Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Abuse-resistance technology/design is encouraged but not required for FDA approval of an oral ER opioid. ♦ All ER opioids must have *in vitro* – and sometimes *in vivo* – alcohol interaction data before FDA approval. ♦ Even opioids with a lower abuse potential than competitors will find it extremely difficult to get a better controlled substance schedule. ♦ Pain doctors are generally receptive to the idea of oxymorphone ER for second- or third-line use. ♦ Doctors want to see functional improvement as well as pain reduction to prove the value of Jazz Pharmaceuticals' Xyrem (sodium oxybate) in fibromyalgia, but doctors will use it if it gets approved. ♦ Advanced Bionics' current steering was a hot topic, and the company is likely to increase market share. ♦ Neurostimulation companies have been trying to spur sales by getting the word out about new Medicare reimbursement rates this year for implantable pulse generators. ♦ Worth watching: Javelin Pharmaceuticals' Rylomine, an intranasal morphine, and Bioness' Bion, a microstimulator for rehabilitation.

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AMERICAN ACADEMY OF PAIN MEDICINE (AAPM)

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There was more news at this meeting on neuromodulation devices than on new pain medications. Chronic pain – pain that persists or recurs for more than six months – afflicts an estimated 75 million Americans. It can be caused by a variety of injuries and diseases, and most commonly affects the lower back and legs. Left untreated or under-treated, chronic pain can destroy a person's life. Beyond the physical disability that often results, it can lead to difficulty holding a job, low self-esteem, strained relationships, depression, and suicide.

Chronic Pain Begins as Acute Pain

Surgical procedure	Patients with chronic pain
Thoracotomy	30% - 67%
Limb amputation	30% - 83%
Mastectomy	11% - 49%
Open cholecystectomy	22% - 37%
Open hernia repair	0 - 37%

Opioids remain the foundation of acute pain management. However, a speaker commented that, when possible, NSAIDs, Cox-2 inhibitors, and regional blockage should be used to provide multimodal augmentation of opioid-based analgesia. New analgesic delivery systems offer advantages of convenience, superior pain relief, and prolonged duration of effect.

Monitoring blood levels of opioids in chronic pain patients may be advisable. A study presented at AAPM found that checking opioid blood concentrations can aid in determining compliance with prescribing instructions, determination of therapeutic effectiveness, and medicolegal protection. In the study, patients had blood samples taken approximately 1-2 hours after a regularly prescribed opioid dose, and researchers found:

- The majority of blood concentrations were above the therapeutic ranges published for non-tolerant people.
- Many concentrations were above levels often described as "toxic" or "lethal."

Depression and Pain

Depression is associated with pain far more than most people realize. About 5%-7% of people in the general population are depressed, but experts estimated that ~20% of chronic pain patients are depressed, and ~45% of psychiatric patients with depressive neurosis have chronic pain. In pain centers, 55%-87% of patients are depressed. About 35% of patients with neuropathic pain are also depressed. An expert said pain often precedes depressive symptoms, and stress predicts the onset of musculoskeletal pain. Mood disturbances also can elicit or exacerbate

Advantages and Disadvantages of Various Delivery Systems

Advantages	Disadvantages
Patient-Controlled Analgesia (IV PCA)	
Patients can self-titrate	Expensive infusion equipment required
Rapid onset of effect	Overdosing may occur when relatives/nurses administer doses for the patient
Compensates for inter-patient differences in PK and PD	Overdosing may occur from programming errors or use of basal infusions
Eliminates dosing peaks and troughs	Elderly patients may not understand the concept of "self-administration"
High degree of patient acceptance, control, and satisfaction	Duration of therapy should be restricted to 24-72 hours
	IV site problems
Epidural PCA	
"Superior" pain control	Invasive and expensive
Reduction in opioid dose	Requires continuous follow-up
Blunts stress/splinting responses in high-risk patients	Catheter migration problems; 30% of epidural catheters do not work adequately
	Contraindication in anticoagulated or systemically infected patients
Regional Analgesia with ketorolac and other NSAIDs	
Reduction in pain intensity scores	200% increase in perioperative bleeding
Reduction in total opioid dose	Increased incidence of wound hematomas
Reduction in opioid side effects (nausea, vomiting, sedation)	Risk of perioperative GI bleeding
Iontophoresis with fentanyl HCl patient-activated analgesic delivery (PATS)	
Therapeutically equivalent to IV morphine	More headache than IV PCA morphine (11.4% vs. 7.5%)
Less nausea than IV PCA morphine (40.8% vs. 45.9%)	

Expert View of Efficacy of Various Non-Opioids in Chronic Pain and Depression

Drug	Efficacy	Number needed to treat
Cypress Bioscience's (milnacipran)	Effective independent of mood.	N/A
GlaxoSmithKline's Wellbutrin (bupropion)	One study showed effectiveness.	N/A
Lilly's Cymbalta (duloxetine)	Approved for diabetic peripheral neuropathic pain. Has an effect early on but has more drug interactions than Effexor.	52 at 60 mg/day 4.9 at 120 mg/day
Lilly's Strattera (atomoxetine)	Pretty good antidepressant, can give results when no results with Effexor or Cymbalta. Can be combined with Forest's Lexapro.	N/A
Pfizer's Lyrica (pregabalin)	First-line treatment for diabetic peripheral neuropathic pain.	N/A
Organon's Remeron (mirtazapine)	Good for sleep or as an adjunct to another antidepressant.	N/A
Bristol-Myers Squibb's Serzone (nefazodone)	Helps improve sleep, but has a black box liver warning.	N/A
SSRIs	Good for depression and anxiety but doesn't do much for pain.	6.8
Tricyclic antidepressants	Effective but safety and tolerability issues.	2.1 - 3.3 for various types of neuropathic pain
Wyeth's Effexor (venlafaxine)	Good data that it works, but it has to be used at a high dose (150-300 mg) to get the effect. May increase the threshold of pain tolerance.	5.5 for polyneuropathy

pain and vice versa; either can make the other treatment-resistant. Pain elicits sleep disturbance, and sleep disturbance promotes pain and impedes coping. A speaker advised, "You should always ask (about depression) when you see a chronic pain patient…If the patient is depressed, the patient should be on an antidepressant. Chose an antidepressant with potentially greater analgesic properties and the lowest side effect profile for that patient." A Florida doctor said, "If a patient is depressed, I give an anti-depressant before an AED (antiepileptic drug). If the patient is not depressed, then I look at efficacy and side effects. The number needed to treat is worse for Neurontin (Pfizer, gabapentin) than tricyclic antidepressants in diabetic neuropathic pain patients."

