

The background of the slide features a series of parallel diagonal stripes. The stripes alternate between a light gray color and a white color, creating a strong visual rhythm. The stripes are oriented from the top-left towards the bottom-right.

Strategic Intent:

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

1997

Straight Talk - What's at Stake

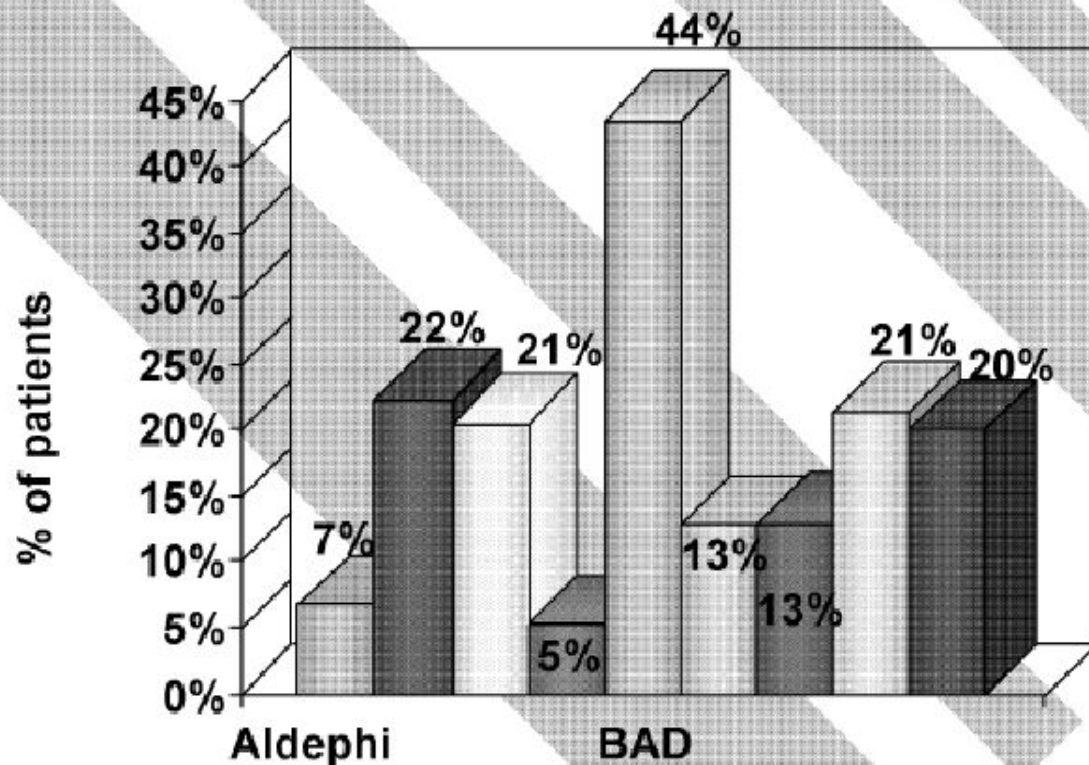
The company is betting the farm on Zyprexa ... the ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve world class commercialization of Zyprexa

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

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.

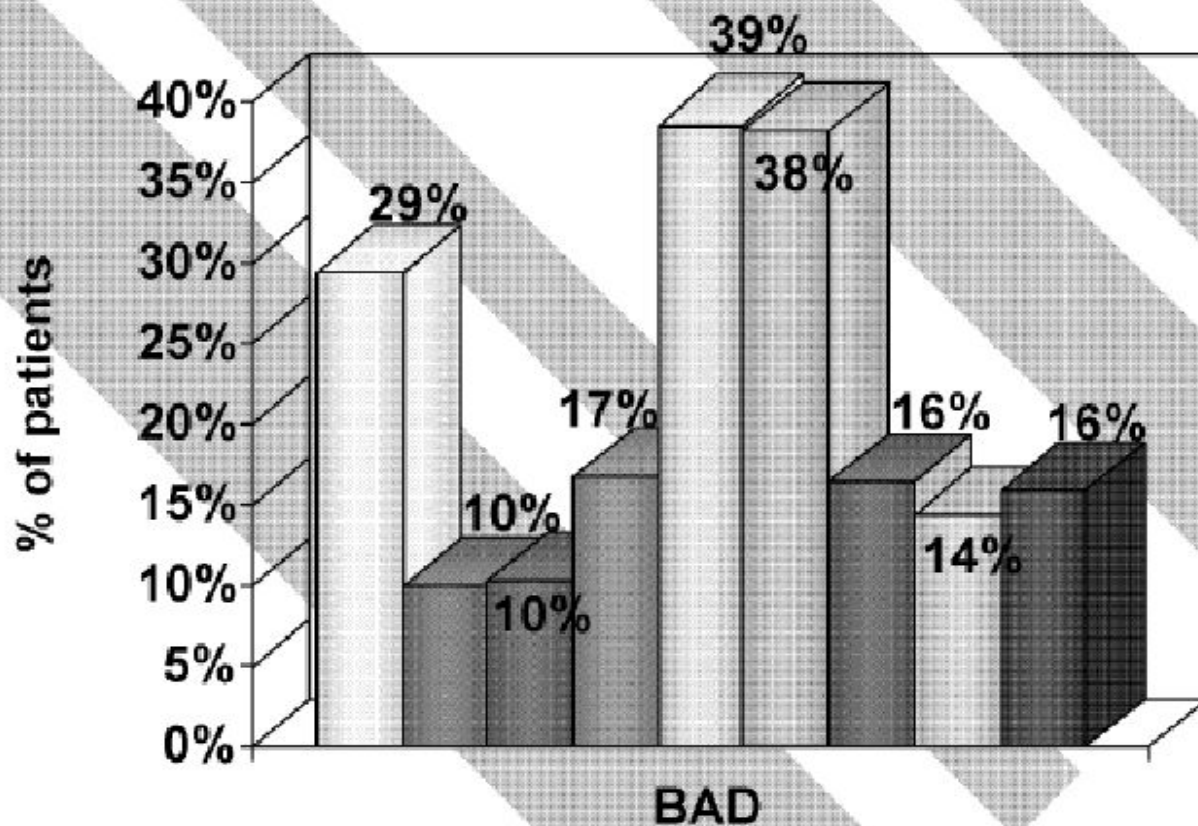
Drugs prescribed for BPD in the Major Markets



THIORIDAZINE	HALOPERIDOL	RISPERIDONE
OLANZAPINE	LITHIUM	Antidepressants
SSRI	SODIUM VALPROATE	Benzodiazepines

- Lithium, a 28 year old product remains the leader

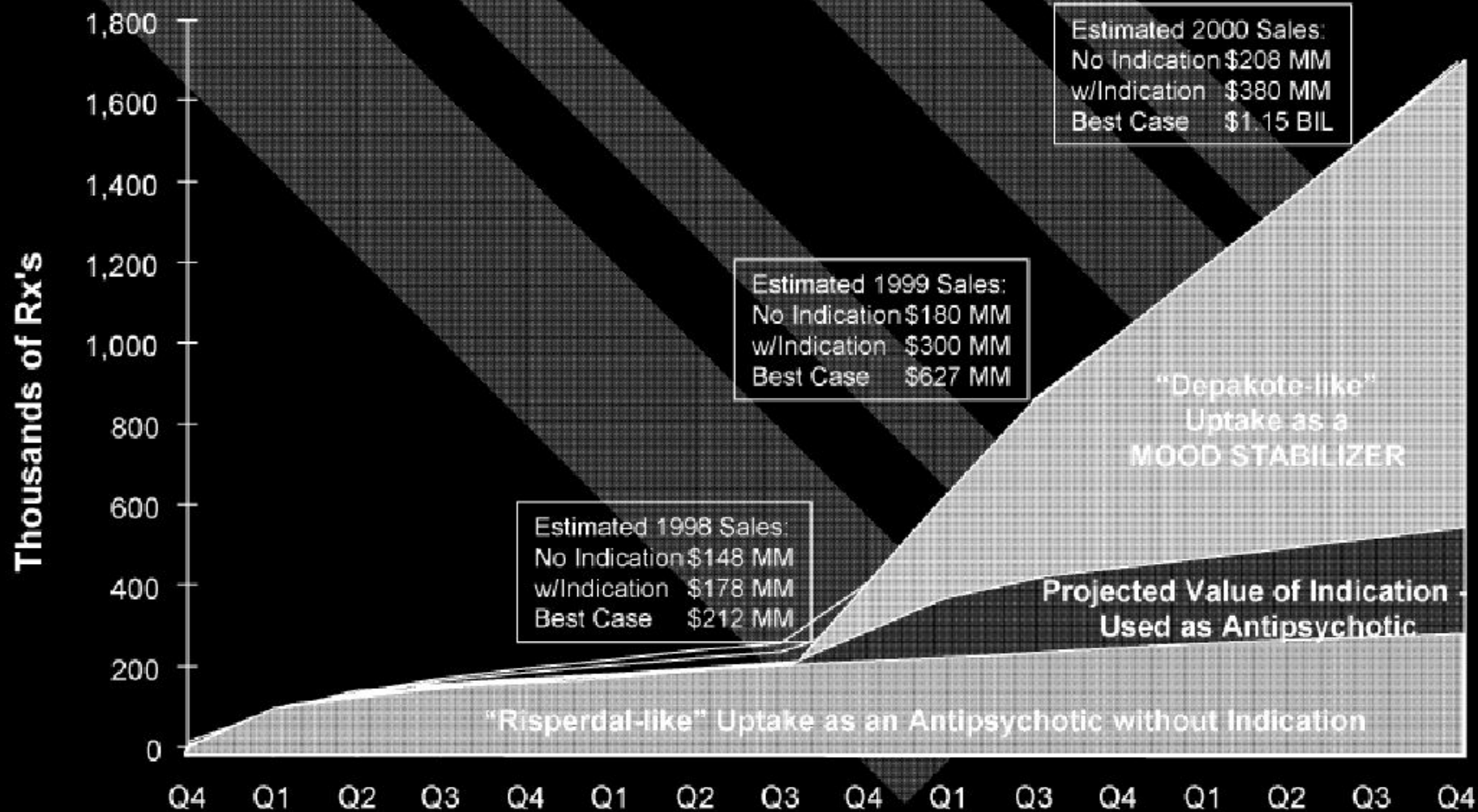
Drugs Prescribed in the U.S. for Bipolar



