Trends-in-Medicine

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by Lynne Peterson and Nigel Staite

SUMMARY

Pain specialists are worried that FDA efforts to limit abuse, misuse, and overdose with long-acting opioids will result in access problems for pain patients, and FDA plans to impose a risk management program for these drugs was an underlying theme at the meeting. This has also caused a lull in new drug development, though the risk management program probably won't go into effect until 2010. FDA officials insisted that approvals are not being held up to wait for finalization of this program. ♦ Immediate-release opioids are still getting approved, like Johnson & Johnson's Nucynta (tapentadol IR), but the FDA does not appear willing to grant an abuse-resistant/deterrent label to ***any*** of the new formulations – and there are quite a few vying for that label. ♦ Pfizer's nerve growth factor, tanezumab, looks very interesting and may be a game changer. ♦ There are now three drugs to treat fibromyalgia, but it is a difficult disorder to treat, and Forest/Cypress has been slow to get its marketing push for Savella (milnacipran) going.

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AMERICAN PAIN SOCIETY (APS)

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Continued patient access to opioids was a big topic of conversation at the APS meeting. Pain specialists are nervous that the FDA will impose new requirements on long-acting opioids – oxycodone, hydromorphone, transdermal fentanyl, methadone, etc. – that will make doctors, particularly primary care doctors, reluctant to prescribe them. There was less news at APS this year than usual on new drugs in development, probably because the field is waiting to see what the new FDA risk evaluation and mitigation strategy (REMS) will be. And the FDA remains unconvinced that it should expand indications to cover non-cancer breakthrough pain. Three drugs have now been approved to treat fibromyalgia, and experts and the pharmaceutical companies were trying to educate doctors about the condition. The most exciting thing was data on Pfizer's tanezumab, a first-in-class antibody to nerve growth factor which looks as if it will have broad utility in pain, with good efficacy and none of the gastrointestinal side effects of opioids.

ABUSE-RESISTANT/DETERRENT OPIOIDS

One thing is clear: The FDA will not give any product an abuse-resistant/deterrent label right out of the box. It will take post-marketing studies to gain that label. Egalet, which is developing an abuse-resistant morphine, met with the FDA during APS, and a researcher said they were told that they will need post-marketing behavioral studies to get an abuse-resistant label. Egalet plans to start early phase U.S. trials later this year.

Nevertheless, doctors should be aware of the different formulations and the potential for abuse-resistance/deterrence. So, once an abuse-resistant/deterrent opioid is available, how quickly will it be adopted? Perhaps surprisingly, there are two very different answers to this.

On one side are pain specialists who say that they will use them little or not at all, citing three reasons:

1. **Not solution.** Some doctors are not convinced these new formulations will solve the problem, which they say is diversion rather than misuse/abuse.
2. **Cost.** The new formulations are expected to be more expensive than other opioids, and doctors said patients may not be willing to pay higher prices or higher copays, and insurers may either not cover them or may put them on a higher copay tier. An expert said, "Managed care needs to step up to the plate and make abuse-deterrent formulations available, and the pharmaceutical industry needs to price them correctly."

3. **Stigma.** By prescribing an abuse-resistant/deterrent formulation, a doctor may be identifying a patient to pharmacies and insurance companies as a drug abuser or potential drug abuser, which could label and stigmatize patients.

On the other side are pain specialists who say they will use abuse-resistant/deterrent formulations for most if not all of their opioid patients, replacing traditional opioids almost entirely. Dr. Joseph Shurman of Scripps Memorial Hospital in La Jolla CA, chair of pain management services at Casa Palmera, a high-end, private-pay rehabilitation center in southern California, said that he will move to 100% abuse-resistant opioids within a year of their approval. He said that cost should be less of an issue with patients and managed care because of the three-fold higher risk of suicide in drug abusers, and he pointed out that sending a patient to a rehabilitation center is far more expensive than abuse-resistant/deterrent drugs are likely to be. Dr. Murray Rosenthal of Millennium Laboratories, a leading urine testing facility, said, "Doctors need to emphasize the positive aspects of the abuse-resistant formulations. Abuse-resistant drugs will get widespread use if they help with sleep and increase pain relief better than immediate-release formulations. Doctors will try them and see what their clinical experience is with them."

Doctors may feel forced to prescribe the abuse-resistant/deterrent formulations out of fear of the DEA. A pain specialist explained that the concern may be that the DEA will examine them, and if they haven't prescribed the "safest" formulation for a particular high-risk patient, then they might get in trouble. Or, they may fear being sued by a high-risk patient/family if that patient gets into trouble with the traditional formulation.

At a seminar on abuse-deterrent/resistant opioids, Steven Passik, PhD, a psychiatrist from Weill Medical College of Cornell University, called these drugs a "nice addition" to the treatment armamentarium but warned against thinking they would solve all the problems with opioids.

Other interesting points made at this session were:

- Patients who refuse certain therapies raise a red flag.
- There has been little concern about creating addiction to opioids in cancer patients, and oncologists rarely screen their patients for addiction, but as cancer patients live longer with their disease this may need to be re-examined. A speaker said, "The risk of abuse, misuse, and diversion is comparable in cancer pain to other pain. There are plenty of people who come to cancer with (an abuse history)."
- High-risk (of abuse) patients are not always the hardest to treat.

Abuse-Reducing Opioid Formulations in Development

Company	Drug	Generic	Formulation	Technology	Status
Akela Pharma	Edacs	Opioid CR	Abuse-resistant	Difficult to crush, chew, extract	Possibly Phase II
Collegium Pharmaceutical/ Endo Pharmaceuticals	COL-003	Oxycodone	Abuse-deterrent	DETERx anti-chewing	Phase II
Egalet	---	Oxycodone, hydrocodone, and morphine	Abuse-resistant	Difficult to extract from impermeable shell	Entering Phase I in U.S.; Phase II in Europe
Elite Pharmaceuticals	ELI-216	Oxycodone CR + naltrexone	Abuse-deterrent	Sequestered antagonist	Phase III
IntelliPharmaCeutics	---	Oxycodone CR	Abuse-resistant	Resists extraction	Pilot
King Pharmaceuticals/Acura	Acurox	Oxycodone IR + niacin	Abuse-resistant and abuse-deterrent	Niacin and becomes viscous	Submitted to FDA in January 2009
King/Alpharma Pharmaceuticals	Embeda	Morphine CR + naltrexone	Abuse-deterrent	Sequestered antagonist	FDA advisory panel favored approval
King/Pain Therapeutics	Remoxy	Oxycodone CR	Abuse-resistant	Viscous gel	FDA advisory panel not positive
Neuromed Pharmaceuticals	Exalgo	OROS Hydromorphone CR	Abuse-resistant	Difficult to crush, extract	To be submitted to FDA in 2Q09 under an SPA
Pain Therapeutics	Oxytrex	Oxycodone IR + naltrexone	Abuse-deterrent	Ultra-low-dose antagonist	Phase III; may be discontinued
Pain Therapeutics/King	PTI-721	N/A	Abuse-resistant	N/A	IND filed August 2008
Pain Therapeutics/King	PTI-202	N/A	Abuse-resistant	N/A	Phase I
Purdue Pharma	OxyContin (new formulation)	Oxycodone CR	Abuse-resistant	Abuse-resistant physical properties	FDA advisory panel recommended against approval
Shire/New River Pharmaceuticals	NRP-290	Hydrocodone IR	Abuse-deterrent	Prodrug	Discontinued
TheraQuest Biosciences	TQ-1015	CR broad-spectrum opioid	Abuse-resistant	Difficult to crush, melt, extract	Phase I
TheraQuest Biosciences	Tramadol ER QD	TQ-1017	Abuse-deterrent	Viscous gel in solvent	Discontinued

FDA Regulation of Opioids

Key takeaways on abuse-resistant opioids:

- An FDA official called the submissions so far on abuse-resistant/deterrent opioid formulations – OxyContin CR, Embeda, Remoxy, and Acurox – "junk science."
- The FDA still has not ruled out applying the opioid REMS to all opioids, not just long-acting formulations.
- No REMS is likely until 2010.
- The FDA is not holding up approvals until a REMS for long-acting opioids is ready.
- To get approval today, generic long-acting opioids will have to have a REMS that is equivalent to the brand REMS. In addition, generics will be subject to the final class REMS when that is determined.
- The uptake of abuse-resistant/deterrent opioids may not be as fast as some have assumed.

