MM&M THERAPEUTIC FOCUS

NEUROLOGY

The neurology space is gearing up to shake free of its decade-long stagnancy, with sector leaders and runners-up alike angling to push the boundaries. What that means: Imminent advances in genetic sequencing, targeted treatments and diagnostics, all designed to get to the biological root of neurological disorders. **Rebecca Mayer Knutsen** explains

Keenly aware that symptomatic patients with complex diseases are taxing neurologists, drug developers are in hot pursuit of discovering needed tools. In the interim, patience is a virtue. The market is starved for novel target-specific products, but the science and technology need a chance to catch up to the hype.

Progress is being made, but treatments for Alzheimer's, schizophrenia and Parkinson's won't be moving the breakthrough needle soon. Late-stage multiple sclerosis drugs, however, may transform the way physicians treat the disease in the next decade, while early clinical work on Tourette's syndrome, ALS and Duchenne muscular dystrophy is sparking interest. And fast-acting antidepressants promise to reduce the clinical impact to hours (see Clinical Corner, p. 40).

While drug firms lay the groundwork for curative breakthroughs down the line, neurology treatments focused on mediating disease symptoms are trickling onto the market. So far, 2015 has witnessed just four neuro approvals.

Eisai's Fycompa (perampanel) is in trials for reducing primary generalized tonic-clonic seizures and partial epilepsy

"The market is so hungry for treatment advances that even modest improvements over current treatments have immediate blockbuster potential," says Loring Cloud, Epic Brand Group partner and clinical brand strategist. "That's enough to keep pharma in the game, even marginally."

The neuro paradox

Treatments for brain and nervous system diseases have evaded drug developers for years—but with the arrival of better diagnostic tools, they are one step closer to understanding their cause. "Identifying biomarkers, which signal the presence of disease, are helping tremendously by taking subjective measures out of the equation," Cloud notes.

Oncology paved the way for exploration of biomarkers in CNS drug development. By helping to identify drug candidates headed for failure in late clinical trials—an issue that has plagued the industry—biomarkers reduce drug-development costs. "Clarity in understanding brain and neurologic pathology and biomarkers emboldens pharma executives to green-light more and more R&D efforts," says Gil Bashe, Finn Partners' managing partner, health.

Neuroimaging technologies may take the top spot among diagnostic and testing tools currently in play. "In ways that were unimaginable not long ago, we can now monitor brain activity to better understand whether therapeutic compounds reach their intended targets, and what effect, if any, they stimulate," explains Dan Brennan, VP and group general manager of neurology, Lundbeck US.

Following the mapping of the human genome, scientists are pinpointing and targeting treatments to specific genetic receptors. According to Digitas Health LifeBrands' VP, group medical director Lee Fraser, emerging technology will allow clinicians to move from lumping disease into broad phenotypes and diagnoses like depression and ADHD into specifically defined subsets of these diseases.

Lundbeck's work with Huntington's disease, a disorder with a known genetic source that has eluded a curative breakthrough, tells a different tale. "Enormous work is required to understand how the genetic mutation operates, and significant challenges must be overcome to arrive at a solution that benefits patients," Brennan says.

Fraser agrees that while helpful, cataloguing hasn't yet led to the explosion of therapies initially promised and expected. But with more rational design and better understanding, he believes the efficiencies and opportunities for success will likely pay off economically.

Pharma invests

The neurology sector has been stuck under a dark cloud of high risk and low approval rates for drugs targeting diseases such as Parkinson's, Alzheimer's and schizophrenia for quite some time. Indeed, we've entered a new era in which pharma is parlaying innovative partnerships and approaches to minimize R&D risk while hedging bets on treatment advances.

The global cost of caring for the roughly 50 million people who suffer from neurologic conditions rings in at $650 billion per year. "There is a mega need and big incentive for biopharma companies to find the grit to invest in R&D," Bashe says.

Novartis, Pfizer, Roche and J&J have strong CNS pipelines, but others—Lilly and Merck among them—are climbing the ranks with in-house innovations and late-stage acquisitions. Still, Bashe notes, the big breakthroughs may come not from Big Pharma but from smaller players like Acadia, Allergan and Biogen, which are making their mark on the sector.

The market opportunities are enormous due to unmet medical needs and a rapidly aging population, says Patrick McEnany, CEO of Catalyst Pharmaceuticals. "In addition to the large indications the big guys are pursuing, the market has plenty of room for orphan-drug opportunities," he says. Catalyst is studying Firdapse for rare neuromuscular diseases Lambert-Eaton myasthenic syndrome and congenital myasthenic syndromes.

As for Alzheimer's ...

Patients with Alzheimer's have faced a dearth of treatment options for some time now—Allergan's Namzaric has been the sole approval since 2004—due to few scientific advances and a series of Phase III flops in 2012. CNS R&D investments are historically high-risk endeavors and most neuropsychiatric candidates in recent years have failed during expensive late-stage clinical trials. "Reasons for these high-profile stumbles range from shifting FDA evaluation standards to insufficient understanding of brain disease pathology," Bashe says.