☐ Risperidone
☒ Fentazin
☐ Sodium Valproate
☒ SSRI
☒ Benzodiazepines

☒ Olanzapine
☐ Haloperidol
☐ Lithium
☐ Antidepressant

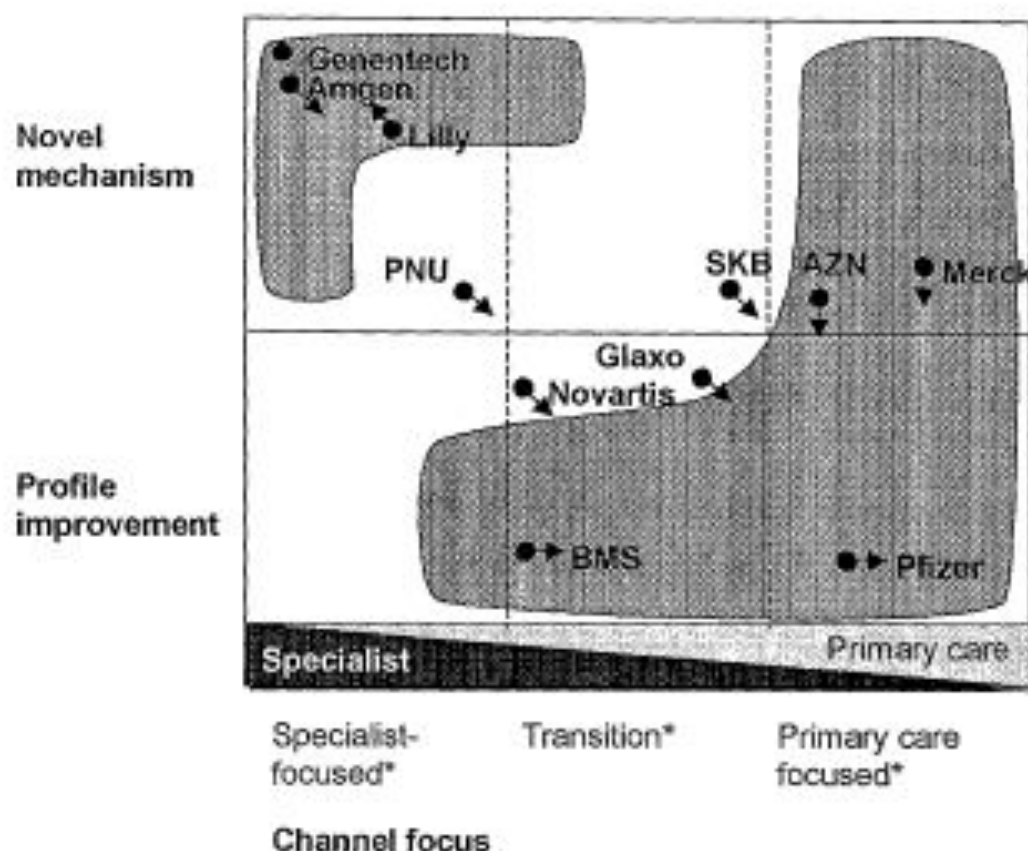
Global Zyprexa Bipolar Forecast



LARGER COMPETITORS ARE MIGRATING TOWARD THE PRIMARY CARE CHANNEL WITH DRUGS DRIVEN BY PROFILE IMPROVEMENTS

- Profit pool
- Current portfolio focus
- Pipeline focus

DIRECTIONAL



Strategic intent:

Offer Zyprexa as a solution to unmet medical need in the office-based primary care environment

Key themes:

- ◆ Symptoms / Behaviors
- ◆ Peer-to-peer emphasis
- ◆ Improve functioning (Thought / Mood / Behavior)
- ◆ Preserve independence, enhance QOL

The following is speculation about patient types, Zyprexa benefits and prescriber perceptions. It is not intended advocate promotion of Zyprexa for non-approved indications, but rather, to illustrate potential symptom and behavior profiles for which Zyprexa may represent a much-needed solution. This is confidential, and not to be reproduced or distributed outside of Eli Lilly and Company.

From a marketing standpoint, there are clearly parallels with the nursing home patient profile. We should reference Zyprexa's effect on hostility, suspiciousness, cognition, confusion, depressive signs and symptoms, etc. We need to be very clear about safety, tolerability and ease of use. A photo of this patient would convey via facial expression the following: uncertainty, aware of illness but lacking total insight, neither physically vigorous nor overly frail.

Mild psychosis

This patient, in his 30s or 40s, is a real pain to treat. He's unpleasant to staff members, high maintenance, and not the kind of patient you want in your waiting room because he's unsettling to other patients. Problem is, he won't accept a psych referral. He doesn't trust "shrinks," which may stem from paranoia and mild delusions of conspiracy. He's in average to below average physical health, generally antisocial, not the best hygiene. He doesn't trust the government or the police, but over time, has come to trust his doctor.

If he has immediate family, their concern is that he's not improving, in fact, may be getting a little worse. His temper is worse, he rambles, his conspiracy theories are getting more grandiose. He's not decompensated to the point of needing hospitalization, but he may "disappear" from time to time.

From a marketing standpoint, there are parallels to the "Jeanine" profile we share with private practice psychiatrists. We should tout Zyprexa's label change to "psychotropic" to address patient stigma associated with antipsychotics. We should highlight the components of efficacy captured in specific BPRS and PANSS measures, describing Zyprexa's broad spectrum of efficacy. Absence of EPS, elevated prolactin and excessive sedation are plusses. Cost will be less of an issue, especially given the doctor's motivation to see this patient less frequently.

Mood swings

Zyprexa is not indicated for bipolar II. Psychiatrists have shared that they have had success utilizing Zyprexa's efficacy in various mood symptoms to improve patients with this somatic complaint. This patient may vary in age, but tends to be employed and relatively highly functioning, but susceptible to mood swings which lead her into bouts of depression, low self-esteem and pessimism about the future, then rebounding with bursts of high energy and social engagement.

The patient's husband is frustrated. He doesn't really care what the causes are (Raging hormones? Stress? PMS?), he just wants relief from the rollercoaster. It's putting a strain on their marriage, and she feels guilty about that. Previous treatment has been aimed at symptoms: antidepressants, anxiolytics, possibly a mood stabilizer.

Primary care physicians may be equipped to treat this patient, but have a poor track record in accurately diagnosis bipolar disorder. The doctor was trained on lithium, but doesn't want to deal with the baggage. Depakote seems like overkill, and there's a lot to manage (incl. Blood monitoring). He's heard of Neurontin, but isn't ready to experiment with it.

4) Anyone in the practice who is currently taking Mellaril

Based on the recent addition of a black box re: Mellaril's questionable cardiac safety profile, we should move quickly to recommend adding on Zyprexa as a first step in titrating the Mellaril to zero.

This is by no means a comprehensive list, nor a validated one. We may find new profiles emerge, or make profound changes to the ones suggested above. The common denominator, though, is the recognition of unmet medical need and the potential value of Zyprexa as a solution for a number of clinical challenges faced by the primary care physician.

Zyprexa's attributes cut across multiple domains of thought disorders, mood disorders and behavior disorders. This can be a source of comfort to a physician who is unsure of a specific diagnosis but needs to recommend therapy, and seeks an option that is safe, well tolerated and offers some hope of efficacy. In many ways, Zyprexa is an ideal primary care agent. Safe. No titration. Well tolerated. Does a lot of different things really well. Millions of patient exposures.

Position: Zyprexa: The safe, proven solution in mood, thought and behavior disorders
We will emphasize safety to address barriers to adoption, and merchandise the brand's "Four years – Four million patients" base of experience. The word "solution" speaks to unmet medical need, and enables the PCP to take control of clinical situations that previously had led to referrals and/or poor outcomes. "Mental disorders" is intentionally broad and vague, providing latitude to frame the discussion around symptoms and behaviors rather than specific indications. We will position Zyprexa as the incremental next step in the PCP's expanding clinical orbit: e.g., SSRIs => 2nd generation antidepressants => safe, gentle psychotropics.

August 2000

Zyprexa PCP Vision

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

The Bipolar Disorder Problem

National Depressive and Manic-Depressive Association (NDMDA) 2000 Survey

- 7 in 10 people with bipolar disorder initially misdiagnosed (30%)
- Most common misdiagnosis is unipolar depression
- On average, 3.5 misdiagnoses and 4 consultations before receiving an accurate diagnosis
- More than 1/3 sought help for more than 10 years before being accurately diagnosed

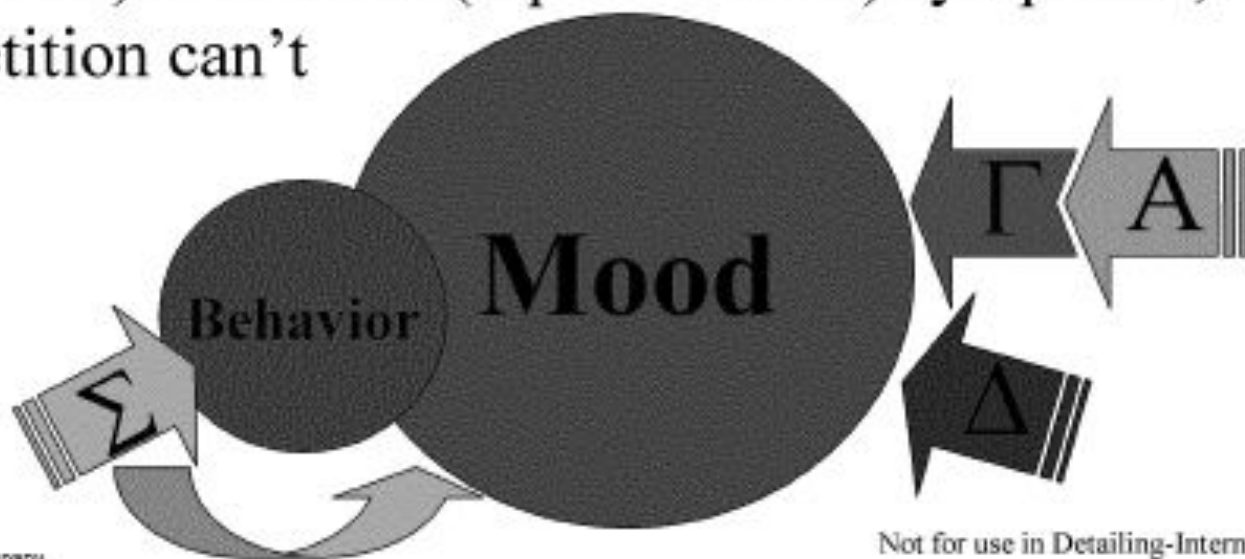
Our challenge

- 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

Our Opportunity/Approach

1. We are filling an unmet medical need
2. We've only scratched the surface of a market with tremendous upside Redacted
3. Zyprexa is a psychotropic – it can treat both behavior (psychosis) and mood (bipolar mania) symptoms; the competition can't



We are the market leaders

- We are creating a market much like Redacted did by highlighting unmet medical need (1/5 pts misdiagnosed)
- The opportunity is huge Redacted
- The competition is close behind and will attempt to draft our profile
 - risperidone launch in Q4 '02
 - aripiprazole launch in Q1 '03
- We can revolutionize the way PCPs view and treat bipolar
- Most importantly, we can help those patients who have been suffering needlessly

Current Managed Care Perceptions of Antipsychotics and Mood Stabilizers

1. Antipsychotics are not on commercial managed care plans' radar screens due to the complicated nature of disease and because patients with schizophrenia are treated by psychiatrists
2. Mood stabilizers are not visible to plans because there are low-cost, generic products available

ZYPREXA Primary Care Unmet Medical Need

ZYPREXA
Olanzapine

Clinical choices in primary care
for mood, thought and behavioral disturbances:

1950's - 1980s	Outdated agents with limited effectiveness, poor safety profile (e.g., Haldol, Lithium, Valium)
Early 1990's	Incremental improvement (e.g., Risperdal, Depakote, Aricept)
October 2000	Paradigm shift - Zyprexa used as a safe, versatile psychotropic

ZYPREXA was originally launched to the primary care audience by the Sigma sales force in November 2000. It has gained over 12 share points since that time. As the current market leader in primary care, ZYPREXA will continue to revolutionize the way complicated mood disorders are treated by primary care physicians. Just as Prozac revolutionized the treatment of depression in the late 80s and throughout the 90s, so too will ZYPREXA forever change the way primary care physicians view and treat bipolar disorder.

The Primary Care sales force will be a major part of helping to improve these statistics, and behind every statistic is a patient and their family struggling with mental illness. Years from now, as Lilly is launching new revolutions in neuroscience, you can look back and say that ZYPREXA changed the way bipolar disorder was viewed, diagnosed, and treated by primary care physicians.

XXX,000 patients say, "Thank You"



Viva
ZYPREXA

Lilly

Answers That Matter.

“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.



Viva
Zyprexa

Whole new purpose gonna set my soul
Set my soul on fire
Got a brand named Zyprexa with a whole new chance
To get those stakes up higher
Thousands of patients waitin' out there
The way they're livin' just ain't fair
But now you bet they can get
Some help from Primary Care
Viva Zyprexa! Viva Zyprexa!

How I wish that there were more
Than twenty-four hours in the day
Cause even if there were forty more
I wouldn't waste a minute away
So much to do, doctors to see
Patients everywhere are depending on me
To be the best that I can be
And talk about Zyprexa faithfully
Viva Zyprexa! Viva Zyprexa!

