Migraine relief builds on acute, preventive drugs

By Amanda Baltazar

CHAPEL HILL, N.C. — Stone Age man cut away pieces of a migraine sufferer's skull to relieve pain, and around 12 centuries ago in Britain, those suffering migraines would drink elderseed juice mixed with cow's brain and goat's dung dissolved in vinegar.

Fortunately today's remedies are a little easier to stomach, and they're becoming more plentiful.

About 30 million Americans suffer from migraines. They usually start between the ages of 5 and 35, according to the National Institute of Neurological Disorders and Stroke, with three-quarters of migraine sufferers being women.

Migraines are usually hereditary. They are debilitating headaches that tend to build up over one to two hours and can last several days. Migraines may be accompanied by other symptoms, such as nausea, vomiting and sensitivity to light or sound. Some migraines are preceded by "aura," in which the sufferer sees lights or lines and may even lose his or her vision.

There are many migraine medications on the market, but a new acute treatment is likely to be approved this year. Trexima from Pozen is currently under final review with the FDA. It's a combination product, consisting of sumatriptan and naproxen sodium, which will likely lead to better compliance since patients only have to remember one drug, not two, according to Dr. Fred Sheftel, director and founder of the New England Center for Headache and president-elect of the American Headache Society.

According to Pozen: "The triptan alters the constriction of the blood vessels, which correlates to the relief of migraine pain. The NSAID inhibits the enzyme responsible for the production of prostaglandins, which are the mediators of pain and inflammation, thereby enhancing the speed, effectiveness and duration of migraine-symptom relief."

"Trexima is an evolution in our treatment," said Dr. Winner, director of the Palm Beach Headache Center and clinical professor of neurology at Nova Southeastern University. "The two [drugs] work better together than each separately. We've seen sustained response over 24 hours, so the sum is better than the parts."

"The market for [Trexima] is potentially as big as the market for triptans," said Dr. Lisa Mannix, medical director of Headache Associates, a medical private practice. And, according to reports by analysts, if approved, Treximа is expected to achieve blockbuster status, with revenues of $1.8 billion by 2008.

The drawback to Trexima is that its two active ingredients have been linked to cardiovascular risks similar to those that led to the downfall of Vioxx in 2004, and FDA regulators previously rejected the drug.

Fortunately for migraine sufferers, the coming years are heralding more medications.

"There are many things currently under study," Winner pointed out, "and there will be a revolution in migraine medications because we're looking at receptors in the brain and completely novel medications. But they're probably three to seven years away."

Another new drug class currently in development is about five years away from approval. Calcitonin Gene Related Peptides (CGRP) are antagonists to stop inflammation and "will be the first really new treatment since Imitrex if they work out," Sheftel said.

"The good news is that with technology advances we now have a better idea of migraines and the brain, so more sophisticated drugs can be developed for prevention and treatment," Sheftel said. These, he said, would probably reduce migraines by around half in about 50 percent of patients who take them.

There are two types of drugs to treat migraines: preventive, which are taken daily, to reduce the frequency of them; and acute medications, to treat the migraine during the attack.

Patients suffering from two or more migraines per month should take preventive drugs. There are a number of medications on the market—methysergide maleate, which counteracts blood vessel constriction; propranolol hydrochloride, which stops the dilation of blood vessels; amitryptyline, an antidepressant; valproic acid, an anticonvulsant; and verapamil, a calcium channel blocker—all of which should be taken daily.

A study sponsored by the National Headache Foundation in 2005 found that 40 percent of people suffering from migraines could benefit from preventive drugs, but only 20 percent actually take them, so there's room for this market to grow.

One of the newer preventative drugs on the market is Topamax (topiramate) from Ortho-McNeil, which had annual sales of around $1.37 billion before generic competition came in. The drug was approved in August 2004 as a migraine preventive. There's also Neurontin (gabapentin) from Pfizer, which had annual sales of over $2 billion at its peak. Neurontin is being used more frequently for migraines, according to Michael John Coleman, executive director and co-founder of Magnum, the national migraine association.

"It's an anti-epileptic, and is the drug of choice for pain," he said. "It's only in the past year that it has started to be used a lot for migraines."

Both of these drugs now have generic competition. Mylan, Barr and Ivax are among the generic manufacturers of topiramate, while Teva, Alpharma and Ivax (owned by Teva) make gabapentin, and Pfizer's Greenstone subsidiary makes an authorized generic.

A surprising migraine therapy is Botox, better known for plumping up the faces of the wealthy. "It's gotten a lot of bad press because it works in a very different way to other preventives," Coleman said. "It's an off-label use and you need a prescription for it from a neurologist, but Botox has been creeping in for years and could be approved [to treat migraines]."