Neuropathic Pain

All the drugs – anticonvulsants, local anesthetics – work about the same (for neuropathic pain), a speaker suggested, citing a 20%-30% efficacy rate and a 20%-30% drop in VAS with treatment. He said, "The selection of an agent is often based on safety, tolerability, ease of use (QD vs. TID), the size of the pills, and efficacy…Neurontin is the most powerful; patients don't tolerate it that well. It is probably the hardest to use, and that is the benefit to Lyrica (Pfizer, pregabalin), which has equal efficacy but is easier to use…Lyrica is a neuropathic analgesic like all the others. It looks like Lyrica is the quickest acting of all, but what is the value of that? I would argue that it is not worth a lot of extra cost, but it is nice. One area where it is nice is in treating herpes zoster where you can't wait. Lyrica is my choice for that, but herpes zoster isn't common compared to chronic neuropathic pain."

Neuropathic Pain Prevalence in U.S.

Pain	U.S. Prevalence
Painful diabetic neuropathy	600,000
Post-herpetic neuralgia	500,000
Cancer-associated pain	200,000
Spinal cord injury	120,000
Causalgia and reflex sympathetic dystrophy	100,000
Phantom pain	50,000
Multiple sclerosis	50,000
Post-stroke pain	30,000
IV-associated pain	15,000
Trigeminal neuralgia	15,000

Breakthrough Pain

At a Cephalon-sponsored session on breakthrough pain, a doctor in the audience asked why doctors should use a drug other than Cephalon's Actiq (fentanyl citrate) or its OraVescent fentanyl for breakthrough pain, which typically lasts <90 minutes.

Comparison of Immediate-Release Medications for Breakthrough Pain

	Drug	Administration	Onset of analgesia	Duration of effect	Advantages	Disadvantages
Hydrophilic	Morphine	Oral	30-40 min.	4 hours	Available in multiple dosage forms, liquid concentrate	Slow onset of analgesia for idiopathic breakthrough pain
	Oxycodone	Oral	30 min.	4 hours	Available in multiple dosage forms, liquid concentrate	Slow onset of analgesia for idiopathic breakthrough pain
	Hydromorphone	Oral	30 min.	4 hours	---	No liquid concentrate, slow onset of analgesia for idiopathic breakthrough pain
	Methadone	Oral	~10-15 min.	4-6 hours	Faster onset of analgesia	Complex pharmacology and PK
Lipophilic	Fentanyl	Sublingual	8-12 min.	N/A	---	Irregular absorption
	Fentanyl	Transmucosal	~5-10 min.	1-2 hours	Fastest onset of analgesia	Requires ongoing patient cooperation in use

A speaker responded, "Part of it may be convention…The bottom line is I'm not sure there is a strong evidence-backed logical answer here. A lot of it is practice patterns based on convention." Another expert said, "People come in for a short-acting opioid, and then get a long-acting opioid, but they keep the short-acting because that is immediate-release morphine."

Even among the experts at this Cephalon-sponsored session, Actiq is not the first-line treatment for breakthrough pain. One said, "It is difficult to take cost off the table. Actiq is more expensive." Another doctor said, "Vicodin (hydrocodone) is cheaper. We commonly use drugs that are cheaper, and refillable. I use immediate-release morphine more commonly (than Actiq)." The moderator said, "Immediate-release hydromorphone and immediate-release morphine are the two most commonly used agents by our group."

Topical Analgesics

- **Topical NSAIDs** (patches) are "modestly effective," according to one speaker, who added, "We've been using a lidocaine patch off-label for hip and back pain with good results in our practice…They are probably better with acute than chronic conditions."
- **Topical nitrates** (ointment). Two studies have shown improvement.
- **Lidocaine patch.** With a lidocaine patch 5%, about 3% of the lidocaine is systemically absorbed. A lidocaine patch was described as effectively treating all neuropathic pain qualities, reducing pain intensity, having less interference with quality of life in post-herpetic neuralgia, significantly improving mean daily diary pain ratings in diabetic polyneuropathy, and effectively treating focal peripheral neuropathic pain syndromes.
- **Clonidine.** This is effective at concentrations of 150-200 µg/g of ointment. The onset of action is within minutes, and there is a significant reduction in hyperalgesia to mechanical and cold stimuli.
- **Resiniferatoxin** (Icos), an ultra-potent analog of capsaicin that is not approved in the U.S.
- **Capsaicin ointment/cream** (Hi-Tech Pharmaca's Zostrix). A speaker said it gives more pain relief in diabetic neuropathy than placebo and has the same analgesia as oral amitriptyline (but fewer side effects). The major limiting factor is burning on application, though use of topical local anesthetics or ice may increase a patient's tolerance for capsaicin.

Regulatory Issues

FDA Deputy Commissioner Scott Gottlieb read a prepared speech in which he called acute chronic pain "an unmet medical need." The problem, he said, is balancing drug approvals and criminal diversion of drugs. He said, "I'm not sure in Washington there is always a clear understanding of the realities of medical practice and the unique challenges patients with pain face. At FDA we are doing what we can…FDA has a culture of medicine, and many (there) still practice medicine. We are trying to strike a delicate balance between access and abuse potential and criminal diversion by a handful of very motivated criminal entities. In the treatment of chronic pain, our goal is to assure that patients who require opioids have appropriate access while misuse and diversion are limited…Our efforts to ensure safety shouldn't inhibit access to important medicines because undertreatment is a concern."

He said the FDA is concerned about legislative proposals that the Agency believes could limit patient access to pain medications while not resolving illegal diversion, "We believe there is a serious problem with people who divert pain medications for illegal purposes, and we see this as a growing threat. We work with DEA (Drug Enforcement Administration), etc., to stamp out this growing problem and to go after people who divert these medications."