Yeah we're helping patients
Viva Zyprexa!
Many wonderful indications
Viva Zyprexa!
Turning night into day
All the hope can remain
You'll never be the same again

Can't rest now I've got to run
I'm gonna tell everyone
Might tell a doctor fifty times
Remember it's about the patients' lives
I'm gonna give it everything I've got
No matter what it takes, I'll never stop
Give a perfect message on every shot
Keep Zyprexa at the top
Viva Zyprexa! Viva Zyprexa!

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ZY 7300 576

Zyprexa Primary Care Overall Strategy



Vision

Expand Zyprexa's market by redefining how primary care physicians treat mood, thought, and behavioral disturbances

Strategy

Establish position of "safe, proven solution for mood, thought, and behavioral disturbances"

- * Strong emphasis on direct to physician marketing; establish Zyprexa as the next incremental step in PCP's treatment and Rx orbit
- * Broad targeting among office based PCPs
- * Message based on patients' symptoms and behaviors (rather than diagnoses)

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.

Zyprexa Primary Care

ZYPREXA
Olanzapine

Why ~~David~~ is the future of Primary Care

Market research on the potential of "David" vs
Martha/Christine

\$ potential, channeling into psychiatry

*How will you
quantify*

David: TRD, Bipolar, Depression with Psychosis

Market research data of the potential of TRD.....

You'll see an old friend (Martha) and meet two new ones: Michael and Kelly. Michael exhibits clear signs and symptoms of bipolar disorder, without appearing to be as threatening as his predecessor (David). Kelly struggles with mild to moderate psychosis, with visible elements of a mood component. Again, the intent was to make Kelly more "treatable" by a PCP (versus the defiant Christine).

You'll see more head-to-head data in the new sales aid, including the results from a recent trial of ZYPREXA versus Depakote. From listening to customers, it's clear that ZYPREXA doesn't get enough recognition as a mood stabilizer. The fact is, ZYPREXA is indicated for the treatment of acute bipolar mania, in the same league as lithium and Depakote but with big advantages. In addition to the data, you'll see more references in the script comparing ZYPREXA favorably with lithium and Depakote.

Michael Spread

This is Michael. Michael is a professional in his mid 30s. He's highly functional, but his wife says that he's always been prone to mood swings, and lately, things have gotten worse.

You rule out substance abuse and possible organic causes, and you're left with a complicated mood disturbance. The last time you saw Michael, he seemed down, unmotivated, detached. You prescribed an antidepressant. Now, 2 months later, he appears "wired," irritable, and anxious, and he hasn't been sleeping much.

His wife is very concerned, not only about Michael's health, but also his recent spending habits and erratic behavior.

Michael says he won't "see a psychiatrist." In fact, he denies that there's anything wrong with him. Simply switching antidepressants may not alleviate his symptoms. Your goals of therapy for Michael may include stabilizing his mood while reducing his agitation.

ZYPREXA, unlike mood stabilizers such as Depakote or lithium, does not carry any black-box or bolded warnings in its package insert. There is no routine blood monitoring required with ZYPREXA, and its cardiovascular safety is proven. ZYPREXA enables you to prescribe with confidence and without hassles. The most common side effect is somnolence, which is dose-dependent, and for a patient like Michael, a calming effect may be desirable.

Doctor, ZYPREXA works. In this head-to-head study versus Depakote, the most widely used mood stabilizer, ZYPREXA was **equivalent or superior in all symptoms** of bipolar disorder. Even if you don't use Depakote, notice how effective ZYPREXA was in treating elevated mood and irritability, and in improving sleep. Would you agree Michael could benefit from a trial of ZYPREXA? Dosing for a patient

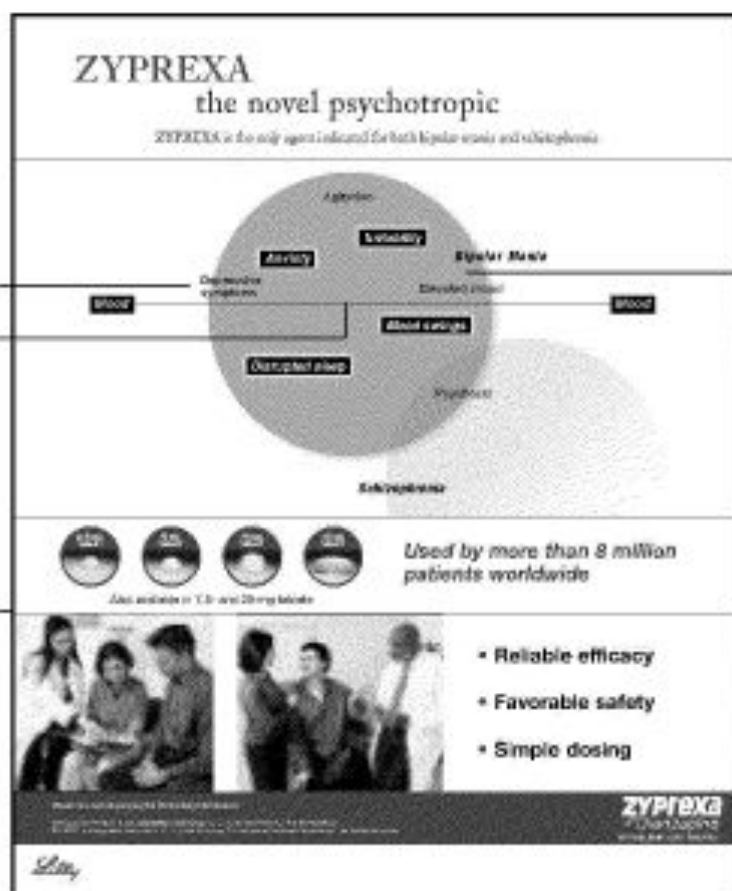
Back Cover

Market Research Key Learning

Many physicians believe that bipolar disorder is more closely related to schizophrenia than depression. The Mood Spectrum is a great tool to communicate the fact that some manic patients may experience psychosis, but these patients constitute a small minority. The facts: up to 30% of patients with a diagnosis of depression or anxiety may actually have bipolar disorder. It is important to note that primary care physicians do not think that these patients are psychotic.

Understanding Needs

- 1 When you look at a spectrum of mood symptoms, you might see a range from unipolar depression, which you treat with antidepressants...
- 2 To pure bipolar mania, where a mood stabilizer may be used. You also have patients exhibiting agitation or poor sleep, for whom anxiolytics may be an option. The closer a patient exists to the edge of the circle, the more clear-cut their diagnoses and treatment options may be.
- 3 But what about patients you treat who exhibit anxiety, irritability, sleep disturbances, and mood swings? Typically, these patients may wind up on multiple meds, or you may be continually switching them from drug to drug or even class to class.



Understanding Needs

- 1 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.

Focused, Open-Ended Question

- ▶ Tell me about the symptoms of a patient like Donna in your practice. How did these behaviors affect her family or personal life?

Follow-Up Questions*

- ▶ What has she been prescribed in the past?
- ▶ What symptoms were still prevalent with medications she had been prescribed?

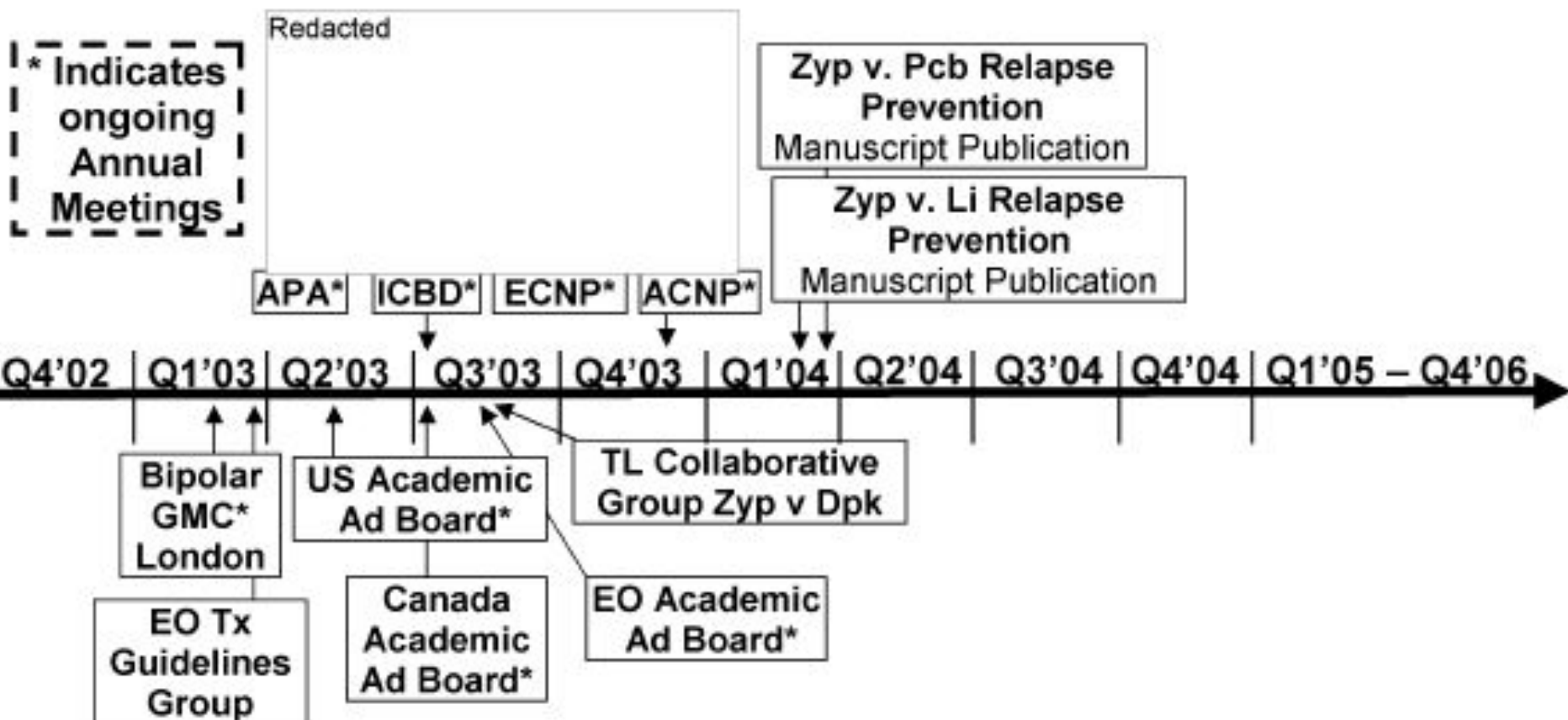
Satisfying Needs

Feature-Benefit-Benefit

- 2 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.

SDDs/Customer Relations Priorities – '03-'06

- TL Collaborative Publications/Alignment Projects
- US Communication Partnership (SDD/PR/IR)
- Bipolar Global Medical Conference, London
- HGGY Primary Manuscripts
- HGHT Primary Manuscripts
- HGHL Primary Manuscripts



Data to Support Message Evolution – '03-'06

Today – BP Mania indication

- Zyprexa treats mania without inducing depression (EH/GW/HQ)
- Zyprexa quickly improves depressive symptoms in mania (EH/GW/HQ)
- Zyprexa reduces the severity of symptoms in both mania and depression (EH/GW/HQ/FU/GY)

New data w/ Maintenance Indication (Q1 2004)

- Better than Lithium for Relapse Prevention (HT) Indication
- Zyprexa prevents bipolar relapse to either mania or depression (HL) Indication
- Zyprexa cuts relapse by 50% when used as a foundation treatment with appropriate combinations (lithium/valproate) (FU) Indication

New data – BP depression (Available today)

- Zyprexa reduces severity of bipolar depression without inducing mania (GY)
- redacted

Level the symptoms of acute mania
associated with bipolar disorder...

with an effective tool for
MOOD STABILIZATION.



