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Eli Lilly: Developing Cymbalta

At 3:55 p.m. on a Thursday afternoon in April 2000, John Kaiser, marketing director at Eli Lilly and Company, spotted the clock in the lower right-hand corner of his computer screen and decided to make one last edit to the PowerPoint presentation he was to give at a 4 p.m. meeting. After editing and sending the slide deck to the color printer, Kaiser quickly reached for his cell phone. The meeting was scheduled to run for two hours, but given the topic—developing a successor to the now-legendary antidepressant Prozac—Kaiser wanted to call home and advise that he might be unavailable until 6:30 or 7:00 p.m. As a former global marketing director for Prozac, Kaiser knew firsthand of its success and that, though certainly possible, replacing it would not be easy. Following his call home, Kaiser quickly walked over to the color printer, picked up copies of the presentation which he had titled "No Pain, No Gain" and headed off to the meeting.

Prozac had only a few years left of patent protection before generic versions of the same molecule, fluoxetine, could be sold in the U.S. Historically, competition by generic manufacturers dramatically reduced the sales of the brand medication that they aimed to replace (Prozac, in this case). Though officially Prozac's patent would expire in December of 2003, no one could be sure exactly how much time Prozac had left. Although a ruling of a U.S. District Court judge in 1999 upheld the patent for Prozac, Barr Laboratories, a manufacturer of generic drugs that hoped to sell its own version of generic fluoxetine, had already filed an appeal with a federal court in Washington, D.C., and a ruling was expected as soon as the summer of 2000.

To management at Lilly, patent expirations were usually just part of the business of pharmaceuticals. However, Prozac was Lilly's flagship product and the market leader in the most popular class of medications used to treat depression—the selective serotonin reuptake inhibitors (SSRIs). Its annual sales of more than $2 billion would create an enormous revenue gap to fill. And although many at Lilly were actively engaged in planning for life after Prozac, pharmaceutical research and development was universally well-known for being an extremely long and risky process. According to one source, experimental drugs took an average of 12 years to travel from the lab to one's medicine cabinet. On average, only one in 1,000 compounds to enter preclinical testing made it to human testing, and only one in five of those tested in humans was ultimately approved by the Food and Drug Administration (FDA) for use in the U.S.[1]

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[1] D. Wierenga and C. R. Eaton, "Phases of Product Development," *Alliance Pharmaceutical Corp*, http://www.allp.com/drug_dev.htm, accessed December 3, 2005.

Professor Elie Ofek and Dr. Ron Laufer prepared this case. HBS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management.

All of this weighed heavily on Kaiser as he walked out of his office toward the conference room for the upcoming meeting. Kaiser was a member of the New Antidepressant Team (NAT), a cross-functional team of Lilly research and development (R&D) and marketing that was formed a couple of years earlier to devise a "successor strategy" for Prozac. Of the five strategic alternatives considered, which included several new compounds developed by Lilly as well as two in-license opportunities, only one product—Cymbalta (duloxetine)[2]—appeared to have the three key ingredients of a potential successor to Prozac: 1) efficacy as good as or better than existing antidepressants, 2) no apparent safety or toxicity issues, and 3) the possibility of meeting a previously unmet patient need.

Despite Cymbalta's potential, Kaiser knew that critical decisions about its future development needed to be made at the meeting. In particular, the NAT members had to decide how to prioritize clinical trials for Cymbalta, including the question of which clinical objective to pursue first. With the cost of a large-scale clinical trial often in the $25–$50 million range and a typical time frame of 15–18 months necessary to design, enroll patients, analyze and document the findings of the clinical trial, each study was a major undertaking and the NAT could only afford to pursue one objective before it planned to submit Cymbalta to the FDA for marketing approval. Since Cymbalta had only been tested thus far with twice daily dosages of 20 mg, 30 mg, and 40 mg, one option was to conduct a new set of clinical trials to establish a once-a-day dosage of 60 mg for Cymbalta to treat major depressive disorder; this would offer more convenient dosing for patients, and in this regard would put Cymbalta on par with its competition. A second option was to invest in clinical trials for a new indication that could potentially establish a point of differentiation between Cymbalta and existing antidepressants; this option was attractive because many physicians viewed the efficacy of current antidepressants as similar to each other with no one product standing out among the others. A third option was to delay the submission of Cymbalta to the FDA for marketing approval so that both objectives could be established before launch, but by then valuable time in the race to market would be lost.

Heading into the meeting, Kaiser had strong feelings about what the direction should be. What Kaiser did not know was that Jim Lancaster, the newly named director of commercial development for Cymbalta—and who had been involved in the launch of Prozac a decade earlier—was walking to the same meeting with a very different direction in mind.

Overview of Depression

The diagnosis and treatment of depression can best be described as having "come a long way" over the past two hundred years. In the early 1800s, there was no recognition of depression as an illness, and patients with the disease either went untreated or, in some cases, were sent to mental asylums. The identification of symptoms and a formal classification of several mental disorders came in the late 1800s and early 1900s. Early treatments specifically for depression included Freud's "psychoanalysis," which held that the source of mental illness was in subconscious thoughts and could be treated through the analysis of one's childhood as well as through the interpretation of dreams. In the 1930s, physical treatments for depression and other mental illnesses included induced seizures and electric convulsive therapy. Pharmacologic treatment of depression was not developed until the 1950s. In the latter half of the twentieth century, psychotherapy—an alternative form of psychoanalysis that focused on one's own behaviors and relationships with others as opposed to subconscious thoughts—and pharmaceuticals became the primary ways to treat depression.

[2] Cymbalta was the brand name chosen by Eli Lilly for duloxetine upon its approval for marketing in the U.S. For simplicity, Cymbalta is the name used throughout this case (vs. duloxetine).

Major Types of Depression, Symptoms, and Disease Prevalence

Although it is not unusual to feel extreme sadness, despair, or to be emotionally overwhelmed in the course of one's life, depression as an illness is characterized by a sustained emotional disturbance that interferes with daily activities such as the ability to work, study, sleep, or eat, for a period of time as short as two weeks or as long as five years or even longer. According to the *New England Journal of Medicine*, depression is a chronic condition second only in prevalence to hypertension (high blood pressure) in general medical practice.[3] Studies in scientific publications have estimated that depression affects anywhere from 10% to 25% of the population at some point in their lifetime, with women twice as likely as men to suffer an episode of depression. At any one time, 10% of the U.S. population is believed to suffer from depression. Despite the prevalence of depression, many of those with symptoms, especially men, do not seek medical attention because of the social stigma associated with the disease. In addition, even when medical help *is* sought, depression often goes undiagnosed because of its complicated set of symptoms, which tend to vary over time and overlap with symptoms of other illnesses. As a consequence, of those with the clinical symptoms of depression, it has been estimated that less than 50% actually receive treatment.[4]

The broad and complex set of symptoms for depression is often described in four general categories: mood changes, cognitive changes, behavior changes, and physical changes.[5] Changes in mood include the typical symptoms that one might envision when thinking about depression: sadness, feelings of helplessness, anxiety, or thoughts of death or suicide. Cognitive changes include the loss of concentration, increased forgetfulness, and the inability to make decisions. Alterations in behavior that result from depression include an increase in interpersonal conflicts with others as well as changes in personal appearance or personal hygiene. Lastly, depression has been associated with physical symptoms such as the loss of sleep or excessive sleep, stomachache and digestive problems, a change in appetite causing weight loss or gain, sexual problems such as decreased sex drive, chronic fatigue, and vague symptoms of pain.

Of the several types of depression, the following represent the most common forms.[6]

- *Major Depressive Disorder*—MDD is generally considered to be the most serious type of depression with respect to the number of symptoms and severity of mood changes. Severe symptoms such as suicidal thoughts or a history of hospitalization are not required for the diagnosis of major depression. If untreated, episodes of MDD can last between 6 and 18 months.

- *Dysthymic Disorder (Chronic Depression)*—This refers to a less severe form of depression that persists for two or more years. While symptoms are not as severe as MDD, the symptoms of dysthymia are enduring and more resistant to treatment. In addition, the low severity of symptoms often results in patients mistaking them for a personality trait or character flaw. Up to 30% of patients with dysthymia develop MDD at some time during the course of their illness.

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[3] M. Goodman et al., "Industry Overview: A Bright Outlook for Depression" *Morgan Stanley Equity Research*, June 7, 2002.

[4] Author's note: estimates in the literature for the prevalence and treatment of depression were varied, likely due to the difficulty in diagnosing the illness.

[5] M. Goodman et al., June 7, 2002.

[6] http://www.psychologyinfo.com/depression/depression_types.html, accessed November 22, 2005.

- *Adjustment Disorder with Depression*—This category describes a specific depression that occurs in response to a major life stressor or crisis such as the death of a family member or the loss of one's job. Short-term counseling or psychotherapy focused on the event or source of the crisis is usually the first line of treatment for adjustment disorder. Adjustment disorder typically lasts less than six months following the identifiable event causing the depression.

- *Bipolar Depression*—This type includes both high and low mood swings, as well as a variety of other significant symptoms not present in other depressions. Patients with bipolar disorder experience excessive elation, a decreased need for sleep, racing thoughts, and aggressive social behavior. Bipolar depression is also called manic depression.

Rating the Severity of Depression

The most commonly used depression rating scale in 2000 was the Hamilton Rating Scale for Depression (HAMD). Introduced by Max Hamilton in 1960, the HAMD was one of the first rating scales developed to quantify the severity of depression. Several versions of the HAMD scale have existed over the years, the most common being the 17-item scale designed to be used by a physician in a clinical interview of a patient. The HAMD-17 evaluates the symptoms of depression, including feelings of guilt, thoughts of suicide, insomnia, difficulties at work or in other activities, as well as the symptoms of related conditions such as anxiety. Items are rated on either a 0–2 or 0–4 scale for severity, and the total HAMD score is the sum of the scores for the 17 items in the survey (**Exhibit 1**). In general, a HAMD score of 10–13 is considered to be the minimum score required for diagnosis of MDD. Clinical trials that study MDD typically use HAMD scores of 15–18 as a minimum requirement for enrollment in the study. Patients with severe depression generally score 25 or higher. In 2000, the pharmaceutical industry widely used the HAMD-17 scale as the standard depression outcome measure in clinical trials presented to the FDA for approval of New Drug Applications.

Pharmacologic Treatment of Depression

The Biochemistry of Antidepressants

Neurotransmitters are "chemical messengers" that are used by the central nervous system (CNS) to activate and modulate the communication between cells, called neurons. A deficiency of the neurotransmitters serotonin and norepinephrine is believed to play an important part in depression, migraine, bipolar disorder, and anxiety. Serotonin is also believed to be influential on sexuality and appetite. Norepinephrine, along with another neurotransmitter called dopamine, has also been acknowledged as playing a significant role in attention and focus.

