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Insight: Antidepressants give drugmakers the blues

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By Kate Kelland and Ben Hirschler
LONDON | Fri Mar 23, 2012 1:27pm GMT

(Reuters) - The development of a novel antidepressant ground to a halt this week when researchers found it did not make patients feel any

The drug firms took the hit, with shares tumbling in Targacept, while AstraZeneca wrote off a total of $146.5 million for the drug's failure.

It was bad news for investors and bad news for patients - and a depressingly familiar tale for drugmakers seeking to develop new treatments for brain illnesses.

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Data from Thomson Reuters Pharma shows returns for pharmaceutical companies in the antidepressant market are collapsing - despite widespread use of pills like Prozac - as patents expire and new drugs fail to make it to market.

Some Big Pharma firms are quitting the field altogether. Others are hacking back investment and shedding jobs.

These might seem like prudent decisions in an increasingly expensive and frustrating field. Other diseases such as cancer and diabetes are reckoned to be better areas to be in these days. Yet some scientists say the timing could hardly be worse.

Researchers who study the brain believe they are finally figuring out the basic mechanics of depression and other mental disorders, discoveries that should open the door to far more effective ways to tackle illnesses that can cripple society.

"It's a great time for brain science, but at the same time a poor time for drug discovery for brain disorders," says David Nutt, professor of neuropsychopharmacology at Imperial College London. "That's an amazing paradox which we need to do something about."

HIGHEST BURDEN

The numbers say it all.

Major depression affects around 20 percent of people at some point in their lives. The World Health Organization predicts that by 2020, depression will rival heart disease as the health disorder with the highest disease burden in the world.

Around a third of all Americans and 40 percent of all Europeans could be classified as mentally ill, with a European study last year finding that almost 165 million people in the region suffer each year from a brain disorder of some kind.

The study covered more than 100 illnesses from insomnia through depression to schizophrenia.

In the developed world, at least, we are popping more pills than ever. One in five adults in the United States is now taking at least one psychiatric drug, according to data from Medco Health Solutions, a pharmacy benefit manager.

But the drugs only work in some of the people some of the time, and there is an urgent need for new, more effective therapies.

"The burden of these diseases is huge, and the costs are enormous -- and it's only going to get worse with increasing life expectancy," said Colin Blakemore, professor of Neuroscience at Britain's Oxford University.

It is a human tragedy that should, in theory, also be a major market opportunity for drugmakers. The problem is that realizing the potential gains is proving extremely hard.

"GIVE A RAT COCAINE"

Just ask investors who took a punt on TC-5214, the failed antidepressant from AstraZeneca and Targacept. Their rollercoaster ride crashed to a halt on Tuesday.

Back in July 2009 things looked very different as Targacept shares more than doubled after TC-5214 tested extremely well in a mid-stage study. That success could not be replicated in later, larger trials.

AstraZeneca and Targacept are not alone. Last October, Novartis halted work on another antidepressant called agomelatine, resulting in an $87 million charge, adding to other high-profile failures, such as Merck & Co's aprepitant.

TC-5214 was designed to work in a novel way by modulating nicotine receptors in the brain - a scientific approach that reflects Targacept's origins inside R.J. Reynolds Tobacco.

The idea seemed good but, compared to testing new medicines in other fields, working out if an antidepressant works is extremely difficult.

The biology of the disease is poorly understood and early tests on animals are not much use either, since mice cannot tell or show scientists what they are feeling.

"Depression is one of the worst areas for animal models," said Nutt. "It contrasts very strongly with addiction, for example. You give a rat cocaine, it behaves like a human -- it gets hyperactive, it runs around, it likes it, it wants more. Whereas in depression, the animal models have ... no obvious validity."

THE PLACEBO EFFECT

Placebo drugs - or sugar pills - typically have a massive impact in lifting depression, underscoring the subtlety of the disease and the suggestibility of patients.

That makes it "very, very hard" to prove that a particular drug is actually working, according to GlaxoSmithKline's research head Moncef Slaoui.

"You can have depression medicines that in absolute numbers may show a 5 percent difference versus placebo because there was a placebo response of 50 percent and a drug response of 55 percent," he told Reuters. "Even with approved drugs sometimes you achieve the endpoint and sometimes you miss it."

As a result, in the absence of compelling new science, GSK decided two years ago to throw in the towel on depression and some other areas of neuroscience.

Others cutting neuroscience work in recent years include Merck, Sanofi, Novartis and AstraZeneca, with the latter deciding in 2010 to stop discovery work in depression even as it continued with development of TC-5214.

The commercial impact is stark. Across the industry, sales are sliding fast as popular selective serotonin re-uptake inhibitors (SSRIs) like Eli Lilly's Prozac and GSK's Paxil are dispensed as cheap generics and new medicines of a similar type, such as Viibryd from Forest Laboratories, fail to bridge the revenue gap.

Worldwide sales of antidepressants, which peaked at $15 billion in 2003, are now expected to fall to under $6 billion by 2016, according to Thomson Reuters Pharma projections, based on consensus forecasts from analysts.

BRAIN SCANS AND MAGIC MUSHROOMS

Brain scientists say it is time for some fresh approaches.

"What we want to do is start from understanding the illness," says Nutt. And he and others are increasingly confident they are starting to do that.

Nutt points to work by psychiatrist Catherine Harmer at Oxford University, who published what one expert commentator called a "paradigm-changing" study in the American Journal of Psychiatry in 2009.

It showed that, counter to previous thinking, antidepressants actually start working instantly even though patients may not notice the effects for months because it takes time for small changes to build up and alter their world view.

In separate research using functional magnetic resonance imaging (fMRI) brain scans, Harmer's team showed that activation of the amygdala - the brain's emotional hub - is blunted by antidepressants even after the first few doses.

Since emotional disorders such as depression and anxiety are linked with hyperactivity of the amygdala, this is thought to have an almost immediate but subconscious effect on reducing patients' negative responses.

"So now we have this new theory - and it has quite a bit of evidence now - that what antidepressants do is to change cognitive bias so that people start to see the world as a more positive place," said Nutt.

In research published in January, Nutt and colleagues scanned the brains of people tripping on psychedelic magic mushrooms and found, counter-intuitively, that the active ingredient psilocybin does not increase but rather suppresses activity in key areas of the brain.

Because the dampening effect of just one small dose of psilocybin was rapid and similar to that prompted by other depression treatments including drugs like Prozac, as well as cognitive behavioral therapy (CBT) and deep brain stimulation, the findings suggest magic mushrooms and other psychedelics could in future also be used to treat depression.

A study out this month found that another controversial treatment - electroconvulsive or electric shock therapy - also appears to turn down overactive connections between parts of the brain that control mood and parts that control thinking and concentrating.

"We're starting to get a new understanding of brain mechanisms - not just in terms of what drugs do, but where they do it," said Nutt. "It's important to see the brain as a whole, and the research benefits of that are going to be quite profound."

(Reporting and writing by Kate Kelland and Ben Hirschler, editing by Peter Millership)

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