Citing an increase in the misuse, abuse, and unintentional deaths from some extended-release pain medications, the FDA announced in February 2009 that it is taking sweeping steps to force 16 manufacturers of two dozen drugs to comply with the new REMS program it intends to impose. At a minimum, the REMS is being designed to apply to long-acting opioids, opioids with high potency, and extended-release opioids. In addition, any new long-acting opioids, including generics, would have to conform with the new REMS.

Earlier this month, the FDA met with manufacturers and representatives from several medical societies, and on May 27-28, 2009, the FDA is holding a public meeting to get input on opioid risk mitigation strategies. Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) in the Office of Drug Evaluation II, Center for Drug Evaluation and Research (CDER), said the meeting is an information-gathering session, "We are looking forward to all the input we can get on that. We have had meetings with patients, pharmacists, pharmaceutical companies, and we have an open public meeting later this month." Dr. Rappaport said the purpose of the public meeting on May 27-28, 2009, is to "hear opinions from stakeholders on what is the right way to do this."

For now, the REMS is only for controlled-release opioids – generic and brand – but in the future experts expect another, probably less stringent, REMS for immediate-release (IR) opioids. However, it is possible, though unlikely, that the FDA will decide to lump all opioids together in one REMS.

So far, the FDA has not indicated what it has in mind for the long-acting opioid REMS, but experts at APS agreed that it is unlikely the FDA will propose any sort of REMS at the May 27-28th meeting. Instead, they expect the FDA to simply listen to public witnesses and to get guidance on what should – and shouldn't – be in the REMS. Then, over the next few months they expect the FDA to craft the REMS.

The APS is preparing its REMS proposal/statement, but no details are available yet. However, it was clear the society is opposed to anything that would negatively affect patient access to opioids, including registries or stringent risk management programs like iPLEDGE – a mandatory distribution program for isotretinoin (e.g., Roche's Accutane) that is designed to prevent use of the drug during pregnancy due to a high risk of birth defects. The focus, APS officials emphasized, should be on diversion, not prescribing practices.

Approved Products to be Affected by the FDA REMS

Generic name	Marketed name	Manufacturer
Brand drugs		
Fentanyl	Duragesic extended-release transdermal system	Johnson & Johnson/Ortho McNeil Janssen
Hydromorphone	Palladone extended-release capsules *	Purdue Pharma
Methadone	Dolophine tablets	Roxane Laboratories
Morphine	Avinza extended-release capsules	King Pharmaceuticals
Morphine	Kadian extended-release capsules	Actavis
Morphine	MS Contin extended-release tablets	Purdue Pharma
Morphine	Oramorph extended-release tablets	Xanodyne Pharmaceuticals
Oxycodone	OxyContin extended-release tablets	Purdue Pharma
Oxymorphone	Opana extended-release tablets	Endo Pharmaceuticals
Generic drugs		
Fentanyl	Fentanyl extended-release transdermal system	Actavis
Fentanyl	Fentanyl extended-release transdermal system	Lavipharm
Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies
Fentanyl	Fentanyl extended-release transdermal system	Teva Pharmaceutical Industries
Fentanyl	Fentanyl extended-release transdermal system	Watson Pharmaceuticals
Methadone	Methadone tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Mallinckrodt
Methadone	Methadone HCL tablets	Novartis/Sandoz
Morphine	Morphine sulfate extended-release tablets	Endo Pharmaceuticals
Morphine	Morphine sulfate extended-release tablets	KV Pharmaceuticals
Morphine	Morphine sulfate extended-release tablets	Mallinckrodt
Morphine	Morphine sulfate extended-release tablets	Watson Pharmaceuticals
Oxycodone	Oxycodone extended-release tablets	Mallinckrodt
Oxycodone	Oxycodone extended-release tablets **	Impax Labs
Oxycodone	Oxycodone extended-release tablets **	Teva Pharmaceutical Industries

* No longer marketed but still approved ** Discontinued

The FDA reportedly has already heard from a long line of people whose loved ones died from an opiate. Dr. Greg Terman, an anesthesiologist from the University of Washington and an APS board member, said, "Many of those people died because they had been given someone else's medication …You can't listen to that without feeling really lousy. But it is important to make clear that it is ***diversion***, not a problem with prescribing. That was not the intention of whoever prescribed or dispensed that drug, which is a huge issue because a part of the REMS is going to have to be what we do about diversion."

APS wants to be sure the FDA hears from other stakeholders, not just the families of opioid victims. David Craig, director of the pain and palliative care specialty residency at H. Lee Moffitt Cancer Center in Tampa and another APS board member, said, "The biggest impact (of a REMS) for my cancer patients would be reduced access. That is the biggest fear I personally have with a REMS. If it is misguided, it could reduce access to pain medications. We've seen a mini-preview with the national shortage of oxycodone…We want the FDA to hear the right message…that having registries, layers of bureaucracy, or a whole host of things that could interfere with access. Tracking prescribers, pharmacies, and wholesalers would wind up with everyone tracking everyone, and no one wants to be tracked. Prescribers don't want to be under the microscope."

That's also the concern of Andrew Bertagnolli, PhD, of Kaiser Permanente, "The fear is that the REMS will cause providers to stop prescribing opioids because primary care doctors already are overwhelmed, and they could decide that the easiest pathway is not to prescribe them." However, a California anesthesiologist said doctors may not be able to simply opt out of prescribing opioids, "There is a standard-of-care use of opioids that has to be met."

The FDA has the authority to take long-acting opioids off the market, but no one really thinks that will happen – unless the REMS being developed doesn't work. Dr. Terman said, "What is driving this (FDA action) is a rapid increase in opioid-associated deaths…The CDC (Centers for Disease Control and Prevention) has given multiple presentations to Congress and in other forums…That is what's driving it…and there is a correlation with the amount of opiates being prescribed…At the moment this class has been singled out – and I don't know why…The FDA…sent letters on 24 products saying, 'Show us what you are going to do to reduce the risk. Then, we'll decide what to do with your product.' Obviously, if they decide to take them off the market, that would reduce access. If they don't go that far but decide doctors need some education, that may still reduce access because you are telling people these are dangerous drugs. What doctor wants to prescribe dangerous drugs? What will compel them (doctors) to take care of a patient's pain if they feel like people are looking over their shoulder?" Robert Jamison, PhD, a clinical psychologist from Brigham & Women's Hospital, said, "The FDA wants to get off the hook (with opioids) and put the problem back on pharmaceutical companies. They want industry to work together and come up with a plan."

