

DEPRESSION

In The Market
for Lifting Moods

The antidepressant market,
while mature, is dynamic.

VARIOUS MARKET SHAPERS —

including increased regulatory
oversight and safety-labeling changes;
imminent loss of patent protection for
some leading products;
and the development of new drug
formulations and classes —
are INFLUENCING RESEARCH and
PROMOTIONAL STRATEGIES.

BY CYNTHIA BORDA

Depression is a debilitating illness that affects a person's body, mood, and thoughts. According to the National Institute of Mental Health (NIMH), in any given one-year period, there are about 19 million adults, or almost 10% of the adult population, who suffer from depression. Children and adolescents also suffer from depression, but the statistics are not as clear.

Of all the therapeutic classes within the broad central nervous system sector, depression is the largest. Analysts at Business Intelligence report that global sales of antidepressants in 2004 were just shy of \$16 billion. The U.S. antidepressant market accounted for 71% of the entire world market.

According to Business Communications Company Inc. (BCC), in 2004 the market for drugs used to treat behavioral and emotional disorders in children and adolescents accounted for \$5.0 billion. Selective

serotonin reuptake inhibitors hold a large share of the behavioral and emotional disorder market, at about 40.5%. In the disorder category, anti-anxiety drugs have about a 25% share.

Taking into account a broader spectrum of symptoms and diseases, it is estimated that the worldwide market for drugs that treat mental, emotional, and behavioral problems in children and adolescents was \$13.4 billion in 2005 and is expected to rise at an average annual growth rate of 7.2% to \$19 billion in 2010, according to BCC.

ADDRESSING PATIENT NEEDS

Growth within the depression market is anticipated despite some major challenges: drug safety issues and a lingering stigma related to the disease.

DR. RICHARD MEIBACH
Roche

IN THE DEPRESSION CATEGORY, WE ARE DEALING WITH THE RULE OF THREES: a third of patients respond to treatment, a third respond but do not do well or relapse, and a third do not respond at all.

The competitive antidepressant market experienced some turbulence during 2005. The Food and Drug Administration (FDA) strengthened antidepressant drug safety labeling for both pediatric and adult patients. Reports linking suicide to the use of antidepressants remain highly controversial. Nonetheless, the FDA has asked that a black-box warning be added to antidepressant medication package inserts for use in children and adolescents.

As a result, companies are providing additional education — unbranded awareness and assistance programs — directed toward patients, physicians, and caregivers.

One of the major challenges for physicians and other healthcare professionals is recognizing and adequately treating depression. Patients often do not seek treatment, nor do they communicate with their physician; therefore diagnosing the disease remains difficult.

“There remains a stigma in the United States related to depression,” says John Hixon, Cymbalta marketing director, U.S., at Eli Lilly and Co. “But there has been some progress made with consumer marketing by pharmaceutical companies.”

Barbara Pagano, VP of digital program development at HealthEd, says the many myths about the condition prevent patients from seeking treatment from their doctors.

“There is a huge need to educate patients and motivate them to go the doctor’s office,” she says. “And education has to continue once they are on treatment to make sure they are taking their medication properly, that they are monitoring their conditions, and that they are aware of possible side effects.”

Suneet Varma, VP and global business manager, neuroscience, for Wyeth Pharmaceuticals, concurs.

“One of the biggest challenges for healthcare professionals is the stigma associated with the disease, which is an obstacle to recognizing and treating depression,” he says. “Much progress has been made in this area. But now we have encountered the problem that patients may think depression is a short-term illness, and they want to move off therapy too early. Depression is a serious, chronic medical condition. If patients aren’t treated to remission, the chance of recurrence is extremely high. All parties, including healthcare professionals, patient advocacy groups, and industry, need to continue to focus on long-term outcomes and to provide patients with information and support to help them benefit patients over the long term.”

Treatment of depression may involve psychotherapy, medication, electroconvulsive therapy, or a combination of approaches. Ini-

tial therapy does not always relieve the patient’s symptoms.

“One of the issues to be dealt with is the low percentage of depressed patients who reach remission,” Mr. Hixon says.

Richard Meibach, Ph.D., VP of pharmaceutical development at Roche, states, “We are dealing with the rule of threes: a third of patients respond to treatment, a third respond but do not do well or relapse, and a third do not respond at all.”

