asked me a question, let me ask you a question: "Unsurpassed," "unsurpassed," what does that mean?
A. It means --
Q. Nobody is better; right?
A. It means equivalent.
Q. So if I really -- I'm trying to think of something. If I tell somebody that I went to a track meet and I saw an athlete that has been unsurpassed, I mean he was -- her, let's say her. Her ability to do the broad jump and the high jump and the relays were unsurpassed, and I was just so impressed and I go and tell you it was unsurpassed, you believe that means I'm saying she was equivalent to everybody

else at the meet?
A. Possibly, yes. That's the correct grammar. Possibly, yes. She was possibly better; she was possibly equivalent.

Omnibus MSJ Exhibit 5

AZ marketing director deposition Apr 2008

Omnibus MSJ Exhibit 14 – reads as though study 15 could not be spun, was "buried" – with others

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From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data.

study published in *Int J Psychiatry in Clin Prac* 2000

The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

M BRECHER,[1] IW RAK,[1]
K MELVIN[2] AND AM JONES[2]

AstraZeneca, [1]Wilmington, DE, USA and [2]Alderley Park, Macclesfield, Cheshire, UK

Correspondence Address
Dr Martin Brecher, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE, USA
Tel: +1 (302) 886 2634
Email: martin.brecher@astrazeneca.com

INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI < 18.5 kg/m^2) and severely obese patients (BMI ≥ 35 kg/m^2).*

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Omnibus MSJ Exhibit 32 weight & diabetes sell sheet Aug 2005

Our objective is to neutralize customer objections to SEROQUEL's weight and diabetes profile This is possible with messages that are supported by data -- the kind of message you can take away from the Weight and Diabetes Sell Sheet

I think you'll appreciate the potential of this tool Then, don't forget to refocus the call on SEROQUEL's Trusted Tolerability profile, highlighting the low incidence of Akathisia and EPS with SEROQUEL

Thanks everyone and good selling!

Omnibus MSJ Exhbit 43 – declaration by expert witness, psychiatrist Dr Wirshing
AZ obscured weight gain & diabetes issues re Seroquel for years

> Since the 2-week long-term placebo-controlled bipolar maintenance trial studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

Thus, the FDA wanted to provide clarity that the already negative blood glucose results stated in the new label—based on studies that effectively prescreened participants who did not well-tolerate Seroquel—actually may be even worse than the label reveals. AstraZeneca has not made the labeling changes that the FDA has requested as of the date of execution of this Declaration. AstraZeneca's evasive treatment and abstruseness with respect to this label change further confirms my opinion that AstraZeneca has not been forthright with physicians

Omnibus MSJ Exhibit 44 testimony of expert witness, pharmacologist Dr Plunkett

AZ aware of Seroquel association with diabetes/hyperglycemia 1999

treated. Further, my review of AstraZeneca's own documents reveals that the company was aware of an association with Seroquel and hyperglycemia/diabetes since at least 1999, when Dr. Small recognized after Trial 8 that Seroquel and two other antipsychotic drugs caused the most weight gain and also were likely to cause diabetes. In 2000, as noted above, the company's Global Drug Safety Physician concluded that Seroquel can cause impaired glucose dysregulation including diabetes. In addition, by November 2002, the Japanese government had evidently reached a similar conclusion, requiring that AstraZeneca send a "Dear Doctor" letter to Seroquel prescribers informing them of the increased risk of diabetes

Omnibus MSJ exhibit 9 statement of expert witness, epidemiologist Dr Arnott

this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

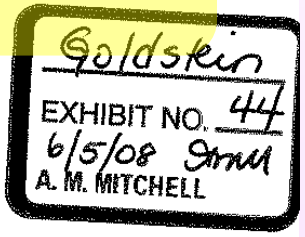
Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

Seroquel global brand team email 8/7/03 re "IIT benchmarking report" avail: www.fdanews.com/ext/files/IIT-Seroquel.pdf

Key messages emerging from the report:

