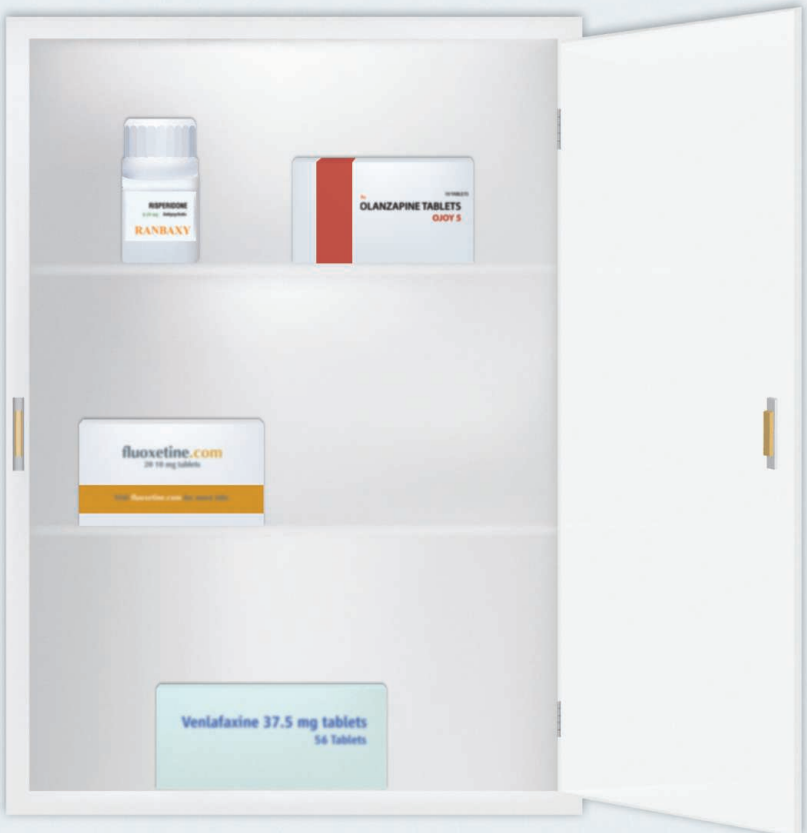

Is Pharma Running Out of Brainy Ideas?

Recent cutbacks raise concerns about the future of drug development for nervous system disorders

WHEN EMILIANGELO RATTI FOUND OUT late last year that GlaxoSmithKline (GSK) planned to pull the plug on drug discovery in some areas of neuroscience, including pain and depression, he knew he had to do something. As a senior vice president and head of the pharmaceutical company's center for drug discovery in neuroscience, Ratti oversaw work at two centers that were targeted for closure, one in Harlow, U.K., and one in Verona, Italy. Ratti scrambled to arrange a deal with an American contract research organization called Aptuit, which took over the Verona facility on 1 July and will provide research for hire for GSK and other companies. "I'm very proud of that because I've been able to secure the future of my 500 people," Ratti says. At the Harlow facility, hundreds of employees have been laid off, while many others have been transferred within GSK, Ratti says.

In announcing the move to investors and analysts on 4 February, GSK Chief Executive Andrew Witty explained that pain, depression, and anxiety were areas where "we believe the probability of success is relatively low, [and] we think the cost of attaining success is disproportionately high." Ceasing research in these areas would save GSK £250 million ($387 million) by 2012. A few weeks later, news came that AstraZeneca was closing research facilities in the United States and Europe and ceasing drug-discovery work in schizophrenia, bipolar disorder, depression, and anxiety.

These cutbacks by two of the top players in drug development for disorders of the central nervous system (CNS) have raised concerns that the pharmaceutical industry is pulling out, or at least pulling back, in this area. In direct response to the cuts at GSK and AstraZeneca, the Institute of Medicine (IOM) Forum on Neuroscience and Nervous System Disorders organized a meeting in late June that brought together leaders from government, academia, and private foundations to take stock. (The forum's chair, Alan Leshner, is also the executive publisher of *Science*.)

"The biggest problem isn't the announcements by GSK and AstraZeneca, it's when you look at the pipeline and see what companies are actually doing in psychiatric drug development," says Thomas Insel, director of the National Institute of Mental Health. "There are very few new molecular entities, very few novel ideas, and almost nothing that gives any hope for a transformation in the treatment of mental illness."

That's worrying, Insel and others say, because the need for better treatments for neurological and psychiatric disorders is vast. Hundreds of millions of people are afflicted worldwide. Yet for some common disorders, like Alzheimer's disease, no truly effective treatments exist; for others, like depression, the existing drugs have limited efficacy and substantial side effects.