Exhibit 2 provides a pictorial representation of the message transmission process between neurons. After their synthesis and transport in vesicles to the boundary of one nerve cell (the presynaptic neuron), neurotransmitters are released and carry "messages" across an intercellular gap (the synapse) to receptors on a connecting neuron (the postsynaptic neuron). Once a neurotransmitter has "carried its message" to the corresponding receptors on the postsynaptic neuron, the neurotransmitter is released back into the synapse and reabsorbed into the sending neuron through a process called *reuptake*. The neurotransmitter is then repackaged into vesicles for future use or broken down by monoamine oxidase (MAO) enzymes. Antidepressant pharmaceuticals generally work to stimulate the transmission of neurotransmitters like serotonin or norepinephrine by (1) promoting receptor binding, (2) inhibiting reuptake, or (3) preventing the

enzymatic breakdown of neurotransmitters. Although each of these approaches attempts to increase the level or activity of certain neurotransmitters, inhibiting reuptake was the target of choice for drug development from the 1970s to 1990s.

Early Pharmaceutical Treatments for Depression

The first use of pharmaceuticals for the specific treatment of depression can be traced back to 1956, when Ronald Kuhn treated a patient, Paula JF, with Tofranil, a drug originally developed as an allergy medication. After several weeks of observing Paula JF, Kuhn wrote to Geigy Pharmaceuticals to suggest that Tofranil might be an antidepressant. Tofranil and other drugs in its class became known as the tricyclic antidepressants (TCAs). TCAs inhibit the reuptake of serotonin, norepinephrine, or both neurotransmitters at the same time. Despite their efficacy, it has been estimated that 75%–80% of patients taking TCAs receive sub-therapeutic doses because of the intolerable side effects associated with higher dosages. These side effects include dry mouth and blurred vision, among many others. In addition, because of the possibility of causing serious cardiac complications, TCAs can be lethal if misused at high doses. In 1983, the annual number of TCA overdoses in the U.S. was estimated to be 500,000.[7]

Around the time of the first use of TCAs for depression, a second class of medications, monoamine oxidase inhibitors (MAOIs), also began to be used for the treatment of depression. MAOIs prevent the breakdown of neurotransmitters (including serotonin), and therefore increase concentrations of the neurotransmitter in the brain. Though efficacious, MAOIs react with certain foods and alcoholic beverages as well as other medications, resulting in side effects as severe as those observed with the TCAs. Due to these tolerability issues, patients often failed to comply regularly with TCA and MAOI medications. Inconsistent compliance often resulted in lowered efficacy rates for both of these treatments. Due to these shortcomings, for many years there was a substantial need for an effective but more tolerable class of antidepressant medications than the TCAs and MAOIs.

The Arrival of Prozac and the SSRIs

Eli Lilly's U.S. launch of Prozac in 1988 dramatically changed the use of antidepressant medications for the treatment of depression. Since this class of drugs selectively blocked the reuptake of serotonin into the presynaptic neuron and had little effect on other neurotransmitters, Prozac and the rest of the subsequently launched SSRI class had comparable efficacy but fewer side effects than the TCAs or MAOIs. Additionally, SSRIs were much safer if overdosed than the TCAs. As a result of these advantages, Prozac became an instant blockbuster, registering first-year sales greater than all previous antidepressants . . . combined(!) And over time, drug therapy increasingly became a common way for primary care physicians to treat depression in addition to referring patients for psychotherapy. Specifically, in 1988 physicians prescribed approximately 2.5 million antidepressant prescriptions per month. By 1998, the number of antidepressant prescriptions had increased fourfold to 10 million prescriptions per month.[8]

After the introduction of Prozac, a number of new SSRIs such as Paxil, Zoloft, and Celexa came to market throughout the 1990s, making it both a large class in terms of sales as well as highly

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[7] D.A. Frommer, K.W. Kulig, J.A. Marx, and B. Rumack, "Tricyclic antidepressant overdose; a review," *JAMA* 257 (1987): 521–5266.

[8] Robert M.A. Hirschfeld, "Antidepressants in the United States: Current Status and Future Trends," chapter in *Treatment for Depression: Bridging the 21st Century*, Myrna Weissman, editor (Washington, DC: American Psychopathological Press, Inc., 2001).

competitive. Total sales of antidepressants in the U.S. in 2000 were close to $9 billion. The SSRI class represented about 50% of all antidepressant prescriptions but more than 70% of antidepressant sales.[9] **Exhibit 3** provides a summary of product market shares in 2000, and **Exhibit 4** gives gross sales forecasts by product. With the future introduction of generic fluoxetine, prescribing was expected to quickly shift from branded Prozac to generic fluoxetine because the latter was expected to be priced significantly lower by competing generic manufacturers—perhaps as much as 80% lower according to Lilly estimates. Industry analysts also expected some prescribing to shift to other existing branded SSRIs, namely Paxil, which was expected to gain approval for a new formulation in 2001, and to a new SSRI, Lexapro, which was expected to be launched in 2002.

A sign that the SSRI class had become highly competitive was the increased spending in advertising and promotion. Total advertising and promotion on SSRIs in 1998, including detailing[10] and direct-to-consumer advertising (excluding free samples), was more than $400 million, second only to the Proton Pump Inhibitor (PPI) class for heartburn.[11] Most SSRIs on the market were regarded as having comparable efficacy relative to placebo and there were very few "head-to-head" comparison trials of the major SSRIs. Many manufacturers sought to establish alternative indications for their product as a source of clinical differentiation. According to IMS Health, SSRIs were prescribed for depression only 65% of the time, with prescribing for other indications such as anxiety, obsessive compulsive disorder (OCD), and premenstrual dysphoric disorder (PMDD) making up the rest.[12] **Exhibit 5** summarizes several product attributes of each of the major antidepressant competitors in 2000, including prescribing indications approved by the FDA (for use in the U.S.). In some cases, drugs were prescribed for indications "off-label," which meant that the manufacturer had not received FDA approval for the claim but doctors chose to prescribe based on some formal research (often published in medical journals) or based on the practices of opinion leaders.

Eli Lilly & Company: Corporate History and Current Pipeline

Colonel Eli Lilly, Lilly's namesake and founder, was a pharmacist who had served in the Union Army during the Civil War. He began Eli Lilly and Company in 1876 when he purchased a laboratory on Pearl Street in Indianapolis, Indiana. The company's first notable success was the creation of a process for applying gelatin-coating to pills for easier swallowing. Lilly's next major success came in 1923 when it introduced Iletin, the first mass-produced insulin developed in collaboration with the University of Toronto. Iletin and Lilly's subsequently introduced insulin products significantly improved the treatment of diabetes.

Throughout the decade of the 1950s, Lilly made a number of scientific advancements, including the development of orally administered penicillin products, the discovery of erythromycin (an antibiotic), and Lilly's partnership in the mass production of the Salk polio vaccine for its first clinical trials. The 1960s brought further innovation with the introduction of a new class of antibiotics. Yet, like most companies, Lilly was not without failure from time to time. For example, Oraflex, an

[9] M. Goodman et al., June 7, 2002.

[10] Detailing sessions are visits to doctors' offices by pharmaceutical sales reps to give physicians information about the appropriate use, efficacy, dosage, side effects, contraindications, and studies regarding new and existing prescription drugs. Most detailing sessions lasted less than two minutes. In this short time a salesperson would primarily discuss one drug and leave material and free samples for other drugs.

[11] J. M. Donohue and E. R. Berndt, "Effects of Direct-to-Consumer Advertising on Medication Choice: The Case of Antidepressants," *Journal of Public Policy & Marketing*, 23 (2), Fall 2004: 115–127.

[12] M. Goodman et al., June 7, 2002.

antiarthritic, was withdrawn from the market in 1982 due to cases of jaundice in patients taking the drug.[13]

With the arrival of Prozac in 1988 and its resounding success in the 1990s, Lilly was often called "the Prozac Company" in the popular press. In the mid- to late-1990s, however, the title "the Prozac Company" was more than just a moniker since a significant portion of Lilly's sales force promoted the product. In 1998, over $150 million was spent on physician detailing and direct-to-consumer advertising.[14] By 2000, Lilly was slowly reducing its dependence on Prozac as sales of newer Lilly products were growing. Zyprexa, a drug used to treat schizophrenia, had worldwide sales of $2.35 billion in 2000, an increase of 25%. Gemzar, a chemotherapy product used in the treatment of certain kinds of cancer, saw its worldwide sales rise 23% in 2000 to $560 million. Sales of the osteoporosis drug, Evista, grew 60% in 2000 and the Lilly diabetes franchise, composed primarily of the synthetic insulin Humulin, grew 22% to $1.76 billion. Overall net sales in 2000 were $10.8 billion, up 8.5% from 1999. In addition to the growth of existing products, Lilly hoped to launch as many as 10 new products over the next five years, which would double the number of new products as compared to the previous five years (**Exhibit 6**).

Finding a Successor to Prozac

The NAT was formed in mid-1998 by two colleagues at Lilly—psychiatrist Mark Demitrack and project development expert Brett Schmidli, who took on the responsibility of being co-leaders of the NAT. John Kaiser was asked to join the team and play a pivotal role, given his previous global experience with Prozac. The fourth member to join was Jim Lancaster, who had prior U.S. Prozac experience. The mission of the team was to find and develop a drug that would better meet the needs of patients suffering from depression; this drug would be Lilly's successor to Prozac and needed to be launched at least 18 months *before* the Prozac patent expired in December 2003. Since that was a date that could change as a result of ongoing court cases challenging the Prozac patent, by April 2000 there was a sense among members of the NAT that the successor should be submitted to the FDA by mid-2001; this was a full year earlier than originally planned. The creation of the NAT also represented a novel approach for new product planning at Lilly because it was the first "cross-functional" team from both R&D and marketing to be formed before completion of Phase 2 clinical trials of a product.[15] In addition, the NAT was not formed with *any particular* drug in mind, but rather had an open mind for developing the best successor to Prozac—no matter what product it eventually turned out to be.

The team began its work by surveying both internal and external opportunities in depression and related illnesses. NAT members quickly zoomed in on what became known as its Five Assets. These assets represented the set of potential product development possibilities for Lilly and each was to be explored in turn. After investigating each of the Five Assets, the NAT planned to disband, and each member would be assigned to a particular asset as it moved further along in its development.

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[13] "Sales of arthritis drug suspended," *The New York Times*, August 5, 1982.

[14] J. M. Donohue and E. R. Berndt, Fall 2004.

[15] Clinical trials conducted as part of a New Drug Application (NDA) in the U.S. are divided into three phases: Phase 1, Phase 2, and Phase 3. Phase 1 clinical trials focus on confirming that an investigational new drug is both tolerable and safe; Phase 1 clinical trials usually enroll healthy volunteers as opposed to patients with the particular condition or disease of interest. In Phase 2, the new drug continues to be tested for safety and tolerability but also begins to be tested for its efficacy, or effectiveness; Phase 2 trials are also used to select an appropriate dose or amount of the drug to use in larger Phase 3 clinical trials. Phase 3 represents the defining moment for an investigational new drug. These trials study a broad population of patients and form the basis for FDA approval of the new drug.

