

# Neurology

New therapies are shaking up MS and insomnia, while the slow pace of progress in Alzheimer's continues to frustrate patients and physicians alike. Welcome to neurology, where, **Joe Dysart** reports, treatment breakthroughs in certain areas are counteracted by setbacks in others

**N**eurology has seen some head-turning new developments during the past year, even as researchers toil on to solve some of its more stubborn mysteries. As Kantar Health medical director Amit Dhawan puts it, the sector is “one of the next frontiers in medicine, with emerging therapies that are transformative—not just in the next few years, but over the next few decades.”

Indicative of that makeover has been Tecfidera, a new drug for multiple sclerosis which became a blockbuster for Biogen Idec in 2014. The pill racked up \$1.2 billion in worldwide sales in just the first half of the year, leaving older competitors like Novartis's Gilenya and Sanofi's Aubagio in its wake. “Currently, and for the foreseeable future, Tecfidera will continue to be the leading oral option for treatment of MS,” says Brian Whalen, vice president, science & medicine, Evoke Health.

The huge sales spike also reflects a larger trend in MS, in which oral drugs have become the fastest growing segment in the market during the past few years—even as injectable drugs hang on to about 50% of patients, according to Ben Weintraub, president, *inThought* Research. Weintraub agrees with Whalen's assessment of Tecfidera, with a small caveat: “Our model has sales increasing from \$2.9 billion worldwide this year to \$3.4 billion in 2015, then peaking in 2017, as competition increases and other fumarate formulations are introduced.” Dhawan's reservations are similarly minor. “As long as the product's safety profile holds and pharmaco-economic benefit data emerges, the drug should continue to position itself as a leading player in the market,” he adds.

But while Tecfidera's future is exceedingly bright, injectable MS treatments are not going away anytime soon, according to Jim Cummings, principal, Evolution Consulting & Research. “My conversations with medical professionals and patients suggest that both audiences are reluctant to switch an established patient from injectable agents that have effectively treated the condition,” he explains.

Weintraub adds that it's rare for any product to topple the status quo overnight. “Most drugs take five to seven years from launch to reach peak sales, and at least two to really make a dent in the current standard of care,” he says. “Interferons and Copaxone have been the standard of care in MS for a long time. So although the oral therapies have had a remarkable start, interferons and Copaxone continue to have the most market share.”

Nonetheless, Tecfidera's immediate impact spurred Biogen Idec to revise its projected earnings northward for this year. Helped along by approval of Tecfidera in Europe in February, Biogen Idec is now estimating company revenue growth for 2014 at somewhere between 38% and 41%, according to Jason Glashow, Biogen Idec's senior director, public affairs.

At the same time, Biogen Idec is making a major play in longer-acting MS treatments with Plegridy, an injectable approved for the US in August. The treatment, which only needs to be administered once every two weeks, is a potent threat to older competitors, which must be injected more frequently.

“Plegridy represents the most significant innovation in the interferon class in over a decade,” crows George Scangos, Biogen Idec's CEO.

Teva's fortune in the MS space hasn't been as good. The company lost US patent protection on the original version of its MS treatment, Copaxone, in May. Additionally, the worldwide patent expires in May 2015. Not surprisingly, generic manufacturers