In acute mania trials, the most common treatment-emergent adverse event associated with ZYPREXA was somnolence. Other common events were dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension.

Recommended starting dose is 15 or 10 mg/day. For patients requiring special consideration, a lower starting dose may be recommended. Daily dosage may be adjusted within the range of 5-20 mg/day, based on individual clinical status. Available in 10-, 7.5-, 5-, and 2.5-mg tablets.

Please see accompanying Brief Summary of prescribing information.

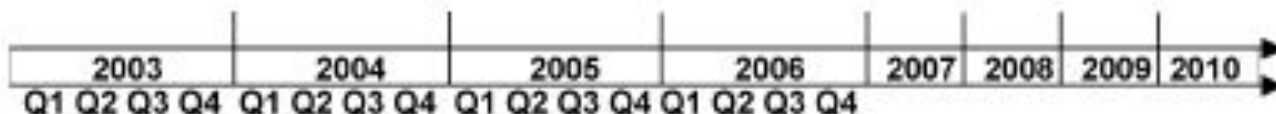
www.ZYPREXA.com

ZYPREXA[®]
Olanzapine 

Bringing life back in balance

Mood Disorders- Zyprexa Lifecycle Map

Areas of Interest



Indications

Redacted

**Mania Combination
Bipolar Maintenance**

redacted

HGFU Complete
US LAUNCH – Q4/03
HGHT & HGHL Complete
US/EU LAUNCH – Q1/04

HDAO
US/ICR LAUNCH – Q1/06

Adolescent – Mania

US LAUNCH Q3/07

Redacted

**Bipolar II (Zyprexa & redacted)
Bipolar depot**

HG??/Other?
US/EU LAUNCH – Q?/0?
HG??/Other?
US/EU LAUNCH – Q?/0?

Competitive

**Lamictal for Bipolar
Maintenance/Relapse**
Lamictal for Bipolar Depression
Lamictal for Unipolar Depression

US/EU LAUNCH – Q2/03

US/EU LAUNCH – Q?/0?

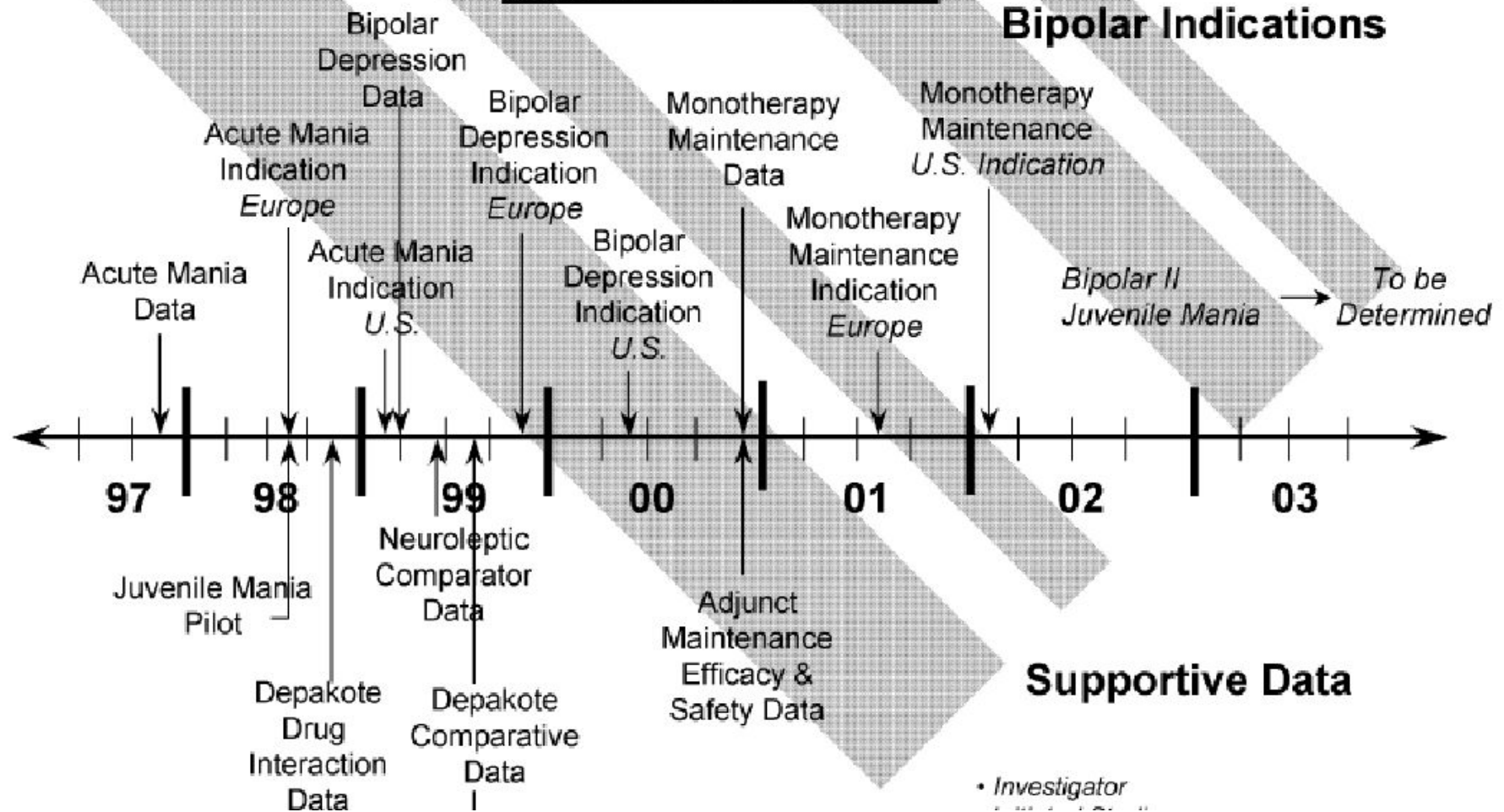
US/EU LAUNCH – Q?/0?

Funded Trial Code ◆————▶
With Start and End Date
Proposed Trial ◆-----▶
Include LAUNCH, if appropriate

Affective Product Program

- Generate the Bipolar Data Needed

Bipolar Data Timeline

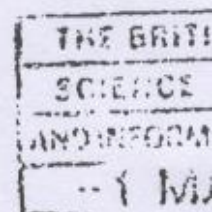


Attention-Deficit Hyperactivity Disorder and Juvenile Mania: An Overlooked Comorbidity?

JOSEPH BIEDERMAN, M.D., STEPHEN FARAONE, Ph.D., ERIC MICK, B.A., JANET WOZNIAK, M.D.,
LISA CHEN, B.A., CHERYL OUELLETTE, B.A., ABBE MARRS, B.A., PHOEBE MOORE, B.A.,
JENNIFER GARCIA, B.A., DOUGLAS MENNIN, B.A., AND ELISE LELON, M.Ed.

ABSTRACT

Objective: To evaluate the psychiatric, cognitive, and functional correlates of attention-deficit hyperactivity disorder (ADHD) children with and without comorbid bipolar disorder (BPD). **Method:** *DSM-III-R* structured diagnostic interviews and blind raters were used to examine psychiatric diagnoses at baseline and 4-year follow-up in ADHD and control children. In addition, subjects were evaluated for cognitive, academic, social, school, and family functioning. **Results:** BPD was diagnosed in 11% of ADHD children at baseline and in an additional 12% at 4-year follow-up. These rates were significantly higher than those of controls at each assessment. ADHD children with comorbid BPD at either baseline or follow-up assessment had significantly higher rates of additional psychopathology, psychiatric hospitalization, and severely impaired psychosocial functioning than other ADHD children. The clinical picture of bipolarity was mostly irritable and mixed. ADHD children with comorbid BPD also had a very severe symptomatic picture of ADHD as well as prototypical correlates of the disorder. Comorbidity between ADHD and BPD was not due to symptom overlap. ADHD children who developed BPD at the 4-year follow-up had higher initial rates of comorbidity, more symptoms of ADHD, worse scores on the CBCL, and a greater family history of mood disorder compared with non-BPD, ADHD children. **Conclusions:** The results extend previous results documenting that children with ADHD are at increased risk of developing BPD with its associated severe morbidity, dysfunction, and incapacitation. *J. Am. Acad. Child Adolesc. Psychiatry*, 1996, 35(8):997–1008. **Key Words:** bipolar disorder, attention-deficit hyperactivity disorder, comorbidity.



JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 8, Number 2, 1998
Mary Ann Liebert, Inc.
Pp. 107-113

Open-Label Olanzapine Treatment in Five Preadolescent Children

JAYANTHI KRISHNAMOORTHY, M.D., and BRYAN H. KING, M.D.

Volume XXXVII
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Newspaper of the
American
Psychiatric
Association

PSYCHIATRIC NEWS

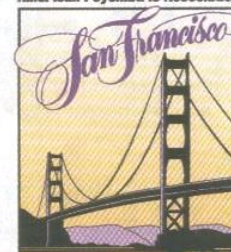
APA's 156th Annual Meeting *in*

May 17-22, 2003

San Francisco

The Promise of Science, The Power of Healing

American Psychiatric Association



The Promise of Science
The Power of Healing

156th Annual Meeting • May 17-22, 2003



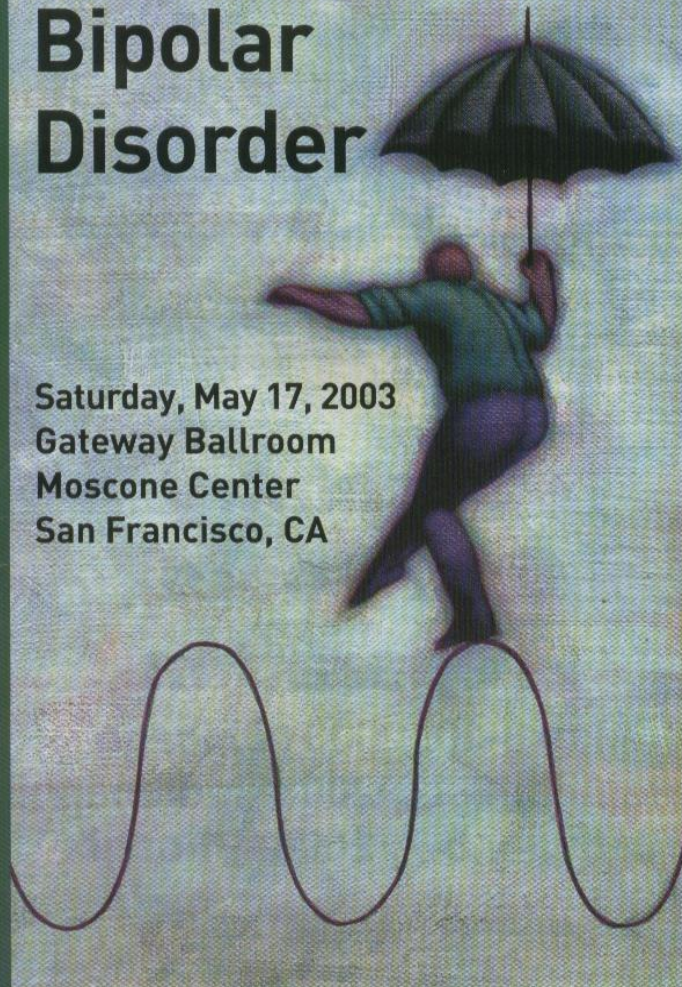
"It's an odd thing, but anyone
who disappears is said to be seen
in San Francisco."