What's in the pipeline?

At first glance, the situation doesn't appear to be so dire. A report released 14 July by the Pharmaceutical Research and Manufacturers of America (PhRMA) touts a record-high 313 drugs in the pipeline for mental health disorders such as depression, anxiety, and addiction. Another report, commissioned by IOM for the June meeting and prepared by the Tufts Center for the Study of Drug Development, identified 1747 drugs in development for a much longer list of disorders, including degenerative diseases like multiple sclerosis and neurological conditions like epilepsy. Indeed, the Tufts report suggests that the pipeline has expanded rapidly for many conditions in recent years (see graph, p. 503). But a closer look tells a different story, says Steven Hyman, a psychiatrist and former NIMH director who is now provost at Harvard University. Many of the drugs in clinical trials have long been approved and are now being tested for a new indication, Hyman says. Looking over the Tufts and PhRMA reports' lists of drugs in

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late-stage clinical trials for depression, he notes that both are loaded with antipsychotic drugs, including Risperdal (risperidone) and Seroquel (quetiapine), two of the first "atypical antipsychotics" approved by the Food and Drug Administration in the 1990s. "People with depression can have anxiety and agitation, and low doses of antipsychotics seem to improve those symptoms," Hyman says. "But they don't necessarily have an independent effect on the core depressive symptoms, and they come with a real side-effect burden."

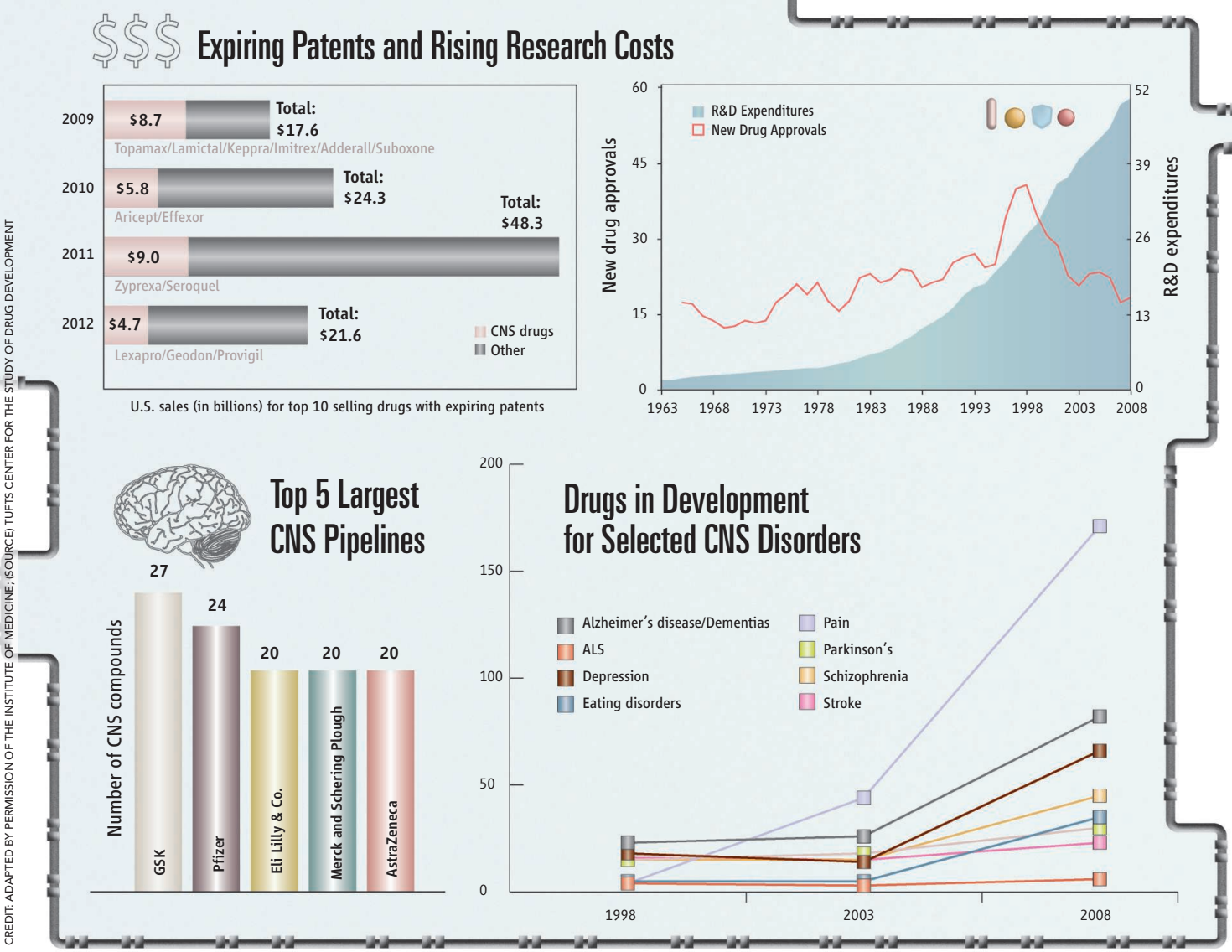
Other treatment candidates have limitations as well. Both lists include Corlux (mifepristone, better known as RU-486, the abortion drug). Even if it proves effective for depression, it couldn't be prescribed for women of reproductive age, Hyman notes. The Tufts list includes Agomelatine, a drug that boosts the effects of the hormone melatonin and blocks receptors for the neurotransmitter serotonin. Hyman says there's little compelling evidence that boosting melatonin has antidepressant effects, and he notes that the drug has had mixed results in European trials for depression. "This is hardly a rich pipeline," Hyman says. "It suggests a sad dearth of ideas and involves lots of attempts at patent extensions and new indications for old drugs."