Asset 1: R-fluoxetine

R-fluoxetine was the same chemical molecule as fluoxetine (the active ingredient in Prozac) but was in a different physical configuration or shape. Because of its distinct physical properties, it was thought that R-fluoxetine might have similar efficacy to fluoxetine and yet avoid some of Prozac's side effects such as sexual dysfunction and insomnia. Another pharmaceutical company, Sepracor, was the holder of the patent for R-fluoxetine. Lilly established a licensing agreement with Sepracor to develop and promote R-fluoxetine if approved; however, its development was soon discontinued in Phase 2 due to tolerability problems in patients.[16]

Asset 2: OFC (olanzapine-fluoxetine combination)

OFC combined the active ingredient in Zyprexa and the active ingredient in Prozac. Although the exact mechanism of OFC was not known, it had been proposed that the simultaneous activation of serotonin, norepinephrine, and dopamine receptors was responsible for its enhanced antidepressant effect. OFC (trade name Symbyax) spawned a formal product team to carry through its development for the treatment of depressive episodes associated with bipolar disorder. Though approved for use by the FDA, bipolar depression represented a much smaller market than MDD (~2.5 million patients for bipolar depression or <1% of the U.S. population, vs. ~10% of the U.S. population for MDD).[17]

Asset 3: 5HT2 antagonist SSRI

Not all SSRI medications were alike. Each one had different specificities in the receptor sites for serotonin, resulting in diverse side-effect profiles and efficacy for targeted symptoms. 5HT1, 5HT2, and 5HT3 were the receptor sites most affected by SSRIs. In particular, stimulation of 5HT2 receptors could cause increased anxiety, restlessness, insomnia, agitation, and sexual dysfunction. Lilly's SSRI-5HT2 antagonist was intended to selectively block the stimulation of serotonin at 5HT2 in order to eliminate these side effects. However, it was discontinued early in its development due to toxicity findings in animals.

Asset 4: Business Development Opportunities

Through market surveillance and due diligence, Lilly identified 13 opportunities to in-license compounds for the treatment of depression from other pharmaceutical companies at various stages of their development. The analysis resulted in two offers made by Lilly but both were declined. There was a sense among NAT members that part of the reason these bids were declined was because the other companies knew that Lilly was working on its own drugs and saw this as a potential area of conflict.

Asset 5: Cymbalta (duloxetine)

Cymbalta was a serotonin and norepinephrine receptor inhibitor (SNRI) that was developed by Lilly in the early 1990s for the MDD market. However, it failed to show

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[16] Tolerability is a general term that refers to the side effects and adverse experiences observed in patients taking a prescription drug.

[17] *Symbyax as a Treatment for Bipolar Disorder*, http://www.vagusnervestimulator.com/topics/symbyax.cfm, accessed December 16, 2005.

satisfactory levels of efficacy for treating MDD at 20 mg/day in Phase 2 trials in 1993. The NAT was in a position to reassess further development plans for Cymbalta.

Other early steps of the NAT in late 1998 and early 1999 included an epidemiological study of depression comorbidities and preliminary market research with physicians to capture the current state of affairs with respect to the treatment of depression. The purpose of the epidemiological study was to understand the broad spectrum of health problems that occurred simultaneously with depression (i.e., comorbid conditions). Since NAT members estimated that any new antidepressant developed by Lilly would compete with at least 8–10 other products, the ability to treat one or more of these comorbidities could represent a potential differentiator over competitors. (The comorbidities identified in the study are summarized in the diagram in **Exhibit 7**.) Interviews with high-prescribing physicians and patients shed more light on these comorbidities, and armed with these findings, the NAT decided to present the Five Assets and a status of its research to the head of neuroscience at Lilly. During the NAT's presentation of its research findings, the comorbidity of "pain" caught the eye of the head of neuroscience. Kaiser and his colleagues were advised to speak with Smriti Iyengar, a senior scientist in basic research at Lilly who had "done some work with Cymbalta and chronic pain."

The Link between Chronic Pain and Depression

In April 1999, Kaiser along with Steve Schaefer and Peter Anastasiou, both marketing colleagues at Lilly, met with Iyengar to discuss her work and its possible relation to their early market research. Dr. Iyengar was a neuro-pharmacologist who had joined the neuroscience group at Lilly in 1991. In 1993, she became aware that Lilly had developed a molecule that could selectively block the reuptake of both serotonin *and* norepinephrine (i.e., SNRI). This immediately reminded Iyengar of the mechanism of action of TCAs. Iyengar knew that TCAs were sometimes used for the treatment of severe pain such as chronic back pain or recurring headaches and that any such use was off-label. Although the mechanism was never fully understood, Iyengar thought that Cymbalta might also be developed for the treatment of pain, especially if it did not cause the same negative side effects as the TCAs. With this rationale in mind, Iyengar requested access to Cymbalta for further testing in rats. Given that Phase 2 trials at that point had not revealed sufficient efficacy for treating depression, Iyengar was granted her request in 1997.

As Iyengar further recalled her story to Kaiser, Schaefer, and Anastasiou, she explained how skeptical her management was to her initial work with Cymbalta. "Pain was a dirty word at Lilly," she told them. "Lilly had so little recent experience in this therapeutic area and since there were no clear guidelines from the FDA for the development of pain indications, there was resistance to working on the treatment of pain," she continued. "After all, Lilly was 'the Prozac Company' and was known for its treatment of depression, right?" In spite of this, over the next several years, Iyengar successfully developed experiments in animals demonstrating the use of Cymbalta for the treatment of pain. Still, after presenting her results, there did not appear to be much interest in her experimental findings or for the clinical development of Cymbalta for a pain indication, and in early 1998 Iyengar was advised to focus on other research. There was little interest, that is, until the meeting with Kaiser and his colleagues, who instantly saw this as an opportunity if Cymbalta could potentially be developed for the treatment of depression *and* pain. "Their enthusiasm and positive feedback to my research came as a huge surprise to me. Marketing was the last place I was expecting to get support for something that seemed to be a scientific issue. Their reaction made all those years of hard work finally seem to be worth it," she later said; "it was wonderful."

Although the sources of chronic pain were not well understood and much controversy surrounded this issue, there was some emerging research in the scientific community connecting aspects of depression to pain. According to one study, the high degree of painful physical symptoms among patients with depression or anxiety was likely due to a shared biochemical cause. Serotonin and norepinephrine had been identified as key neurotransmitters in depression, but it was hypothesized that they also played a role in regulating pain. Some researchers thought that imbalances in serotonin and norepinephrine throughout the central nervous system reduced pain thresholds and increased sensitivity to pain. As a result, it was conceivable that depression represented a state in which lower levels of serotonin and norepinephrine led to both emotional symptoms and painful physical symptoms.[18]

Even more telling were anecdotal stories of the link between severe pain and depression. In one example, a letter to the editor of *Diabetes Care*, two physicians in private practice in Oklahoma explained the success of Effexor, another SNRI already on the market, in treating a painful condition associated with diabetes called diabetic peripheral neuropathic pain (DPNP). They wrote, "when [Effexor] was added, all patients had a 75%–100% reduction in pain within 3–14 days. . . . One patient stopped the medication after being pain-free and after two days had a recurrence of the pain. [Effexor] was restarted, and the discomfort was promptly relieved."[19] Effexor currently had no approved indication to treat chronic pain. Though efficacious, Effexor was also viewed by physicians in Lilly's research to have higher discontinuation rates than SSRIs due to tolerability issues.

Other examples of the link between pain and depression came from Lilly's own focus groups with patients. One such story of a middle-aged African American woman clearly made an impression on Kaiser. "With tears in her eyes," Kaiser recalled, "she told me that no one ever believed that the pain was real. All the doctors kept telling her that because she suffered from depression the pain was 'all in her head.'"

Since there appeared to be a link between pain and depression, the NAT was eager to determine to what extent the medical community had reported evidence that these symptoms were present together. In reviewing medical literature and databases on depression, Kaiser came across an item that caught his eye. There was a study involving a primary care physician, Dr. Kurt Kroenke, from Indiana University that indicated a correlation between chronic pain and depression. When Kaiser realized that the potential evidence he was looking for was "right in Lilly's back yard," he immediately scheduled a meeting. Dr. Kroenke presented to Kaiser and Anastasiou the data he had compiled on how a significant proportion of patients that his group treated for depression had also exhibited symptoms of pain. As they listened to Kroenke's presentation for nearly three hours, Kaiser and Anastasiou found it difficult to contain their excitement. To Lilly, it now appeared as though the link between depression and chronic pain was real.

Cymbalta R&D—Next Steps

Subsequent to the meeting with Iyengar, Kaiser was hopeful that Cymbalta would be the "Holy Grail" of the quest for Prozac's successor. A significant breakthrough was provided in early 1998 when (Mark) Demitrack initiated an assessment of Cymbalta's relatively low efficacy in treating depression in previous clinical trials. Internal and external scientific experts determined that the once

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[18] H. L. Fields and A. I. Basbaum, "Central nervous system mechanisms of pain modulation," in: P.D. Wall and R. Melzack (ed.), *Textbook of Pain* (New York, 1999), pp. 309–329.

[19] J. L. Davis and R. L. Smith, "Painful peripheral diabetic neuropathy treated with venlafaxine HCL extended release capsules," *Diabetes Care*. 22(11), 1999, p. 1909.

daily 20 mg dose of Cymbalta previously investigated, which was identical to the dosing of Prozac, was probably too low. The rationale: unlike the SSRIs which only blocked the reuptake of serotonin, Cymbalta required a greater dose to block the reuptake of both serotonin and norepinephrine and, thus, to produce a strong efficacious response.

This expert assessment proved to be true in subsequent clinical trials of Cymbalta. In one notable clinical study, Cymbalta was tested at doses ranging from 20 to 40 mg twice daily as compared with 20 mg of Prozac once daily. As shown in **Exhibit 8**, the primary endpoint of this study revealed greater reductions in the symptoms of depression with Cymbalta as compared with both Prozac and placebo (as measured by the average reduction in HAMD-17 scores). Cymbalta also achieved a better overall response rate than both Prozac and placebo in the study (defined as the proportion of patients with at least a 50% reduction in HAMD-17 scores). These results were also supported by a promising safety and tolerability profile for Cymbalta since the frequency and severity of side effects remained low.

The NAT now had a definite sense that Asset 5 would be the main candidate for a Prozac successor. Two things were clear—Cymbalta was effective for treating MDD if proper dosing was administered, and it had the potential for treating a common aspect associated with depression, namely, painful physical symptoms. On the first issue, by the fall of 1999 Phase 2 trials were well underway to formally show the efficacy of Cymbalta for treating MDD with dosing twice daily (also called BID). It was yet to be determined whether once-daily dosing of 60 mg should be investigated in subsequent clinical trials before submitting Cymbalta to the FDA for marketing approval. It was generally believed that patient compliance in continuing drug therapy decreased significantly when a product had to be taken twice or more in a single day as opposed to just once daily, and the lack of a once-daily dosing regimen for Cymbalta was viewed by some at Lilly as a negative differentiator relative to the leading SSRIs on the market (**Exhibit 5**). According to one member of the NAT, at twice-daily dosing "it would be like evaluating a new car that is otherwise a superb car but has a gas tank that is half the size of other cars on the market, thus requiring you to go to the gas station twice as often." But pursuing clinical trials to establish a once-daily dose of Cymbalta was not without risk of failure. First, taking 60 mg once daily as opposed to, for instance, 30 mg twice daily might create issues of tolerability or potential side effects since literally twice the medication would be taken at a single time. Second, if the half-life of Cymbalta was not long enough, then with single dosing its efficacy might wear off without providing relief of symptoms over an entire 24-hour period.

Before committing virtually all of its R&D funding for the next year to test a once-daily 60 mg dose of Cymbalta, the NAT sought to better understand the implications of pursuing the newly established link between depression and pain, from both the market and R&D standpoints.