Dr. Gottlieb stressed that the FDA's decision to approve pain medication is not a law enforcement issue, but the FDA is trying to work with law enforcement. He said, "We are also sorry about delays in approval. The process for approving new pain medications already is among the most challenging approval pathways that any drug must go through. We have discussed ways to collaborate with DEA and bring them in early in the process…We are eager to find creative ways to get DEA involved early while protecting the approval process. We are already doing a lot to help DEA."

The approval process for medical devices is "much more modern" than the drug approval process, Dr. Gottlieb said. He explained, "(The device statute) allows us to calibrate to the perceived level of risk…There are a number of different pathways on the device side that calibrate premarket requirements to the level of risk, and that gives FDA more tools to minimize risk. The drug side is a less flexible statute, a one-size-fits-all approach."

➢ **Role of DEA.** Asked about efforts by DEA to have a say in the approval and marketing of new controlled substances, to interfere in FDA's approval process, Dr. Gottlieb said, "Having law enforcement take on an explicit role in the approval presents challenges and problems…These are innately public health decisions that require a careful balance of risk:benefit and that we and Congress thought was better left to FDA…These are dual challenges. The law enforcement challenges are distinct from the public health challenge, and they need to be dealt with in a different sphere."

➢ **Anti-abuse measures.** Asked what the FDA is doing to stop the conversion of long-acting pain medication to short-acting drugs by crushing them, Dr. Gottlieb said, "It is challenging if you have a motivated criminal who is trying to outsmart whatever safeguards are built in…Crushing or altering the product, especially when (the product is) intended for long-acting use. On the scientific side, we will promulgate guidance to sponsors on how to develop technologies that could be abuse-resistant – and there are a number in development – but I don't think there is any way to completely eradicate the problem."

➢ **Abuse resistance.** Asked if some form of abuse-resistance technology or design will be necessary for approval of any oral extended-release opioid, Dr. Gottlieb referred the question to the Agency's Controlled Substance Staff (CSS) which responded, "No. While we are encouraging sponsors to incorporate abuse-resistance technology, we are not requiring this for approval of extended-release opiates. We can imagine a time in the future when there may be many abuse-resistant formulations available, making the approval of products without this feature questionable; but that's a long way off."

However, Dr. Gottlieb said the science of evaluating abuse potential has changed since the FDA issued its guidance years ago, and that is being updated, with new guidance expected later this year. He said, "Our role could be better guidance, and how to develop abuse-resistant products."

➢ **Alcohol interaction studies.** The FDA's Controlled Substance Staff was also asked what the key issues (beyond the normal showing of risk:benefit) are in the review of extended-release opioids. For example, do all extended-release opioids have to have alcohol interaction data before approval? Their response was, "All extended-release opioids would need to have *in vitro* alcohol interaction data prior to approval, or provide a strong rationale for why the product's specific formulation would merit an exemption. The need for pre-approval (or any) *in vivo* alcohol interaction data would be based on the results of the *in vitro* data. The other key issue for these products is the development of an adequate and appropriate Risk Management Plan that addresses diversion, abuse, misuse, and accidental pediatric exposure."

➢ **DEA scheduling.** If an opioid were to demonstrate a lower abuse potential (than competitors), would DEA give it better scheduling? The FDA's Controlled Substance Staff said, "We are assuming that the question is specific to products involving reformulation of already scheduled opioid drugs and substances as opposed to new molecular entities which require initial scheduling…FDA/HHS (CDER/CSS) has a significant role in this process as well as in other medical/scientific aspects of the drug scheduling process mandated by the CSA (Controlled Substances Act)…The Controlled Substances Act of 1970 – the law under which DEA regulates and enforces drug control – specifies the schedules for all of the opiate/opioid drugs and substances, in conformity with international drug control treaties. Formulation and concentration are not factors which modify scheduling under the CSA, with rare exceptions. Differential (lower) scheduling exists under the CSA for a couple of opioid drug products (e.g., hydrocodone, codeine) when the product combines one of these drugs with an unscheduled analgesic within a concentration/dose range specified within the CSA. Hence, neither FDA nor DEA has the authority to control a reformulated scheduled opioid drug product in a lower schedule...DEA regulates the manufacturers of controlled drugs in various ways including establishing production and import quotas…The aspects which FDA does regulate are the product labeling and Risk Management Plans. We certainly encourage innovations in product formulation which enhance product safety and decrease the risks of abuse, overdose, and accidental ingestion. However, the bar for a comparative labeling claim with respect to 'relative abusability' would be quite high."

SPECIFIC DRUGS

ALPHARMA'S Kadian (sustained-release morphine). MGI Pharma stopped co-promoting, but doctors are still using it – some, though there is no excitement about it. A doctor said, "Kadian is for people who generally don't have significant ups and downs in pain, who have steadier pain. Kadian peaks in

about 8 hours, so it is good for people who can start the day but are in pain later in the day."

ALTHEA THERAPEUTICS' hydromorphone transdermal patch. A poster reported on a 3-day, randomized, dose-response study in acute post-operative pain. The study found the need for rescue medication was reduced, but only when 4 patches were used (not 1 or 2 patches), and 21% of patients had site reactions.

AVANIR'S Neurodex (dextromethorphan hydrobromide + quinidine sulfate). In addition to pseudobulbar syndrome, Neurodex is being studied in neuropathic pain. A doctor said, "The mechanism is attractive. NMDA antagonists are 'dirty' drugs, and there has been neurotoxicity when they are given intrathecally, so they have gone a little out of favor, but the theory is not yet wrong. Neurodex is worth watching. If it works, it will work in chronic neuropathic pain."

Asked what they think of NMDA and/or sigma-1 as targets for neuropathic pain, experts were cautiously optimistic. A West Coast doctor said, "I think the NMDA receptor is a key target, but it is a complicated receptor, with at least six different sites affected. Inhibiting the NMDA receptor without making the person crazy (psychotic) is the issue. The FDA is probably willing to look at it, but the process is too expensive. So many potential side effects means a lot of hoops (for sponsors to jump through). It would be incredibly expensive to get it through Phase III. If it is as effective in humans as in animals, it would be very popular. But rats don't say if they are hallucinating." Another expert said, "It has been proven in animal models that targeting NMDA will reduce central sensitization. Methadone – which has NMDA effects – doesn't appear to be effective. So the data are mixed."