Recognizing the challenges practitioners and patients face, pharmaceutical companies

operating in this therapeutic category have initiated various programs to help clinicians with these issues.

Ms. Pagano says an effective education program should work to dispel myths, provide basic facts about the disease, and address managing patient expectations.

“As with any condition, there is no magic pill that makes the difference,” she says. “There have to be lifestyle changes as well.”

THE LEADING ANTIDEPRESSANTS

(BY U.S. SALES DOLLARS, JANUARY 2005 TO SEPTEMBER 2005)

Category	Product	Marketer	Rank Jan to Sept 2005	Jan to Sept 2005 Total \$	Jan to Sept 2005 % Market Share	Jan to Sept 2005 Total % Growth Over Jan to Sept 2004	Year 2004 Total \$	Year 2004 % Market Share
SSRIs				\$5,154.6	100.0%	(19)%	\$8,330.5	100.0%
	Zoloft	Pfizer	1	2,319.5	45.0	(2)	3,149.0	37.8
	Lexapro	Forest	2	1,558.3	30.2	22	1,761.2	21.1
	Paroxetine HCL	Generic	3	394.3	7.6	(32)	698.1	8.4
	Paxil CR	GlaxoSmithKline	4	250.3	4.9	(62)	876.2	10.5
	Fluoxetine HCL	Generic	5	164.5	3.2	(9)	224.7	2.7
	Others			467.7	9.1	(65)	1,621.3	19.5
SNRIs				\$2,497.1	100.0%	20%	\$2,845.9	100.0%
	Effexor XR	Wyeth	1	1,932.0	77.4	(1)	2,612.3	91.8
	Cymbalta	Lilly	2	454.3	18.2	999	80.7	2.8
	Effexor	Wyeth	3	110.9	4.4	(5)	152.9	5.4
Newer Generation Antidepressants				\$1,682.0	100.0%	0%	\$2,212.7	100.0%
	Wellbutrin XL	GlaxoSmithKline	1	1,072.1	63.7	44	1,060.7	47.9
	Bupropion HCL SR	Watson Labs	2	158.7	9.4	22	168.2	7.6
	Budeprion SR	Teva	3	120.1	7.1	31	124.4	5.6
	Wellbutrin SR	GlaxoSmithKline	4	105.8	6.3	(80)	620.4	28.0
	Bupropion HCL SR	Generic	5	102.9	6.1	28	112.6	5.1
	Others			122.3	7.3	24	126.4	5.7

Notes: Information in National Sales Perspectives is derived from IMS Health’s DDD service and is the most comprehensive, national-level prescription sales database. The National Sales Perspectives tracks sales activity for all pharmaceutical distribution channels, including major retail food stores and chains, mass merchandisers, independent pharmacies, mail-service pharmacies, hospitals, clinics, closed-wall HMOs, long-term care, home healthcare, and prisons/universities. Sales information is compiled from more than 100 pharmaceutical manufacturers and more than 300 wholesaler and chain warehouses. Dollars are in millions.

Source: IMS Health Inc., Fairfield, Conn.; IMS National Sales Perspectives Audit November 2005. For more information, visit imshealth.com.



SUNEET VARMA
Wyeth

The biggest challenge is suboptimal outcomes. **THERE ARE STILL MANY WHO THINK OF DEPRESSION AS A SHORT-TERM ILLNESS, BUT REALLY IT IS A LONG-TERM MEDICAL CONDITION.** We need to think more about long-term outcomes and maintaining wellness.

Education plays an important role in the overall treatment of the

condition.”

Mr. Varma says Wyeth is aligning good

clinical practice with good marketing practice to benefit patients and physicians alike.

“With the knowledge that depression can return to a patient up to a year and a half after treatment, it is important that we evaluate the

long-term benefits of our medicines,” he says. “We’ve conducted several long-term prevention studies with this in mind. In fact, Effexor XR is approved for the use of prevention of recurrence for up to one year.”

Partly inspired by a number of published clinical studies, Wyeth launched in June 2005 an unbranded support and education program for patients diagnosed with depression. Wyeth’s program, Dialogues: Time to Talk, is designed to increase patients’ understanding of their illness and therapy and to assist in tracking patients’ progress.

Patients taking Effexor have the option to enroll in Wyeth’s telephone support services, which can be accessed through a series of calls from nurses or unlimited calls into the Dialogues: Time to Talk help line.