Continued Market Research Efforts for New Product Planning

Creation of the New Product Planning Division

The NAT approached product development as a combined R&D and marketing endeavor. Kaiser firmly believed that further R&D on Cymbalta should be guided by a thorough understanding of the market forces. This philosophy was shared by senior management at Lilly who advocated the formation of a separate entity within the company that would offer counsel and expertise on such matters for all drugs, particularly in early development. Sheri Morin, who later became the director of New Product Planning, explained:

Though basic science will always be the engine of medical discovery, drugs often fail to achieve commercial success because their market potential had not been assessed properly or because specific indications critical to satisfying unmet patient needs were not built into the drug or were not tested for. That's where the New Product Planning (NPP) division comes in. First and foremost, NPP seeks to uncover patient needs, either directly or through the eyes of physicians. It is also charged with understanding how well competitive offerings are perceived as satisfying the diverse set of patient needs. In addition, NPP provides competitive intelligence as to which drugs are being developed by company rivals. The goal of the analysis is to focus the work of Lilly's scientists by identifying those drug indications that would be most valued by physicians and patients when launched. In some cases, the findings could suggest discontinuing development of a drug, either because the demand would be too low, the selling and communication effort would be too high or too complex, or because a rival firm was already ahead of the game and close to an FDA submission. The NPP division is there to assist Lilly in its mission to develop "first or best-in-class" drugs.

Given its status within Lilly, the NAT was in an ideal position to lay the foundation and establish processes that would later be followed in the new product planning of other drugs.

Relative Importance of Antidepressant Attributes to Physicians

As part of its new product planning process for Cymbalta, NAT members felt that it was important to determine which characteristics of current antidepressants were most important in the prescribing decisions of physicians. And given what Kaiser and his colleagues now knew, the importance of "pain" would now be measured. The results of the conjoint study are shown in **Exhibit 9**. The study revealed that tolerability and the avoidance of certain side effects of antidepressants were often perceived as more important to physicians (47% weight in prescribing decisions) than a drug's primary or secondary efficacy in treating depression (18% each). Dosing (8%) and safety (9%) received less weight in prescribing decisions. According to some physicians interviewed in connection with the study, these last two factors were given less importance because the SSRIs were generally thought to be safe as compared with previous classes of antidepressants, and almost all were available in once-daily (or QD) dosing formulations. Further research broke out and quantified via a numerical score the positive or negative impact of each factor on prescribing decisions. For example, the occurrence of weight gain as a side effect of some antidepressants had a significant negative impact on physicians' decision to prescribe a product (score of -62.7), while the occurrence of weight loss had virtually no effect on their prescribing patterns (score of +1).

Patient Segmentation Study

The NAT also examined the needs of patients through the eyes of physicians and, as a result of their analysis, developed seven definitive patient segments to characterize the market (**Exhibit 10**). Descriptive names such as "Functioning Fran" and "Addicted Denise" were given to each segment, and a profile of each segment was developed that included demographic data, types of symptoms present, the extent of pharmaceutical treatment used in the segment, as well as expected patient response to antidepressant therapy. The symptom of pain was present in virtually all of the segments but was most apparent in the segment called "Hurting Helen."

Antidepressant Axis of Competition

Integrating all of the research to-date on the needs of patients, the prescribing habits of physicians, and an understanding of the competition, Kaiser and his colleagues developed what they called the "axis of competition" for current antidepressants (**Exhibit 11**). Specifically, the axis of competition was a schematic that visually depicted the perceived differentiation between products in the antidepressant marketplace. Along the primary axis, products were placed based on their efficacy in treating MDD (i.e., the greater the perceived efficacy in treating depression, the further along the axis a product was placed). In addition to the main axis for the treatment of depression, other axes were placed on the diagram to describe the treatment of other patient needs: the greater the difference in orientation between each axis (i.e., the angle between each axis), the greater the observed differentiation between the products. Kaiser, Schaefer and Anastasiou were hopeful that Cymbalta would not only be positioned far along the axis for depression but that it would also create a new and robust axis nearly orthogonal to the others due to its strength in the treatment of pain. The NAT referred to this new axis as the "mind-body link."

The Implications of Pursuing Pain

Comparison against Existing Antidepressants

If the NAT decided to conduct human testing of Cymbalta for pain, it was important to determine which angle of "pain" to pursue. As Kaiser and his team soon discovered, there appeared to be two major alternatives, but both of these alternatives were complex and not without difficult trade-offs. The first alternative was to compare Cymbalta to existing SSRIs and SNRIs in the treatment of pain specifically related to depression. That is, Lilly could attempt to prove that Cymbalta was better than Paxil, Zoloft, or another antidepressant in treating the painful symptoms that occur simultaneously with MDD. One difficulty with pursuing this approach was that there was only one item on the HAMD-17 survey that specifically addressed pain (**Exhibit 1**). A second disadvantage of this alternative was that there was not a clear consensus among physicians as to the nature of the link between depression and pain; specifically, different physician specialties viewed this mind-body link in very different ways as described below.

In interviews with physicians, primary care physicians (PCPs) estimated that approximately 50% of patients suffering from depression who came to their office also suffered from pain symptoms, most commonly tension headache, neck/shoulder pain, and back pain. Psychiatrists estimated that only 5%–20% of their patients needed pain therapy. Moreover, most psychiatrists did not subscribe to the mind-body link and thought the apparent pain associated with depression was "in the head of the patient" and didn't really exist. They simply instructed their patients to "take an aspirin" if they felt symptoms of pain. Many psychiatrists commented that depressed patients tended to focus attention on themselves and the pain they felt was a by-product of that. "Treat the underlying depression and the pain will go away," one psychiatrist told Kaiser during an interview. Neurologists, on the other hand, thought that feelings of depression were often caused by underlying physical pain—the reverse of the psychiatrists. Neurologists estimated that 20%–30% of their patients had chronic pain.

Lastly, attempting to compare Cymbalta to an existing SSRI on pain might fail to conclusively separate Cymbalta from the comparator, thus giving the rival drug an implicit endorsement for treating pain.

Pursuing a Separate Pain Indication

The other alternative for Lilly was to pursue an indication for pain that was independent of depression. This path would be akin to showing that Cymbalta was effective as a pain reliever (i.e., when measured against other pain relievers/placebo) in addition to pursuing an indication for Cymbalta as an antidepressant, resulting in two separate FDA filings. In Kaiser's view, if Cymbalta was indicated for the treatment of a specific pain condition separate from the treatment of depression, then it would not matter whether one's pain was caused by depression or vice versa; Cymbalta could be used in either case. Of course, given the time and budget constraints, the remaining trials for establishing the depression indication in this alternative would have to proceed with twice-daily dosing.

Separate from depression, the treatment of pain represented a large and fragmented market. According to the National Institutes of Health, over 40 million Americans were unable to find relief from their pain.[20] Many conditions caused painful symptoms. Some of the most common were osteoarthritis (inflammation of the joints due to wear and tear) and rheumatoid arthritis (inflammation of the joints due to an overactive immune system). In addition, there were many other conditions that involved painful symptoms, including fibromyalgia (severe muscle pain and chronic fatigue) and the lesser-known condition of diabetic peripheral neuropathic pain or DPNP (a painful and debilitating complication of diabetes).

Pharmaceutical treatments for pain in 2000 included a myriad of medicines, some of which were available over the counter. Opioid painkillers represented a sizable market in the U.S.—nearly $2.5 billion—but were highly addictive. Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, were commonly used for pain but often caused side effects such as upset stomach or, more seriously, gastrointestinal (GI) bleeding. The need for better medications to treat pain was best exhibited by the recent rise of the COX-2 class of drugs, which included Celebrex and Vioxx. Celebrex was indicated for the treatment of rheumatoid arthritis and osteoarthritis, while Vioxx was approved to treat chronic pain and osteoarthritis. Both medications claimed to have fewer GI complications and were actively marketed to consumers via television and print advertising. In only 20 months, the COX-2 class became the 11th-largest therapeutic class of drugs in the U.S. with sales of $3 billion.[21] Combined sales of prescription NSAIDs and COX-2s exceeded $6 billion in 1999.

Lilly could alternatively decide to pursue an indication for fibromyalgia or DPNP—conditions afflicting far fewer than the approximately 20 million patients suffering from osteoarthritis. On the plus side for fibromyalgia was that it was well-known to rheumatologists and other specialists that treated depression. Though the causes of fybromyaligia were not well understood, an improper balance of neurotransmitters was hypothesized by some, and recent studies were investigating the effect of SSRIs on fibromyalgia. In addition to pain (commonly in the neck, shoulders, chest, legs, and lower back), the symptoms of fibromyalgia were broad and also included sleep disorders, fatigue, and gastrointestinal disorders. DPNP, on the other hand, was a "pure pain" condition. It was a complication of diabetes that caused damage to the nervous system, which in turn resulted in pain. This "forgotten complication" of diabetes, as it was sometimes called, affected 10%–20% of diabetic patients.[22] Existing pain relievers were not considered effective for treating DPNP. No medication had yet been approved by the FDA for the specific treatment of DPNP. Therefore, if pursued, Lilly could hope for a relatively fast review from the FDA.

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[20] "Pain Therapeutics Initiates Phase II Clinical Trial for New Painkiller," Business Wire, October 18, 2000.

[21] "US sales of COX-2 arthritis drugs swell to $3 bln in H1, 2000," Reuters News, October 17, 2000.

[22] A. J. M. Boulton et al., *Diabetes Care*, 27 (2004): 1458–1486.

Decision Time!

By 8:30 pm, the meeting that was supposed to last for a couple of hours had now turned into a four- and-a-half-hour marathon, and the four NAT members present at the meeting had not reached anything close to resembling a consensus as to how to proceed with the clinical development of Cymbalta. One option was to invest in Phase 2/Phase 3 clinical trials to test depression efficacy of a once daily (QD) 60 mg dosing regimen of Cymbalta instead of the existing 20–40 mg twice-daily (BID) dosing regimen. Jim Lancaster, a former marketing director on the Prozac brand team, was firmly in support of this option. The main argument put forward was that all of the leading SSRIs and the only SNRI on the market, Effexor, were QD. Therefore, it was important to first establish Cymbalta as an effective once-daily antidepressant, and that no doctor was going to prescribe Cymbalta if it was BID due to compliance concerns.

Kaiser shook his head as he read the question posed on the overhead projector: "Can We Risk Launching a BID drug into a QD Market?" He quickly replied, "No pain, no gain." "Pursuing an indication for pain will be the only way for us to differentiate ourselves against the competition. Unless we are going to have efficacy astronomically better than the others in the market, which I don't think will happen, then having a unique point of differentiation will be the only way to succeed in this competitive marketplace. Efficacy for treating pain in depressed patients should be our main message."

Another period of silence fell on the group, and Kaiser pondered what he was up against. Several of the senior leaders at Lilly, including John Hayes, one of its most respected neuroscientists, had expressed optimism that Cymbalta could actually work *better* than existing products against depression, including Prozac. However, Kaiser felt that those opinions were based on early comparative data against Prozac (**Exhibit 8**) and could change as further development of Cymbalta proceeded. Although Kaiser had been praised by many at Lilly for the market research analysis that he and his colleagues had prepared, the other counterargument to his proposal was that Lilly could always pursue a pain indication sometime down the road after submitting the NDA for Cymbalta to treat MDD, since at that point they would have additional resources. But Kaiser believed that two to three years could make or break this drug given the expected arrival of much less expensive generics to the market. Having the unique differentiator of pain would be the only way to avoid this from happening, in his view.