Preventive medicines work well, but only for about half of the patients who take them. Anyone who suffers from migraines will need to take acute therapies, too.

One of the most commonly used classes of acute drugs is triptans, which include GlaxoSmithKline's Amerge and AstraZeneca's Zomig. The FDA has approved seven of these drugs, the first of which was Imitrex (sumatriptan) from GSK, which was approved in 1992 and had annual sales of approximately $910 million for the 12 months ended September 2006, according to IMS Health. Generic versions of Imitrex became available last year from companies including Teva, Dr. Reddy's and Ranbaxy.

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Migraine treatments in clinical trials

- A double-acting cox-2 inhibitor from GlaxoSmithKline, currently known as 406381.
- Aricept from Eisai, which is indicated to treat Alzheimer's disease, but could soon be used as a migraine preventive using neurostabilizers.
- A nasal spray containing butorphanol from IntraNasal Therapeutics.
- Frovatriptan from Endo, which already is approved to treat migraines. The drug maker is seeking a specific approval to market it as a five- to seven-day preventive for menstrual migraines.
- An auto injection system for Imitrex from Aradigm.

A new acute treatment for migraine sufferers likely will be approved this year.

Migraine

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Triptans should be taken soon after symptoms start, and generally take effect within one to two hours. Since seven are available, if one doesn't work for a patient, he or she can try another.

Triptans are not a save-all. They should not be used more than twice a month and should not be taken by anyone with cardiovascular problems.

One of the biggest problems physicians and pharmacists see is overuse or misuse of migraine medications, according to Sheftel.

"I think pharmacists have a role in identifying this and can counsel patients. It's certainly not the way to treat recurrent headache," he said. "One of the risk factors is the daily use of medication. Many people start with intermittent migraines and these become regular because of their medications."

One of the biggest problems, according to Mannix, is that people wait too long to take acute medication and if they take it when their migraine is severe, the efficacy goes down. "If they take it before the pain becomes severe, they will get better results," she said. "Migraine is a process and it's better to get it early in the attack. The further it goes into the brain, the harder it is to treat."

She also advised that migraine sufferers do not routinely take pain killers. "There's some evidence that pain killers may make the brain so sensitive that triptans won't work, so it's really important that people don't take them.

"I think the future will be more focused on prevention," Mannix said. "Clinical trials show around a 50 percent reduction in the frequency of migraines in people who take preventative medications."

Wellness

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consumer preferences, ahead of clinical pharmacies and chain drug stores. Consumers polled for the survey reported that they were offered the opportunity to speak with the pharmacist in their supermarket more often than they were in chain drug store, mass merchant or clinical pharmacies.

It's all well and good, but challenges abound for food store pharmacy operators as they do for other trade channels. One key factor roiling the food/drug combo arena is clearly Wal-Mart Stores, which learned long ago how to leverage its commanding market position in general merchandise retailing by broadening its grocery and drug store offerings.

Wal-Mart eclipsed Kroger as the nation's leading supermarket chain nearly a decade ago by diverting much of the daily torrent of customer traffic flowing through its supercenters into its expanding food aisles and capturing their loyalty with the everyday low prices that proved effective in the general merchandise aisles.

The same applied to pharmacy. Wal-Mart has muscled its way into the elite ranks of prescription outlets, topped only by Walgreens and CVS, by applying its massive clout with vendors, its technological prowess and its one-stop-shopping convenience.

That prowess was on full display late last year, when Wal-Mart launched a $4 pricing campaign that included 331 generic prescriptions in 26 therapeutic categories.

Thanks to the generic promotional pricing, "The business is up 50 percent in prescription units in some of my pharmacies," one Wal-Mart pharmacy district manager told *Drug Store News*. "We're seeing a nice increase in our OTC business, as well."

Many combo store retailers, including Kroger Co., Publix, Meijer, Wegmans and Pathmark—which agreed in February to be acquired by A&P—launched their own generic promotions. Some went further. San Antonio-based H-E-B launched a new, chainwide discount program last fall that revolves around a membership card, called the My H-E-B Pharmacy Rewards Card. With the card, consumers will have access to a total of 500 generic drugs at a flat rate of $5 per prescription, along with savings of up to 50 percent on all other branded and generic drugs.

Rochester, N.Y.-based Wegmans also responded in dramatic fashion, slashing prices on nearly 200 me-too maintenance medications to $11.99 for a 90-day supply. Not to be outdone, Pittsburgh-based supermarket chain Giant Eagle and Grand Rapids, Mich.-based Meijer began offering pediatric cough syrups and some other prescription medicines for children free of charge.