What do experts expect the REMS to contain? Among the things being discussed:

- A registry, or even several different registries. This is not favored by doctors but is likely.
- Physician education on prescribing pain medications. This is almost a certainty. The question is whether this is a one-time event or something that has to be repeated yearly. A California anesthesiologist said, "If it is just a doctor education program and not too difficult, then there is no problem. California already requires 12 hours of pain and end-of-life education (one time), and people would do that unless the course has to be repeated all the time or the doctor rarely prescribes opioids."
- An opioid prescribing licensing exam, perhaps tied to the doctor's DES license/number. This was predicted to significantly dampen doctor willingness to prescribe opioids. The FDA reportedly has floated this idea.
- A restricted delivery system. This appears unlikely.
- A restrictive program like iPLEDGE, the STEPS program for Celgene's Thalomid (thalidomide), or the TOUCH program for Biogen Idec/Elan's Tysabri (natalizumab). This also appears unlikely, though a unique program for opioids is likely.
- Patient information materials. And there may need to be some form of proof that doctors have given patients the information.
- Patients may have to have had a minimum amount of another opioid before being prescribed a controlled-release opioid.

The Veterans Administration, Kaiser Permanente, and Brigham & Women's Hospital have all instituted multifaceted opioid abuse mitigation programs. Each is different, but each has been successful. Yet, none of these meet the FDA criteria, Dr. Jamison said, explaining, "The FDA wants something ***proven*** to work."

Jennifer Bolen, a legal expert in pain medicine from Legal Side of Pain and a former federal prosecutor, said there already has been behind-the-scenes compromising on the new REMS and described the negotiations as a war, "The FDA knows what it wants, but it doesn't know how to get there… The FDA and DEA are under pressure to get companies to do something (about opioid abuse and misuse). The REMS is a form of control not exerted except with a very few drugs. It would be okay if it were the right kind of education, but the FDA has clipped the wings on education because of restrictions on drug company education…What is percolating under all of this is a high degree of control of medicine if some of these (items) get in the REMS."

APS is not the only group working to ensure that the FDA's long-acting opioid REMS is not oppressive. Dr. Terman said that Pain Care Forum, a group of >30 organizations – professional associations, consumer organizations, industry members, etc., focusing on pain policy issues – is working "to craft more general recommendations that we can all submit together."

There was also talk at APS of another FDA meeting on opioid REMS in July 2009, but that could not be confirmed.

The FDA has not approved any new long-acting opioids since the Agency announced in early February 2009 that it wants a single REMS program for this whole class of long-acting/extended-release agents. Experts predicted it will be 2010 before a long-acting opioid REMS is finalized, and they do not believe that the FDA will hold up action on all new drugs in the class until then. One expert who met with the FDA recently said the FDA was specifically asked if new drugs are on hold for the REMS, and FDA officials said, "No, we are not holding up any approvals."

How quickly will the FDA issue guidance on the new REMS for long-acting opioids? Dr. Rappaport said it probably will be next year. First, the FDA has to collect information, then review the docket (which he called a "massive task," and then there may be another FDA advisory committee meeting or possibly another public meeting. Meanwhile, the FDA "won't hold up anything for a substantial amount of time," Dr. Rappaport said. However, the company will have to propose an acceptable REMS that would be implemented until it is supplanted by the class REMS.

Asked how the FDA decided with which stakeholders to meet so far about the REMS, Dr. Rappaport said, it has been restricted to pharmaceutical companies with approved long-acting or extended-release opioids or who have submitted an application for one of these drugs to the FDA. Companies with products in development (even under an IND) have not been included in these discussions, nor have consultants.

Asked how generic long-acting opioids are affected, Dr. Rappaport said they have to have a REMS just like a brand drug. They are not being held up, but they are being held to the same criteria as a brand.

Asked about plans for a REMS for immediate-release opioids, Dr. Rappaport said that was discussed at the stakeholders meeting, "There are reasons to do that because of the possible risk that a REMS for long-acting opioids would cause people to switch to short-acting opioids. But pharmacy groups are already concerned about the additional responsibility. It is still a possibility that the REMS will be extended to all opioids."

Asked why no abuse-resistant/deterrent opioids have been approved yet, Dr. Rappaport said, "They need adequate science on the benefit. Look at the OxyContin CR (Purdue), Remoxy (King Pharmaceuticals/Pain Therapeutics, oxycodone hydrochloride controlled-release, or PTI-821), and Embeda (King/Alpharma, controlled release morphine + naltrexone) submissions…The problems are in the science, not regulatory hold-ups. I urged companies to do (develop) these products, but they can't come in with junk science and say you have a benefit."

Asked whether an FDA official said recently that if the dying doesn't stop, he is prepared to take opioids off the market, Dr. Rappaport said, "I don't think that is exactly what he said…I doubt he would say that we would take these drugs off the market. I think what he said is that that is one possibility if we don't get this problem under control…The object is to figure out the right way to do that."

BREAKTHROUGH PAIN

There is no point in Cephalon resubmitting Fentora for breakthrough pain until the FDA decides how it wants to handle the REMS; nothing is getting approved for breakthrough pain in the near future.

APS sponsored a "debate" on the issue of opioids in non-cancer breakthrough pain. To set the stage for the debate, the FDA's Dr. Rappaport provided an overview of the FDA position and thoughts on this issue.

He emphasized that the FDA's goal is to ***maintain access*** to important opioid drugs and to ***reduce the abuse and misuse*** of the products that have led to the current public health crisis of overdose and death, "This is all about maintaining access to these drugs, and neither I nor anyone at the Agency is looking to make these drugs less available or more restricted. But there are people who would like to do that, and if we don't step in and maintain some mitigation and balance, there is a chance that they will be so restricted that the average practitioner and pain patient won't have access to them."

Dr. Rappaport suggested looking at this website: **www.bluelight.ru**.

The FDA is ***very*** concerned about abuse and misuse of fentanyl. Dr. Rappaport said, "Fentanyl is one of the most sought after drugs by abusers. It has high potency, and it is very likable. People pay a lot of money for this stuff. When Actiq (Cephalon's fentanyl lollypop) was first approved, we were looking at $45,000 street value (sic) for a single Actiq. It is really this that is driving our concern."

Currently, fentanyl products are FDA approved for use in the cancer population, which Dr. Rappaport said "at least to some degree" provides some restricted access and restricted use in the community, "So we don't have so much fentanyl out there in the community that it will have a serious impact on misuse and abuse and the public health."

The FDA is concerned that approving fentanyl products for non-cancer breakthrough pain could significantly expand the number of patients exposed to the products – and significantly increase misuse, overdose, and deaths. Before the FDA agrees to extend the indication for fentanyl and other opioid products to non-cancer breakthrough pain, Dr. Rappaport said the FDA needs more data on safety and efficacy and a better definition of the breakthrough pain population:

- *Who are they?*
- *Do they experience the same phenomenon as cancer patients?*
- *How many of them are there?* A pharma told an FDA advisory panel that expanding the indication could result in an increase in patients, from 2 million to perhaps 11 million or more.
- *Who is prescribing for non-cancer breakthrough pain patients?* Dr. Rappaport said, "At the moment, most generalists (doctors) are kind of afraid of these patients… but once (these drugs) are approved for the chronic low back pain patient, they will have to get used to them. There will be pressure for them to use them, and there will be expanded use."
- *Is the non-cancer pain population at increased risk of adverse effects or abuse and addiction?*
- *Will there be problems in the community?* He said, "Inadvertent exposure is a concern."