Brett Schmidli and Mark Demitrack, the co-leaders of the NAT and the only other members present at the meeting, sat quietly; it wasn't evident from their demeanor which side they favored. Finally, Demitrack spoke up and proposed to put it to a vote. There were three options regarding the direction of clinical trials to be conducted before NDA submission: (1) prove efficacy for treating MDD using QD dosing, (2) pursue a separate pain indication (in addition to submitting for an MDD indication using BID dosing), and (3) delay NDA submission, by potentially several years, until both issues were established. And with those options in mind, the group started with Demitrack and proceeded to go around the room, each stating which option in their opinion was the best strategy to pursue.

Exhibit 1 Hamilton Rating Scale for Depression (HAMD-17)

1. **DEPRESSED MOOD** (Sadness, helplessness, despondency)
   0= Absent (Neutral mood)
   1= Indicated only on questioning
   2= Spontaneously reported verbally
   3= Communicates non-verbally (facial expression, tendency to weep, at times is overpowered by hopelessness)
   4= Patient reports virtually only these feelings either verbally or non-verbally

2. **FEELINGS OF GUILT**
   0= Absent
   1= Self reproach, feels as if he/she has let people down
   2= Ideas of guilt over past errors or deeds
   3= Presents illness is a punishment—delusions of guilt
   4= Hears accusatory voices or experiences threatening visual hallucinations and paranoia

3. **SUICIDE**
   0= Absent (No suicidal impulses)
   1= Feels life is not worth living, but does not wish to die
   2= Wishes he/she were dead/thoughts of possible death
   3= Suicidal ideas or gesture
   4= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**
   0= No difficulty falling asleep
   1= Complains of occasional difficulty falling asleep
   2= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE (Midnight—5 am)**
   0= Absent
   1= Complains of being restless and disturbed during night
   2= Waking during the night/getting out of bed

6. **INSOMNIA LATE / PREMATURE AWAKENING**
   0= Absent
   1= Wakes in early hours but goes back to sleep
   2= Consistently waking early and unable to fall asleep again

7. **WORK AND ACTIVITIES**
   0= Normal work activity
   1= Thoughts and feeling of incapacity, fatigue, weakness related to activities, hobbies or work
   2= Clear loss of interest in activities, hobbies or work
   3= Decrease in actual time spent in activities or decreases in productivity, or the patient is sick-listed
   4= Stopped working completely because of present illness

8. **RETARDATION**
   0= Normal speech and thought
   1= Slight retardation at interview, slightly reduced speed
   2= Obvious retardation at interview, slow pace
   3= Interview difficult due to long latencies/brief answers
   4= Complete stupor, interview cannot be completed

9. **AGITATION**
   0= None (Normal motor activity)
   1= Fidgetiness, changing position in chair
   2= Playing with hands, hair, etc.
   3= Moving about, can't sit in chair during interview
   4= Hand wringing, nail biting, hair-pulling, biting of lips, almost continuous pacing, pulling off clothes

10. **ANXIETY (PSYCHOLOGICAL)**
    0= No difficulty
    1= Subjective tension and irritability
    2= Worrying about minor matters
    3= Apprehensive attitude apparent in face or speech
    4= Fears markedly interfere with daily life

11. **ANXIETY (SOMATIC):** Physiological signs of anxiety
    0= Absent
    1= Mild
    2= Moderate
    3= Severe
    4= Incapacitating

12. **SOMATIC SYMPTOMS: GASTROINTESTINAL**
    0= None
    1= Loss of appetite but food intake about normal
    2= Marked reduction of appetite and food intake

13. **SOMATIC SYMPTOMS: GENERAL**
    0= None
    1= Heaviness in limbs, back or head. Backaches, headache, muscle aches, loss of energy
    2= Any clear-cut symptom rates 2

14. **GENITAL SYMPTOMS:** Loss of libido, impaired sexual performance, menstrual disturbances
    0= Absent
    1= Mild
    2= Severe

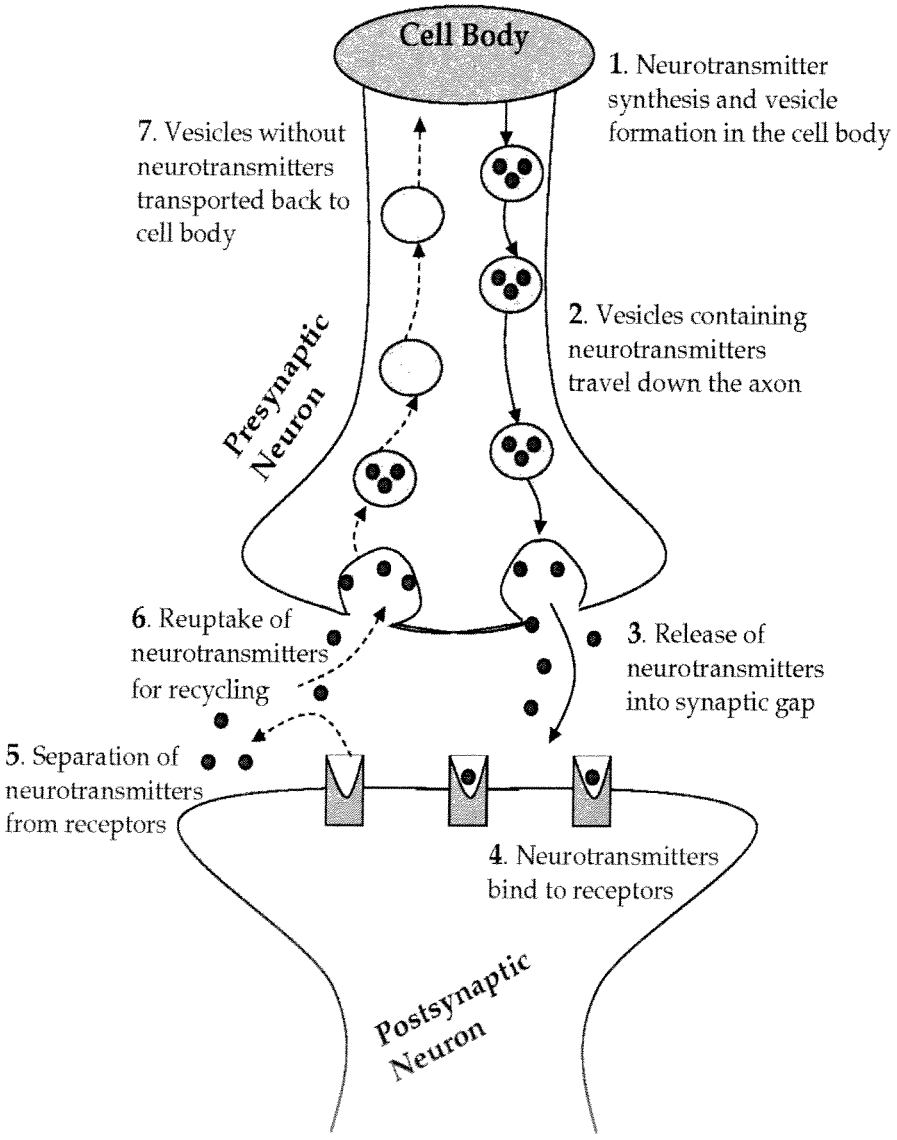
15. **HYPOCHONDRIASIS**
    0= Not present
    1= Self-absorption (bodily)
    2= Preoccupation with health
    3= Frequent complaints, requests for help, etc.
    4= Hypochondriacal delusions

16. **LOSS OF WEIGHT**
    0= No weight loss
    1= Weight loss likely caused by depression (1–2.5 kg)
    2= Definitive weight loss (>3 kg)

17. **INSIGHT**
    0= Acknowledges being depressed and ill
    1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    2= Denies being ill at all

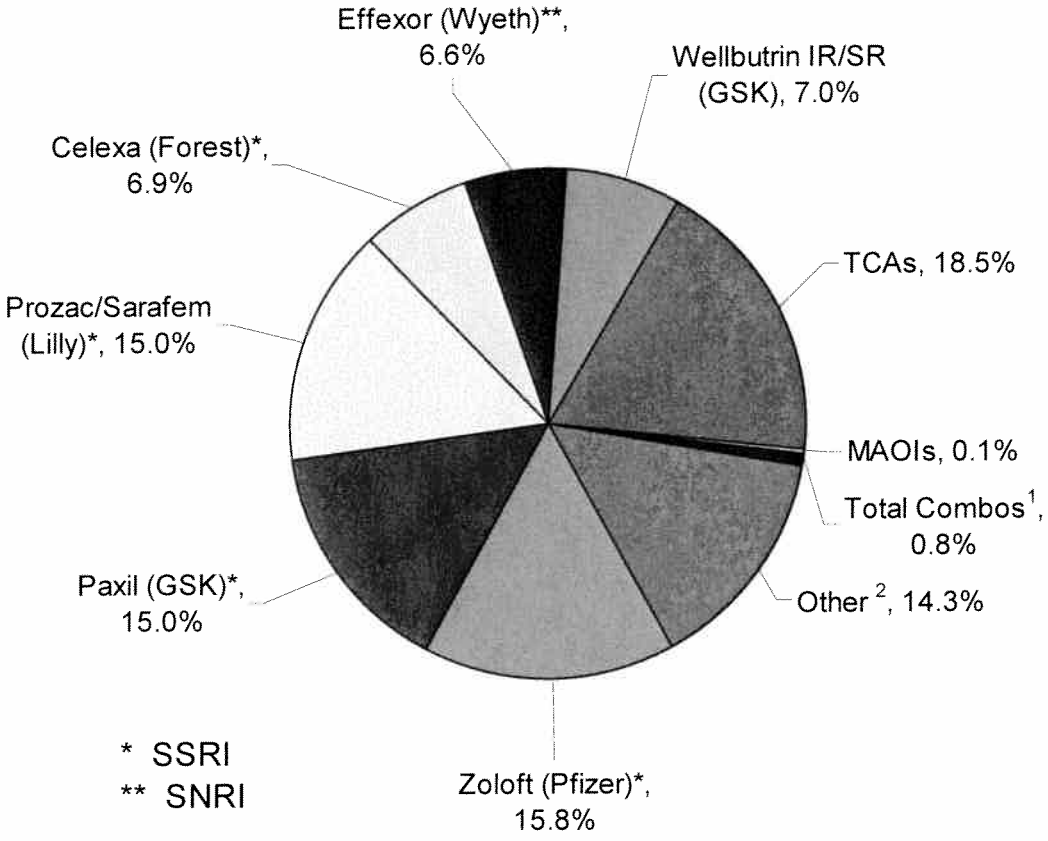
Source: Compiled from Hamilton, "A rating scale for depression," *J Neurol Neurosurg Psychiatry*, 23 (1960), pp. 56–62, and Hedlung and Vieweg, "The Hamilton rating scale for depression," *Journal of Operational Psychiatry*, 10 (2), (1979), pp. 149–165.

