Getting Personal with Pain

Pain research seems to be ideal for the application of pharmacogenomics, but pharmaceutical companies have invested little research in the area. The authors discuss opportunities and approaches in the pain management market.

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A recent *Newsweek* cover story speaks of, "moments in medical history when science morphs into magic," and goes on to describe the first use of ether in 1846: "Gilbert Abbott, a Boston printer, walked into Massachusetts General Hospital … [and] became the first human being to go under the knife without feeling a shred of pain." (1)

The article quotes London's *People's Journal*, which wrote at the time, "We have conquered pain." The *Newsweek* journalist opens the discussion that we'd like to continue in this column.

"If only it were that simple," writes Claudia Kalb. "Surgery may not hurt the way it used to, but pain remains a blight on countless lives. In its many guises — migraine, arthritis, back pain — it causes more disability than cancer and heart disease combined. The psychological effects can be devastating, ranging from depression to anxiety and sleeplessness. And the annual cost, including treatment and lost workdays, now hovers around $100 billion in the United States. No wonder the medical world is so keen on the problem."

Indeed, the medical world is putting considerable focus on "conquering" pain. Even Congress got into the act. On 1 January 2001, a Congressional resolution signed by then-President Bill Clinton went into effect, declaring this the "Decade of Pain Control and Research." Unfortunately, there doesn't yet seem to be increased funding from the National Institutes of Health for pain research. Speaking at the 2003 meeting of the American Pain Society in Chicago, Illinois, USA, neurosurgeon John D. Loeser said that for years, researchers simply stopped the search for new analgesics. "Opioids, aspirin and acetaminophen were considered adequate," he explained, "but something more is needed. Whatever health care delivery system we work in, we must labor to have both acute and chronic pain management included within funding guidelines." (2)

At the research level, at least, there seems to be a reversal of what Loeser described. "Harnessing high-tech imaging equipment and stunning advances in genomics, scientists are detangling the pain system at its molecular level," writes Kalb. They are coming up with more targeted treatments and creating more efficient drug delivery systems. But, to be sure, there's still plenty of pain out there, despite the advent of ether. How will we get to the time when science again morphs into "magic?"

We think the answer lies in what we wrote of in an earlier column about the "pharmacy of the future" and the individualized medicine it will make available. As pain research moves forward, it makes the most sense to focus on the individual patient and her genetic makeup if, indeed, we are to capture the opportunities for magic.

Basic Elements of Pain Research

From the patient's point of view, one can argue that "pain is pain," whatever the cause. Scientists and physicians, though, correctly see pain as a highly complex panoply of cause and effect. To do the most for patients, research ought to follow a more or less sequential and logical path,

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looking at determinants of pain, pain's impact and the remediation of pain. Let's look at each of these elements in a bit more detail; within each, the opportunity to employ the expanding knowledge of genomics should be evident.

Researchers first must explore the determinants of pain. This includes the mechanisms of pain generation and the different ways of classifying types of pain, the nature of stimulus and the varying disease processes, such as inflammation. Taking off from that knowledge base, we need to understand everything possible about individual differences in the way the pain mechanisms occur. For example, what are the genetic variations in inflammatory response? We'd also want to get a firm grasp on individual susceptibilities to specific disorders characterized by pain, such as arthritis or endometriosis.

That leads us logically to the impact of pain. What are the individual differences in how people experience pain? How can we measure these different reactions, both to pain and to pain therapies? What do the answers tell us about remediation?

To capture the opportunities for using "omics" in pain remediation, researchers need to apply the full spectrum of new science and technologies to uncover new therapies, the degree of efficacy and effectiveness that can be predicted by individual characteristics and the adverse effects that similarly can be predicted. To execute this focus on the individual will require new diagnostic tests.

On top of these elements are questions that touch on what this all means for quality of life and how it affects the world on a social level. That's why, beyond the scientific work, there are researchers looking at the impact of pain and its treatment on patients' daily quality of life, as well as the economic impact on society — both direct and indirect — of pain and its treatment.

Optimism Over Today's Opioids

Of course, it is difficult to believe that the challenges inherent in all of these questions are on the verge of being surmounted. The new sciences and technologies are moving forward at a rapid pace, but to think we will have conquered pain completely by the end of the Congressionally mandated "Decade of Pain Control and Research" surely is something quite beyond optimism.

What, then, can we be more immediately optimistic about? We suggest research into existing pain medications — especially opioids — that explore how to individualize these therapies and thus maximize their benefits to suffering patients.