Dr. Rappaport reviewed the problems with the original Actiq approval, saying the delay in approval was over the risk management plan (RiskMap), particularly the risk of accidental exposure of children. He noted, "Actiq is used widely off-label. It is used in opioid non-tolerant patients. There have been pediatric exposures and deaths. But there is limited abuse because there is limited product on the market so far."

Cephalon's Fentora (buccal fentanyl) was approved in 2006 with a similar RiskMap, and that is also causing problems that concern the FDA. Dr. Rappaport said, "In less than two years, we have seen an increase in cases of off-label use, overdose, death, and accidental exposures. Maybe it is the formulation. We are not really sure."

He said the FDA rejected Cephalon's request for an expanded indication for breakthrough pain in non-cancer patients, despite a proposal for a RiskMap that included a controlled launch, controlled physician detailing, and education plus a proposal for RFID tracking and a patient/prescriber registry because of a continuing concern about abuse, misuse, and overdose. He emphasized that these problems were even seen in the clinical trials, "It is very rare to see any abuse or diversion (in clinical trials), and here you see a significant problem. The advisory committee's conclusion was that expanded use of this product will raise serious safety concerns and will result in significant abuse and misuse and further impact public safety."

In addition, there has been increasing use of fentanyl products in patients non-tolerant of opioids. Dr. Rappaport said the FDA's Division of Risk Management in the Office of Surveillance and Epidemiology has warned that "non-tolerant patients are at a greater risk for life-threatening adverse events" and "urged additional strategies, such as mandatory enrollment in order to prescribe, requiring training or certification – not just attending a CME (continuing medical education) course, falling asleep, and signing a paper you were there…(but) taking a legitimate test that you understand how to use a product, treat pain, and the risk of misuse/diversion – and pharmacy requirements that could include mandatory enrollment of pharmacies and mandatory training or certification…no therapeutic substitute, patient counseling, etc."

Is this type of RiskMap or REMS feasible? Dr. Rappaport said, "We are not sure. We are still debating this. It is not likely to be feasible for a REMS for all potent opioids, but for the narrow indication here (breakthrough pain), it might be possible. But what happens if it is approved for non-cancer patients? You have to consider the numbers and the impact on the healthcare system…These are suggestions, things we are talking about internally and externally. They are not written in stone."

Is the FDA really considering a requirement for a patient/prescriber registry that would track opioid use? Dr. Rappaport said that idea actually first came from Cephalon, which proposed that as part of its RiskMap for an expanded indication for Fentora in breakthrough pain in non-cancer patients, "That (registry) proposal was a surprise to us…We didn't hear about it until the advisory committee. And that seemed something worth considering if this product had a broad indication …Some of the problems that are pushing us as possibly doing a patient registry as part of a REMS is that (in 2007) a majority of prescribers for Fentora are anesthesiologists…and oncologists ranked 14th in use."

FDA Figures on Fentora and Actiq Use

Category	Use
Fentora use by physician type	
Anesthesiologists	35%
Neurologists	5%
Internal medicine	5%
General practitioners, family medicine, doctors of osteopathy	9%
Physical medicine and rehabilitation	21%
Other (including oncologists)	25%
Fentora use by disease state	
Cancer-related	38%
Surgery	17%
Back pain	8%
Other	37%
Actiq use by disease state	
Cancer-related	14%
Surgery	14%
Other	72%

One advisory committee member suggested that the breakthrough pain risk management program be tested in the cancer population and then tested in the non-cancer population before any expanded indication is approved. Dr. Rappaport said, "I'm not quite sure how to do that without quarantining off an entire state. How do we test this before implementing it? We don't want to implement any program that causes more problems than benefits."

With respect to a REMS for breakthrough pain, under the FDA's new authority to mandate risk management programs, Dr. Rappaport said the FDA is currently discussing that internally.

The debate

Two pain specialists debated three questions, but neither position was clear or concise.

1. ***Is there science/clinical information that flares of pain intensity in patients with chronic non-cancer pain and cancer pain differ?***

CON: Dr. John Markman, director of the Pain Management Center at the University of Rochester Medical Center, argued that there isn't clear evidence that these two types of patients are the same. He compared the case of a woman with metastatic cancer of the spine and a women with chronic low back pain, both of whom experienced sharp breakthrough pain if they bent the wrong way. Among the points he made were:

- "Breakthrough is one term for a complex problem…There is a huge evidence gap between breakthrough pain in non-cancer patients and cancer patients…The main justification for demonstrating the unmet need of non-cancer breakthrough pain rests on a single 2006 telephone survey of chronic pain outpatients (n=229)…We need to have a better handle on the need before we go forward and expand indications."
- "We know that like heart rate and blood pressure, there is something about pain that is intrinsically variable…You do not give every patient who comes to the office with a heart rate of 120 adenosine…because the risk:benefit profile is not appropriate for every patient."

PRO: Dr. Charles Argoff, a neurologist from Albany Medical College, argued, "We don't have concrete evidence that there is a difference between non-cancer and cancer breakthrough pain." Among the points/comments he made were:

- "This is an individualized process (treating these patients)."
- Pain medication should be handled by pain specialists. "When you do surgery in a hospital, you have to prove you can do the surgery. People who prescribe a treatment should know what they can prescribe."
- "This is a class of medication I want to be able to use, and we have to learn how to titrate."
- "Do you do risk analysis on cancer patients? Why not? What about (cancer patient) family members? We don't have any information on how often medications might be diverted when prescribed for cancer patients."
- "I think everyone who prescribes (fentanyl) needs to understand basic documentation."

Dr. Argoff's Algorithm for Treating Breakthrough Pain

<table>
<tr><th colspan="3">Initial patient assessment</th></tr>
<tr><td colspan="3">Comprehensive pain management plan</td></tr>
<tr><td colspan="2">Trial of opioid therapy</td><td rowspan="3">Alternatives to opioid therapy</td></tr>
<tr><td colspan="2">Patient reassessment</td></tr>
<tr><td>Continue opioid</td><td>Exit strategy</td></tr>
</table>

2. ***Should the indications for treatment of breakthrough pain with opioids be expanded to include non-cancer patients?***

CON: Dr. Markman argued that the evidence does not support this. He said, "We are introducing a new class, and the benefit, to me, was uncertain…The definition and scope of breakthrough pain in chronic non-cancer patients is not sufficiently characterized." Among the other points he made were:

- "The trials to potentially show a benefit were based on $SPID_{60}$ (pain intensity at 60 minutes)…As someone who manages chronic pain, I don't think of it as a series of $SPID_{60}$s over time." Instead, he suggested a parallel group design trial be conducted comparing short-acting to rapid-acting opioids in a relevant patient population already on optimized medical therapy.
- The time to first perception of breakthrough pain maximum intensity is 0-5 minutes, but a clinically important reduction in pain takes longer than that with the fentanyl products.
- "I don't think it is okay to let the marketplace decide this …The evidence gap will prevent clinicians from safely weighing the risk of prescribing the rapid acting opioids for the proposed indication. We don't want to put the whole class in jeopardy for this small, marginal benefit."
- "There are many other opioid treatments available...It is not about not treating this at all…It is where is the extra value?"