Current treatments, including cholinesterase inhibitors and Namzaric, an N-methyl-D-aspartate receptor antagonist, mask the symptoms of Alzheimer's but fail to treat the underlying disease or delay cell damage. "Now scientists are approaching Alzheimer's with the goal to arrest and even reverse these conditions," Bashe continues.

Biogen is acutely aware that focusing on one Alzheimer's development pathway could be the developer's kiss of death. The company is making a big bet with its anti-amyloid agent aducanumab (BIIB037) in Phase III trials for dementia. In previous anti-amyloid news, of course, Lilly's solanezumab and Pfizer and Johnson & Johnson's bapineuzumab each went down in a ball of flames in late-stage trials.

Biogen is simultaneously developing treatments targeting tau and BACE proteins. Merck leads the BACE inhibitor pool, with Lilly's in-licensed program from AstraZeneca lurking close behind. Lundbeck's late-stage candidate idalopirdine is an antagonist for the 5-HT6 receptor, found mostly in the areas of the brain involved in cognition.

TOP 25 NEUROLOGY PRODUCTS

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

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 mos.	TRx	Vs. prior 12 mos.	US journal media $ (000s)	Vs. year-ago period
1	Abilify	Otsuka	$7,758.6	9.4%	8,762,907	0.2%	$1,674.0	-49.0%
2	Lyrica	Pfizer	$3,376.5	24.8%	10,048,959	4.1%	$3,430.0	4.9%
3	Tecfidera	Biogen Idec	$3,226.2	65.8%	442,903	57.5%	$812.0	-32.6%
4	Suboxone	Indivior	$1,446.1	4.3%	6,981,450	-0.1%	$0.0	N/A
5	Namenda	Forest	$1,410.2	-22.6%	5,563,773	-31.7%	$0.0	N/A
6	Seroquel XR	AstraZeneca	$1,355.8	7.9%	2,372,325	-0.1%	$0.0	N/A
7	Latuda	Sunovion	$1,330.9	79.3%	1,715,924	61.6%	$2,483.0	-29.1%
8	Avonex pen	Biogen Idec	$1,299.3	20.6%	181,466	-2.6%	$0.0	N/A
9	Invega Sustenna	Janssen	$1,102.3	27.2%	632,065	21.2%	$329.0	3,576.2%
10	Duloxetine HCL	generic	$1,049.8	-33.1%	20,646,670	156.6%	$0.0	N/A
11	Avonex	Biogen Idec	$1,027.1	-19.3%	167,267	-27.2%	$0.0	N/A
12	Rebif	Pfizer	$965.6	-14.6%	168,504	-23.0%	$0.0	N/A
13	Namenda XR	Forest	$824.0	231.1%	3,404,245	208.9%	$65.0	-93.7%
14	Strattera	Eli Lilly	$790.9	20.6%	2,417,852	1.2%	$0.0	N/A
15	Pristiq	Pfizer	$742.8	9.5%	2,720,364	-10.8%	$723.0	29.2%
16	Vimpat	UCB	$692.0	27.0%	1,042,229	18.6%	$931.0	N/A
17	Betaseron	Bayer	$672.5	-20.8%	97,380	-23.7%	$0.0	N/A
18	Exelon	Novartis	$639.5	11.3%	1,768,963	-7.9%	$690.0	-65.1%
19	Invega	Janssen	$595.1	18.4%	612,578	1.1%	$332.0	N/A
20	Divalproex Sodium ER	generic	$541.9	-16.5%	4,821,030	1.1%	$0.0	N/A
21	Intuniv	Shire	$533.5	-18.1%	1,809,902	-31.6%	$0.0	N/A
22	Risperdal Consta	Janssen	$474.8	-1.0%	474,621	-8.6%	$0.0	N/A
23	Chantix	Pfizer	$464.2	19.8%	2,196,998	2.3%	$0.0	N/A
24	Bupropion HCL XL	generic	$457.0	17.3%	18,236,604	9.7%	$0.0	N/A
25	Gabapentin	generic	$390.8	-3.2%	52,866,839	14.7%	$0.0	N/A

Sources: Sales, IMS Health; journal media spend, Kantar Media
Sales and TRx data run from June 2014–May 2015; journal data run from January–September 2015

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

CLINICAL CORNER

While many companies have paid their entry fees in the antidepressant R&D race, Allergan has taken a bold step forward. The big wait-and-see innovation in combating depression will likely result from Allergan's acquisition of Naurex, according to Gil Bashe, managing partner, health, Finn Partners. "[It] could be a game-changer," he says.

Allergan gained rapastinel, a targeted modulator of the brain receptor N-methyl-D-aspartate, or NMDA, which plays a role in the brain's ability to form memories. Experts are touting the fast-acting drug candidate for its ability to work quickly in the treatment of depression.