—Oscar Wilde

A symposium to be held during
the APA 2003 Annual Meeting

New Strategies for Managing Bipolar Disorder

Saturday, May 17, 2003
Gateway Ballroom
Moscone Center
San Francisco, CA



Agenda

5:30 – 6:00 PM

Dinner

6:00 – 6:10 PM

Welcome and Introduction

S. Nassir Ghaemi, MD (Chair)
Cambridge Hospital

6:10 – 6:40 PM

Clinical Management of Bipolar Patients: A Difficult Task

Dwight L. Evans, MD
University of Pennsylvania

6:40 – 7:10 PM

Rational Polypharmacy in the Treatment of Patients With Bipolar Disorder

S. Nassir Ghaemi, MD

7:10 – 7:40 PM

Emerging Treatments for Bipolar Disorder: A New Role for Atypical Antipsychotics

Lakshmi N. Yatham, MB, FRCPC
University of British Columbia

7:40 – 8:10 PM

Complexities in the Treatment of Juvenile Bipolar Disorder

Robert L. Findling, MD
University Hospitals of Cleveland

8:10 – 9:00 PM

Questions and Answers

At the conclusion of this
symposium, the participant
should be able to:

- Implement new strategies for the management of acutely ill bipolar patients
- Implement new strategies for the maintenance treatment of bipolar patients
- Understand challenges in diagnosis and describe current research data and treatment options in juvenile bipolar disorder

Juvenile Bipolar Disorder: Contemporary Issues in Research

Presented at the APA 156th Annual Meeting



Wednesday, May 21, 2003

7:00 PM – 10:00 PM

Moscone Center (Hall E, Exhibit Level)
San Francisco, California

Faculty and Agenda

Reception and Dinner: 6:30 PM – 7:00 PM
Symposium: 7:00 PM – 10:00 PM

- 7:00 PM Welcome and Introduction**
Timothy E. Wilens, MD, Boston, Massachusetts
- 7:15 PM Pediatric Mania: A Developmental Subtype of Bipolar Disorder?**
Joseph Biederman, MD, Boston, Massachusetts
- 7:40 PM Diagnostic and Treatment Implications of Psychiatric Comorbidity in Juvenile Bipolar Disorder**
Timothy E. Wilens, MD, Boston, Massachusetts
- 8:05 PM Treatment of Pediatric Bipolar Disorder with Anticonvulsant Mood Stabilizers**
Joseph M. Gonzalez-Heydrich, MD, Boston, Massachusetts
- 8:30 PM The Therapeutic Role of Atypical Antipsychotic Medications in Pediatric-onset Bipolar Disorder**
Janet Wozniak, MD, Boston, Massachusetts
- 8:55 PM Genetics of Early-onset Bipolar Disorder**
Stephen Faraone, PhD, Boston, Massachusetts
- 9:15 PM Question-and-Answer Session**



Sponsored by the American Psychiatric Association

 **NOVARTIS** Supported by an unrestricted educational grant from Novartis.

Overview

Despite the increasing recognition of bipolar disorder (BPD) in youth, controversy and clinical confusion exist as to its clinical presentation, comorbidity, biological underpinnings, and treatment. In this symposium, recent information on the similarities and differences of BPD in youth and adults will be evaluated. The neurobiology and familial evidence of BPD and subtypes of BPD will be explored. The literature suggests very high levels of psychiatric comorbidity with BPD in youth. The overlap of specific comorbidities with BPD will be presented, with an emphasis on the clinical presentation and treatment implications. Treatment of youths with BPD continues to be a complex issue. A review and recent work on the use of lithium and anticonvulsants—alone and in combination—in children and adolescents with BPD will be presented. Contemporary findings on the use of atypical antipsychotics in youth with BPD will also be reported, as well as data on efficacy and adverse effects of the various medications used in this group and on the treatment of special cases (eg, preschoolers, comorbidity).

Target Audience

This continuing education activity is designed for psychiatrists and other clinicians who diagnose and treat juvenile BPD.

Learning Objectives

Upon completion of this symposium, the participant should be able to understand the:

- Clinical presentation of juvenile BPD and how it relates to the adult form of the disorder
- Major comorbid conditions with BPD in youth and treatment strategies
- Treatment issues in managing mania, depression, and comorbidity in youth with BPD

Accreditation

The American Psychiatric Association (APA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The APA designates this educational activity for a maximum of 3 category 1 credits towards the AMA Physician's Recognition Award and for the CME requirements of the APA. Each physician should claim only those credits that he/she actually spent in the educational activity.

Registration Policy

Attendees must be registered for the APA Annual Meeting to attend this symposium. Seating is limited and will be on a first-come, first-served basis. For more information about the meeting, please visit the APA Web site at www.psych.org or contact the APA toll-free at (888) 357-7924 (within the US or Canada) or (703) 907-7300.

P51

Open trial of atypical antipsychotics in preschoolers with bipolar disorder

E. Mick, J. Biederman, M. Aleardi, M. Dougherty

Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston, MA, USA

Objective: To evaluate the short-term safety and efficacy of atypical neuroleptics in a single-site, prospective, open-label, eight-week study of risperidone and olanzapine monotherapy in preschoolers with bipolar disorder (BPD).

Methods: Risperidone was initiated at an open-label dose of 0.25 mg/day to be increased weekly according to response and

Poster session

tolerability to a maximum dose of 2.0 mg/day. Olanzapine was initiated at 1.25 mg/day and increased to no more than 10 mg/day.

Results: Twelve children with a mean age of 4.5 ± 0.8 years were treated with olanzapine ($n = 4$) or risperidone ($n = 8$). By week 8, the mean YMRS score was reduced from 31.1 ± 5.6 to 17.6 ± 8.1 . We failed to detect a statistically significant effect of type of atypical neuroleptic ($t = -0.3$, $P = 0.7$). According to the CGI, there was no difference in overall rate of improvement ('Much' or 'Very Much' improved) in the risperidone (63%) and olanzapine (75%) groups of children. The most frequently reported adverse were headache (33%), insomnia (25%), and stomach ache (25%).

Conclusion: Atypical neuroleptics were effective in treating symptoms of bipolar disorder in very young children with mild, infrequent adverse events. This study suggests that treatment promising treatments for child and adolescent onset cases of BPD may be equally effective and safe in preschool children.

SPEAKERS & CHAIRS - 1

1. Michael Allan	1. Joseph Goldberg	1. Robert Perlis
2. Lori Altschule	2. Joseph Gonzalez-Heydrick	2. Robert Post
3. Claude Baldassano	3. Eric Hollander	3. Mark Pollack
4. Ross Baldessarini	4. Douglas Jacobs	4. Nathalie Rasgon
5. John Beyer	5. Kay Jamison	5. Michael Ryan
6. Joseph Biederman	6. Paul Keck	6. Gary Sachs
7. Pierre Blier	7. Terrence Kettler	7. Kirti Saxena
8. Charles Bowden	8. Hussaini K Manji	8. Hans Steiner
9. Joseph Calabrese	9. Susan McElroy	9. Trisha Suppes
0. James Chou	10. Shishkula Malhotra	10. Allan Swann
1. Lee Cohen	11. Herb Meltzer	11. Carol Taminga
2. Melissa DelBello	12. Hugh Meyrick	12. Rajiv Tandon
3. Dwight Evans	13. David Miklowitz	13. Adele Viguera
4. Stephen Faraone	14. Martha Morrell	14. Janet Wazniak
5. Jan Fawcett	15. Henry Nasrallah	15. Peter Weiden
6. Robert Findling	16. Charles Nemeroff	16. Timothy Wilens
7. Ellen Frank	17. Ruta Nonacs	17. John Zajecka
8. Mark Frye	18. Maria Oquendo	18. Carlos Zarata
9. Nassir Ghaemi	19. Diana Perkins	
0. Fred Goodwin		

Depression and Bipolar Support Alliance Consensus Statement on the Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents

JOSEPH T. COYLE, M.D., DANIEL S. PINE, M.D., DENNIS S. CHARNEY, M.D., LYDIA LEWIS, CHARLES B. NEMEROFF, M.D., GABRIELLE A. CARLSON, M.D., PARAMJIT TOOR JOSHI, M.D., DAVID REISS, M.D., RICHARD D. TODD, M.D., Ph.D., MARTHA HELLANDER, J.D., AND THE DEPRESSION AND BIPOLAR SUPPORT ALLIANCE CONSENSUS DEVELOPMENT PANEL

J American Academy of Child & Adolescent Psychiatry
42, 1494-1503

THE SKINNY ON THE
ANTI-FAT HORMONE

TIME

Inside the Volatile
World of the
**YOUNG
AND
BIPOLAR**

Why are so many kids
being diagnosed with the
disorder once known as
MANIC DEPRESSION?

Ian Palmer, 9, is
being treated for
bipolar disorder







**Rebecca Riley
Boston
February 2007**

Phased Approach for Growth in Bipolar

Brand Equity Dependent	PHASE I: Introduction	PHASE II: Accelerate Conversion	PHASE III: Foundation Differentiation
PATIENT TYPE	Acute manic patient + Rapid cycling (Stabilize, Hope)	Expand: + Acutely symptomatic bipolar patient with frequent relapses (Stabilize, Hope, Motivate)	Expand: + Symptomatic bipolar patients with a need for long-term control and mood stabilization (Stabilize, Hope, Motivate)
WHERE BUSINESS COMES FROM	Conversion Displace current market leaders in bipolar mania	Deeper Conversion First line mania and maintenance for many customers	Market Leadership + Aggressive Grow the Market Establish as foundational therapy for mood stabilization for most customers

Comparative efficacy of atypical antipsychotics for paediatric bipolar disorder

E. Mick, J. Biederman, M. Dougherty, M. Aleardi

Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston, MA, USA

Objective: The objective of this study was to assess the relative impact of atypical antipsychotics in paediatric bipolar disorder.

Methods: This was an randomized, open-label, eight-week study of monotherapy with an atypical neuroleptic (olanzapine ($n = 19$), quetiapine ($n = 19$), risperidone ($n = 42$) and ziprasidone ($n = 21$)) in the treatment of youth with mania.

Results: One-hundred one subjects were enrolled in the study. They were 10.2 ± 2.7 years of age and predominantly male (67%). 71% of subjects completed the study with no differences in rate of drop-out between the medication arms ($P = 0.7$). There were significant reductions in symptoms for each treatment arm that were not statistically significantly different [$F(3,96) = 2.2$, $P = 0.09$]. However, clinical ratings on the CGI indicate that the effect was strongest for risperidone (75% much or very much improved) followed by ziprasidone (57%), quetiapine (56%) and olanzapine (50%). Olanzapine was associated with marked increase in weight (4.9 ± 2.1 kg increased) that was statistically significantly greater than the weight gain for risperidone (2.2 ± 2.1 kg), quetiapine (1.4 ± 1.6 kg), and ziprasidone (0.6 ± 2.1 kg).

Conclusions: This study suggests that atypical antipsychotics reduce manic symptomatology in children and adolescents with bipolar disorder and that this effect may strongest for risperidone. Future placebo-controlled, double blind studies of these compounds are warranted in this population.

Phased Approach for Growth in Bipolar

	PHASE I: Introduction	PHASE II: Accelerate Conversion	PHASE III: Foundation Differentiation
MARKET CONDITIONING (DTP) One step ahead of the field	<ul style="list-style-type: none">• Share data on maintenance and expanded patient types• Share combination data• Clear competitive differentiation from other AP	<ul style="list-style-type: none">• Share data on bipolar depression and expanded patient types• Establish spectrum of bipolar efficacy• Clear competitive differentiation from other traditional mood stabilizers	<ul style="list-style-type: none">• Significant expansion of bipolar spectrum of efficacy and patient types

Zyprexa Primary Care Site Selection Criteria

High antidepressant writer

good relations with sales rep.