PRO: Dr. Argoff argued, "I don't understand why we are singling out this group in terms of potentially depriving a large group of people from the benefits of this type of treatment...If a (rapid-acting) opioid can be used successfully in even 45% of patients, (it is worthwhile). We have many treatments that we are able to use as tools for migraine – valproic acid for example has less than a 50% response rate, topiramate about 50%, gabapentin 50+%. What we want to do is understand how to use these tools better…That doesn't mean immediately restricting them to patients who can benefit from them now. It

does mean for people to be able to use these having the skill set to do so and the skill set to evaluate and monitor, and the skill set to pick the patient who should remain and those who shouldn't…The incremental benefit is worth it to many patients. We should not be pontificating…The point I got from the FDA was that many people who don't have the skill set to prescribe are prescribing."

3. (a) Is the risk:benefit assessment of an opioid with non-cancer patients different from that with cancer patients, and (b) Is there a negative impact on public health if these opioids are indicated for non-cancer breakthrough pain?

CON: Dr. Markman argued that these opioids have a high rate of adverse events (63%-65%), a risk for long-term side effects (tolerance and hyperalgesia), and may affect a patient's craving or likability sense, "Will these formulations…increase the tendency in patients predisposed to aberrant drug taking behavior? Are we increasing the risk profile?...Will this new formulation exacerbate the (abuse) problem?" Among the points he made were:

- In 2007, 40% of Fentora patients and 75% of Actiq patients were not taking another opioid.
- "Problems with the new formulation may have a chilling effect on the use of other opioids…You advance this (Fentora or Actiq) to the marketplace (for non-cancer breakthrough pain), and the adverse consequences are so great that the patients most likely to benefit from opioids don't receive them."

PRO: Dr. Argoff argued that not making these products available is the problem.

Survey results

Cephalon sponsored a symposium on breakthrough pain, with the goal of raising physician awareness of non-cancer breakthrough pain – the issues and the controversies – to promote non-cancer breakthrough pain as a real entity, and, perhaps, get some off-label use of Fentora. During the symposium, doctors were asked to participate in an "outcomes research activity" for which each medical office could earn $200. The "chart audit" is being conducted by MediCom Worldwide (i.e., Cephalon). To qualify, a clinician, nurse, or "manager" has to complete a 10-question "chart review tool" on 5 chronic pain patients managed "immediately following and for 6 weeks after the symposium."

Attendees at the symposium were also surveyed, and 362 pain specialists participated. Some of the findings from this survey were:

- Nearly two-thirds rely on literature and only 10% rely on labeling to make a decision to prescribe an opioid for non-cancer patients.
- More than half felt there is no concrete evidence that there is a difference between non-cancer and cancer breakthrough pain, while 25% said there is evidence of a difference, and about one-sixth were not sure.
- One-third said the primary reason not to use opioids for breakthrough pain is insufficient data, while one-third said the abuse potential was a reason not to use opioids for that purpose.
- 50% said there is no negative impact to public health if opioids (fentanyl) were approved for non-cancer breakthrough pain, about one-third thought there would be a negative impact, and about one-sixth were unsure.

Doctors were asked the same questions before and after the symposium, and, not surprisingly, the voting didn't change by more than ~2% in either direction.

The bottom line

It is extremely unlikely that the FDA will grant an indication for non-cancer breakthrough pain until there is some consensus about whether the condition is real, what short-acting opioids are appropriate treatment, and what type of REMS should be required. It appears that Cephalon understands this and is actively engaged in trying to change medical opinion/practice from the bottom-up, rather than trying to get an FDA indication and then changing practice top-down.

FIBROMYALGIA

Fibromyalgia remains a controversial disease/disorder. European regulators have refused to approve any drugs to treat or manage fibromyalgia specifically. The FDA has approved three drugs.

- **Pfizer's Lyrica (pregabalin)**
- **Lilly's Cymbalta (duloxetine)**
- **Forest Laboratories/Cypress Bioscience's Savella (milnacipran)**

Jazz Pharmaceuticals plans to file Xyrem (JZP-6, sodium oxybate) with the FDA by the end of 2009 for the treatment of fibromyalgia. A second Phase III trial has been completed, with results expected in mid-2009.

Fibromyalgia is estimated to affect 3%-4% of women (7%-8% of women age 55-75) but only 0.5%-1.5% of men. The key diagnostic criteria are: "pain all over," sleep disturbances, chronic fatigue, and cognitive/mood complaints. There is some evidence of a genetic predisposition to fibromyalgia, increased levels of pro-nociceptive neurotransmitters (e.g., substance P, glutamate) and decreased levels of anti-nociceptive neurotransmitters (e.g., serotonin, norepinephrine).

The APS meeting coincided with the launch of Savella, which was approved by the FDA to treat fibromyalgia in January 2009 but was not available in pharmacies until late April 2009,

and doctors did not start getting detailed until early May. However, the sales reps at the Savella booth did not appear very knowledgeable about their new product and did not appear to have a very compelling story to tell. The biggest advantage to Savella appears to be pricing – it is reported to be 10%-15% less than Cymbalta.

At a Forest-sponsored breakfast on fibromyalgia, Dr. Lesley Arnold, a psychiatrist from the University of Cincinnati College of Medicine and an opinion leader in the fibromyalgia field, noted that fibromyalgia treatment is evolving and requires an interdisciplinary approach. She said fibromyalgia is more likely to be treated effectively if it is identified by a primary care doctor who manages it and intervenes early.

Asked about the efficacy of Tramadol and Tramadol/ acetaminophen in fibromyalgia, Dr. Arnold said, "There are studies showing efficacy in fibromyalgia, so that is another option. It is not FDA-indicated, but there is evidence in the literature to support that."

Researchers from Stanford University School of Medicine presented their research – not supported by industry – on the off-label use of compounded low-dose naltrexone for fibromyalgia, and the results were very interesting. It was a small, single-blind, placebo-controlled study in 10 women. Naltrexone 4.5 mg QD was administered ~1 hour before bedtime. Side effects were described as mild and transient, with the most common side effect vivid dreams. The researchers have started another, larger, double-blind trial which will be completed by December 2009.

Low-Dose Naltrexone in Fibromyalgia

Measurement	Placebo	Naltrexone (p-value vs. placebo)
Reduction in fibromyalgia symptom severity	2.3%	32.5% (p<0.0005)
Reduction in daily pain	---	(p=0.001)
Reduction in highest pain	---	(p=0.005)
Reduction in fatigue	---	(p=0.008)
Reduction in stress	---	(p=0.003)
Reduction in Fibromyalgia Impact Questionnaire	--	8.96 (p<0.0005)
Increase in mechanical pain threshold	---	5.88 (p<0.001)
Reduction in thermal pain threshold	---	3.86 (p<0.013)

Who Makes the Diagnosis of Fibromyalgia

Physician	Making diagnosis
Rheumatologists	42%
Family physicians	23%
Internists	12%
Other	23%

Treatment of Fibromyalgia

Measurement	Historical	Today
Understanding of disease	Poor	Better, with greater disease awareness
Treatment approach	Focused on relieving pain	Should address constellation of symptoms
Drugs	Tricyclic antidepressants were the cornerstone and first-line therapy	Cymbalta, Lyrica, Savella replacing tricyclic antidepressants as first-line therapy