Loring Cloud

Selective serotonin reuptake inhibitors, the gold standard in depression treatment, can take several days if not weeks or even months to chip away at symptoms. Furthermore, currently marketed SSRIs, such as Lexapro and Prozac, increase levels of the neurochemical serotonin in the brain but are only effective in about one-third of all patients with depression.

Rapastinel (GLYX-13), a once-weekly intravenous molecule, performed well in multiple Phase II clinical studies for major depressive disorder. When compared with traditional antidepressants, it could potentially spur a faster onset of action, equal or greater efficacy and a more favorable safety and tolerability profile for patients.

SSRIs act on serotonin and related neurotransmitter pathways. But rapastinel mobilizes glutamate pathways to enhance synaptic plasticity and improve communication between neuronal cells.

In the long term, hopes have turned to rapastinel's application in suicide prevention—a growing problem, particularly among teenagers. "Even though clinicians want to get depression under control quickly because of the suicide potential in patients, they have become very accepting of an onset of effect that takes two to four weeks to achieve," says Loring Cloud, partner and clinical brand strategist at Epic Brand Group. In the highly genericized antidepressant market, he adds, clinicians often cycle through at least two different generic antidepressants before considering a more aggressive treatment.

For a patient who has failed treatment on his second bout with major depression, data show the chances of obtaining control over the depression drops to one in eight. "Clinicians need to have a much stronger sense of urgency about treatment," Cloud stresses.

Speed of onset will be the first barometer of success for a faster-acting antidepressant. "If the speed of onset is a significant improvement, then the market will be very accepting," Cloud continues. "Smart marketers will realize they can leverage this onset of effect to create more urgency around better outcomes, and sooner."

As for the marketing around these treatments, Bashe believes that campaigns must raise societal sensitivity that depression and other neurologic conditions do not result from lifestyle choices. "They are biologic responses and demand medical care and innovation," he says.

Allergan acquired another targeted NMDA modulator—NRX-1074—with Naurex. Phase III rapastinel trials are expected to begin in 2016.

"Disease-modifying compounds are a long way off and mostly promise to delay the progress of the disease rather than prevent or cure it entirely," Brennan says. "Symptomatic treatments are critical tools now and will be far into the future."

MS and more

Much of the multiple sclerosis care plan focuses on improving dose and frequency deliveries, but drug developers are making gains in reversing the damage done by MS patients' overactive immune system. Roche favors developing ocrelizumab for the primary progressive form of the disease. The company's anti-CD20 MAb has shown positive results in Phase III trials. Biogen's MS candidate anti-LINGO, being studied in patients with optic neuritis, relapsing remitting MS and secondary progressive MS, may reverse immune system damage and help nerve cells regrow.

Fraser points to research using stem cells as an experimental platform to test hypotheses early in development and screen drug candidates in MS. "Researchers have identified drug candidates that can trigger stem cells in the patient's nervous system to form new myelin," he says.

Eisai's Fycompa, the only anti-epileptic on the market that selectively targets AMPA receptors, is currently in a Phase III trial for reducing the frequency of seizures in patients with primary generalized tonic-clonic seizures and partial epilepsy. Lundbeck's IV carbamazepine, a novel formulation of the oral antiepileptic drug carbamazepine, is in pre-registration with FDA.

The migraine market is preparing for a race to market for a new class of drugs called calcitonin gene-related peptide (CGRP) monoclonal antibodies but lost one of its big players when Merck bailed out. The company sold its portfolio and two experimental drugs to Allergan, which leaves Lilly, Teva, Amgen and Alder Biopharmaceuticals in the hunt.

Allergan's Vraylar snagged FDA approval for the treatment of schizophrenia and bipolar disorder in September. Otsuka and Lundbeck's Rexulti gained FDA approval in July for schizophrenia. The compound is also in late-stage trials for Alzheimer's, post-traumatic stress disorder and adjunct major depressive disorder.

Parkinson's

Parkinson's saw two approvals in 2015: Impax Labs' Rytary (carbidopa and levodopa) extended-release capsules and AbbVie's Duopa (carbidopa and levodopa) enteral suspension. Although at first glance that seems like a triumph, most new advances in Parkinson's disease simply continue to progress levodopa delivery—and, as such, do not qualify as major breakthroughs.

"Levodopa is the best weapon doctors have to treat symptoms," says AbelsonTaylor vice president and account director Eric Densmore. "The problem is, over time, patients become resistant and the efficacy wanes. There's a constant search for ways to preserve and maximize the utility of levodopa."

Acorda Therapeutics is exploring an inhaled version of levodopa that might be effective longer, while Voyager Therapeutics is testing a gene therapy to assist patients who have developed a resistance to levodopa. Biogen is exploring ways to slow progression by clearing toxins that build in the brain.

"The subjective nature and varying degrees to which patients [can] cope with PD symptoms make it difficult to find concrete clinical endpoints upon which decisions can be made," Densmore says. ■