• Lilly run a large and highly effective IIT program

• Significantly higher (x3 in some markets) investment than AZ
• They are perceived as open and flexible to receiving proposals but will often impose strict design changes before approval
• They impose few restrictions on the investigator once design changes are communicated and agreed
• They are fast and effective in turning studies around centrally and locally
• They offer significant financial support but want control of the data in return
• They are able to spin the same data in many different ways through an effective
publications team
• Negative data usually remains well hidden



• Janssen have a well organised IIT plan

• Significant spend in some markets but variable in others
• Well structured, protocol-driven program that turns proposals around quickly through a very small approval team
• Local investment decisions are allowed on small IIT's
• No IIT data is allowed to be published without going through Janssen for approval, and communication is controlled by Janssen
• High expectations are set on investigators who publish favorable results but they are well rewarded for their involvement
• They seem less concerned than Lilly about negative data reaching the public domain

• BMS IIT program is growing very fast in launched markets

J&J Risperdal documents

re J&J Pediatric Psychopharmacology Research Program at the Massachusetts General Hospital

- Released from a court case involving Johnson & Johnson (Janssen) in Masachussetts, Nov 2008
- Available at:
  - http://psychrights.org/Research/Digest/NLPs/Risperdal/081112Opp2BiedermanQuash-Seal.pdf
  - Further information:
  - http://ahrp.blogspot.com/2008/12/j-j-risperdal-documents-biederman.html

JJRE02256029 rationale to generate data supporting use of risperidone

-----Original Message-----
From: Gharabawi, Georges [JANUS]
Sent: Tuesday, February 05, 2002 7:42 AM
To: Vergis, Janet [JANUS]; Cote, Christine [JANUS]
Cc: Mahmoud, Ramy [JANUS]; Pandina, Gahan [JANUS]; Kovacs, Clare [JANUS]; Deloria, Carmen [JANUS]; Kalmeijer, Ronald [JANUS]
Subject: Janssen-MGH Child and Adolescent Bipolar Center - Dr Joe Biederman

Subject
Invitation to a meeting with Prof Biederman and his team at Janssen on March 14 or March 28, 2002 (date pending your approval) to agree on the main deliverables from the Janssen/MGH Center for Child and Adolescent Bipolar Disorders and prioritize the different activities - Your attendance of the 1st hour is needed.

Background
Dr Biederman is the pioneer in the area of C&A Bipolar Disorders. He approached Janssen multiple times to propose the creation of a Janssen-MGH center for C&A Bipolar disorders. The rationale of this center is to generate and disseminate data supporting the use of risperidone in this patient population. I met with Dr Biederman in August 2001 and discussed with him the feasibility of this center and agreed that, should Janssen decide to support it, the main focus will be on 2 topics: 1) Diagnostics, including the creation of a screening/diagnostic tool to train clinicians (Pediatricians and General Psychiatrists) on how to diagnose C&A BPD, use of genetics and Neuro-Imaging techniques to recognize C&A BPD and the different variants of the disorders and 2) Therapeutics, including short and long-term outcomes of the management of C&A BPD with risperidone including the long-term prophylactic effect on drug abuse. Following a number of internal discussions within the Brand team and with Janet, it was decided to 1) explore the feasibility of involving other J&J companies that would be interested in participating in the center and share the financial support and 2) fund the center pending the submission of a 5-year plan of deliverables including retrospective analyses and prospective exploratory research.

Annual Report 2002: The Johnson and Johnson Center for Pediatric Psychopathology at the Massachusetts General Hospital

Director: Joseph Biederman. MD

CQ˜Drreetor; Stephen V. Faraone,. PhD

Overview

The mission of the Center is to create a common ground for a strategic collaboration between Johnson & Johnson (J&J) and the Pediatric Psychopharmacology Research Program an at the Massachusetts General Hospital (MGH). The Center provides an infrastructure for MGH