Risky business

The reasons for the seeming lack of innovation are partly historical, says William Potter, who retired in January from Merck, where he was vice president for neuroscience. In the 1980s and '90s, drug companies realized that they could make billions of dollars a year off drugs that were slightly modified versions of already-approved medications, particularly the SSRI antidepressants like Prozac, Potter says: "The investment in truly innovative projects was not as deep as it might have been because you could make so much money from 'me, too,' drugs."

The current climate for innovation may be even worse. Companies will soon lose billions of dollars in revenue as patents expire on dozens of blockbuster drugs (see figure, below). Meanwhile, the costs of research and development are rising. "Most companies don't see where they're going to be getting the cash flow, so they're having to be more conservative," Potter says. "You can't just ask companies to throw money at something that might not pay off."

The Tufts report suggests that pharma executives have good reason to see investments in CNS drug development as riskier



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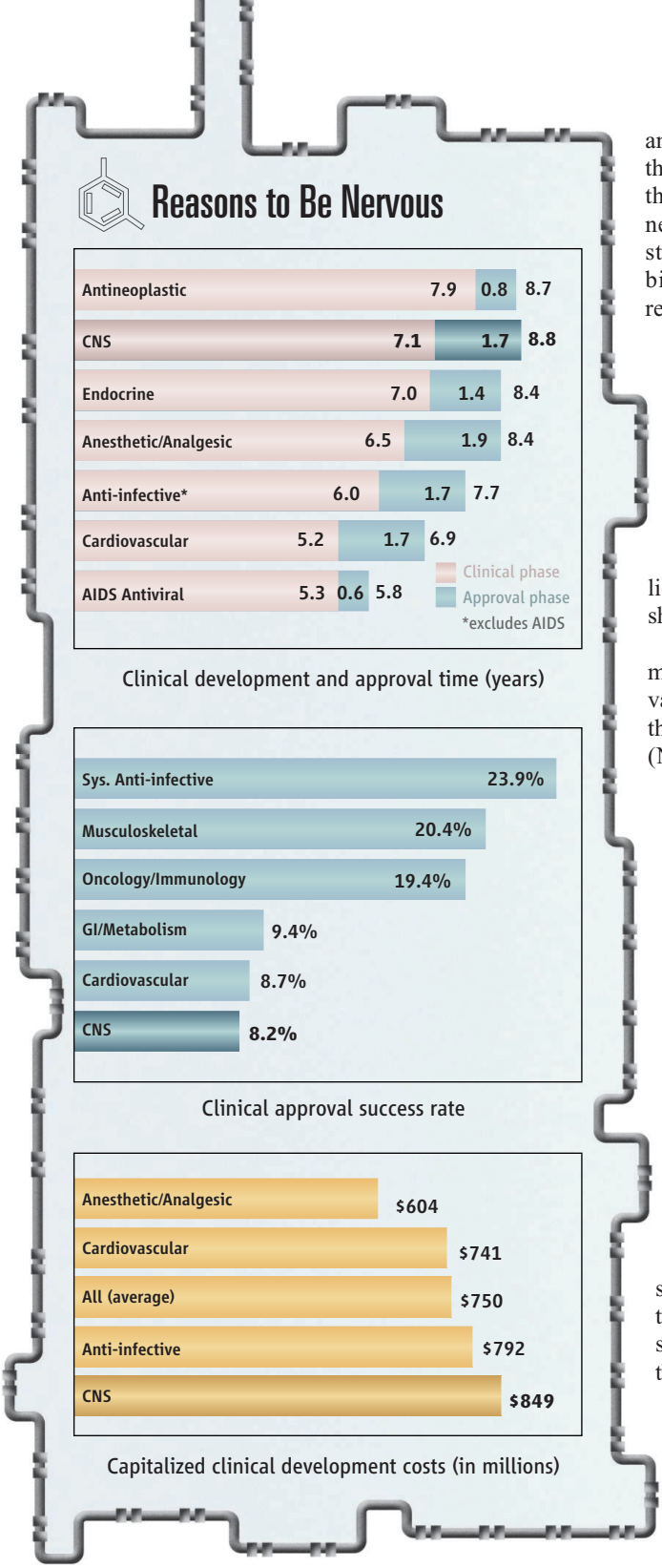
than investments in other areas. CNS drugs cost more and take longer to bring to market than other types of drugs (see figure, right). And only 8% of CNS drugs that make it to clinical trials end up being approved, about half the average success rate across all therapeutic areas. Moreover, when CNS drugs fail, they tend to do so in late-stage clinical trials, after a significant investment has been made, says Kenneth Kaitin, director of the Tufts center.