Exhibit 2 Schematic of the Role of Neurotransmitters in the Transmission of Information from One Neuron to Another



Source: Casewriter.

Exhibit 3 U.S. Antidepressant Market Shares in 2000 (as a Percentage of Total Rxs)

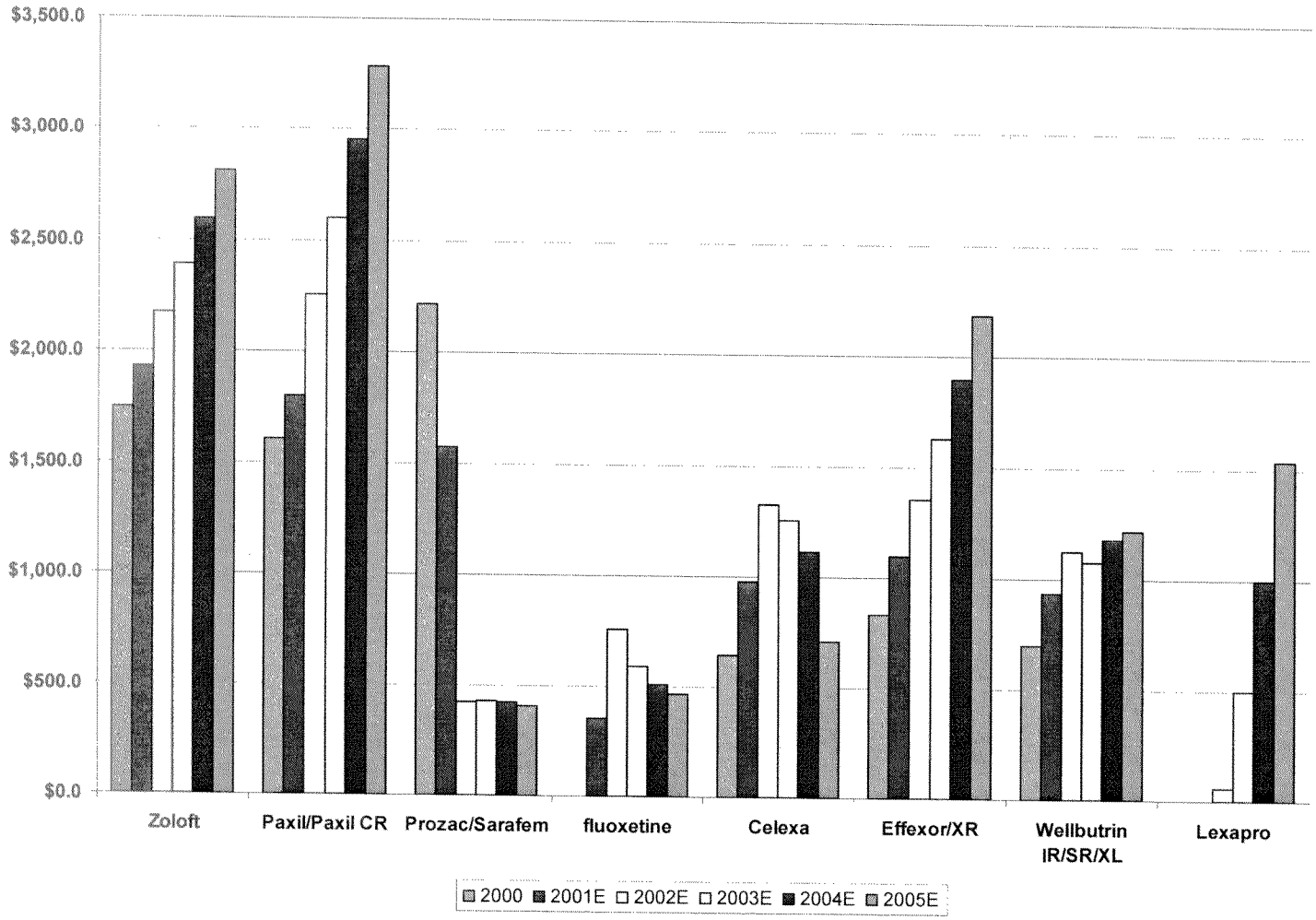


Source: Compiled from Pharmaceuticals, Specialty, Morgan Stanley (June 7, 2002), IMS America (original source).

[1] Combos include: Deprol, Etrafon, Etrafon Forte, Etrafon-A, perphenazine/amitriptyline, Limbitrol, Limbitrol DS, Triavil, and amitriptyline/chlordiazepoxide.

[2] Other includes: Luvox, Fluvoxamine, Desyrel, trazodone, Remeron, Remeron Soltab, and Serzone.

Exhibit 4 U.S. Antidepressant Market—Total Sales (millions)



Source: Compiled from *Pharmaceuticals, Specialty*, Morgan Stanley (June 7, 2002) and IMS America.

Exhibit 5 Antidepressant Competitor Characteristics

Product	Year Introduced	Mechanism of Action	Administration	Indications
Prozac (fluoxetine)	1988	Selective Serotonin Reuptake Inhibitor (SSRI)	Oral Once Daily	Major Depressive Disorder Obsessive Compulsive Disorder Bulimia Nervosa Panic Disorder[a]
Celexa (citalopram hydrobromide)	1998	SSRI	Oral Once Daily	Major Depressive Disorder
Zoloft (sertraline hydrochloride)	1992	SSRI	Oral Once Daily	Major Depressive Disorder Obsessive-Compulsive Disorder Panic Disorder Posttraumatic Stress Disorder[b] Premenstrual Disphoric Disorder[c] Social Anxiety Disorder[d]
Paxil / Paxil CR (paroxetine hydrochloride)	1993 (CR formulation expected in 2001)	SSRI	Oral Once Daily	Major Depressive Disorder Panic Disorder Social Anxiety Disorder Premenstrual Dysphoric Disorder
Wellbutrin IR/SR (bupropion hydrochloride)	1989 (SR formulation introduced in 1996)	Inhibits Reuptake of Serotonin, Norepinephrine, and Dopamine	Oral 2–3 times daily	Major Depressive Disorder
Effexor / Effexor XR (venlafaxine hydrochloride)	1994 (XR formulation expected in 2001)	Selective Norepinephrine Reuptake Inhibitor (SNRI)	Oral Twice Daily (XR expected to be Once Daily)	Major Depressive Disorder Generalized Anxiety Disorder[e] Social Anxiety Disorder Panic Disorder

Source: Compiled by casewriter from manufacturer and FDA-approved prescribing information for each product.

[a]*Panic disorder* causes unexpected and debilitating feelings of terror including chest pains, sweating, and dizziness.

[b]*Posttraumatic stress disorder* occurs following a terrifying event and can include nightmares and emotional numbness.

[c]*Premenstrual dysphoric disorder* is more severe than premenstrual syndrome (PMS) and is linked with severe emotional and physical problems that typically occur in the second half of the menstrual cycle.

[d]*Social anxiety disorder* causes overwhelming anxiety and excessive self-consciousness in everyday social situations.

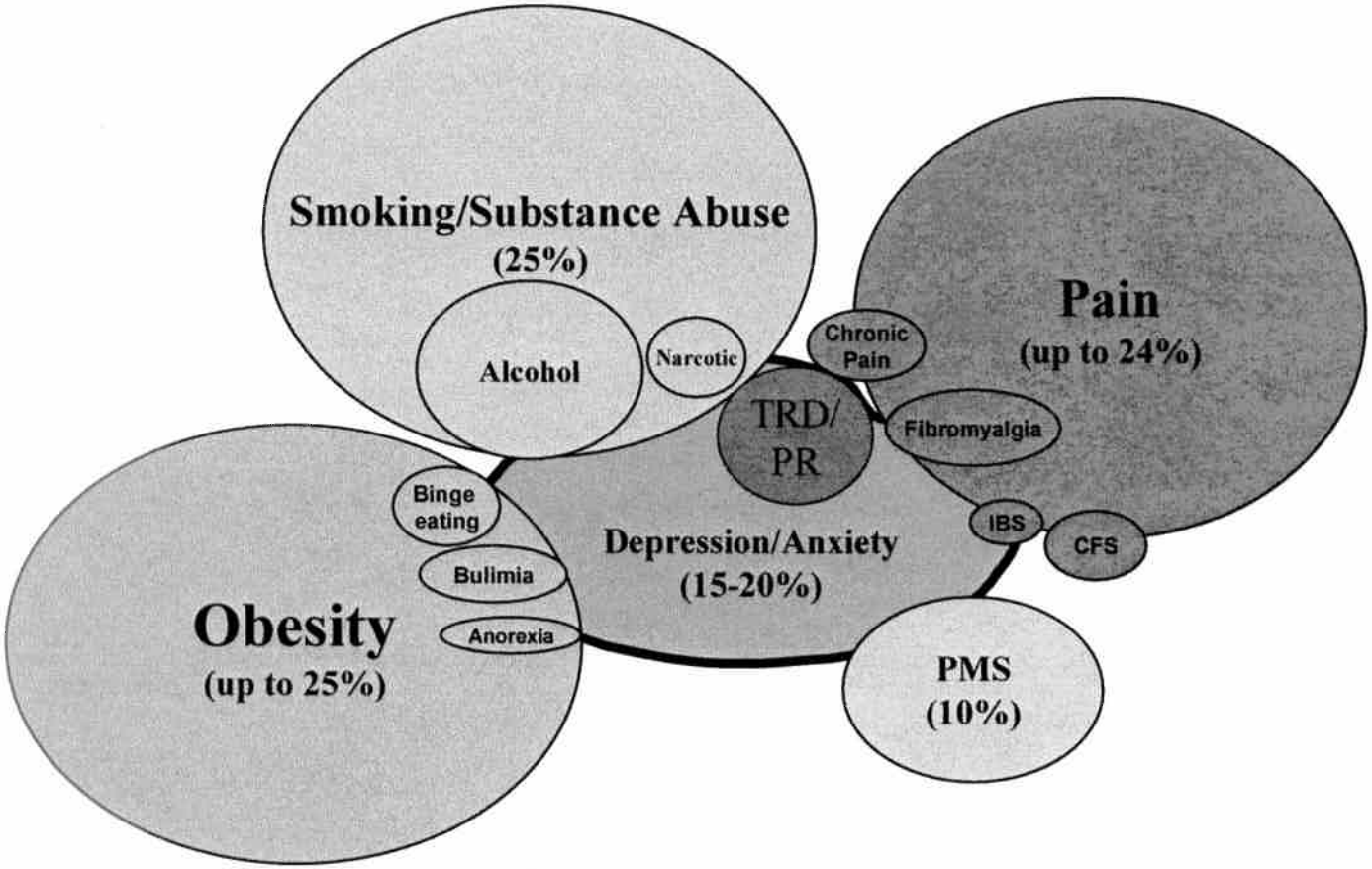
[e]*Generalized anxiety disorder* causes excessive worrying that interferes with daily activities.