An essential feature of the Center is its ability to conduct research satisfying three criteria: a) it will lead to findings that improve the psychiatric care of children; b) it will meet high levels of scientific quality and c) it will move forward the commercial goals of J&J. We strongly believe

disorders. Because parents, patients and clinicians are exposed to a media that frequently questions the validity of childhood disorders, genetic and brain imaging studies are needed to show the validity of these disorders as brain disorders that respond to medication. Epidemiologic studies are needed to show that childhood disorders are frequently chronic and severely debilitating. Without such data, many clinicians question the wisdom of aggressively treating children with medications, especially those like neuroleptics, which expose children to

From Wall Street Journal, avail at: http://s.wsj.net/public/resources/documents/WSJ_Risperdal125-127-112408.pdf

JJRE02510305 anxiety over loss of a KOL's favour to a competitor

The check has been authorized and should be sent out in three business days.
Sohel

----Original Message----
From: Bruins, John [JANUS]
Sent: Wednesday, November 17, 1999 11:49 AM
To: Sachak, Sohel [JANUS]
Cc: Burgos, Licette [JANUS]; Mahmoud, Ramy [JANUS]; Wolfe, Michael A. (JAN)
Subject: Dr. Joseph Biederman payment

Sohel;

As I am writing this memo, I am FAXing you all the documentation which I have on this Grand Rounds Program.

As of yesterday, 11/16/99, Dr. Biederman was promised delivery via Federal Express a check for $3K. I made this promise to him since I was assured that this matter would be resolved. It has not.

Let me start from the beginning so that it is crystal clear with everyone involved:

-Dr. Biederman is not someone to jerk around. He is a very powerful national figure in child psych and has a very short fuse.

-Three or four years ago Janssen H.O. requested that he put together a study to evaluate RIS in the child and adolescent population. He submitted a thourough and lengthy proposal which amounted to approximately $280K. We dragged our heels on this request (which we made) for over a year. He finally recieved a standard ding letter. By the time I found out about it a week later and went to see him his secretary advised me of his fury. The sales representative who called on him and I took an hour of verbal beating. I have never seen someone so angry.

-Dr. Biederman is the Head of Adolescent Psych at MGH. Since that time our business became non existant within his area of control. He now has enough projects with Lilly to keep his entire group busy for years.

-Although I occasionally call on him and invite him to our Ad Boards, he acts with scepticism about our sincerity.

JJRE02510306 we have jerked him around…afraid of repercussions

-Six months ago I recieved a call from Leighton Huey (the Chairman at UConn). He informed me that Dr. Biederman was coming to give GR in September of this year. According to him, some previous discussion had taken place between the Boston rep (covering Dr. Biederman) and the Hartford rep (covering UConn). The Boston rep was doing everthing she could think of to get Dr. Biedreman back in our graces. Anyway they had done some behind the scenes negotiating to schedule this program. Dr. Huey informed me that Dr. Biederman recieved commitment that Janssen would pay for this program. This included a promise of $2.5K honorarium and expenses. Dr. Huey and I were both surprised by the figure but we were not part of the negotiating and stayed out of it. Dr. Huey FAXed me the e-mail correspondance. I told him that I would take care of it since the sales reps were no longer working.

-I then filled out the grant request paperwork and sent it to you for approval. This was about three months ago and well before the program on September 20, 1999.

-You then returned to paperwork to me and requested me to get the sales force to pay for it.

-I discusses the issue with Mike Wolfe (new RBD for New England) and forwarded the materials to Rick Atkinson (new DM for Hartford).

-At a sales meeting in Boston which was addressing finances I committed to taking back this Grant Request since no one was willing to champion this program and pay for it.

-On or about September 20 I resubmitted the paperwork to you with a verbal explaination.

-A month later you requested further documentation.

-Over a week ago Dr. Biederman was on his way back to tirade. He was calling me and Dr. Huey's office and was starting to ruffle Dr. Huey's feathers that we had not payed him. I asked Dr. Biederman for further documentation and committed to him that we would get his check to him by yesterday in exchange for documentation from him. In two lengthy voice mails to you I explained the situation and promised the documentation to pass in the mail with the check.

-Dr. Biederman paged me yesterday and I did not know why he had not recieved his check. I told him to call you.

