Trends-in-Medicine

May 2005
by Lynne Peterson

SUMMARY

The head-to-head and sleep data on **Ligand's** Avinza may help with marketing, but doctors were underwhelmed. ♦ The pivotal trial of **Cephalon's** OraVescent fentanyl is expected to be completed by summer, with a 3Q05 filing. ♦ The launch of **Pfizer's** Lyrica (pregabalin) has been delayed while the DEA determines what Schedule it will get because of the euphoria side effect, and this is frustrating doctors. ♦ **GlaxoSmithKline** still has confidence in Lamictal (lamotrigine) for neuropathic pain and will repeat the two failed trials, but doctors are dubious they will be sufficient for approval. ♦ Pain doctors are interested in **Johnson & Johnson's** ionophoretic transdermal fentanyl for post-op pain, and they want to use it for outpatients as well as inpatients. ♦ Generic fentanyl matrix patches are not perceived to be as effective as J&J's Duragesic, but cost is driving usage. ♦ Interest in rechargeable spinal cord stimulators is growing, and they are expected to take ~30% market share.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

AMERICAN PAIN SOCIETY
Boston, MA
March 31-April 2, 2005

The American Pain Society (APS) meeting is a good forum for checking on the status of drugs in development to treat pain. This year there were few truly new agents reported, but there was a lot of data on pain indications for agents already approved for other indications plus new formulations of existing pain medications.

A former FDA official said, "In my opinion, the pipeline is dry – or maybe more dormant than dry." He predicted further FDA approval delays ahead, "It's been an ugly year, and I think it will be an ugly next couple of years…(But) the federal government loves generic drugs…In the next four or five years, the government has to start fixing Medicare, and generics are cheaper, so guess who is going to use them – the Medicare and Medicaid population because the government has to pay for those."

Impediments to development and approval of new pain medications:

- Complex pain processes vs. specific analgesic drug mechanisms.
- Higher throughput R&D vs. limited predictive value of preclinical screening methods and clinical models.
- Extrapolating from "clean" clinical models to a heterogenous disease and to patients.
- Complex regulatory processes.
- Lack of financial incentives for non "blockbuster" indications.
- Increased FDA emphasis on safety after concerns were raised about the cardiovascular safety of coxibs.
- Wide variation in response (on VAS) to pain across subjects.

BACK PAIN

Back pain ranks second only to headaches as the most frequent pain complaint, with more than 65 million Americans experiencing it every year. Oxycodone sales reportedly total about $2 billion annually, but the drug, like all opioids, has its problems, chiefly tolerance, physical dependence, drowsiness, and severe constipation – plus abuse.

In late March 2005, Pain Therapeutics reported positive results from a Phase III trial of Oxytrex (oxycodone) which showed it eased back pain without nearly as many side effects as "plain" oxycodone (e.g., Purdue Pharma's OxyContin) because of the addition of minuscule amounts of an ingredient that counter the side effects without reducing the analgesic properties of oxycodone.

However, critics pointed out that there was a high dropout rate in the placebo-controlled trial. Pain Therapeutics did not have a booth at APS.

LIGAND'S Avinza (morphine sulfate extended-release capsules). Three Avinza studies were presented at APS:

➢ **ACTION.** An interim analysis was presented from this randomized, parallel-group, multicenter, head-to-head comparison of Avinza QD and Purdue Pharma's OxyContin (oxycodone) BID in 212 patients (age 30-70) having a suboptimal response to NSAIDs, acetaminophen, and/or prior intermittent IR opioids. In this study, sponsored by Organon, researchers found that Avinza provided statistically significant better pain relief, better quality of life, and better quality of sleep but required less rescue medication and a lower total daily opioid requirement. Discontinuation rates were not reported, but a researcher said they were comparable.

8-Week Results of ACTION Trial

Measurement	Avinza n=105	OxyContin n=107	p-value
Average	49	50	---
Back pain history	8 years	7 years	---
Median BPI pain score at baseline	7	7	Nss
Median time to stabilization	27 days	28 days	Nss
Dose changes during stabilization	105	107	Nss
Increased dose	48%	57%	---
Decreased dose	0	1%	---
Average global quality of sleep *(lower is better)*	-33%	-18%	<.001
Number of rescue doses per patient at Week 8	2.6	3.9	---
Morphine equivalent mean total daily dose	72 mg	88.5 mg	---
Adverse events			
Constipation	86%	88%	---
Dizziness	58%	63%	---
Drowsiness	86%	84%	---
Dry mouth	84%	75%	---
Itchiness	62%	55%	---
Nausea	48%	44%	---
Vomiting	23%	20%	---

A researcher explained that there were more peaks and troughs with OxyContin than Avinza, and Avinza had more stable plasma concentrations. A doctor commented, "The (study) findings are not dramatic, but they are clinically significant."

➢ **Avinza vs. Alpharma's Kadian** (sustained-release morphine). A head-to-head, Phase IV, randomized, double-blind, two-way crossover, comparative bioavailability study of Avinza and Kadian in 40 healthy, opioid naïve patients (age 19-40) was sponsored by Alpharma. Researchers found both drugs were bioequivalent by FDA standards, both could be dosed once-daily, and both were well-tolerated.