Exhibit 6 Anticipated Launch Dates of New Lilly Products

Year	Product	Indication
2001	Xigris Forteo	Severe Sepsis Osteoporosis
2002	Cialis Strattera	Male Erectile Dysfunction Attention-deficit hyperactivity disorder (ADHD)
2003	Alimta Symbyax	Mesothelioma, other cancers Bipolar depression
2004	Oritavancin	Bacterial infections

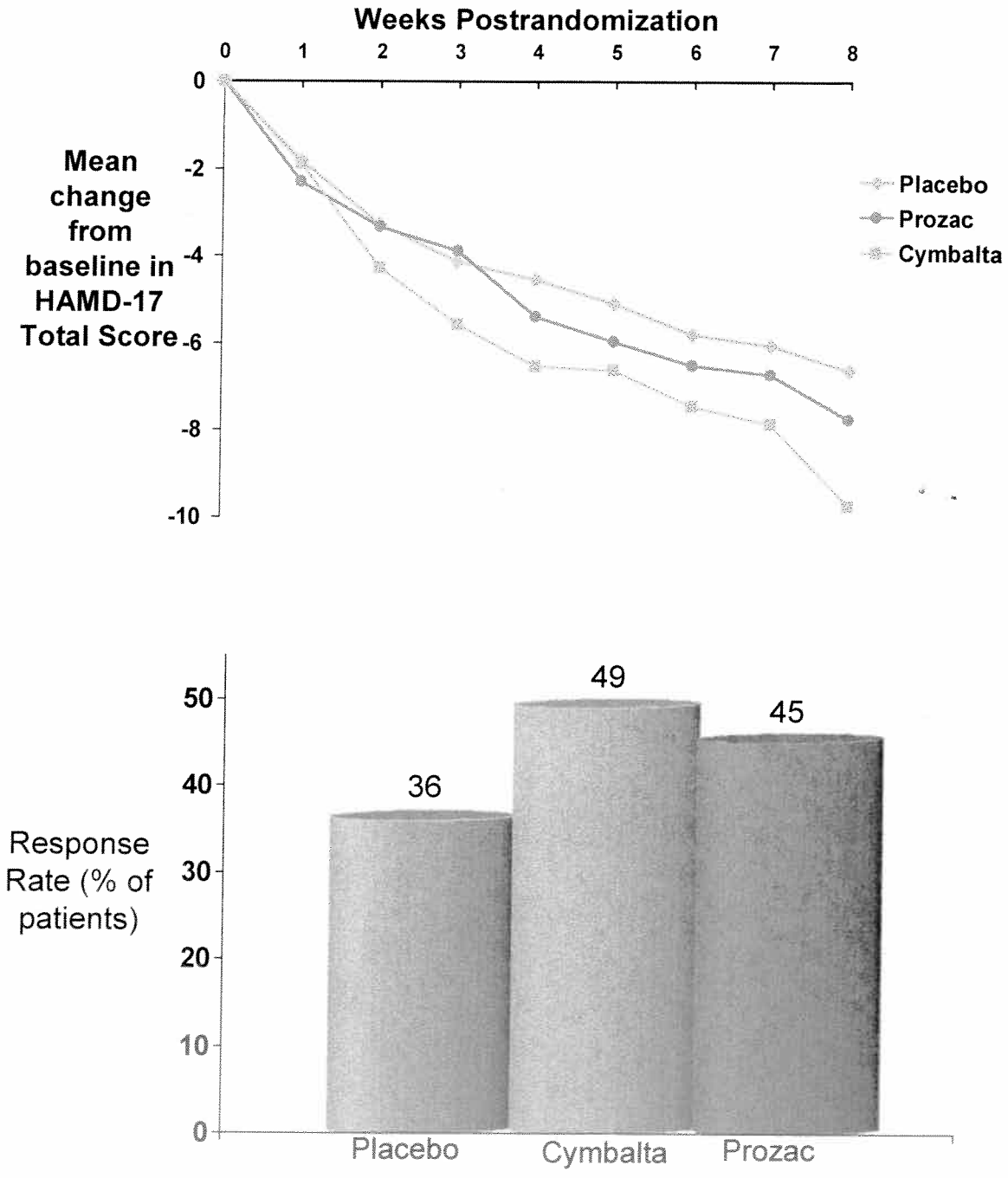
Source: Company documents.

Exhibit 7 Incidence of Comorbidities in Epidemiological Study



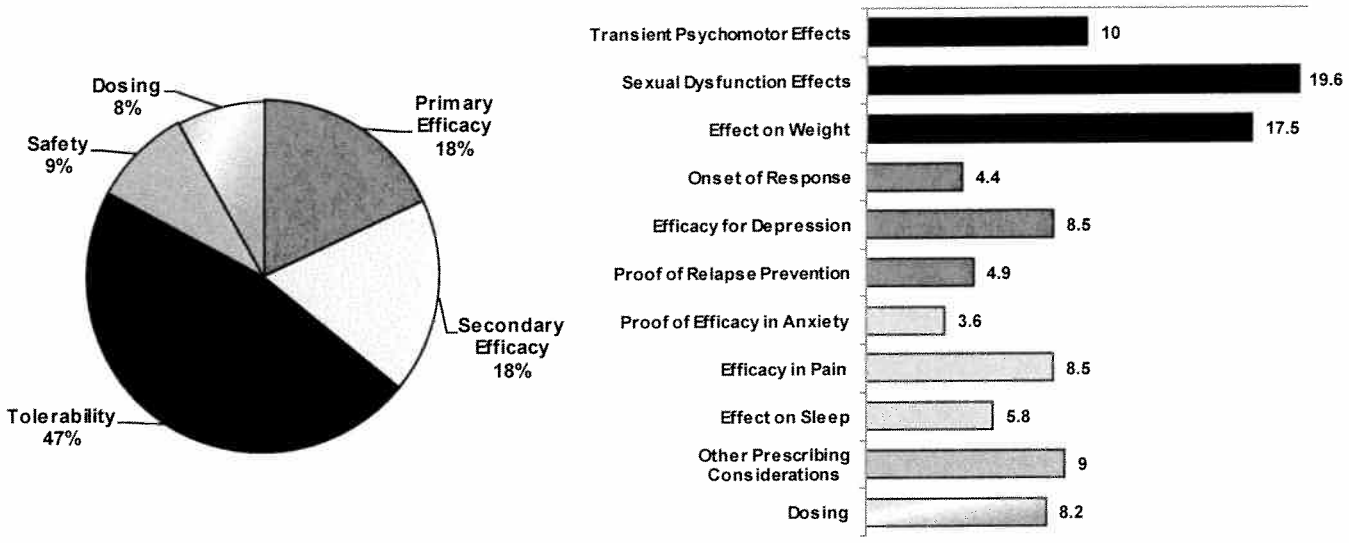
Source: Company documents.

Exhibit 8 Cymbalta Phase II Study—Key Efficacy Findings



Source: Company documents.

Exhibit 9 Conjoint Study—Relative Importance of Antidepressant Attributes to Physicians



Percentages above reflect the relative weight in prescribing for that aspect/attribute (out of 100)

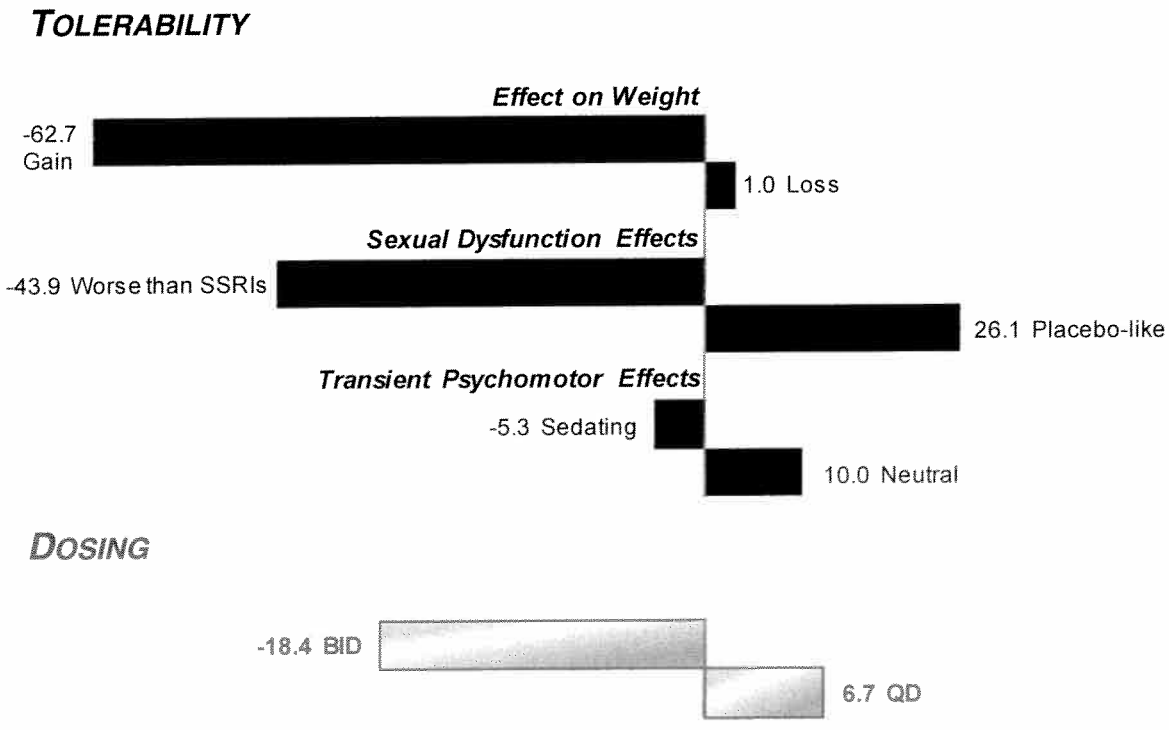
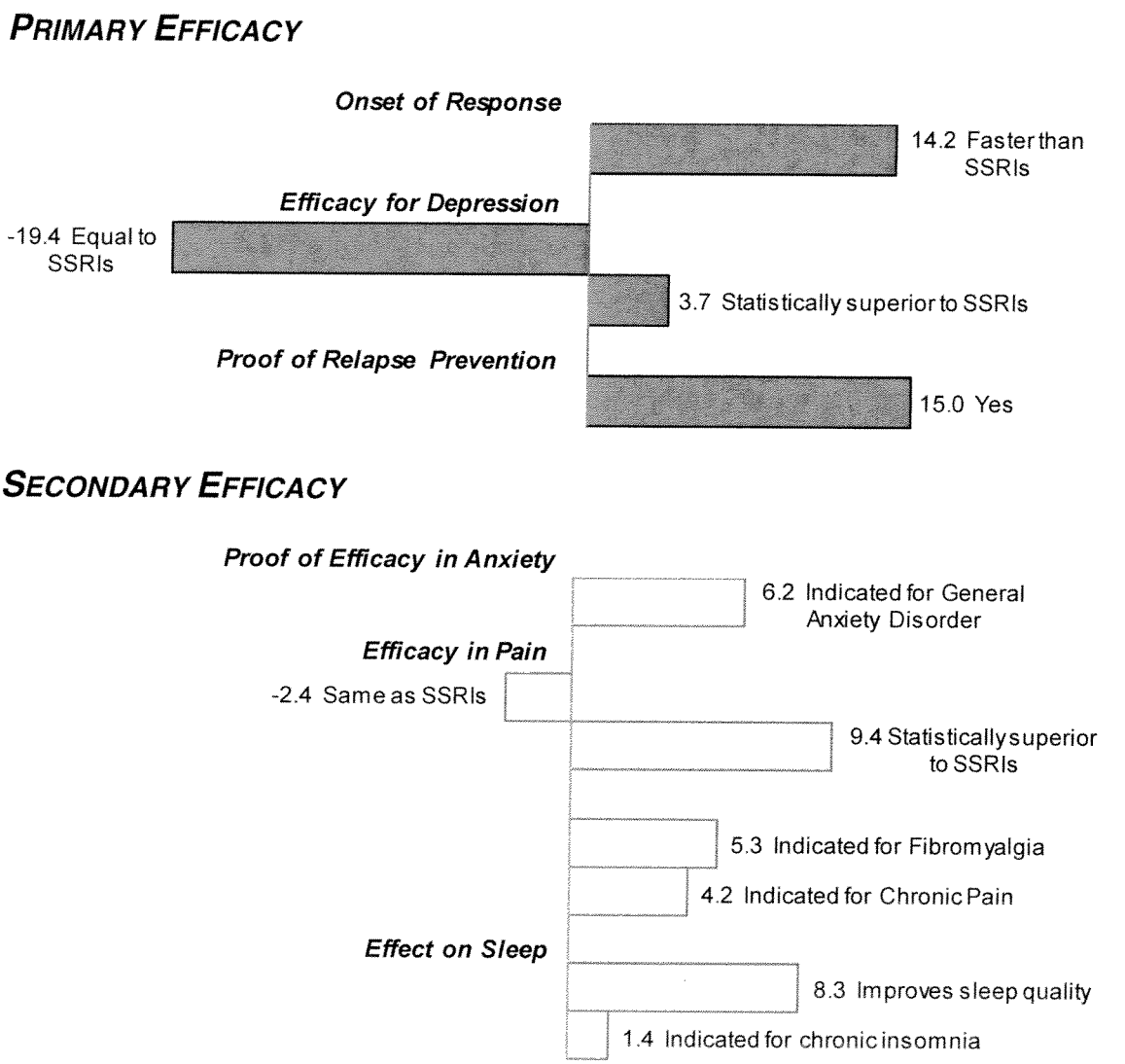