## TOP 25 NEUROLOGY PRODUCTS, 2013

Category leaders, ranked by 2013 US sales and their media spend

Rank	Product	Manufacturer	US sales \$ (millions)	Vs. prior 12 months	TRx (000s)	Vs. prior 12 months	US DTC media \$ (000s)	Vs. prior 12 months	US journal media \$ (000s)	Vs. prior 12 months
1	Abilify	Otsuka	\$6,547.8	15.0%	8,737.0	1.0%	\$121,370.0	5.0%	\$0.0	-100.0%
2	Cymbalta	Eli Lilly	\$5,274.0	14.0%	18,554.0	0.0%	\$34,551.0	-55.0%	\$0.0	N/A
3	Copaxone	Teva	\$3,710.2	6.0%	111.0	-15.0%	\$0.0	N/A	\$674.0	-1.3%
4	Namenda	Forest	\$1,867.9	9.0%	8,555.0	12.0%	\$0.0	N/A	\$414.0	-82.3%
5	Rebif	Merck/Serono/Pfizer	\$1,273.6	4.0%	43.0	-21.0%	\$0.0	N/A	\$0.0	-100.0%
6	Avonex	Biogen Idec	\$1,245.6	-25.0%	58.0	-31.0%	\$0.0	N/A	\$900.0	-2.3%
7	Seroquel XR	AstraZeneca	\$1,238.3	6.0%	2,457.0	-9.0%	\$6,415.8	-12.0%	\$0.0	N/A
8	Gilenya	Novartis	\$1,060.7	26.0%	15.0	10.0%	\$27,470.5	164.0%	\$734.0	-13.7%
9	Stelara	Janssen	\$966.6	43.0%	13.0	71.0%	\$20,557.4	-25.0%	\$241.0	-48.0%
10	Tysabri	Biogen Idec	\$936.2	123.0%	0.0	3.0%	\$0.0	N/A	\$789.0	-3.1%
11	Tecfidera	Biogen Idec	\$905.2	N/A	15.0	N/A	\$0.0	N/A	\$1,323.0	N/A
12	Betaseron	Bayer	\$902.9	-4.0%	32.0	-21.0%	\$0.0	N/A	\$0.0	-100.0%
13	Lunesta	Sunovion	\$867.2	13.0%	3,288.0	-11.0%	\$25,659.8	-46.0%	\$0.0	-100.0%
14	Invega Sustenna	Janssen	\$780.6	39.0%	448.0	30.0%	\$546.0	44.0%	\$0.0	N/A
15	Avonex Pen	Biogen Idec	\$771.1	215.0%	16.0	175.0%	\$0.0	N/A	\$0.0	-100.0%
16	Synagis	MedImmune	\$770.5	-1.0%	22.0	534.0%	\$347.3	-61.0%	\$439.0	50.7%
17	Pristiq	Pfizer	\$643.9	12.0%	3,216.0	-9.0%	\$43,986.0	52.0%	\$567.0	-9.0%
18	Strattera	Eli Lilly	\$624.2	10.0%	2,421.0	-2.0%	\$0.0	N/A	\$0.0	N/A
19	Intuniv	Shire	\$588.3	27.0%	2,614.0	8.0%	\$0.0	-100.0%	\$0.0	-100.0%
20	Exelon	Novartis	\$563.2	11.0%	1,891.0	-1.0%	\$19,159.7	-51.0%	\$793.0	211.0%
21	Revlimid	Celgene	\$546.3	-2.0%	28.0	-4.0%	\$0.0	N/A	\$1,155.0	N/A
22	Latuda	Sunovion	\$504.1	1.0%	788.0	70.0%	\$0.0	N/A	\$5,278.0	116.1%
23	Risperdal Consta	Janssen	\$483.9	2.0%	521.0	-4.0%	\$0.0	N/A	\$0.0	N/A
24	Vimpat	UCB	\$474.2	40.0%	822.0	25.0%	\$0.0	N/A	\$113.0	82.4%
25	Invega	Janssen	\$473.6	13.0%	600.0	-1.0%	\$0.0	N/A	\$0.0	N/A

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journals, Kantar Media.

Note: List includes products FDA indicates as approved for treating MS, Parkinson's disease, Alzheimer's disease, depression, schizophrenia, bipolar and insomnia.

Mylan and Sandoz are closing in with formulations of their own. Indeed, Mylan has already signed a license and supply agreement with NATCO Pharma to distribute generic Copaxone in the US, Europe and other key markets.

Teva is taking a simultaneous bruising with its new formulation of the same drug, three-times-a-week Copaxone. Teva's original plan was to migrate current Copaxone users over to the newer, longer-acting formulation, and hopefully dodge some profit losses when standard Copaxone went generic. By late summer, Teva had made significant headway: 51% of original Copaxone patients had made the switch to the newer version, according to a Zacks Investment Research Report.

### Generics move in on the market

But it turns out some generic manufacturers — Mylan, as well as the joint partnership of Momenta and Novartis — want a piece of that three-times-a-week Copaxone market, too. Chances are that Teva will sue for patent infringement on the newer Copaxone, which would stop generic manufacturers in their tracks for 30 months. Even so, a generic version of the newer, longer-acting version could go on the market as early as 2017.

Weintraub advises the industry to closely follow MS research that emerged at the European Committee for Treatment and Research in Multiple Sclerosis meeting in September. It revealed new insights into the genetics of MS, he says. "Understanding how the immune

system goes awry and which environmental and genetic factors increase MS risk will lead to even better therapies and possibly even ways to prevent MS in the first place."

Meanwhile, in insomnia, Sanofi's Ambien, Sumitomo Dainippon's Lunesta and generic knock-offs are facing increased competition from Belsomra, a new drug from Merck. The manufacturer finally won FDA approval for its sleep medication in August. But Merck enters the race a few lengths behind, given that the FDA refused to approve its pills at a potency greater than 20 mg. The reason: studies show that taking the drug at levels greater than 20 mg can leave users dangerously groggy the next morning.

Even after a 20-mg dose, both men and women who take Belsomra can experience impaired driving performance, according to the FDA. "Using the lowest effective dose — 5 mg — can reduce the risk of side effects, such as next-morning drowsiness," says Ellis Unger, a director at the FDA's Center for Drug Evaluation and Research.

In Alzheimer's, the slog has been even tougher. Eli Lilly is experimenting with solanezumab, while Genentech and Roche have two similar compounds under development, according to Weintraub. But "Alzheimer's Disease Drug-Development Pipeline: Few Candidates, Frequent Failures," a comprehensive study of all recent efforts to treat Alzheimer's, revealed that 99.6% of all attempts for meaningful treatment have failed. Even more alarming: there are only 80 to 100 Alzheimer's drugs currently in clinical trials.