There have been past failures using this theoretical mechanism, so an expert suggested one issue to watch with these investigational agents is their impact on other pain medication use: "I would watch the effect on opioid use, though that is hard to study because it is always changing."

CEPHALON'S Actiq (fentanyl citrate) and **OraVescent fentanyl (OVF).** Doctors offered mixed answers to questions about whether OVF is superior to Actiq and the effect OVF will have on Actiq usage. One expert insisted OVF is superior, but others prefer Actiq because it is titratable by patients. The bottom line is that price may be the deciding factor. A source said, "OVF is highly abusable, but if the price is low, there will be a lot of use in hospices. It may not replace Actiq, but it will cannibalize it. How much it will expand the market is a question. The indication will be cancer, but it is too early to say how much use there will be in non-cancer. For me, it will expand the market. It will be the quickest thing we have. Endo is further behind with its (competing) product. The only downside is Actiq patients can self-titrate, and you can't do that with OVF. OVF has better bioavailability (than Actiq) – 25%-50% of Actiq gets lost in the GI tract, but OVF is half the dose of Actiq." Another source said "The advantage of Actiq was that it was absorbed slowly."

ENDO PHARMACEUTICALS/PENWEST'S oxymorphone ER/IR. Both the extended-release and IV reformulations have been in FDA "approvable" status since 2003. The most recent complete response was submitted by the companies to the FDA in December 2005. No information has been available as to what was required/submitted as part of the complete response, but there has been a buzz about a concern over alcohol interaction. Endo said it did a study on the ER formulation, and the results were good, but that study was ***not*** part of the complete response letter and supposedly will be submitted prior to the late May PDUFA date. An expert said, "I've heard there is less effect with alcohol, but I haven't seen the data." Another expert said, "I expect every extended-release drug will have to do the same studies as Palladone (Purdue Pharma, hydromorphone ER)."

Reportedly, the FDA wanted titration studies, but those resulted in increased side effects and dropouts. Too many dropouts confounded the results, and new studies were undertaken. Endo also is reported to have described those as positive. An expert said the FDA issues with oxymorphone ER are what he called "picky issues" – titration and dropouts.

Palladone was withdrawn from the U.S. market in July 2005 after it was discovered in a post-market study that the drug had a potential for severe side effects if taken with alcohol. PK data indicated that the co-ingestion of Palladone and alcohol results in dangerous increases in the peak plasma concentrations of hydromorphone. These elevated levels may be lethal, even in opioid-tolerant patients.

Pain doctors are generally receptive to oxymorphone ER. They indicated oxymorphone ER most likely will fit in after Percocet (oxycodone + acetaminophen) and Vicodin, as second- or third-line therapy – at least at first – but it will move to first-line. A source said, "Methadone has dysphoria. This has a little euphoria, which is good for patient acceptance. But if it gets too much market share, the addicts will catch on. The company has to walk a line: Sell it, but not too much." A California doctor said, "I greatly look forward to it. It is another choice, and it is not more or less abusable…I want that option for patients…The abuse resistance (proposal) with OxyContin (Purdue Pharma, oxycodone) is a lot of smoke. It won't make the drug safe for people who don't inject it, and most abusers swallow it. What we need is better awareness by doctors, tools to screen patients, and good consent forms." Another doctor said, "I would use the IR for breakthrough pain or start with IR and then go to ER."

Price will be a key issue in how well oxymorphone ER does, doctors insisted. They agreed it is a pretty price sensitive market. One commented, "There are two groups of patients:

(1) The 1/3 to 1/2 of patients where price is an issue, and they can't afford this, so their choice is methadone, and (2) The other 1/2 to 2/3 of patients who don't care about price, mostly because they have insurance." Another doctor said, "Most pain drugs are on formularies now, but I'm not sure how the carriers will handle the new drugs, if they are expensive. Probably they will tier them high."

Sources believe the data on oxymorphone ER support BID dosing. A doctor said, "I'm pretty comfortable with BID dosing. It doesn't seem to peak and trough a lot, but some doctors will dose TID."

However, it was not clear to doctors that oxymorphone ER is superior to OxyContin. An expert said, "I can't say it is better, but it works well."

Most chronic pain patients cycle through the various higher-order pain products before oxymorphone is prescribed. A doctor explained, "I start patients on Vicodin or a low dose Percocet, and then a sustained-release opioid. It's a sequential trialing." Another doctor said, "For moderate-to-severe pain patients, I start with something like hydrocodone, but if the patient has a more severe need for something stronger, then I use oxycodone or morphine. If it is chronic pain, it is foolish to use a short-acting medication. We currently have Duragesic – matrix, not the Johnson & Johnson patch – Avinza (Ligand, morphine sulfate extended-release), and Kadian. Avinza works 24 hours, but Kadian doesn't." A third source said, "About 10% of my patients get Avinza SR, 30% get OxyContin, but <5% of my new patients get OxyContin now. If OxyContin were 10% ER and couldn't be crushed, I'd use it more…I'm writing less Kadian because patients have trouble filling the prescription. A lot of pharmacies don't carry it." A West Coast doctor said, "Kadian made a special deal with MediCal on price and got the contract. Kadian is not a bad drug, but it has never worked for my patients. It doesn't work 24 hours, and it is not as effective as Avinza or other morphines. We use Avinza by preference now for long-acting morphine; it's good because it is QD."

Endo claims that both the *in vivo* and the *in vitro* data demonstrate no risk of dose dumping with oxymorphone ER, but at the highest levels of alcohol there was a transient increase in blood levels. An expert said this doesn't appear to be of clinical significance, but he insisted the FDA will want this studied further, "The company seems convinced it isn't, but the FDA will want that data. It does look like not all these drugs cause dose dumping…I think all the companies will be held to the Purdue (Palladone) standard. They will need to show there is not huge dose dumping. A little will probably be okay, and I think they could do a kinetic study to show the effect."