Patients are asked assessment questions by phone and can enter responses via the touch pad. Within 48 hours, the responses are sent to the patient’s primary physician regarding the patient’s therapeutic progress. Over the course of several months, patients who enroll receive educational materials that have been developed in consultation with physicians and patients to address common therapeutic needs.

Lilly also has unbranded consumer campaigns to provide patient support. Support Partners offers step-by-step guidance to help people with depression, and their loved ones, build partnerships that help make recovery more achievable. Lilly’s Depression Hurts Website offers tools for patients to explore information about some of the common emotional and painful physical symptoms of depression, a self-assessment, the causes of depression, and how to get help.

“We have the Support Partners program designed to guide friends or loved ones through steps to help patients who are depressed,” Mr. Hixon says. “Depression Hurts is a program that guides patients through physical symptoms associated with depression. Expedition Hope is a program to raise awareness and help erase the stigma of depression.”

Ms. Pagano says the Web lends itself very well to education by being able to combine interactive video and audio with text-based learning.

“Research has shown that it’s the No. 2 place that people seek healthcare information,” she says. “Having that presence online is essential. Particularly with a condition like depression, people want to be able to have that access to explore that condition in the privacy of their own home.”

Mr. Hixon says Lilly’s “Welcome Back Awards” program is another initiative that the company has undertaken to mitigate the stigma associated with the disease.

ABOUT DEPRESSION

- ▶ Depressive disorders affect about 19 MILLION AMERICAN ADULTS.
- ▶ NEARLY TWICE AS MANY WOMEN (12%) AS MEN (7%) are affected by a depressive illness each year. At some point during their lives, as many as 20% OF WOMEN HAVE AT LEAST ONE EPISODE of depression that should be treated. Although conventional wisdom holds that depression is most closely associated with menopause, in fact, the childbearing years are marked by the highest rates of depression, followed by the years before menopause.
- ▶ Large-scale research studies have reported that UP TO 2.5% OF CHILDREN AND UP TO 8.3% OF ADOLESCENTS IN THE UNITED STATES SUFFER FROM DEPRESSION. In addition, research has discovered that depression onset is occurring earlier in individuals born in more recent decades. There is evidence that depression emerging early in life often persists, recurs, and continues into adulthood and that early-onset depression may predict more severe illness in adulthood.
- ▶ DEPRESSION IN CHILDREN AND ADOLESCENTS IS ASSOCIATED WITH AN INCREASED RISK OF SUICIDAL BEHAVIORS. Over the last several decades, the suicide rate in young people has increased dramatically.
- ▶ In a given year, BETWEEN 1% AND 2% OF PEOPLE OVER AGE 65 LIVING IN THE COMMUNITY (those not living in nursing homes or other institutions) SUFFER FROM MAJOR DEPRESSION, AND ABOUT 2% HAVE DYSTHYMIA. Additionally, recent studies show that 13% TO 27% OF OLDER ADULTS HAVE SUBCLINICAL DEPRESSIONS that do not meet the diagnostic criteria for major depression or dysthymia but are associated with increased risk of major depression, physical disability, medical illness, and high use of health services. Suicide is more common among the elderly than any other age group.
- ▶ Brain-imaging technologies are revealing that in depression, THE NEURAL CIRCUITS responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly and that CRITICAL NEUROTRANSMITTERS — chemicals used by nerve cells to communicate — ARE OUT OF BALANCE.
- ▶ Genetics research indicates that VULNERABILITY TO DEPRESSION RESULTS FROM the influence of MULTIPLE GENES ACTING TOGETHER WITH ENVIRONMENTAL FACTORS.
- ▶ One of the most challenging problems in depression research and clinical practice is refractory — hard to treat — depression. While about 80% OF PEOPLE WITH DEPRESSION RESPOND VERY POSITIVELY TO TREATMENT, A SIGNIFICANT NUMBER OF INDIVIDUALS REMAIN TREATMENT REFRACTORY. Even among treatment responders, many do not have complete or lasting improvement, and adverse side effects are common.

Source: The National Institute of Mental Health, Bethesda, Md.
For more information, visit nimh.nih.gov.



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Each year, Mr. Hixon says, an independent committee of national mental health leaders selects honorees in the following categories: lifetime achievement, community service, destigmatization, primary care, and psychiatry.