Adding to those troubles, the animal models, particularly for psychiatric disorders, are far from perfect at predicting which compounds will be effective in humans, and the clinical trials are often more complicated for CNS disorders, says Ratti. These disorders tend to be complex and intermittent, and their symptoms often defy objective measurement. "All these things together are making discovery and development in neuroscience significantly risky," he says.

Many companies see areas like oncology and autoimmune disorders as safer bets, says Steven Paul, who stepped down in February as executive vice president for science and technology for Eli Lilly and Co. "Their perception is that the science is a little richer and the odds are less daunting in some of these other areas," he says. Even within neuroscience, Paul says, some companies may see psychiatric drugs as a bigger gamble than drugs for neurological conditions. Paul, who is a psychiatrist, says he doesn't necessarily agree with that assessment: "I personally believe there are compelling pathways and new targets to pursue."



Seeking a new model

Given the economic challenges, experts inside and outside pharma say the old model of drug development, in which companies assume all the risks and costs of searching for new drugs and shepherding them from test tube to clinic, is no longer viable. "Traditionally, they would have significant internal research groups that would be as good as anyone at doing some of the basic research that might lead to new targets," says Adrian Ivinson, who directs the Harvard NeuroDiscovery Center. "We're seeing less and less of that."

Many companies are trying to reduce costs by outsourcing R&D. AstraZeneca and GSK both set up R&D centers in Shanghai, China, in 2007, for example. The GSK center focuses on developing treatments for multiple sclerosis, Parkinson's, and Alzheimer's diseases; its work on those disorders will continue despite the recent cutbacks in other areas of neuroscience. Another outsourcing strategy involves contracting with biotech companies and academic researchers to do some of the early drug-discovery work that was previously done in-house. "They are sending scouts out into the community to talk to groups like ours and many others to identify projects with potential for drug discovery," Ivinson says. In a typical arrangement, a company funds a research project in exchange for the right to license any resulting compounds that show therapeutic potential.

At the IOM meeting, there was much discussion about public-private partnerships. Insel notes that the U.S. National Institutes of Health (NIH) already has a drug-discovery effort that might serve as a model, the Therapeutics for Rare and Neglected Diseases project launched last year. A measure in the new U.S. health-care legislation could expand NIH's role: It authorizes up to $500 million a year for a "Cures Acceleration Network" aimed at speeding drug development (*Science*, 26 March, p. 1562). "It's a strong message from Congress that they would like to see NIH more involved in drug discovery and drug development," says Insel.

Another possibility might be a shared repository of compounds. "Pharma has thousands and thousands of compounds that are leads they've decided not to follow," Insel says. "Would it make sense to put those into a resource that other people could begin to mine?" In May, GSK made public a library of potential malaria drugs, but neurology and psychiatry are far more lucrative markets. An open-access library of compounds would involve a host of challenges, not the least of which are questions about intellectual property, Insel says. "These are big and thorny issues, but we have got to grapple with them so that 10 years from now we're not looking at the same list of compounds that we know don't work well enough and hoping that if we just give them to a different group of patients we'll get a better outcome."

–GREG MILLER

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