"The pipeline is almost dry," says Kate Zhong, a co-author on



## CLINICAL CORNER

The same technology that has helped industries unearth patterns buried in mountains of data is now being used to forge better treatments for Parkinson's. "We're on the verge of a paradigm shift in the pharmaceutical industry, where insights gleaned from Big Data, rather than hypotheses, will drive scientific drug discovery," says Niven Narain, co-founder, president of Berg, one of the companies driving the analytic revolution.

Berg is employing those techniques to crunch data and statistics as part of an effort to find biomarkers for Parkinson's disease. Its Berg Interrogative Biology Platform compares skin, blood and urine measurements from Parkinson's patients with data accumulated in other Parkinson's studies. "Berg's novel approach provides valuable insights to assess and accelerate the R&D process," says Cecilia Van Cauwenberghe, senior research analyst at Frost & Sullivan, which gave the technology its North American Drug Technology Innovation Award for 2013.

Berg hopes to point to biomarkers for Parkinson's in much the same manner that, say, heart specialists identify high cholesterol as a known indicator for heart troubles. According to Narain, there are currently no known biomarkers for Parkinson's.

Compared with traditional clinical efforts, researchers could find a drug for Parkinson's much faster using Berg's method. The reason: biomarker research enables drug makers to assess how a drug impacts a specific biomarker associated with a disease, according to Chelsea Kasai, a spokesperson for The Parkinson's Institute and Clinical Center.

Berg's work is also helping advance insights being uncovered by the Parkinson's Progression Markers Initiative (PPMI), a biomarker study sponsored by The Michael J. Fox Foundation for Parkinson's Research. That initiative's impact has been one of the most significant developments in neurology in the past year, according to Amit Dhawan, medical director at Kantar Health.

Todd Sherer, CEO, the Michael J. Fox Foundation, agrees: "It is evident that a large-scale biomarker study is not only possible in Parkinson's disease, but is already yielding scientific insights." Currently, 32 clinical facilities around the world are driving the initiative. One of those, the Parkinson's Institute, is supplying Berg with the skin, blood and urine samples being used as part of its comparative analyses. "Through our collaboration with Berg, we hope to identify predictors for the disease and potential new drug targets," says Birgitt Schuele, director of gene discovery and stem cell modeling at the Parkinson's Institute. "Armed with this information, we will be able to better diagnose and develop therapies that can treat—and perhaps even halt—the neurological damage caused by Parkinson's."



the study, published in *Alzheimer's Research & Therapy*, and senior director, clinical research and development, Cleveland Clinic Lou Ruvo Center for Brain Health.

Too, the need is profound: Given that Alzheimer's levies a greater toll on the US economy than heart disease, the development of an effective drug ranks among the highest of high priorities, according to Cleveland Clinic director Jeffrey Cummings. "With an estimated 44 million people living worldwide with the condition, the Alzheimer's disease drug development ecosystem needs more support," he says.

### Reasons for optimism

Despite the setbacks, Weintraub is optimistic. "In Alzheimer's disease, we've seen industry and academia joining forces to do large, long, expensive trials of promising agents in patients with very early-stage disease, in some cases even before symptoms of cognitive decline are evident," he says. "This kind of teamwork is exciting not just because it may lead to a disease-modifying therapy for Alzheimer's, but also because it will become a road map for collaboration on difficult clinical trial situations." Efforts may also lead to new therapies to complement existing products, such as Forest's Namenda.

Some hope can be seen in results from a recent Case Western study, which successfully removed amyloid beta—a substance believed to cause Alzheimer's—from mouse brains. Researchers effected the change by using the cancer drug bexaroten. Duly inspired, the Cleveland Clinic is currently attempting to replicate those results in the human brain. The move is consistent with the Clinic's belief that the most effective path towards an Alzheimer's treatment may be to re-indicate an already approved FDA drug for use with Alzheimer's.

But Whalen is skeptical about the theory that amyloid beta is a cause of Alzheimer's. He points to four recent failed clinical trials that tried to treat Alzheimer's by targeting amyloid beta with antibodies (Aβeta). "These failed trials have provided the ultimate support for shifting the focus and funding away from Aβeta as a therapeutic target," he says.

### An Alzheimer's experiment

Nonetheless, Whalen supports Lilly's recent decision to experiment with Aβeta on extremely early-stage Alzheimer's patients: "Lilly's new focus on patients who may be in the earliest, asymptomatic stages of the condition is one that I fully support as the best approach to evaluating an anti-amyloid therapy." Overall, he adds, solanezumab "continues to be one of the best options for impacting the progression of Alzheimer's disease."

In schizophrenia, Cleveland Clinic's Cummings sees researchers and drug companies going beyond simple treatment of symptoms in coming years. "In schizophrenia, the so-called atypical antipsychotics—the cornerstone of treatment—have been quite effective in treating the positive symptoms and modestly effective in treating the negative symptoms," he notes. At the same time, he says that these agents have "done very little to address the progressive cognitive impairment."

Researchers hope newer drugs in development will be able to neutralize that impairment. It's also believed that non-drug treatments—such as brain games that are said to "work out" the brain—can be developed to neutralize the ailment.

"If effective, this one-two punch may improve overall patient function, thus offering a benefit to patients, caregivers and society at large," Cummings says. ■