CVS

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In terms of synergies, CVS expects to realize between $800 million to $1 billion in revenue synergies in 2008, and significantly more thereafter. The company expects about $500 million in cost savings, largely related to better purchasing.

"We would like to note that every deal that both CVS and Caremark have done historically has yielded synergies significantly in excess of original guidance," stated Citigroup analyst Deborah Weinswig in a recent research note. "We believe this deal will be no exception."

Charles Boorady, also of Citigroup, believes that if the company achieves cost savings from the drug-procurement process, it likely will come from a combination of the following: manufacturers accepting the lower price or offering greater rebates, the wholesalers and distributors accepting lower prices and manufacturers bypassing the wholesalers and selling directly to the combined CVS/Caremark entity.

While many industry observers view the merger as a boon for the companies, it undoubtedly will have major implications on the industry, in general, as vertical integration is a new paradigm that—if successful—could clear the way for more mergers moving forward, with Medco and Express Scripts likely being the next targets.

"The fragmentation in the past may be the reason why vertical integration did not work, but the sheer scale of the CVS/Caremark company may be able to make it work," Boorady said. "The only test will be whether customers buy into the concept or the concerns over the perceived channel conflict will outweigh it."

Either way, Boorady sees it as a win-win for rival PBMs. "I see Medco and Express Scripts winning either way. If this integration works, they are likely to be the ones that are acquired next. If it doesn't work then they could stand to gain customers that prefer a standalone [PBM] instead of a vertically integrated model."

Another issue such a deal brings to the forefront is network restriction. If customers are willing to restrict the retail pharmacy so that employees can get their prescriptions filled at a single chain, or just a few chains in the market, then it will make the synergy from a vertical integration more obvious, according to Boorady.

However, this has been a concern for several years and has yet to materialize.

"I think most employers have concluded, and will continue to conclude, that the sheer hassle factor that you are putting on your employees by making them go to a CVS instead of a Walgreens, or vice versa, isn't really worth what little savings you can get relative to other things you can do that present less of a hassle to the employee but can save a lot more money," Boorady said.

However, prior to the deal, CVS Pharmacare controlled a provider network of more than 56,000 retail pharmacies. Meanwhile, Caremark's network numbered more than 60,000 retail pharmacies, so it is unlikely that the combined company, post-merger, would suddenly pull back the size of its network—particularly, if the end goal is to remain attractive to insurers and payers and competitive with stand-alone PBMs.

According to William Blair & Co. analyst Mark Miller, the combined company is facing its first big test as it expects an announcement on the large Federal Employee Program contract—currently up for negotiation—as early as May. Three years ago, Caremark won this contract from Medco and it is likely that the two PBMs, among others, will bid for this business aggressively.

"While there are many moving parts to these types of negotiations, this will be the first big test for the new CVS/Caremark, and may provide some incremental perspective on the current state of the competitive environment," Miller stated in a research note.

In related news, CVS/Caremark has announced the members of the company's board of directors. As previously disclosed, the 14-member board was evenly split among designees from CVS and Caremark.

Former Caremark chairman and chief executive officer Mac Crawford has been elected chairman of the board of the combined company. Ryan will continue to serve as president and chief executive officer.

The following individuals named to the board from CVS are:

- Ryan, president and chief executive officer of CVS/Caremark Corp.
- David W. Dorman, senior advisor and partner, Warburg Pincus LLC.
- Marian L. Heard, president and chief executive officer, Oxen Hill Partners.
- William H. Joyce, chairman and chief executive officer, Nalco Co.
- Terrence Murray, former chairman and chief executive officer, FleetBoston Financial Corp.
- Sheli Z. Rosenberg, former vice chairman, president and chief executive officer, Equity Group Investments LLC.
- Richard J. Swift, former chairman, president and chief executive officer, Foster Wheeler Ltd.

The following individuals named to the board from Caremark are:

- Mac Crawford, chairman of CVS/Caremark Corp.
- Edwin M. Banks, founder, Washington Corner Capital Management LLC.
- C. David Brown II, chairman, Broad and Cassel.
- Kristen E. Gibney Williams, former executive of Caremark's Prescription Benefits Management division.
- Roger L. Headrick, managing general partner, HMCH Ventures; president and chief executive officer, ProtaTek International
- Jean-Pierre Millon, former president and chief executive officer, PCS Health Systems
- C.A. Lance Piccolo, chief executive officer of HealthPic Consultants