Comparison of FDA-Approved Fibromyalgia Therapies

Measurement	Pfizer's Lyrica (pregabalin)	Lilly's Cymbalta (duloxetine)	Forest Labs/Cypress Bioscience's Savella (milnacipran)
When FDA approved	2007	2008	2009
Mechanism of action	Anticonvulsant	SNRI	SNRI
Efficacy	Monotherapy significantly reduces pain, sleep disturbance, and improves sleep quality at doses of 450 and 600 mg/day	Significantly reduces pain starting at Week 1. Superior to placebo in improvement in function and reduction of total impact of fibromyalgia on patients	Significantly more patients are fibromyalgia composite responders and pain composite responders. Significant improvement in global status, physical function, and fatigue. Improvements seen in Week 1.
Adverse events	Dizziness, somnolence, weight gain	Nausea, dry mouth, constipation	Nausea, headache, constipation
Dose	225 mg - 300 mg BID	60 mg/day QD	100 mg - 200 mg BID
Advantages	Efficacy	Amount of data, approval in multiple indications, one-step titration, balanced SNRI	10%-15% less expensive than Cymbalta
Disadvantages	Side effects, titration schedule	Side effects, boxed warning for risk of suicide, increased bleeding risk	BID dosing, titration schedule, boxed warning for risk of suicide, increased bleeding risk

SPECIFIC DRUGS

ABBOTT's Vicodin CR (acetaminophen and hydrocodone controlled release)

Abbott did not have a booth at APS this year, probably in reaction to the FDA rejection of its Vicodin CR. But it is quite a contrast to last year, where Abbott had a big booth and a strong presence. Sources believe Vicodin CR is dead. The problem with Vicodin CR may have been a demand by the FDA for analysis using baseline observation carried forward (BOCF), instead of last observation carried forward (LOCF).

BOCF is a more conservative analysis and is considered a very tough hurdle rarely employed outside of pain studies. It is usually used when dropouts are high. In a BOCF analysis, any dropouts are treated as non-responders, regardless of what response they had when they discontinued the trial. The FDA likes to look at both an LOCF and a BOCF analysis to make sure the effect sizes and p-values are somewhat consistent. If not, that signals a large number of patients may have dropped out, and the LOCF is putting a rosier picture on the data, so the results may not be generalizable to the entire study population.

CADENCE PHARMACEUTICALS' IV acetaminophen

Phase III trials are complete and indicate that a pre-made solution in IV bottles of 650 mg or 1000 mg acetaminophen (infused over 15 minutes) is effective for pain relief and is opioid-sparing. The safety profile also looked good, with no liver toxicity. Cadence has filed for a label in acute pain and fever and to market it in the peri-operative setting for surgical pain relief, starting in the operating room and continuing into recovery and until patients can take oral medications.

Pain specialists described IV acetaminophen as an important addition to surgical pain management. Dr. Raymond Sinatra of Yale University said, "It is a very powerful drug, very similar to ketorolac (Toradol) but without the same side effects. It has been used in Europe for many years (where it is sold by Bristol-Myers Squibb's subsidiary, UPSA, as Perfalgan). We were involved in a very large orthopedic trial, and we saw an opioid-sparing effect up to 28%...(But) I would avoid it in patients with severe hepatic disease. This is a very useful multimodal analgesic…Orally, it contributes 5%-10% of the analgesia, but IV, it contributes about 30%."

All the doctors questioned predicted that IV acetaminophen will find wide use and be adopted fairly quickly, by surgeons mostly but also by anesthesiologists.

- "The problem is how to manage postop pain. You can use opioids, but doctors are reluctant to prescribe them. The rationale for a multimodal approach is that you can decrease opioid use with safe adjuvants. IV acetaminophen doesn't interfere with platelet function like NSAIDs, doesn't cause GI bleeds, and doesn't interfere with renal function…The ambulatory market will be sizeable, but more doses will be given inpatient, so perhaps 60% inpatient, 40% ambulatory."
- "There is so much bad press about opioids that anything we can do to reduce use will do well. Anything opioid-sparing is a big deal. Everyone will tune in."
- "It will be used quite a bit. People will take to it very quickly."

For what types of procedures is it most likely to be used?

- "It would have very wide application – all one-day surgery, almost all orthopedic surgery, some gynecologic surgery, and laparoscopic surgery. It would most likely be used single-dose in the ambulatory setting, and in multiple doses for inpatients. It will probably be given by the anesthesiologists in the operating room, with subsequent doses in recovery."
- "It will be used for both inpatients and outpatients."
- "It will be used in both complex, invasive surgeries and for milder procedures, but it will be more likely used in outpatient surgery centers where they don't want people held up in recovery because of side effects."

The only other FDA-approved non-opioid, infusible analgesic is Toradol (ketorolac), but Toradol has a boxed warning for bleeding risk. Experts predicted that IV acetaminophen will not only take market share from Toradol but will expand the market. A doctor said, "A lot of doctors know about Toradol but won't use it because of the risk, even before the black box." Another commented, "It will expand the market because it will really represent a new alternative. People won't too often weigh it against Toradol. They will just use it wherever it is indicated."

Cadence is a small company, and sources were mixed on whether it will be able to handle marketing without a major partner, though one source suggested this would be a perfect fit for J&J. One expert said, "Everyone knows acetaminophen. It's a trusted molecule, and it is recognized as safe. The education needs to be that this is not only safe but also has powerful effectiveness. But it will need a big educational initiative, and that will be hard. This will be a hospital or ambulatory surgery center drug, so Cadence will need people with access. But the message will resonate."

What might the issues be for FDA approval? Experts couldn't think of any.

EGALET

This Danish company is working on morphine, hydrocodone, and oxycodone formulations that are abuse-resistant. The formulations are based on a proprietary injection molded polymer system, consisting of an erodable matrix partly covered with a water-impermeable, non-erodable shell. The tablet is cylindrical, with fixed surface erosion areas at both

ends, allowing a tightly controlled, extended-release for up to 12 hours and a potential for QD dosing. Egalet is looking for a partner to fund further development studies of its candidates.

FOREST LABORATORIES/CYPRESS BIOSCIENCE's Savella (milnacipran)

Savella wasn't getting much attention at the American Academy of Neurology meeting in April, but the drug wasn't available in pharmacies until that meeting, and the companies hadn't started detailing doctors yet. Pain specialists at APS were much more aware of Savella, even though the company only started detailing doctors on the day before the APS meeting started.

JOHNSON & JOHNSON's tapentadol

The IR formulation (Nucynta) was approved by the FDA in November 2008, but it has not yet been launched because it is still waiting for Drug Enforcement Administration (DEA) scheduling. Nucynta is expected to be a Schedule II drug, like morphine and fentanyl. A speaker said, "It is not a weak opioid. It is powerful…This is a very powerful opioid…And it shows up as a drug that is liked." Another expert said, "In preclinical data it looked like it might not be as 'likable' (as oxycodone), but in liking studies vs. hydromorphone, it was virtually indistinguishable. So I think it will properly be scheduled as Schedule II."

Other interesting points about tapentadol include:

- Nucynta is as efficacious as oxycodone 10 mg-15 mg but has fewer side effects, notably less constipation.
- Four Phase III trials of tapentadol ER have been completed (2 in osteoarthritis, 2 in low back pain, 1 in diabetic peripheral neuropathy), and a 12-month safety study is underway. J&J has not yet submitted tapentadol ER to the FDA, but it is not waiting for the safety study. Rather, the submission, which will be for moderate-to-severe chronic pain, is waiting for resolution of some "formulation issues." A speaker predicted it is 1-2 years away from the market.
- A question about tapentadol ER that a researcher couldn't answer: Is there any respiratory effect?
- A tamper-resistant formulation of tapentadol ER is in development.
- Grünenthal has conducted cancer pain studies, which are required for European approval in chronic pain.