A MATURING MARKET

With many of the major products in the later stages of their life cycles, pharmaceutical companies are evaluating strategies to maximize their positions as well as evaluating compounds in the pipeline to replace market-share leaders upon patent expiration.

A report by Espicom says there are five key areas of unmet clinical need that will have to be addressed to drive further growth of the market. These include improvements in the efficacy, speed of onset, and safety/tolerability of drugs as well as reductions in remission rates and relapse/recurrence.

“The biggest challenge for the pharmaceutical industry in the depression arena is finding new targets, something that works,” Dr. Meibach says.

The monoamine oxidase inhibitors and tricyclics work well, but the dosing and side effects are inconvenient.

The selective serotonin reuptake inhibitors (SSRIs) are probably the best known subclass of depression treatments. Current IMS Health data (January to September 2005) show Zoloft (sertraline) in the top spot, with more than \$2.3 billion in sales to date.

SSRIs work by inhibiting the reuptake of serotonin and allowing for more enhanced serotonergic activity. Selective inhibition has decreased the side effects associated with earlier medications that inhibited other neuroreceptors as well.

There is another class of compounds known as the serotonin and noradrenaline reuptake inhibitors (SNRIs), also referred to as dual uptake inhibitors. Current IMS data have Effexor XR (venlafaxine) in the No. 2 spot with almost \$2 billion in sales.

These sales data make clinical sense since some reports indicate that SNRIs are often not the first drug of choice among clinicians but are reserved for patients refractory to SSRIs. The SNRIs work by inhibiting the uptake of both serotonin and neuroadrenaline, both of which are implicated in depression.

Finally, several medications with different mechanisms of action are often categorized into what is known as the newer generation antidepressants. Included in this group are the noradrenaline plus specific serotonin-2 and -3 antagonism Remeron (mirtazapine) and the selective norepinephrine and dopamine reuptake inhibitor Wellbutrin XL (bupropion),

which defines a novel class of antidepressant that has no direct actions on the serotonin system. IMS data show Wellbutrin XL ahead in this class with more than \$1 billion in sales.

MOVING FORWARD

Several new molecules or compounds are being studied for use in depression. The compound that is most likely to hit the market first is a triple reuptake inhibitor. These medications inhibit three neurotransmitters linked to depression: serotonin, norepinephrine, and dopamine. They are still selective, thereby limiting side effects, yet they potentially can reach therapeutic effect faster than the dual reuptake inhibitors.

According to a report by Decision Resources Inc., the two companies most likely to reach the market first are GlaxoSmithKline and Merck, with launches estimated in 2009 and 2011, respectively.

Substance P antagonists or neurokinin (NK)-1 antagonists have been studied for about a decade for use in depression and other illnesses, such as chemotherapy-induced nausea and vomiting as well as anxiety.

“Placebo responses are higher than in any other area of research, as much as 50%,” Dr. Meibach says. “So we have to conduct two or three trials just to get one positive trial.”

Other areas of focus for depression treatment include selective adenosine A(2A) receptor antagonists, beta-3 agonists, 5HT-1A compounds, CRF-1 antagonists, and NMDA antagonists, which already are being studied and used in moderate-to-severe Alzheimer’s dis-

ease patients. Research also shows that NMDA antagonists have an antidepressant effect.

Another novel approach to treatment is a topical selegiline product by Bristol-Myers Squibb. Selegiline is a monoamine oxidase (MAO) inhibitor that has excellent antidepressant properties but is limited in use because of the issues with dietary restrictions associated with tyramine ingestion. Using a topical product provides the benefits of an MAOI without the dietary restrictions since the intestinal mucosa is not directly involved.

The future of all of these drug classes and products rides on safety, efficacy, minimal side effects, and a different mechanism of action.

“The future direction for antidepressants has to be innovative,” Mr. Varma says. “Hopefully, there will be drugs offering improved efficacy, perhaps with multiple and novel mechanisms of action, which will come to market for the treatment of depression.”

Dr. Meibach says the category will benefit from drugs that can target specific populations, for example patients who have comorbid conditions along with depression, such as heart disease: postsurgical patients; or patients who are refractory to treatment.

“A more comprehensive wellness plan needs to be developed for patients,” Mr. Hixon adds. “Depression is not going away, so companies need to get patients into programs that include cognitive therapy, diet, and exercise, and partner support along with medication.” ♦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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