Low Zyprexa uptake

Key Takeaways

- **Bipolar opportunity is tremendous**, and the market dynamics are shifting
- Customer Target: **Patient (symptoms) + Brand promise**
- **Phased approach is critical** to achieve goals, with established triggers and metrics for moving on to next phase
- **Significant data is available**, with exciting new indication for maintenance expected early 2004
- We have an opportunity to **establish and differentiate** before new competition enters the market (Lamictal, Seroquel BP, Risperdal BP)

Disease State Summary – Insights and Implications for ZYPREXA

- Lifelong therapy is required for Schizophrenia and Bipolar Disorder.
- There are significant unmet needs in these populations and there are significant opportunities for therapies that go beyond symptom control (e.g. improved attention).
- Bipolar Disorder represents a huge market potential and it is currently in the early stages of development. Treatment for Bipolar Disorder will grow dramatically if a solution to under- and misdiagnosis is created.
- There is a high degree of symptomatology overlap in Schizophrenia, Bipolar Disorder and other related disorders. This overlap provides ZYPREXA with access to a wider market beyond these two indications.
- Schizophrenia and Bipolar Disorder are associated with stigma – it is important for ZYPREXA to support efforts to reduce this stigma.
- With suicide so prevalent among patients suffering from schizophrenia and bipolar disorder, it is critical to: 1) ensure patients stay on their medications to help prevent suicide and 2) provide data showing ZYPREXA's role in suicide prevention.
- The economic impact of Schizophrenia, Bipolar Disorder and Dementia is profound. With access and pricing pressures escalating, health outcomes data showing the value of ZYPREXA will become increasingly important.

Capabilities

Strengths

- Core message development
- Branding
- Publications Strategy
- Presentations
- Long term product strategy

Opportunities to further upgrade

- Competitive analysis
- Market research
- Customer relations
- Communications
- HE / DSM
- Line Extensions

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

APA 2003: Key Learnings

This year's APA was marked by a significant emphasis on (1) bipolar disorder, (2) weight gain and diabetes, (3) attempts to commoditize efficacy, and (4) overall limited media coverage for the event.

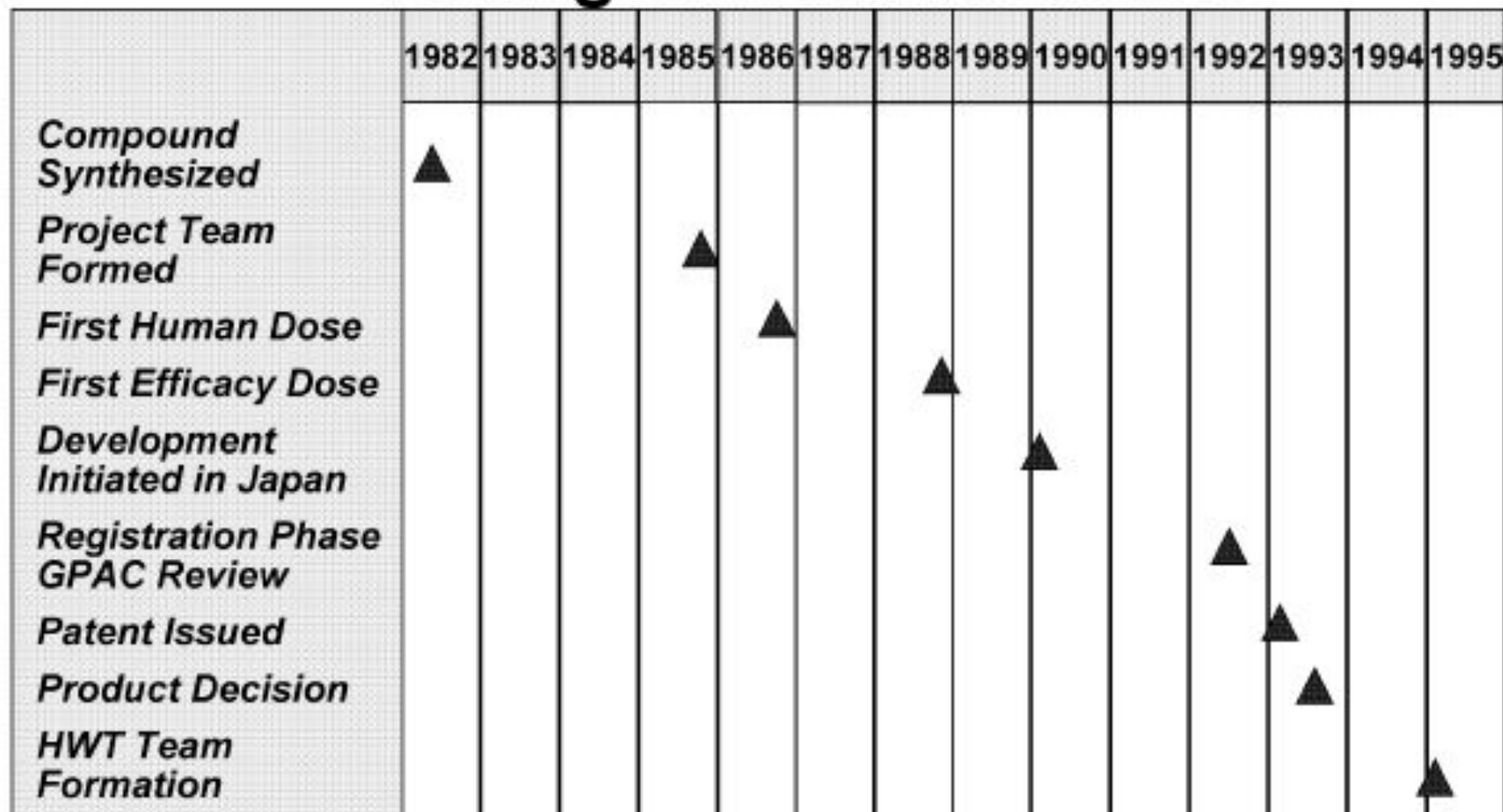
The Lilly-sponsored symposium on bipolar disorder was acclaimed by attendees to be outstanding in terms of quality and breadth of data. With expected 2003 launches of new indications in bipolar mania, Astra Zeneca (Seroquel) and Janssen (Risperdal) seemed to have a strategy of providing much less significant data of their own and use Zyprexa data to establish a "me-too" carry-over of equity.

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Background Milestones



FDA Approves Zyprexa(R) for Maintenance of Bipolar Disorder

First Atypical Antipsychotic Approved for Treatment of Bipolar Mania Is First Mania Treatment in 30 Years to Receive Additional Approval for Bipolar Maintenance

INDIANAPOLIS, Jan. 14

The U.S. Food and Drug Administration (FDA) has approved Zyprexa(R) (olanzapine) for maintenance in the treatment of bipolar disorder, Eli Lilly and Company announced today. This FDA approval recognizes that Zyprexa is an effective treatment to delay relapse into either mania or depression in patients with bipolar disorder. Zyprexa is the first treatment in nearly 30 years to be recognized by the FDA as a treatment for both acute mania and maintenance treatment in bipolar disorder.

"Bipolar disorder is a serious condition that can be difficult to treat. For those who achieve stability on existing medications, relapse of symptoms is all too common," said Frederick K. Goodwin, MD, Director, Center on Neuroscience, Medical Progress and Society, at the George Washington University Medical Center, Washington, D.C. "It is good news that the FDA has now approved Zyprexa as a new tool for physicians to use to delay relapse and prolong periods of stability and wellness."

Zyprexa was approved by the FDA in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder and is the first medication approved to both treat acute mania and delay relapse of symptoms associated with bipolar disorder since lithium received approval from the FDA in 1974.

FDA Approves Zyprexa(R) for Maintenance of Bipolar Disorder

About Bipolar Disorder

Bipolar disorder, also known as manic-depressive illness, is a complex mental illness characterized by debilitating swings in mood. These swings range from manic episodes, marked by abnormal euphoria, elation and irritability, to episodes of deep depression, marked by extreme sadness and difficulty functioning. These periods of illness are interspersed with periods of normal mood. Although a lifelong illness, bipolar disorder typically emerges in adolescence or young adulthood, and episodes continue intermittently throughout life. More than 2.5 million Americans live with a diagnosis of bipolar disorder but recent research indicates the real number may be as high as 10 million. The results of untreated bipolar disorder can be catastrophic. According to the National Institute of Mental Health, nearly one in every five people with the illness ends their life by suicide. The World Health Organization estimates that bipolar disorder is the sixth leading cause of disability in the world.

CSF 5: Fuel the Future/Build the Business

Grow the Zyprexa franchise in schizophrenia and bipolar and realize two significant new opportunities for brand expansion.

Marketing Objective #5: Develop the brand map for new opportunities (Q3 2002) and commercialize two opportunities by 2004.

Metric: Evolve and implement the product life cycle plan to achieve linear growth through '06.

Areas of Focus

- High Dose
- Borderline
- Bipolar Depression
- Child and adolescent

Zyprexa Product Team 4 Column Summary

Gary D. Tollefson, M.D., Ph.D.

**Vice President,
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana**

Comparative efficacy of atypical antipsychotics for paediatric bipolar disorder

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Methods: This was an randomized, open-label, eight-week study of monotherapy with an atypical neuroleptic (olanzapine ($n = 19$), quetiapine ($n = 19$), risperidone ($n = 42$) and ziprasidone ($n = 21$)) in the treatment of youth with mania.

Results: One-hundred one subjects were enrolled in the study. They were 10.2 ± 2.7 years of age and predominantly male (67%). 71% of subjects completed the study with no differences in rate of drop-out between the medication arms ($P = 0.7$). There were significant reductions in symptoms for each treatment arm that were not statistically significantly different [$F(3,96) = 2.2$, $P = 0.09$]. However, clinical ratings on the CGI indicate that the effect was strongest for risperidone (75% much or very much improved) followed by ziprasidone (57%), quetiapine (56%) and olanzapine (50%). Olanzapine was associated with marked increase in weight (4.9 ± 2.1 kg increased) that was statistically significantly greater than the weight gain for risperidone (2.2 ± 2.1 kg), quetiapine (1.4 ± 1.6 kg), and ziprasidone (0.6 ± 2.1 kg).

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Conclusion: Atypical neuroleptics were effective in treating symptoms of bipolar disorder in very young children with mild, infrequent adverse events. This study suggests that treatment promising treatments for child and adolescent onset cases of BPD may be equally effective and safe in preschool children.

were maintained for 28 days on a lithium diet or control diet. Half of the lithium treated animals were switched to control diet from day 25 of the treatment period. *In vivo* microdialysis was used to measure basal DA levels and the increase in DA release in response to a 20 min potassium induced depolarization. *In situ* hybridization histochemistry using a 35S labelled cDNA probe was used to quantify the abundance of rat tyrosine hydroxylase (TH) mRNA in the ventral tegmental area (VTA). Basal DA levels did not differ between any of the treatment groups. During the 20 min potassium perfusion, whilst DA levels in control animals increased to 804% of basal values, those in lithium treated and lithium withdrawn animals increased to only 420% and 313% respectively. One-way ANOVA revealed a main effect of group ($F_{2,19} = 5.47$ $P < 0.05$). There was no difference in the abundance of TH mRNA in the VTA in any of the groups. These studies suggest that there is impaired DA release in rats during chronic lithium treatment and this impairment persists after lithium withdrawal. However, it is unlikely that such changes are the result of a difference in the production of the DA synthetic enzyme tyrosine hydroxylase.

P50

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P51

Open trial of atypical antipsychotics in preschoolers with bipolar disorder

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Methods: Risperidone was initiated at an open-label dose of 0.25 mg/day to be increased weekly according to response and

tolerability to a maximum dose of 2.0 mg/day. Olanzapine was initiated at 1.25 mg/day and increased to no more than 10 mg/day.

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P52

Valproic acid inhibits the enzyme prolyl oligopeptidase-a new drug target?