Doctors didn't think that it would be a big problem for oxymorphone ER marketing if Purdue were to start promoting OxyContin again because doctors and patients are still leery of the issues surrounding OxyContin. A source said, "There is a lot of patient resistance to OxyContin because of the (negative) press, especially with little old Moms and Dads. There is a fair bit of pause with this."

Endo's Lidoderm (lidocaine patch) lost orphan drug status in March 2006, but there were no indications at this meeting that a competitor is on the near horizon, except for reports of an unidentified sterile lidocaine patch in Phase III for post-operative pain. A source said, "It is sterilely applied to reduce pain around the incision site."

FOREST LABORATORIES' Combunox (ibuprofen + oxycodone). This has not done well in the market, and doctors indicated that was due to at least two factors: lack of marketing support by Forest, and physician dislike of combination pain medications. An expert said, "People never really embraced combination products, and Forest didn't really support it with marketing." Another expert said, "We like to titrate both drugs, and you can't do that with a fixed dose combination. Ibuprofen is a potentially very dangerous drug. If you take too much, it is dangerous, especially if a patient takes 18 a day."

JAVELIN PHARMACEUTICALS' Rylomine. This intranasal morphine is in development as an alternative to IV morphine. A researcher said, "Rylomine has a 'secret ingredient' – a long-charged polymer from shellfish (GRAS), which allows the morphine to adhere to the nasal passage until it is absorbed." The company is seeking an indication for acute moderate-to-severe pain in a supervised healthcare setting.

A study was presented looking at post-orthopedic surgery patients with moderate-to-severe pain which found Rylomine (15 mg and 30 mg) superior to both placebo and IV morphine. The minimum effective dose of Rylomine was 7.5 mg (which is roughly equivalent to 5.0 mg of IV morphine). Adverse reactions to Rylomine were dose-related and consistent with general opioid effects (dizziness, nausea, sedation, vomiting). The company hasn't done vasoconstrictor or rhinitis studies yet, and those will be necessary, the researcher said.

Javelin also has an intranasal ketamine in development.

JAZZ PHARMACEUTICALS' Xyrem (sodium oxybate). Among the comments about Xyrem were:

- "The results could have been more robust. Anecdotally, my patients were very pleased, and I use it off-label in fibromyalgia patients with refractory insomnia." He called fibromyalgia a "dopamine deficiency" and said new PET studies would be out soon, adding, "I think we should treat the organic disease, and Xyrem does that."
- *California:* "I want to see the effect on pain and sleep. It will need a 30% reduction in pain to be meaningful. Use will be problematic – but I would use it."

- *Florida:* "It is very exciting data, but I don't understand the mechanism or what it means. We need more studies. We need outcomes data. But even with efficacy data, that drug will be problematic in terms of aberrant behavior …There may be some abuse of the drug, some diversion. Patient selection also may be an issue. There may be some patient mis-selection, and that may bite them (Jazz) …The FDA is on the verge of approving duloxetine (Lilly's Cymbalta) for fibromyalgia, and you could give Xyrem and duloxetine together."
- "Data are always mixed in fibromyalgia. I want to see a change in energy, pain, and mood – improved functioning as well as less pain. We decided against using it off-label because of the abuse issue – users could be abused by others. It is a scary drug to me not just because it puts a patient in a dissociative state, but it also would be released to the world. You can't just open Pandora's box. Pharmacy controls would not be sufficient. If the drug is really beneficial, it will get used…Demand will outstrip supply, and that could lift any restrictions…Marijuana is not a dangerous drug; this is."

Duloxetine in the Treatment of Women with Fibromyalgia

Measurement	Duloxetine 60 mg QD n=118	Duloxetine 60 mg BID n=116	Placebo n=120
Current MDD	26.7%	24.8%	27.6%
12-Week results			
Primary endpoint: Brief pain inventory (BPI) 24-hour average pain severity	Down ~3.0 (p<.001 vs. placebo)	Down ~3.0 (p<.001 vs. placebo)	Down ~1.5
Secondary endpoints *			
Fibromyalgia Impact Questionnaire (FIQ) total score	Down 18.72 (p<.001 vs. placebo)	Down 18.81 (p<.001 vs. placebo)	Down 8.35
BPI severity: average pain	-2.30	-2.40	+1.16
BPI severity: worst pain	-2.53	-2.37	+1.35
BPI severity: least pain	-1.77	-1.76	+0.58
BPI severity: pain right now	-2.40	-2.33	-1.15
Average interference	-2.57	-2.58	-1.43
Mean AUC	152.2	160.5	79.8
Patient Global Impression of Improvement (PGI)	3.11	3.06	3.71
HAMD total score	-3.79	-2.97	-2.24
SF-36 Health Status Survey (p-value vs. placebo)			
Physical	0.127	0.087	---
Mental	<.001	0.002	---
Bodily pain	0.001	0.004	---
General health perceptions	0.202	0.099	---
Social functions	0.019	0.217	---
Side effects			
Any discontinuation	21.2%	23.3%	11.7%
Discontinuations due to lack of efficacy	5.9%	3.4%	15.0%
Nausea	~45%	~37%	~13%
Dry mouth	~20%	~23%	~6%
Constipation	~14%	~17%	~2%
Diarrhea	~15%	~13%	~5%

* All p<.05 vs. placebo

- *Illinois:* "We're still trying to understand what fibromyalgia is…Functional improvement is more important than pain reduction, which is more subjective. Xyrem needs to show an effect on at least two of these three things: pain, function, and sleep…We use both Lyrica and duloxetine for fibromyalgia, too. Lyrica 425 mg reduces pain and increases sleep. We are using that off-label…Most fibromyalgia patients have lethargy and decreased mood."

KING'S Remoxy (abuse-resistant oxycodone)

The purported advantage of Remoxy (which was licensed from Pain Therapeutics) over OxyContin is an abuse-resistant formulation. Doctors are watching abuse-resistance proposals but with a wary eye. An expert said, "I'm not sure (about the outlook for Remoxy). It (sentiment) could go either way. If the abuse-resistance is real, it might get embraced. But it may just be that the company hopes to capture market share."