-Dr. Biederman has done everything we have asked of him. Again, we have jerked him around. I am truely affraid of the repercussions.

-I beg you to approve the payment of his ckeck.

JJRE04017358 – how to "handle" improvement in placebo issue "if it occurs" – why raw data & trial protocols would end suspicion

From: Biederman, Joseph,M.D. [BIEDERMAN@HELIX.MGH.HARVARD.EDU]
Sent: Wednesday, June 12, 2002 1:34 PM
To: 'Pandina, Gahan [JANUS]'
Subject: RE: AACAP 2002 Draft Abstract

I will review this morning. I will be happy to sign the forms if you could kin
them to me

> -----Original Message-----
> From: Pandina, Gahan [JANUS]
> Sent: Tuesday, June 11, 2002 5:50 PM
> To: Biederman, Joseph,M.D.; Stephen V. Faraone Ph. D. (E-mail); Mick, Eric
> Cc: Gharabawi, Georges [JANUS]; Bossie, Cyndi [JANUS Non J&J]
> Subject: AACAP 2002 Draft Abstract
>
> Dear All,
>
> I am sending the most recent draft of the abstract for AACAP 2002, with some missing data (analyses were supposed to be completed this evening, but will be here in the morning instead). I was able to have our statistics department generate the summary data for each of the two symptom areas (depression and mania), but this resulted in the delay. Please take a look, and provide any comments you think appropriate. We have generated a review abstract, but I must review this longer abstract before passing this along (this is less crucial). Based upon the improvement in the placebo group, both groups may demonstrate significant improvement overall on the two domains, so, if you could, please give some thought to how to handle this issue if it occurs. I will send the results as soon as possible. Dr. Biederman, if you could be prepared to sign and fax a disclosure form as presenting author, unless you would rather have another present the data then assign a designee, as we cannot submit without a signed disclosure. I will be at an off-site meeting tomorrow, but available

BRIEF ABSTRACT

JJRE 04017359

American Academy of Child and Adolescent Psychiatry Conference - 2002

Symptoms of affective instability respond to risperidone treatment in children with disruptive behavior disorders.

Biederman1, J., Faraone1, S., Mick1, E, van Patten1, S., Pandina2, G., Gharabawi2, G.

1Massachusetts General Hospital, Boston, MA

> 2Janssen Pharmaceutica Inc., Titusville, NJ

> Objective: To examine the response of affective symptoms to risperidone treatment in children with disruptive behavior disorder (DBD).
>
> Method: Children with DBD (oppositional defiant disorder/conduct disorder/disruptive behavior NOS; n=118; mean, age 8.6 years, 97 males) and subaverage IQ were randomized to placebo or risperidone in a 6-week, double blind study. Weekly assessments were made with the Nisonger Child Behavior Rating Form (NCBRF), along with other efficacy, safety and cognitive assessments. While the NCBRF Conduct Problem Subscale was the primary outcome measure, secondary analyses were performed on items classified as symptoms of depression or mania. Change in symptoms from baseline to endpoint was evaluated.
>
> Results: Analysis of covariance for symptoms of depression and mania showed significant improvement at endpoint in the risperidone group (depression: p=0.0001; mania: p=0.0001), while the placebo group did not (ns). Individual symptom analysis showed a greater improvement in children treated with risperidone than placebo. Example: the risperidone group improved significantly on "crying, tearful" (p<0.05), "irritability" (p<0.001) "feels worthless or inferior" (p<0.001), while the placebo group showed no improvement in these symptoms.
>
> Conclusions: Risperidone is effective in the treatment of manic and depressive symptoms frequently found in children with DBD. Implications for treatment are discussed.