A. W. Mudge*, L. Cheng*, M. Lumb*, L. Polgar†, J. Thomas*

*University College London, MRC Laboratory for Molecular Cell Biology, London, UK, †Institute of Enzymology, Hungarian Academy of Sciences, Budapest, Hungary

We showed that the three mood stabilizers used to treat bipolar disorder-lithium, valproic acid (VPA) and carbamazepine (CBZ) – all share a common mechanism of action: Each drug depletes inositol in cultured neurons (*Nature* 2002;417:292–295). We therefore proposed that the phosphoinositide (PI)s signalling pathway is likely to underlie the therapeutic action of the mood stabilizers and that defects in the regulation of PI)s signalling in mood-related circuits may contribute to bipolar disorder. We also reported that small-molecule inhibitors of prolyl oligopeptidase (PO) acted in the same fashion as inositol and reversed the action of all three mood-stabilizers. PO is a cytoplasmic enzyme and PO inhibitors increase intracellular levels of the second messenger inositol-1, 4, 5-trisphosphate (InsP3) by an unknown mechanism. We now report that VPA directly inhibits recombinant PO with a K_i of approximately 1 mM, consistent with VPA's therapeutic blood level. This result was at first surprising because it is the opposite of the previously reported inositol-depleting action of VPA. Identification of this new molecular target of VPA suggests a mechanism for how VPA could act to stabilize both the manic and the depressive poles of bipolar disorder, however. We now propose that the action of VPA in depleting inositol levels may underlie the antimanic action of this drug, while the effect of VPA in increasing PI)s signalling by inhibiting PO may underlie VPA's ability to limit mood swings to depression. We also present evidence that the response to VPA varies with the ongoing activity in the neuron.

P53

Double-blind, placebo-controlled study of quetiapine in bipolar depression

J. R. Calabrese*, W. Macfadden†, R. McCoy†, M. Minkwitz†, E. Wilson†, J. Mullen†

*University Hospitals of Cleveland, Cleveland, OH, USA, †Astrazeneca, Wilmington, DE, USA

Learning objectives: At the conclusion of this session, the participant should be able to: (1) recognize that quetiapine is an effective and well tolerated treatment for bipolar depression and is not associated with treatment-emergent mania; and (2) understand that

Martha Spread

This is Martha. Martha is a widow who lives independently and has been your patient for some time. She is becoming more complicated to manage, and you note increasing agitation. Her sleep is disturbed; she dozes during the day and is up most of the night. Her family has shared their concerns with you, saying, “She thinks we’re trying to take advantage of her.”

Martha’s family doesn’t want to send her to a nursing home, but her agitation and confusion must be addressed. Your goals of treatment for Martha may include reducing her behavioral disturbances without impairing her cognitive functioning.

PROBE: Do you see patients like Martha? What medication(s) do you prescribe in treating her behavioral disturbances?

ZYPREXA is a safe choice for Martha. It has a low potential for drug interactions and anticholinergic side effects. Unlike drugs such as Haldol or Risperdal, ZYPREXA has an **EPS profile that is comparable to placebo** across the full dosing range.

As I said before, ZYPREXA is quite different from older antipsychotics, so you can be confident treating Martha with a low dose. The most common side effect is somnolence, which is dose-dependent, so a starting dose of 5 mg—or even 2.5 mg—at bedtime is appropriate. In fact, this could help Martha’s poor sleep.

Doctor, ZYPREXA works. It has proven effective in reducing hostility as early as the first week. Early improvement will give Martha—and her family—confidence in the treatment you’ve prescribed. And ZYPREXA won’t impair Martha’s cognition; in fact, it actually improved cognition in prelaunch trials. (If the physician asks, a medical letter on the use of ZYPREXA in older populations is available.) Would you agree that these are important benefits for this patient?

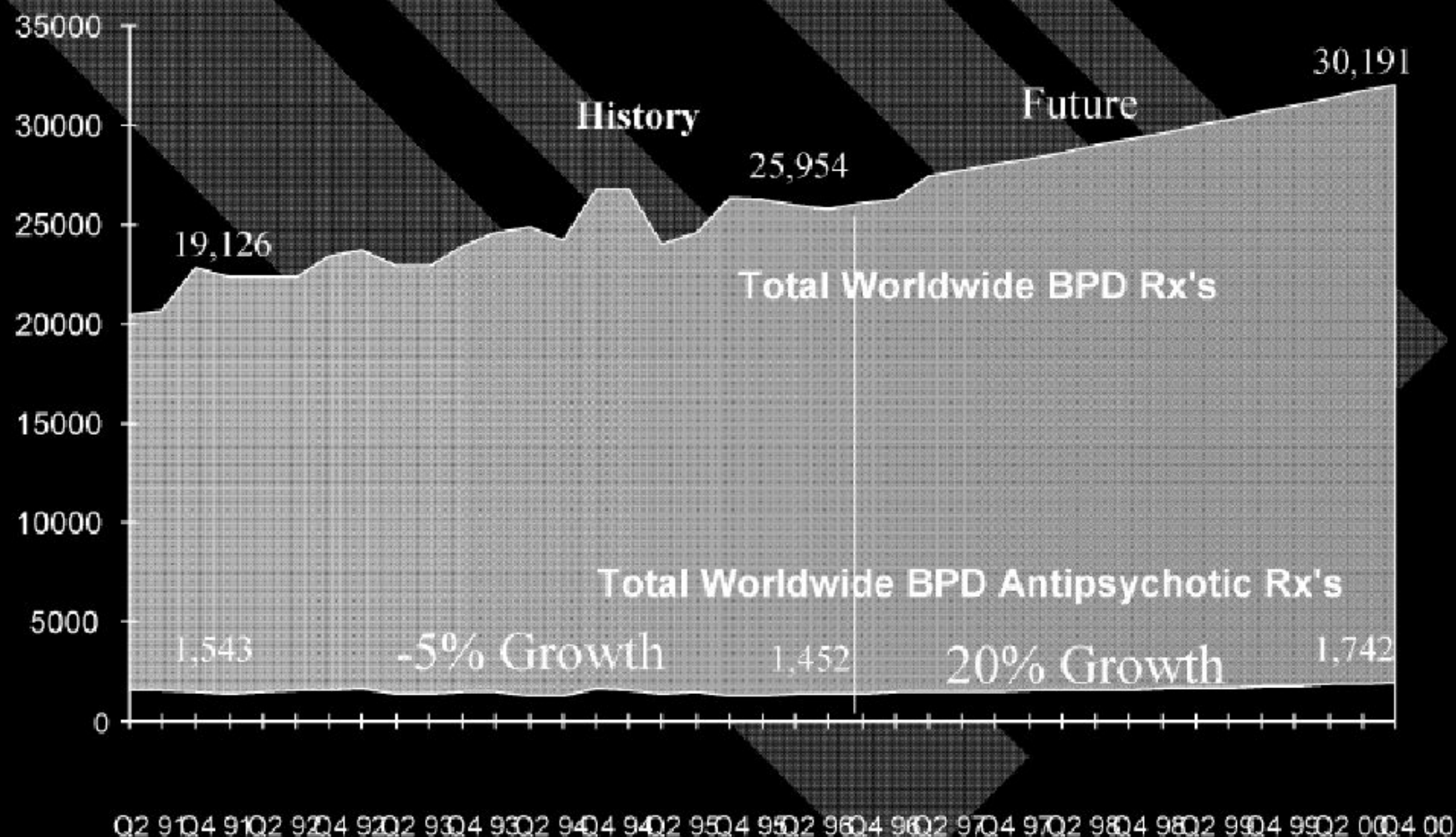
Clinical Studies Stages II and III



Examples - 1996 Plan

Objective	Locale	PI
• Emerging market registration	Hong Kong/China Mexico	Lieh-Mak
• New indication	global	many
– mania		
– psychosis in Alzheimer's	global	many
• Expand the package insert wording	U.S.	Lieberman, et al,
– relapse prevention	Neth	Kahn
– refractory	U.S.	Tamminga
• Commercialization -	multistate	many
• Local opinion leader involvement - templates	global	many

Global Market Trends in Bipolar Disorder



Michael Spread

This is Michael. Michael is a professional in his mid 30s. He's highly functional, but his wife says that he's always been prone to mood swings, and lately, things have gotten worse.

You rule out substance abuse and possible organic causes, and you're left with a complicated mood disturbance. The last time you saw Michael, he seemed down, unmotivated, detached. You prescribed an antidepressant. Now, 2 months later, he appears "wired," irritable, and anxious, and he hasn't been sleeping much.

His wife is very concerned, not only about Michael's health, but also his recent spending habits and erratic behavior.

Michael says he won't "see a psychiatrist." In fact, he denies that there's anything wrong with him. Simply switching antidepressants may not alleviate his symptoms. Your goals of therapy for Michael may include stabilizing his mood while reducing his agitation.

ZYPREXA, unlike mood stabilizers such as Depakote or lithium, does not carry any black-box or bolded warnings in its package insert. There is no routine blood monitoring required with ZYPREXA, and its cardiovascular safety is proven. ZYPREXA enables you to prescribe with confidence and without hassles. The most common side effect is somnolence, which is dose-dependent, and for a patient like Michael, a calming effect may be desirable.

Doctor, ZYPREXA works. In this head-to-head study versus Depakote, the most widely used mood stabilizer, ZYPREXA was **equivalent or superior in all symptoms** of bipolar disorder. Even if you don't use Depakote, notice how effective ZYPREXA was in treating elevated mood and irritability, and in improving sleep. Would you agree Michael could benefit from a trial of ZYPREXA? Dosing for a patient like Michael should be higher than in a patient like Martha; in fact, efficacy in bipolar mania was demonstrated at a dose range of 10 to 15 mg in clinical trials.

ZYPREXA has not been studied in bipolar depression, but it's worth noting that in bipolar mania trials, there was actually **improvement in depressive symptoms**. Does this give you enough information to try ZYPREXA in a patient like Michael?

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

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 paradigm

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)

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

A Potted (& Selected) History of LY170053

1982 -Project team formed in Erl Wood

1986 -IND submitted in U.S.

A staid schizophrenic named Struther
When told of the death of his brother,
Said: “Yes, I am sad.
It makes me feel bad,
But then, I still have each other.”