The results of a randomized, multicenter, 981-patient, double-blind, placebo- and active-controlled Phase III trial of tapentadol ER in chronic low back pain was presented at APS, showing efficacy superior to placebo and comparable to oxycodone CR and with fewer GI side effects. Tapentadol ER patients had numerically ***less*** nausea, constipation, vomiting, dizziness, pruritis, somnolence, insomnia, fatigue, and hyperhydrosis, and numerically ***more*** headache, dry mouth, diarrhea, and dyspepsia than oxycodone CR patients.

Results of Phase III Trial of Tapentadol in Low Back Pain

Measurement	Placebo n=319	Tapentadol ER n=318	Oxycodone CR n=328
Discontinuations	49.5%	45.9%	56.7%
Discontinuations due to adverse events	4.7%	16.7%	32.3%
Discontinuations due to adverse events during the 12-week maintenance period	2.2%	6.0%	5.8%
Primary endpoint: Change from baseline in pain intensity at Week 12 of the maintenance period	---	0.8 more than placebo (p<0.001)	0.9 more than placebo (p<0.001)
Secondary endpoint: Change from baseline in average pain intensity over the 12-week maintenance period	---	0.7 more than placebo (p<0.001)	0.8 more than placebo (p<0.001)
Treatment-related adverse events			
Any	59.6%	75.5%	84.8%
Serious adverse events	0.9%	2.2%	3.4%
Death	0	0	0
Nausea	9.1%	20.1%	34.5%
Constipation	5.0%	13.8%	26.8%
Headache	13.8%	19.8%	16.8%
Somnolence	2.5%	13.2%	16.2%
Dry mouth	2.2%	8.2%	3.7%
Diarrhea	7.2%	6.0%	2.4%
Dyspepsia	2.5%	5.0%	1.8%

KING/ACURA's Acurox (oxycodone IR + niacin), an abuse-resistant/deterrent opioid

Acurox has been submitted to the FDA, and the PDFUA date is June 30, 2009. Acurox is an immediate-release, so a REMS is not required for approval. Data from a study in bunionectomy surgery patients were presented. The efficacy looked good, but the side effects were high, though fairly typical of opioids. There were no serious adverse events, and only 2.2% discontinued for adverse events. (*See chart on page 12*)

NEUROGESX's NGX-4010, a capsaicin patch for pain

This was filed with the FDA on October 28, 2008, for the treatment of post-herpetic neuralgia (PHN), but it has an FDA problem that could delay approval. A topical lidocaine was used to prep the patient, but the lidocaine that was used is not FDA-approved, so it can't be listed in the label instructions. Thus, the FDA wants the company to do a small study using a different lidocaine – one that is approved and that is comparable to the lidocaine used in the studies already submitted.

Furthermore, although the company has a positive opinion from European regulators, making approval likely, it still does

Acurox in Bunionectomy Surgery Patients

Measurement	Placebo n=136	Acurox 2 x * 5/30 mg Q6H n=135	Acurox 2 x ** 7.5/30 mg Q6H n=135
Discontinuations	8 patients	8 patients	3 patients
Primary endpoint: $SPID_{48}$	604.5	998.5 (p<0.0001)	1225 (p<0.0001)
Secondary endpoint: Response to treatment	2.9%	9.6% (p=0.0212)	10.4% (p=0.0105)
TOTPR core (pain relief)	2.0%	3.9% (p=0.0005)	5.1% (p<0.0001)
Adverse events			
Any	38.2%	77.0%	87.3%
Nausea	10.3%	50.4%	61.9%
Vomiting	3.7%	34.1%	50.0%
Dizziness	4.4%	16.3%	23.9%
Flushing	1.5%	16.3%	11.2%
Pruritis	0.7%	12.6%	9.7%
Headache	2.2%	9.6%	8.2%

* 5 mg oxycodone IR, 30 mg niacin ** 7.5 mg oxycodone IR, 30 mg niacin

not have a partner in Europe and reportedly won't (or can't) launch without one. It also has no U.S. partner yet.

Reportedly, the cost of the patch, including the office visit, will be about $6,000 a year.

PFIZER's tanezumab (PF-4383119), a humanized monoclonal antibody targeting nerve growth factor

This looks like it has the potential to be a very successful drug for Pfizer. Even competitors described it as a "game changer." Phase II data in osteoarthritis (OA) were presented at the American College of Rheumatology meeting in November 2008, showing good efficacy and very minimal side effects (nothing concerning) with a single intravenous (IV) infusion (5-minute push) once every 8 weeks.

The results of a randomized, double-blind, 217-patient, placebo- and active-controlled, multicenter, Phase II trial of tanezumab in lower back pain were presented at APS. A single IV infusion of tanezumab 200 µg/kg provided durable efficacy over 12 weeks, and the efficacy of tanezumab was clearly better than either naproxen or placebo. There were some sensation-related side effects, but a researcher said they start with the first dose, last 2-4 weeks, and then go away. With the second dose, these side effects are seen much less

Results of Phase II Trial of Tanezumab in Chronic Low Back Pain

Measurement	Placebo n=41	Naproxen 500 mg BID n=88	Tanezumab 200 µg/kg n=88	p-value
Primary endpoint: Mean change in LBPI at Week 6 *	-1.96	-2.54	-3.37	0.004 vs. naproxen, <0.001 vs. placebo
Secondary endpoints				
≥30% reduction in LBPI at Week 6	31.7%	56.8%	73.9%	0.013 vs. naproxen, <0.001 vs. placebo
≥30% reduction in LBPI at Week 12	48.8%	51.1%	67.0%	<0.05 vs. placebo and naproxen
≥50% reduction in LBPI at Week 6	19.5%	34.1%	56.8%	0.002 vs. naproxen, <0.001 vs. placebo
≥50% reduction in LBPI at Week 12	29.3%	34.1%	48.9%	<0.05 vs. placebo and naproxen
Mean change in RMDQ at Week 6 **	-3.93	-4.69	-7.70	<0.001 vs. naproxen, <0.001 vs. placebo
≥1 category improvement in Patient's Global Assessment of LBP	64.5%	62.6%	75.5%	Nss vs. naproxen, Nss vs. placebo
≥2 category improvement in Patient's Global Assessment of LBP	25.8%	38.7%	44.6%	
Safety				
Discontinuations due to adverse events	4.9%	3.4%	4.5%	---
Any adverse event	65.9%	60.2%	55.7%	---
Arthralgia	0	6.8%	13.6%	---
Headache	19.5%	5.7%	11.4%	---
Abnormal peripheral sensation	2.4%	3.4%	12.5%	---
Abnormal peripheral sensation side effects				
Hyperesthesia	0	0	6.8%	---
Paresthesia	0	1.1%	4.5%	---
Dysesthesia	0	0	2.3%	---
Neuralgia	0	0	1.1%	---
Peripheral neuropathy	0	0	1.1%	---
Pallanesthesia	0	2.3%	0	---
Hypoesthesia	2.4%	0	0	---

* LBPI = lower back pain intensity score ** RMDQ=Roland-Morris Disability Questionnaire total score

frequently. She described the side effects as, "a first-dose phenomenon." There is also some mild-to-moderate arthralgia, but that appears to be some overlap with the abnormal peripheral sensation side effects, and it also resolves in 2-4 weeks.