LIGAND'S Avinza (morphine sulfate extended-release capsules). Doctors are still interested in Avinza. They were not concerned about possible dose-dumping with either Avinza or Kadian. A doctor said, "Four or five years ago, I switched from OxyContin to Avinza, and (with Avinza) I could give less medication with fewer side effects." Another source said, "Kadian has no ER, and Avinza has 10% ER. In patients who have trouble getting up in the morning who want both a short-acting and a long-acting pain medication, I give Avinza." A third doctor called Avinza and OxyContin "comparable," with individual variations.

LILLY'S Cymbalta (duloxetine)

A Lilly official said there is no problem with the combination of duloxetine and Lilly's Lyrica (pregabalin) in fibromyalgia. A Midwest doctor said duloxetine is his treatment of choice in depressed pain patients.

Another poster reviewed a 12-week study of duloxetine treatment of fibromyalgia in women with or without major depressive disorder (MDD).

PURDUE PHARMA'S hydromorphone Hcl ER (HHER)

Purdue is developing 12-, 16-, 24-, and 32-mg QD capsules for the treatment of adult opioid-tolerant patients with persistent moderate-to-severe pain who require continuous analgesia. A poster presented the results of a 464-patient, randomized, double-blind, placebo-controlled, parallel-group study in two groups: HHER vs. HHER

placebo and fentanyl transdermal patch (FTS) vs. FTS placebo. The maximum duration of the study was ~43 days.

The study found:

- The primary endpoint – days from initial dose to adequate and stable analgesia – was not statistically different in either group.
- Physicians were more satisfied with FTS and HHER than the respective placebo groups.
- In a post-hoc analysis, the mean HHIR rescue drug used daily was 1.7 mg less with HHER than with FTS (p=0.003).
- Pain scores throughout the study were lower with HHER than HHER placebo (p=0.002), but the HHER scores were not statistically significantly lower than FTS.
- Sleep question scores of the BPI-SF throughout the study were lower with HHER than HHER placebo (p=0.001), but the HHER scores were not statistically significantly lower than FTS.
- $PASS_{24h}$ scores throughout the study were lower with HHER than HHER placebo (p<0.001), but the HHER scores were not statistically significantly lower than FTS.

Purdue Pharma's Extended-Release Hydromorphone Study

Measurement	FTS placebo n=75	FTS n=154	HHER placebo n=76	HHER 12 mg n=157
Primary endpoint: Days from initial dose to adequate and stable analgesia	Nss difference		Nss difference	
Subjective results				
Physician satisfaction with medication subscale score	34.2	49.7	41.9	58.2
Physician overall subjective ease of medication use subscale score	75.7	77.3	82.6	86.4
Adverse events				
Constipation	0	4%	1%	10%
Nausea	7%	13%	14%	8%
Headache	7%	8%	4%	6%
Dizziness	1%	3%	6%	4%
Deaths	0	0	0	0
Serious adverse events	1%	<1%	3%	7%
Adverse events leading to discontinuation	13%	6%	9%	7%

Peripherally selective opioid antagonists in development include:

ADOLOR/GLAXOSMITHKLINE'S Enterge (alvimopan). The FDA issued an approvable letter this for post-operative ileus (POI) in July 2005. It is administered orally pre- and post-operatively.

PROGENICS/WYETH'S methylnaltrexone. A subcutaneous version of this peripheral opioid receptor antagonist is in development to treat the side effects of opioids without interfering with pain relief. The companies plan to submit the drug to the FDA in early 2007.

Paracetamol (IV acetaminophen). This non-opioid, non-NSAID is approved in Europe but not the U.S.

PFIZER'S paracoxib. The FDA issued a non-approval letter for this in September 2005. A speaker said, "In the current environment, I would have trouble seeing the FDA approve this drug despite the track record outside the U.S."

DEVICES FOR NEUROMODULATION

Twenty pain specialists at a pre-conference symposium on neuromodulation were asked about their use of each of the rechargeable neurostimulation devices – Restore by Medtronic, Eon by St. Jude/Advanced Neuromodulation Systems (ANS), and Precision by Boston Scientific/Advanced Bionics. Interestingly, very few of these doctors use all three implantable pulse generators (IPGs); most use devices by just one or two manufacturers.

- On average, their use was: 41% Medtronic, 33% ANS, and 26% Advanced Bionics.
- Doctors using one device exclusively had no plans to try another IPG.

Advanced Bionics' current steering was a hot topic at the meeting, but other technology on the horizon that doctors were talking about included:

- Smaller batteries and generators.
- Percutaneous surgical implantation of leads.
- Bion, a small microstimulator being developed by **BIONESS** for rehabilitation (e.g., movement disorders) and by Advanced Bionics for neurostimulation. Advanced Bionics already has a C.E. Mark for the use of Bion as a pudendal nerve stimulator in the treatment of urinary incontinence, and a U.S. trial is ongoing. Advanced Bionics' founder Al Mann is also the founder of Bioness.

ADVANCED BIONICS' Precision

A third of the doctors questioned who were not currently using Advanced Bionics planned to try it, and several said they expect to increase their use of Advanced Bionics' Precision, at the expense of both Medtronic and ANS. Doctors had high praise for Precision's current steering and fractionalization technology. Current steering offers the ability to control electric current and steer it along the spinal cord in real time. A doctor said, "Steering current is very exciting." Another doctor said, "Steerability is just so amazing." A third source said, "I think current steering will be important, but most implanters are not sophisticated enough to understand it."

Until Advanced Bionics raised its prices earlier this year, its prices had been lower than ANS or Medtronic. A company vice president said, "We entered the market at a price point that allowed us to work with clinicians and show the value of the R&D effort we put behind a rechargeable system with constant current output…The price increase timing is a function of us being out there a year – out 18 months – well below the competition price point, and we made a decision to fund future R&D, and that is why the price increase…That was something we, as an organization, believe we needed to do."