Media reports of psychiatrists' earnings from pharmaceutical companies

A Doctor's Underreported Transactions

Three Harvard child psychiatrists originally reported to Harvard little consulting income, but when Senator Charles Grassley pressed, they amended their disclosures to show millions in total fees. But some of the amended entries contradict payment records from drug makers. Examples for one of the doctors:

DR. JOSEPH BIEDERMAN'S DISCLOSURES

COMPANY	YEAR	INITIAL REPORT	AMENDED	RECORDED BY DRUG COMPANY
Johnson & Johnson	'01	Not reported	$3,500	$58,169
Eli Lily	'00	Less than $10,000	3,500	14,105
Eli Lily	'03	Less than $10,000	8,250	18,347
Eli Lily	'01	No amount provided	6,000	14,339
Eli Lily	'04	No amount provided	8,000	15,686
GlaxoSmithKline	'00	Not reported	2,000	3,328
Pfizer	'04	Not reported	3,000	4,000

In Their Own Words

What the doctors and the Senator who lead the investigation had to say:

Senator Charles E. Grassley Republican of Iowa

"It looked like they had taken a couple of hundred thousand dollars. But last March, Harvard and Mass General asked these doctors to take a second look. ... Dr. Biederman suddenly admitted to $1.6 million dollars from the drug companies. And Dr. Spencer also admitted to over $1 milion. Meanwhile, Dr. Willens also reported over $1.6 million."

Dr. Joseph Biederman

"Through my full and complete disclosure of the requested information, I hope that Senator Grassley will recognize my long term intention to comply fully with and adhere to the conflicts of interest policies of those institutions."

Dr. Timothy Wilens

"In accepting these invitations to speak, and in what I reported on my disclosure forms, I have always believed that I was acting within the applicable relevant guidelines and rules."

Dr. Thomas J. Spencer

"I am deeply committed to helping children with A.D.H.D. and other similar disorders find treatments that can help improve their lives. ... It was my sincere belief that I was at all times complying with the relevant policies and procedures as to outside income."

THE NEW YORK TIMES

The New York Times

- **June 8, 2008: Researchers Fail to Reveal Full Drug Pay** by Gardiner Harris & Benedict Carey

- A world-renowned Harvard child psychiatrist whose work has helped fuel an explosion in the use of powerful antipsychotic medicines in children earned at least $1.6 million in consulting fees from drug makers from 2000 to 2007 but for years did not report much of this income to university officials,

- In the last 25 years, drug and device makers have displaced the federal government as the primary source of research financing
- "The price we pay for these kinds of revelations is credibility, and we just can't afford to lose any more of that in this field," said Dr. E. Fuller Torrey, executive director of the Stanley Medical Research Institute, which finances psychiatric studies. "

Symbiotic relationship between pharma and medical profession has a long history.

He was a perfect practicing physician.
These causes being known for what they were,
He gave the man his medicines then and there.
All the apothecaries in a tribe
Were ready with the drug he would prescribe
And each made money from the other's guile;
They had been friendly for a goodish while.

Geoffrey Chaucer c. 1390

from The General Prologue to The Canterbury Tales

Conclusions

1. **Pharmaco's bottom line appears to be prime dynamic and drives search for as wide as possible indications including subsyndromal and soft syndromes.**
   - In the case of Zyprexa the expiration of the Prozac patent fuelled this move beyond previous antipsychotic salesplan.
2. **Drive for wider indications and defence against adverse publicity re ADEs appears to set research agenda.**

Conclusions

3. **CME in its broadest sense (advertising, sales reps, key opinion leaders/thought leaders, meetings, conferences, journals) is approached with sophisticated marketing strategies.**

Conclusions

4. **Academic psychiatrists with interests that are "confluent" with pharmacos are sought out and feted with grants, consultancy fees etc.**
   - Does this skew the weight of research/teaching in an overly biomedical direction and away from the biopsychosocial model?
5. **ADE's are approached defensively.**
   - Unclear how much group think/institutional pressure effect rather than overtly conscious/deliberate.
     - Analogy with "one eyed" football fans?

Conclusions

7. **Evidence (from Seroquel documents) that some unfavourable in-house studies are "buried".**
8. **"Competitive reviews" of other pharmacos' research and claims appear hypercritical** but
   - at least show competition can help balance selective information from competitor pharmacos.
   - suggests pharmacos know or assume each other's methodology to be biased/flawed.