The study found:

- There were no discontinuations for adverse events.
- ~10% of patients had hypersensitivity sensation to pain – a pins and needles-type of feeling, which the researcher said could be related to nerve growth factor.
- There is no muscle weakness, but Pfizer plans to do nerve conduction studies to better understand the side effects.
- Infusion reactions have been mild so far.

Pfizer researchers offered some additional facts:

- Very large people (≥125 kg) may require a larger dose, but all other people should be able to be treated with the same fixed IV dose (10 mg).
- IV dosing will be flat, fixed dosing, not weight-based dosing.
- All the sites for the Phase III osteoarthritis trial have been selected, and that trial is almost fully enrolled.
- For low back pain, Pfizer expects a 20 mg dose to be used.
- At the request of a fibromyalgia expert, Pfizer also is considering the idea of a trial of tanezumab in fibromyalgia. And there are mechanistic reasons to think it may work in fibromyalgia.
- Pfizer also is studying tanezumab in cancer pain. The sites have been selected for a cancer pain study – in people with bone metastases because there "is some scientific rationale" for that – and the trial is now enrolling patients.
- There is no interaction with the immune system, so there are no immunosuppressive properties.
- The drug is not disease-modifying; it just provides pain relief.
- Pfizer plans to file for both osteoarthritis and lower back pain at the same time.
- Pfizer has been discussing with managed care companies what it wants to see in terms of pharmacoeconomics. A tanezumab researcher said, "It won't be priced as high as biologics for rheumatoid arthritis (RA), but it will be more expensive than orals for osteoarthritis or low back pain…Insurance companies and managed care really would like to see patients get off chronic opioid therapy …The impact on worker productivity may offset some of the cost of this vs. opioids."
- The Phase III in lower back pain is scheduled to start in June 2009.
- Tanezumab needs to be refrigerated.
- Pfizer expects that eventually patients will be able to self-inject with pre-filled syringes.
- Pfizer plans to position tanezumab not as first-line but for people who don't respond to NSAIDs or are opioid failures.
- No switching studies have been done, but Pfizer plans an opioid comparison study in the future.

A subcutaneous (SQ) formulation is in development but is about a year behind the IV formulation. The SQ formulation is already in the clinic being tested in humans. Pfizer is doing bridging studies and does not plan a full program as with the IV formulation.

Can Pfizer use PK and bridging studies to get a subcutaneous formulation approved? Experts were divided. Some researchers said no because the IV and SQ formulations will have different bioavailability and local effects, though noting the decision will be up to the FDA. A former tanezumab researcher said it depends on "which way the wind is blowing at the FDA; there is nothing set in stone." Others thought PK/bridging studies would be sufficient. A Merck researcher said, "It has to do with the size of the molecule. Most can do with a PK study." A J&J researcher agreed.

That may be tougher for tanezumab as a biologic (antibody) than it would be for a small molecule. For example, Bristol-Myers Squibb is developing a subcutaneous version of its IV Orencia (abatacept) for RA. Reportedly, the company thought it could just submit a bridging/PK study and get approval, but the FDA wanted full-blown clinical efficacy and safety data which Bristol is currently doing. Tanezumab may well be asked to do the same, but Pfizer doesn't have anything to lose by submitting a bridging/PK package on the off-chance FDA approves it.

PURDUE PHARMA

➢ **Transdermal buprenorphine (BTDS) for moderate-to-severe pain.** The results of a randomized, double-blind, double-dummy, Phase III trial of BTDS in moderate-to-severe pain were presented at APS. The study found that 20 µg/hour transdermal BTDS significantly reduced pain over 24 hours ($p<0.001$). IV and intramuscular buprenorphine is FDA-approved for the relief of moderate-to-severe pain, and sublingual formulations are approved for the treatment of opioid dependency. In addition, Purdue's 7-day buprenorphine patch has been marketed in Europe for years as BuTrans for osteoarthritis by Mundipharma/Napp. In comparison to oxycodone IR, BTDS significantly decreases average pain over 24 hours ($p<0.001$). Four sensitivity analyses were conducted, and all showed a robust effect of BTDS.

➢ **Ryzolt (once-daily IR/ER tramadol).** Purdue launched this at APS. The product is formulated in Labopharm's Contramid dual matrix technology and was shipped to pharmacies in mid-April. It is available in 100 mg, 200 mg, and 300 mg tablets. Despite availability of Ryzolt, Purdue only had "coming soon" signs in its booth and no sales literature other than the FDA label and packages of its *Value Program* (14 days of free tablets and a $35 copay voucher). Detailing by sales reps was merely "Ryzolt is a unique formulation of immediate-release and controlled-tramadol. We don't have any head-to-head data vs. Ultram ER. We are a unique formulation."

XENOPORT/GLAXOSMITHKLINE'S XP-512 (gabapentin enacarbil, a prodrug of gabapentin), for diabetic peripheral neuropathy (DPN)

The brand name was going to be Solzira, but the FDA objected to the name, so there will be a new name. There were no new data at APS on this – just 2 posters that had previously been presented at the American Academy of Neurology meeting. A DPN expert/researcher was not very optimistic about XP-512, but he didn't really have any data on which to base that.

TIDBITS

ATLANTIC PHARMACEUTICAL is working on an oxycodone IR that is abuse-resistant. There were no data on this at APS; it is just getting ready to start human clinical trials.

Data from **CEPHALON's** head-to-head trial of Fentora (buccal fentanyl) vs. oxycodone IR is not expected until fall 2009.

ENDO PHARMACEUTICALS did not have any posters at the meeting on any drugs it has in development.

A military doctor said **JAZZ PHARMACEUTICALS' Xyrem** (sodium oxybate) can't be used in PTSD (post-traumatic stress disorder) patients because it causes nightmares.

Purdue Pharma has filed a Citizen's Petition against **KING PHARMACEUTICALS' Remoxy** (abuse-resistant oxycodone CR) claiming that Remoxy should have used oxycodone CR as the comparator in its pivotal trials, not oxycodone IR.

THERAQUEST has given up on its TQ-1017, a once-a-day, abuse-deterrent Tramadol ER. The company is continuing to investigate TQ-1015, a controlled-release broad-spectrum opioid it claims is abuse-resistant. A Phase I trial in healthy patients was started in March 2009, and results are expected in June 2009. Once that is complete, TheraQuest plans to go straight to a Phase III using a 505(b)2 strategy.

VERTEX PHARMACEUTICALS is working on a pain drug, but no details were available on it. This may be VX-702 which failed to show sustained efficacy in rheumatoid arthritis but is now being explored in pain. A dental pain study was positive.

The FDA is increasingly requiring the use of **baseline observation carried forward (BOCF)** instead of the more usual last observation carried forward (LOCF). Researchers agreed that the FDA has begun applying BOCF to pain trials frequently, especially, but not exclusively, when dropout rates are high, so this is something that needs to be watched with all trial data for the future. Researchers are not happy with the mandated use of BOCF, but they recognize it is a reality. One said, "Overall, we got to a certain (data) level, and then the FDA changed the rules. But it is a good time to do that. By being a little stricter, we will improve research. The FDA is asking pharma to kick research up a notch…But it's a little onerous."

Apparently, BOCF has caused problems with pain drugs for companies other than Abbott. On the other hand, BOCF may have ***helped*** Cypress Bioscience, which was reportedly told by the FDA to use BOCF for a milnacipran fibromyalgia trial. However, Cypress resisted, insisting it wanted to use LOCF. Then, it turned out that the BOCF analysis was more favorable for milnacipran than the LOCF analysis!

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