Other comments about Advanced Bionics and Precision included:

- *Oregon:* "I like Advanced Bionics' tightly spaced leads. I think I get better back pain control with them than with the Medtronic leads…The differences in the devices are subtle, and a lot comes down to support and the availability of the rep."
- *Wisconsin:* "I plan to try Advanced Bionics because of the potential to steer leads. I did my first Advanced Bionics patients last week."
- *California:* "I use Advanced Bionics exclusively. I used to use Medtronic and ANS, but I get good axial pain control with Advanced Bionics. Steering and control of the leads are better with Advanced Bionics."
- *Nevada:* "I use mostly Advanced Bionics and some Medtronic but no ANS because their service is poor."
- *West Coast:* "We love our ANS rep, so it is difficult to reduce our ANS use, but we like the steerability of the Advanced Bionics device."
- *New Mexico:* "Advanced Bionics has the smallest unit, and the leads fracture less."

Advanced Bionics also has a new cochlear implant under review at the FDA which increases the maximum number of channels from 22 to 120. The target release date is September 2006 – if it isn't delayed by the FDA hold on Boston Scientific approvals, though an Advanced Bionics official thought it was exempt from the hold on Boston Scientific approvals.

MEDTRONIC'S Restore

Comments about Medtronic and Restore included:

- *California:* "I use Medtronic devices mostly because I'm very familiar with them, the company provides excellent support, and I've had good outcomes. I've had less exposure to Advanced Bionics, and the one patient we tried did not have a good result."
- *Virginia:* "I use Medtronic and ANS devices equally. I haven't tried Advanced Bionics yet. I wasn't trained on it, and I want to use what is proven."

Comparison of Rechargeable Neurostimulation Devices

Feature	Medtronic's Restore	ANS's Eon	Advanced Bionics' Precision
Battery capacity	300 mA-hours	325 mA-hours	200 mA-hours
Contacts	Up to 16	Up to 16	Up to 16
Pulse width	60-450 µs	50-500 µs	20-1,000 µs
Weight	72 g	75 g	36 g
IPG engine	Constant voltage	Constant current	Constant current
Amplitude	0-10.5 V	10-25.5 mA	0-12.7 mA per channel (0-120 mA total)
Number of programs *	1-2	1-24	1-4
Programmer communication	Near-field	Near-field	Far-field
Device life	Up to 9 years at medium settings	7 years at high settings	>20 years at medium settings
Compatible percutaneous leads	2	5	1
Compatible surgical leads	2	10	1
Implantation depth	0.4 in (1.0 cm)	1.0 in (2.5 cm)	0.75 in (2.0 cm)
Multiplexed channels per program	Up to 4	Up to 8	N/A
Recharge burden at medium settings (60 H, 300 µs, 4.0 mA, 750 Ω)	1 hour every 14 days or 4 hours every 56 days	1 hour every 19 days or 4 hours every 76 days	1 hour every 4 days or 4 hours every 16 days

* Described as not very important to patients

- *Texas:* "We currently use only Medtronic, but I'll try the others because of their technology."
- *New York:* "Medtronic's steering technology is not good."
- *Utah:* "I've been using almost no Medtronic lately because I've had better results with the Advanced Bionics device, especially in axial pain."
- *Minnesota:* "We use only Medtronic, and I don't see a big reason to change."
- *Mississippi:* "Medtronic has a longer track record, but the newest guys (Advanced Bionics) with current steering and fractionalization may be worth trying. But we tend to go with the cheapest device so we can provide care to more people."
- *West Coast:* "I don't use Medtronic because there is no sales rep near me, and ANS and Advanced Bionics have better products right now. The Medtronic reprogrammable device is more bulky and has a few glitches that make it not as user-friendly as the others."

Shortly after AAPM, the FDA approved Medtronic's RestorePrime, a programmable – but not rechargeable – stopwatch-sized device. RestorePrime is a 16-electrode unit designed for patients with low-to-moderate energy requirements and who have chronic, bilateral back pain associated with failed back surgery, disc problems, etc.

ST. JUDE/ANS'S Eon

Most sources considered St. Jude's purchase of ANS neither a negative nor a positive. However, a Medtronic user said, "St. Jude will be great for ANS, which has brilliant ideas but a limited resource base. St. Jude will make ANS a serious competitor for Medtronic. ANS has exciting, dedicated people, a remarkable CEO, and a lot of vision."

ANS may have an advantage with its three contact lead. A speaker emphasized this technology, but doctors didn't mention it.

Other comments about ANS and Eon included:

- *New York:* "I use only ANS. I'm really happy with my reps, and the Medtronic reps are not very user-friendly."
- *Utah:* "We use 70% ANS and about 30% Advanced Bionics. Both companies have better reps and service than Medtronic, and we have the perception they are more advanced."
- *California:* "ANS has better technology than Medtronic, but I'll start using some more Advanced Bionics because they have features that ANS doesn't – steerable current and fractionalization."
- *Mississippi:* "I like the Advanced Bionics products, and the technology is very intriguing, but can they keep up the development pace?"

Miscellaneous

Among the other interesting points speakers and other sources made about neurostimulation were:

- Spinal cord stimulation (SCS) is effective in neuropathy, ischemia, and some other visceral pain syndromes (e.g., irritable bowel syndrome).
- Oral administration of Pfizer's Neurontin (gabapentin) and Pfizer's Lyrica (pregabalin) were reported to facilitate SCS in some patients. A Utah doctor said, "Lyrica is very good in combination with SCS."
- Use of certain medications is a growing problem for SCS:
  - Bleeding risks due to patient use of anticoagulants – Sanofi-Aventis's Plavix (clopidogrel) or Coumadin (warfarin).
  - Glucose levels due to newer diabetic medications that must be stopped before surgery, which can cause sugar to rise and increase the risk of infection.
- The mechanism of action of SCS is partially mapped, but much is still unknown.
- SCS reduces the frequency of angina by diminishing coronary ischemia, and there are some indications of a cardioprotective role.
- SCS seems to possess the capacity to inhibit viscero-somatic reflexes to various organs (e.g., irritable bowel syndrome).

Dr. John Oakley, past president of the North American Neuromodulation Society, suggested that patients should be encouraged to spend 30 minutes a day "topping" off their rechargeable battery devices to prolong the battery life.