Postscript re Atypical Antipsychotics

- All $multi-billion earners for pharmacos. Yet:
- Tyrer P & Kendall T. The spurious advance of antipsychotic drug therapy. *Lancet* Jan 4, 2009.
  - **"The spurious invention of the atypicals can now be regarded as invention only, cleverly manipulated by the drug industry for marketing purposes and only now being exposed. But how is it that for nearly two decades we have, as some have put it,[9] "been beguiled" into thinking they were superior?"**

- They answer their own question with similar conclusions to those we have come to from reading the above internal pharmaco documents.

American Journal of Psychiatry

March 2009 Editorial board commentary (26 signatories)


Commentary

Conflict of Interest—
An Issue for Every Psychiatrist

- "There is no clearer example of conflict of interest than the participation of prominent psychiatrists in pharmaceutical company speakers bureaus, which supply academic opinion leaders to deliver company-approved presentations that market their drugs to their clinical colleagues in the guise of medical education."

American Journal of Psychiatry

March 2009

Editorial board commentary:

Conflict of Interest—An Issue for Every Psychiatrist

- "The interacting system of industry-supported clinical trials, advisory boards, and speakers bureaus not always, but nonetheless too often, has resulted in conflicts of interest that have demeaned both psychiatry and the pharmaceutical industry."

"Each of us must acknowledge...our own responsibility to limit conflicts of interest in order to preserve the integrity of the field that is so important to us all."

The Profession and Industry

(DeAngelis CD & Fontanarosa PB, JAMA 2008; 299:1833-1835)

- Some proposals
  - Prospective registration of all clinical trials with principal investigator(s) listed
  - Primary data should be analyzed by investigators and not company
  - Honest authorship and financial disclosure
  - Independent statistical analysis by journal
  - Meaningful punishment for errant
    - Authors
    - Peer reviewers
    - Journal editors
  - Professional organizations to prohibit industry input into educational activities

Slide courtesy Prof Felix Bochner, pharmacology, Adelaide University

Institute of Medicine
of The National Academies (USA) April 2009

- Because of "risk of bias…loss of trust…risk to public's health":
  - Public disclosure all finance between industry & physicians, researchers etc (all "keyplayers" in Zyp docs parlance)
  - "Prohibit…gifts…industry controlled presentations…ghost written papers…"
  - "Restrict…contact with sales reps, drug samples…"
  - CME to be "free of industry influence", needs "alternative sources of funding"
  - Clinical practice guidelines committees to have no members with conflicts of interest, and to be free of industry sponsorship

APA severely restricts future industry sponsorship of CME

- From 2010 (2011 at latest) no industry sponsored symposia at APA.
    - i.e. Similar to original plan for RANZCP Congress 2009
    - + at Adelaide plan to not accept naming rights

www.the-scientist.com/blog/print/55679/

Elsevier published 6 fake journals

sponsored by Merck and un-named pharmacos

- Australasian Journal of Bone & Joint Medicine
- Australasian Journal of General Practice
- Australasian Journal of Cardiology
- Australasian Journal of Clinical Pharmacy
- Australasian Journal of Cardiology
- Australasian Journal of Cardiovascular Medicine

- Fortunately we already have ***Australasian Psychiatry*** !

THE AUSTRALIAN

April 1, 2009

Vioxx maker Merck and Co drew up doctor hit list

Staff at US company Merck &Co emailed each other about the list of doctors - mainly researchers and academics - who had been negative about the drug Vioxx or Merck and a recommended course of action.

The email, which came out in the Federal Court in Melbourne yesterday as part of a class action against the drug company, included the words "neutralise", "neutralised" or "discredit" against some of the doctors' names.

It is also alleged the company used intimidation tactics against critical researchers, including dropping hints it would stop funding to institutions and claims it interfered with academic appointments.

"We may need to seek them out and destroy them where they live," a Merck employee wrote, according to an email excerpt read to the court by Julian Burnside QC, acting for the plaintiff.

- **However no similar emails seen in the Zyprexa, Seroquel or J&J-MGH documents.**