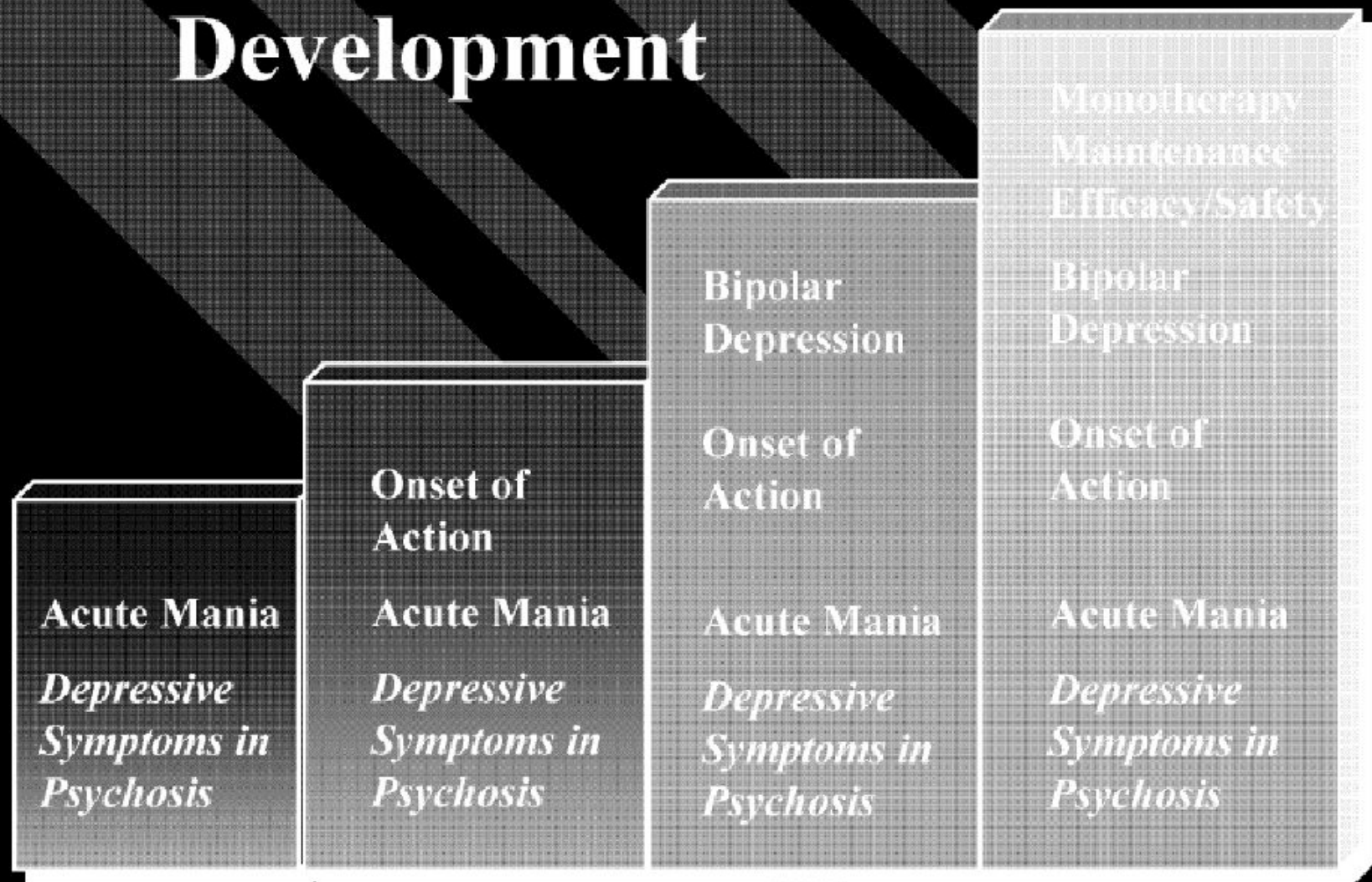
Competitive Message Analysis

Key Criteria	Zyprexa	Lithium	Depakote	Carbamazepine	Haldol	Risperidal	SSRIs
EFFICACY							
Acute Mania	+++	++	+++	++	++	+	-
Acute Depression	+	+	-	-	-	ND	++
Maintenance	ND	+	+	+	ND	ND	ND
Doesn't Induce Change of Polarity	++	++	++	++	--	+	--
SAFETY							
Blood Monitoring	+++	--	-	---	+++	+++	+++
Drug Interactions	+++	--	+	---	+	+	+
TD	+++	+++	+++	+++	---	-	+++
Toxicity	+++	---	-	-	++	+++	+++
PATIENT ACCEPTABILITY							
Tolerability	+++	-	++	--	-	++	+++
Convenience (dose/titration)	+++	-	-	-	-	-	++
Monotherapy Acute Mania	++	+	++	--	-	ND	---
Weight Gain	---	--	--	+++	+	-	+++
EPS	+++	++	+++	+++	---	-	+++
Cost	---	+++	-	+++	+++	---	--

+++ = definitive evidence/advantage

ND = No Data

Bipolar Message Development



Launch



PLC Management Priorities for Exploration

Funded

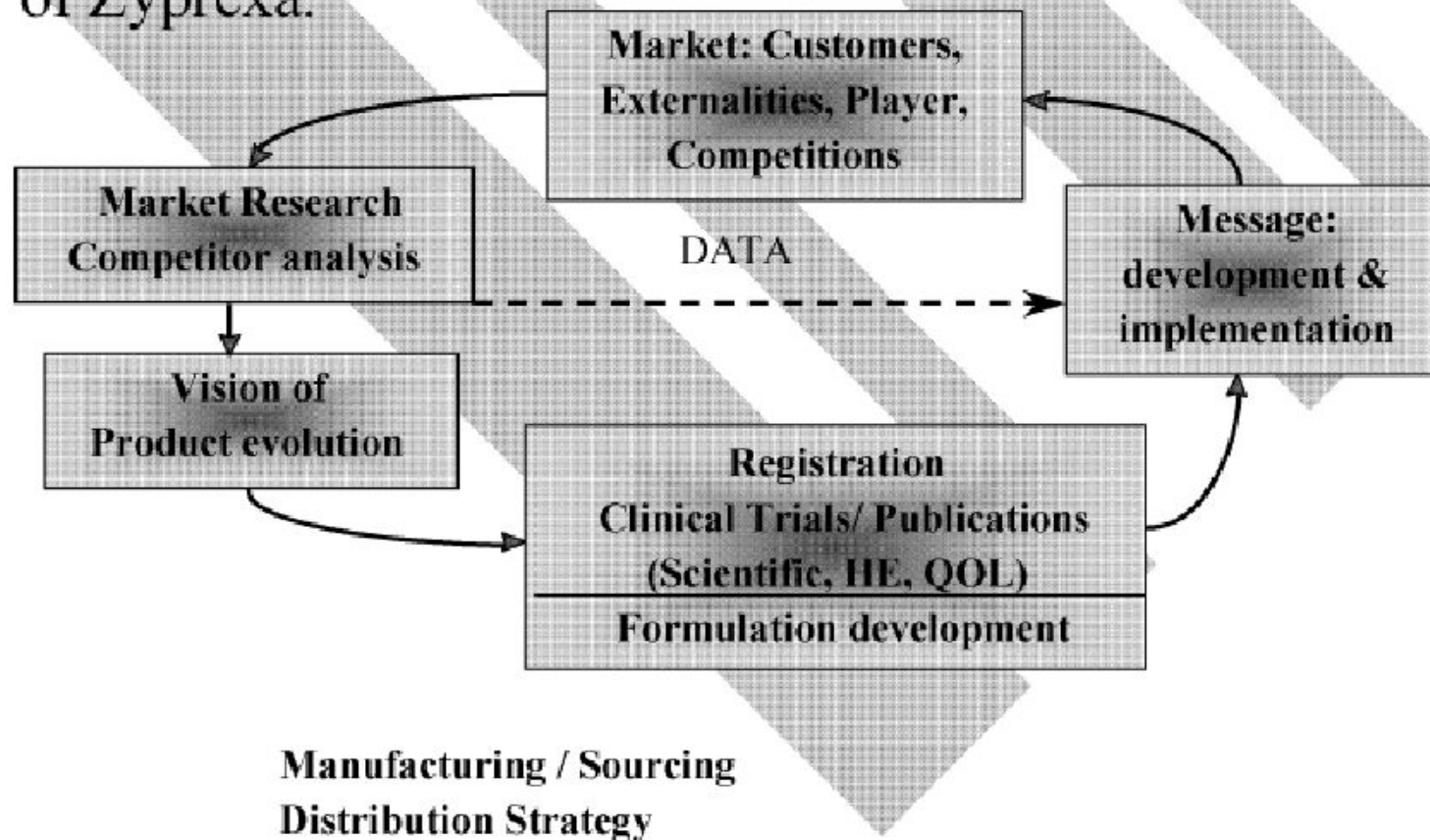
- HDAO Treatment-Resistant Depression (TRD)
- HGIU Child & Adolescent Bipolar I
- 8004 PET Study (FPV 4/03)

Unfunded

- *Bipolar Depression (EU)*
- *Bipolar II*
- *Schizoaffective*
- *Depot Bipolar*

I. Vision of the Value Cycle

- The Value cycle is defined as the list of all the activities that should be conducted in the areas of discovery, development, demand creation and sourcing in order to optimize the value of Zyprexa.



Better *Suzanne Clifford*
**Management
of Psychoses
in the Elderly**



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Delusions in Alzheimer's Disease

- 30-85% of patients have delusions
- Common beliefs/behaviors
 - Marital infidelity
 - Patients, staff are trying to hurt me
 - Staff, family members are impersonators
 - Personal harm
 - People stealing things
 - My house is not my home
 - Strangers living in my home
 - Misidentification of people
 - People on TV are real

Deutch LG, et al. Am J Psychiatry. 1991;148(3):1155-1163

Drevets WC, Rubin EH. Biol Psychiatry. 1999;25(1):38-48

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- **No medication is approved by the U.S. Food and Drug Administration for the treatment of behavioral disturbance in dementia**



JALeming@aol.com on 08/21/2001 09:05:31 PM

To: medwatch cc: taylor_anne_elizabeth

Dear Medwatch:

I was detailed today by an Eli Lilly Senior Sales Representative (ELIZABETH TAYLOR - taylor_anne_elizabeth@lilly.com) on the product Zyprexa. During the detail presentation she presented me with a promotional brochure (which she said had been reviewed and approved by the FDA for use detailing physicians).

This brochure presented an elderly female patient who was presented to her physician by her family complaining of insomnia, agitation, slight confusion and had no physical finding to explain her state. She then proceeded to tell me what other physicians might prescribe for her (i.e., Zyprexa) and she attempted to engage me in the conversation by asking what I might prescribe for the sample patient. I indicated that I would try to arrive at a working diagnosis after history, physical examination and appropriate diagnostic testing and then prescribe for that tentative/working diagnosis.

I inquired what Zyprexa was indicated for she then indicated that many physicians might prescribe an antipsychotic for this patient. I then asked for the package insert and read to her that her product was indicated for schizophrenia and bipolar mania -- neither of which the presented patient had been diagnosed with. She then indicated that some physicians might have prescribed the patient Haldol (by name) or Risperdal (also by name) or other antipsychotic drugs that have been on the US market longer (she referred to these as "older" antipsychotics) and all she really wanted to do was to get physicians to prescribe the safest product for their patients. I am not aware of any head-to-head double-blind controlled studies comparing the

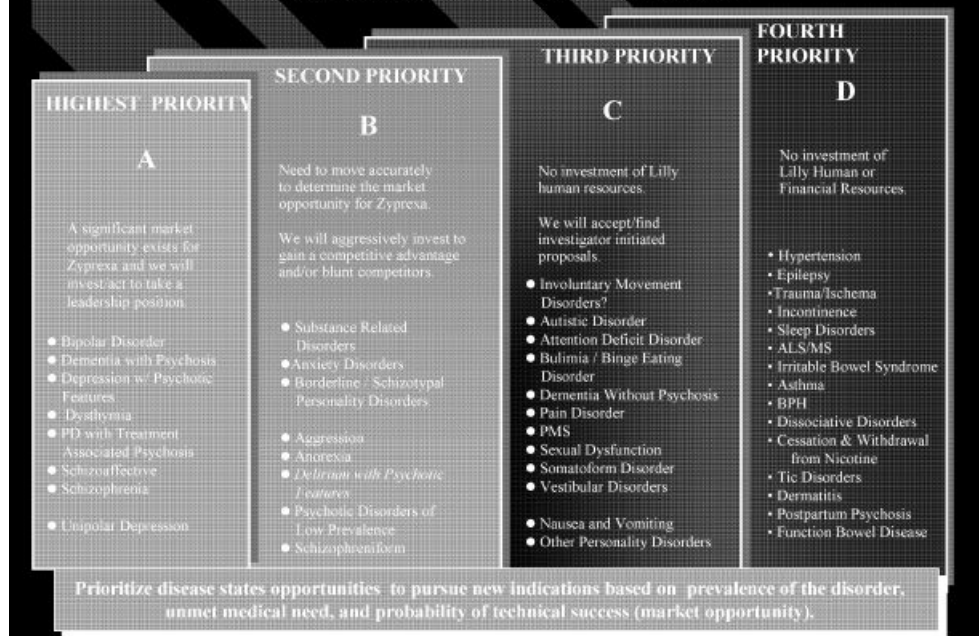
HIGHEST PRIORITY

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

Disease State Prioritization



Date: 10/02/2002 02:40:52 PM
From: CN=Anita L Johnson NONLILLY/OU=AM/O=LLY
Subject: Off-Label Strategy Workshop

Walter,

1. I do not like "off-label" term - "Elderly and new domains" maybe.
2. This is not a US priority but I would appreciate regular team updates to Rob Distefano.

Thanks,
Jill