A recent issue of *The New England Journal of Medicine* features several articles examining chronic neuropathic pain — which affects more than two million Americans — and the use of opioids in its alleviation. In the issue, Kathleen M. Foley editorializes that "despite advances in our understanding of the pathophysiology and molecular biology of neuropathic pain, its clinical management remains disappointing and controversial…Opioid treatment of neuropathic pain often is discouraged because of concern about ineffectiveness, the potential for the development of tolerance, the risk of addiction and limiting side effects." (3)

What if there was a way to determine before prescribing them whether opioids would help a patient suffering from neuropathic pain, without the problems Foley describes? A group of students in the MIT Program on the Pharmaceutical Industry's (POPI) course on "Principles and Practice of Drug Development" — Sunil Jain, Paige Fenghui Koh, Kevin Taback and Ajay Wasan — explored the development of a commercial assay for genetic sensitivity to opioid compounds (4).

"There has been an explosion in the prescription of oral opioids for pain," write the students, "with an estimated 170 million prescriptions written last year." Patients with myriad "nonmalignant chronic painful conditions, such as rheumatic or degenerative arthritis, are increasingly prescribed opioids." However, pointing to the crux of the problem from an individualized medicine point of view, "there is a great individual variability in the response to a particular opioid. A patient may have poor pain relief with morphine but good pain control with equianalgesic doses of oxycodone. This variability is thought to be partially related to genetic polymorphisms for the mu opioid receptor. Such polymorphisms encode single amino acid substitutions that, in animals, have been correlated to an enhanced response to particular opioids."

The students imagine that pharmacogenomics could help solve this problem and thus considerably enhance the medical value of existing therapies. Not only that, there could be significant societal benefits. After all, they note, patients often are given increasingly higher doses of opioids to achieve relief. "Clinicians decide to switch opioids only after pushing the doses as high as a patient can tolerate without excessive side effects," they write. "High doses also are expensive to insurance companies. For instance, many patients with severe pain at the Brigham and Women's Hospital Pain Management Center (Boston, Massachusetts, USA) have opioid prescription bills of several thousand dollars per month." That has an impact on the health care costs for everyone.

Who Will Meet the Challenge?

To meet the challenge, the POPI students propose a strategy to determine a patient's "opioid susceptibility profile." It involves taking a blood sample, identifying the patient's polymorphisms, correlating the polymorphisms profile to known responses to various opioids and then recommending an optimal opioid therapy. They outline the steps for developing the tests: First, identify the polymorphisms efficiently, reliably and inexpensively. Then conduct clinical studies to correlate the mu opioid receptor (MOR-1) polymorphisms to pain relief from var-

ious compounds. Next, win FDA approval under the Clinical Laboratory Improvement Amendments (CLIA). And finally, commercialize the test.

Going further, they detail the science of three possible screening tests. Much of what they suggest involves the new technological tools of pharmacogenomics research, such as single nucleotide polymorphism (SNP) tests. "If the polymorphism profile of MOR-1 in an individual patient predicts response to a particular opioid, then this information can be used as a test to guide the decision to prescribe a specific opioid," the group writes. "This test will allow opioid therapy to be tailored to the genetic opioid susceptibility profile of an individual patient, thus improving her pain control, minimizing side effects, decreasing the risk of addiction and saving insurance companies money."

That is individualized medicine. That is the beginning of the pharmacy of the future. It makes one wonder how the pharmaceutical industry is evolving with the science.

These students looked far and wide but found that "little work has been done correlating the expression of MOR-1 polymorphisms to response to various opioids. We are aware that a pharmaceutical company is using data on polymorphisms in combination with PET scanning for activation of opioid receptors in the brain to test the analgesic properties of new compounds. Yet, we know of no company trying to use information on polymorphisms to tailor individual treatment in choosing an opioid already available."

This makes little sense, unless one believes — as we do — that the industry is moving far too slowly in making the paradigm shift we described some months ago in this column. How little sense? Consider that, "the commercial potential of such a test is enormous," as the students write. They estimate that two million U.S. patients with chronic pain would be eligible to receive the assay and another 13 million post-operative surgical patients would be "included in the annual addressable market. Given our initial pricing estimates, the potential market value is $400 million to test the current stock of chronic pain patients, and an annual market in the billions of dollars to test the post-operative surgical population. This is relative to a current market of opioid drugs of more than $3.5 billion, growing at a rate of 10–20% annually." (5)

Here's the bottom line: "With an estimated 40 million Americans with undertreated chronic or acute pain and a doubling of the market size for opioids over the past three years, we project the market opportunity to be $70 billion over the next 10 years." (5)

Maybe that's one of the blockbusters on which pharmaceutical firms ought to be working. It promises big revenue returns and tremendous societal value while helping move forward the technological and scientific advances of the past several years. With the industry under attack on several fronts, it would be nice to see "science morph into magic" for everyone involved —patients, providers, physicians and the industry itself.

References

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5. The authors base their numbers on an analysis of the data provided in three sources: SunTrust Robinson Humphrey, "Company Report on Pain Therapeutics, Inc., July 9, 2002; National Center for Health Statistics, 1999 International Classification of Diseases (9th revision); and information on methylnaltrexone available at http://www.progenics.com/MNTX.htm.

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