A debate over **rechargeable vs. non-rechargeable generators** ended with both speakers concluding that there really is a place for both, and in complicated situations, probably a rechargeable device is better.

Key **problems for programmers** that were cited by a speaker included:

- Incorrect lead location.
- Wrong choice of components.
- Poor patient selection (wrong control device).
- Too few anode or cathode choices.
- Inability to increase pulse width without shortening device life.
- Inability to provide high-frequency stimulation. Sometimes the treatment effect diminishes over time but increasing the frequency can restore response.

When doctors consider the various devices for neurostimulation, Dr. B. Todd Sitzman of Forrest General Cancer Center in Hattiesburg MS advised them to keep in mind that complex pain syndromes may be best treated with leads that:

- Have closer contact spacing. Another speaker added, "Small, closely spaced electrodes provide more precise targeting."
- Are positioned midline.
- Are positioned in contact with the dura.
- Are programmed as a tripole ("guarded cathode"). Another speaker said, "There is an advantage to a transverse tripole, but no company has a true lead that does it yet. The closest right now is the ANS lead with three contacts."

Other indications for neurostimulation devices

New uses for spinal cord stimulation (SCS) also are being investigated, including coronary disease (angina), irritable bowel syndrome, pelvic pain, urinary incontinence, endometriosis, peripheral vascular disease, and migraine headaches. There is anecdotal information (but no studies) that SCS improves peripheral circulation and reduces ischemia. Devices are also being used off-label for deep brain stimulation. Dr. Mikhail Fukshansky of M.D. Anderson Cancer Center said, "Neurostimulation may also be useful in post-thoracotomy pain syndrome and in post-mastectomy patients. About ~25% of post-mastectomy patients are reported to have some neuropathic pain for years." A Midwest doctor said, "Motor cortex stimulation and occipital nerve stimulation for migraine are promising, and angina is a big area. There is clear evidence neurostimulation works in angina, but use of devices for that is off-label."

Migraine headaches are a particularly interesting area. One of the speakers concluded, "We believe SCS for other indications will have a future. I think it is under-used presently, and the fragmentary knowledge of the mechanisms of action is one reason for the under-use." A Midwest doctor said, "I already use neurostimulation for migraines, but only transformed (daily) migraines." A West Coast doctor added, "Only one of 10 migraine referrals turns out to really be migraine." A New York doctor said, "I haven't used neurostimulation for migraines or for occipital neuralgia yet, but I'm considering it." Another doctor said, "I haven't tried this (stimulation for migraine), and I won't."

Advanced Bionics has started enrolling patients in the multicenter, randomized, double-blind PRIZM migraine trial. The first implant was expected to be done shortly after AAPM. PRIZM compares the Precision device to sham stimulation. The trial will enroll ~180 migraine patients (using HIS criteria) with or without aura. The primary endpoint is the decrease in severity and frequency of migraines at three months. After three months, all patients will get active stimulation.

Medtronic also is conducting a neurostimulation trial for migraine headaches, and at the time of AAPM it was almost fully enrolled.

New Medicare Reimbursement Rates for IPGs

Medicare code	Description	Reimbursement
	Ambulatory Surgery Center	
L8685	IPG single array, rechargeable, includes extension	$9,532 - $12,709
L8687	IPG dual array, rechargeable, includes extension	$12,405 - $16,540
L8680	Implantation of neurostimulator electrode, each	$335 - $446
L8686	IPG single array, not rechargeable	$6,082 - $8,110
L8688	IPG dual array, not rechargeable	$7,915 - $10,554
	Hospital outpatient	
CPT-63650	Implantation of neurostimulator electrode array, epidural	$3,025
CPT-63655	Laminectomy for implantation of neurostimulator electrode, plate/paddle, epidural	$5,559
CPT-63685	Insertion or placement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling	$11,456
C1820 Pass-through code (for the next 2-3 years)	Rechargeable IPG ***and*** charging system	Variable but can be ~$10,000 or more (in addition to the APC payment)
	Hospital inpatient	
DRGs 499 and 500	Back and neck procedures except spinal fusion with or without complications and comorbidities	Varies but usually ranges from $4,660 - $7,126
DRGs 531 and 532	Spinal procedures with or without complications and comorbidities	Varies but usually ranges from $7,313 - $16,115
New technology add-on (added to the DRG)	Dual array rechargeable IPG	Up to $9,320 added to the DRG, depending on the hospital cost-to-charge ratio

Reimbursement

New Medicare reimbursement rates went into effect for neurostimulation IPG implantation on January 1, 2006, and the companies have been trying to get the word out about the changes in the hope that this will spur usage. Medicare officially concluded that rechargeable neurostimulators present "a substantial clinical improvement" for Medicare patients and significantly increased 2006 facility payments for dual array rechargeable IPGs, including:

1. New pass-through payments for hospital outpatients.

2. New technology add-on payments for hospital inpatients.

3. New HCPCS "L codes" with improved DMEPOS payment rates for Ambulatory Surgery Centers (ASCs). This means total reimbursement for implantation of a dual array rechargeable device with two leads at an ASC would increase from ~$14,000 to ~$21,000.

For doctors, the payments are the same whether the testing or permanent IPG placement is done at an ASC, as a hospital outpatient procedure, or as a hospital inpatient procedure. For facilities, a reimbursement expert said the new Medicare rates make it more financially attractive to do the testing at an ASC and to do the permanent implant in a hospital inpatient setting, but testing is profitable at both an ASC and a hospital outpatient facility. Physicians who own or have a partial interest in an ASC may find that they lose a little money on permanent implants in Medicare patients at the ASC, so they may want to do those patients at the hospital. An expert said Medicare reimbursement for a permanent IPG "is still below the cost in many circumstances."

Medicare patients are generally only part of a pain doctor's practice, though, and experts said reimbursement tends to be better with commercial patients. One expert said, "Medicare is traditionally the worst payor." Another expert said, "We are communicating with different payors to see if we can get improved reimbursement from them as well."

Some doctors are doing IPG trials in their office. CMS has not issued a decision or rate for that, but some – but not all – commercial carriers are paying for it.

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