Exhibit 9 (continued)



The impact of each aspect is further broken out by a positive vs. negative or neutral level on that characteristic. Numbers indicate the effect on the likelihood of prescribing (for example, -62.7 means the average physician is 62.7% less likely to prescribe the drug).

Source: Company documents.

Exhibit 10 Patient Segmentation Study—Segment Profiles

Functioning Fran

duloxetine

Segment Size Relative to Sample:	**28%**
Demographics	
Average Age:	39
% Female:	73%
% PCP:	67%
Treatment History	
Average # regimens:	1.7
Average # episodes:	3.1
Average Length of Depression:	5 yrs.
Last Tx Change b/c Side Effects:	45%
Current Presentation	
Global Severity:	Mild to Moderate
% Considered TRD:	5%
% with any Anxiety Symptom:	60%
% with any Pain Symptom:	24%
Top Primary Rx:	fluoxetine, citalopram
% with Secondary Rx:	18%

- Easy to treat, with long term remission expected
- Mild severity of depression and symptoms
- Fewer anxiety symptoms
- Younger, much less chronic and higher functioning
- Many fewer regimens
- Very compliant

Lilly

Addicted Denise

duloxetine

Segment Size Relative to Sample:	**4%**
Demographics	
Average Age:	37
% Female:	62%
% PCP:	52%
Treatment History	
Average # regimens:	2.1
Average # episodes:	3.7
Average Length of Depression:	7 yrs.
Last Tx Change b/c Side Effects:	36%
Current Presentation	
Global Severity:	Moderate
% Considered TRD:	14%
% with any Anxiety Symptom:	86%
% with any Pain Symptom:	35%
Top Primary Rx:	fluoxetine, bupropion
% with Secondary Rx:	30%

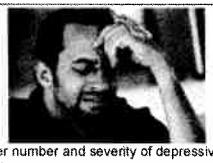
- Abuses drugs and/or alcohol
- Smokes
- Younger
- Many comorbidities and external stressors
- Poor compliance (30% vs. 17%)
- Greater likelihood of being from a minority group (still only 21% minority)

Lilly

Complex Carl

duloxetine

Segment Size Relative to Sample:	**10%**
Demographics	
Average Age:	46
% Female:	42%
% In GP Care:	48%
Treatment History	
Average # regimens:	4.1
Average # episodes:	6.2
Average Length of Depression:	10 yrs.
Last Tx Change b/c Side Effects:	16%
Current Presentation	
Global Severity:	Moderate to Severe
% Considered TRD:	71%
% with any Anxiety Symptom:	95%
% with any Pain Symptom:	68%
Top Primary Rx:	SSRI's, venlafaxine
% with Secondary Rx:	62%



- Higher number and severity of depressive symptoms
- More likely to have comorbid psychotic features, bipolar disorder, or borderline personality
- Very chronic with multiple therapies
- Frequent combination therapy
- Very often considered both TRD and very "Difficult to Treat," with lower expectations for improvement
- Much more likely to have been hospitalized (37% vs. 13%)
- Suspected poor compliance

Lilly

Anxious Anne

duloxetine

Segment Size Relative to Sample:	**19%**
Demographics	
Average Age:	49
% Female:	73%
% PCP:	66%
Treatment History	
Average # regimens:	2.1
Average # episodes:	3.4
Average Length of Depression:	7 yrs.
Last Tx Change b/c Side Effects:	29%
Current Presentation	
Global Severity:	Mild to Moderate
% Considered TRD:	10%
% with any Anxiety Symptom:	82%
% with any Pain Symptom:	34%
Top Primary Rx:	fluoxetine, sertraline
% with Secondary Rx:	30%

- Mild symptoms and severity of depression
- Older, but fewer regimens
- Anxiety often present, but not severe; fatigue absent
- More energy and motivation
- More cost sensitive and likely to pay full amount for Rxs

Lilly

PCP=receive treatment from primary care physician; GP=from a general practice physician
TRD=treatment resistant depression
Rx or Tx=drug prescribed by physician
Secondary Rx =more than one drug prescribed simultaneously to a patient to treat various aspects of their depression symptoms

Exhibit 10 (continued)

Hurting Helen

duloxetine

Segment Size Relative to Sample:	**8%**
Demographics	
Average Age:	54
% Female:	88%
% PCP:	71%
Treatment History	
Average # regimens:	2.6
Average # episodes:	3.5
Average Length of Depression:	9 yrs.
Last Tx Change b/c Side Effects:	24%
Current Presentation	
Global Severity:	Moderate
% Considered TRD:	33%
% with any Anxiety Symptom:	86%
% with any Pain Symptom:	100%
Top Primary Rx:	fluoxetine, sertraline
% with Secondary Rx:	40%

- Always pain, typically severe, and often fatigue/low energy symptoms
- Older, longer length of suffering
- More likely to be overweight and female
- Somewhat difficult to treat, lower expectations on outcome, and consume more than average health care resources
- Disability more common

Lilly

Classic Carol

duloxetine

Segment Size Relative to Sample:	**20%**
Demographics	
Average Age:	44
% Female:	65%
% PCP:	64%
Treatment History	
Average # regimens:	2.0
Average # episodes:	3.6
Average Length of Depression:	7 yrs.
Last Tx Change b/c Side Effects:	28%
Current Presentation	
Global Severity:	Moderate
% Considered TRD:	16%
% with any Anxiety Symptom:	89%
% with any Pain Symptom:	42%
Top Primary Rx:	paroxetine, citalopram
% with Secondary Rx:	28%

- Many classic depression symptoms, i.e. restlessness, appetite change, anhedonia, concentration problems, worry/guilt, irritability/nervousness, low energy, etc.
- Some symptoms, but not all, may be severe
- Average severity overall
- Fewer regimens, less length of depression suffered
- Viewed as easy to treat, consuming fewer resources, with remission expected

Lilly

Non-Responding Nancy

duloxetine

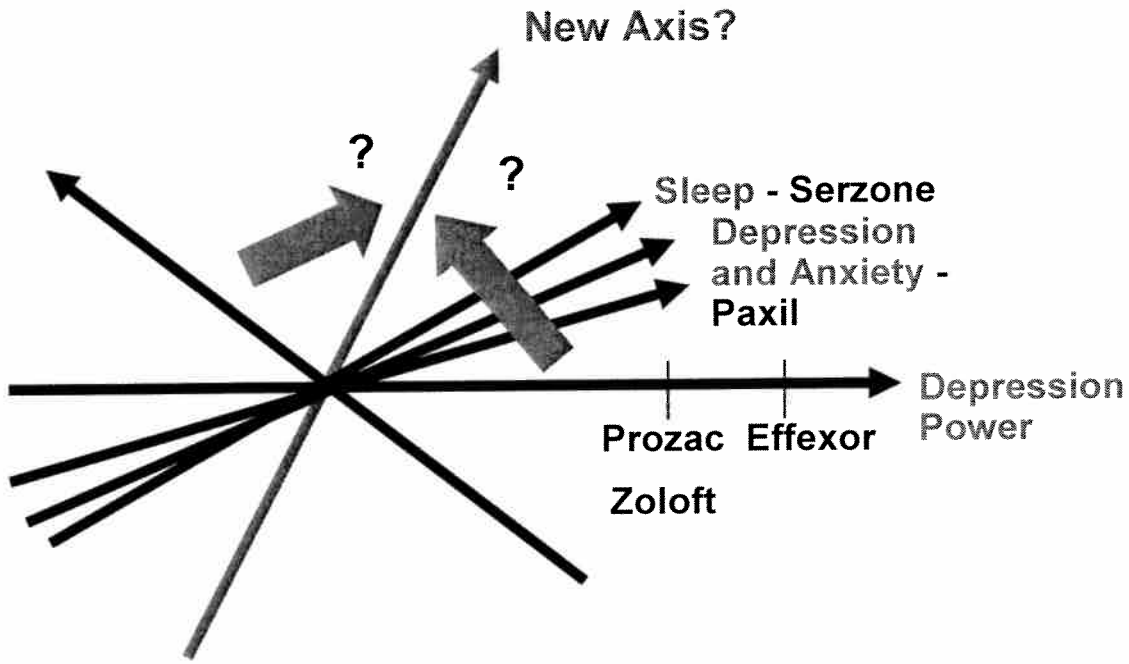
Segment Size Relative to Sample:	**11%**
Demographics	
Average Age:	47
% Female:	81%
% PCP:	47%
Treatment History	
Average # regimens:	4.2
Average # episodes:	5.5
Average Length of Depression:	10 yrs.
Last Tx Change b/c Side Effects:	30%
Current Presentation	
Global Severity:	Moderate to Severe
% Considered TRD:	94%
% with any Anxiety Symptom:	86%
% with any Pain Symptom:	42%
Primary Rx:	fluoxetine, citalopram, venlafaxine
% with Secondary Rx:	50%

- Considered to be TRD
- Very chronic with multiple therapies
- More severe overall and in classic depressive symptoms
- Considered "Difficult to Treat" with lower expectations for improvement
- Frequent combination therapy
- Much more likely to have been hospitalized (29% vs. 13%)
- Suspected poor compliance

Lilly

Source: Company documents.

Exhibit 11 Antidepressant Axis of Competition



Source: Company documents.