8-Week Results of Avinza vs. Kadian Trial

Measurement	Avinza	Kadian
Mean morphine T_{max}	6.7 hours	12.9 hours
Mean plasma morphine level from 8-60 hours	Slightly higher with Kadian	
Mean morphine C_{max}	3.9 ng/mL	4.3 ng/mL
$T_{1/2}$	15.6 hours	14.5 hours
Adverse events		
Headache	5 patients	7 patients
Nausea	4 patients	5 patients
Dizziness	3 patients	3 patients
Light-headedness	4 patients	2 patients
Vomiting	4 patients	2 patients
Upset stomach	3 patients	2 patients

➢ **Sleep study.** An interim analysis of an ongoing Avinza sleep study in osteoarthritis (OA). This is a 30-patient, single-center, placebo/baseline-controlled, single-blind study. Researchers reported on 24 patients (of 27 enrolled) who had completed the study per protocol; two patients withdrew for adverse events, and one patient discontinued due to a protocol violation. Researchers reported:

- BPI average pain decreased significantly in all groups.
- Overall quality of sleep increased significantly in all groups.
- Mean hours of sleep increased in all groups, and it increased significantly in the 30 mg and 60 mg x 14 days groups.
- Avinza given QD in the morning produced significant improvement in pain control, sleep quality, and sleep duration.
- Polysomnographic results found trends in favor of:
  - Shortened latency to persistent sleep.
  - Reduced night awakenings.
  - Increased sleep efficiency, total sleep time, and Stage 2 sleep duration.
  - Decreased total wake time.
  - No significant decrease from baseline in REM duration.

Doctors asked about the Avinza sleep study and the head-to-head study vs. Kadian found the results interesting but not particularly compelling. Several said they already use Avinza. However, Ligand sales reps said they believe this study will help them market Avinza.

ALPHARMA'S Kadian (sustained-release morphine). Two posters offered a little more information on this FDA-approved medication.

➢ A re-analysis of the four-week KRONUS-MSP trial looking at neuropathic pain patients who were poor responders to other medications (hydrocodone and oxycodone). Researchers found:

- 56% of patients with peripheral neuropathy (PNP) and 58% of all other pain (AOP) patients remained on QD dosing.
- Patients with PNP were started on a mean daily dose of 61.5 mg, and AOP patients were started on a mean dose of 56.4 mg.
- At Week 4, the PNP mean dose was 108.3 mg, and the AOP mean dose was 98.6 mg.
- About 29% of all patients reported at least one adverse event.
- The most common treatment-related adverse events were constipation (~12%) and nausea (~7%).
- Kadian was effective and well-tolerated in relieving pain and improving sleep and quality of life.
- Patients and physicians expressed a greater degree of satisfaction with Kadian than with their prior treatment.
- Determining the precise type of pain – nociceptive vs. neuropathic – may not be critical when considering the use of opioids, but patients with neuropathic pain may require a higher dose than patients with other types of pain.

➢ A study of patient and physician satisfaction with Kadian in chronic, non-malignant, moderate-to-severe pain. This was another re-analysis of the KRONUS-MSP trial, this time looking at under-treated patients. Researchers reported Kadian was effective and well-tolerated whether dosed in the morning or at night in relieving pain and improving sleep and quality of life.

BREAKTHROUGH PAIN

The characteristics of breakthrough pain are:

- Moderate-to-severe intensity.
- Rapid onset (<3% in 43% of patients).
- Relatively short duration.
- 1-4 episodes per day.

Cephalon acquired Cima Labs, but part of that deal includes an irrevocable license to Barr Laboratories to manufacture and sell a generic formulation of Actiq (oral transmucosal fentanyl) in the U.S. Cephalon/Cima is currently developing OraVescent fentanyl, a fast-dissolving, effervescent, fentanyl tablet. A Cephalon official said the pivotal trial of OraVescent is expected to be completed in mid-2005, and the company hopes to file in 3Q05.

However, OraVescent was not mentioned by any of the speakers at a Cephalon-sponsored seminar on breakthrough pain, except during the question-and-answer period. One speaker said only, "The latest I heard was that it is coming." Another commented, "This is an investigational product now. What I know is that it is another orally administered fentanyl."

Rather, speakers at that session focused on the problem of breakthrough pain and the advantages of fentanyl, a lipophilic drug, over hydrophilic drugs such as codeine, hydromorphone, oxycodone, meperidine, and methadone. Among the points that speakers made were:

➢ 52%-64% of inpatients referred to a cancer pain service suffer from breakthrough pain.

➢ Breakthrough pain can be identified in 74% of non-cancer patients with controlled baseline pain.

➢ The analgesic options for breakthrough pain include: tramadol, opioids, aspirin, acetaminophen, NSAIDs, and Cox-2 inhibitors.

➢ IR oxycodone is not really an immediate release agent. A speaker said, "There is nothing immediate release about them, but they will probably be used in breakthrough pain."

➢ Buprenorphine is absorbed quite well in the mouth and is quite lipophilic – and controversial.

➢ There are no reports of people feeling "stoned" or giddy on oral fentanyl. A speaker said, "I've not had people say that with extensive use it caused any kick or boost to them."

➢ Patients who use more than three or four Actiqs a day probably need to have their round-the-clock medication reviewed.

It was a convincing talk. More than one doctor in the audience said he would go home and start using Actiq, feel more comfortable about using it, or would increase use.

CHRONIC NON-MALIGNANT PAIN

ENDO PHARMACEUTICALS' Oxymorphone ER. Endo has an approvable letter from the FDA on this. An official said the FDA requested additional clinical data, so the company is doing another trial which is well underway, with results expected before the end of 2005.

A six-month, multicenter, non-randomized, open-label study evaluated oxymorphone ER in terms of efficacy, tolerability, and the effect on quality of life in opioid-naïve outpatients with moderate to severe chronic, non-malignant pain. This is not the trial the company needs to satisfy the FDA, but it is new data since the drug was submitted to the FDA. Researchers reported that oxymorphone ER:

- After the initial titration phase, there was little evidence of dose escalation or development of opioid tolerance.

- Patients were maintained on dosing every 12 hours with minimal use of rescue medication.
- Produced a statistically significant ($p<.001$) and clinically significant (60%-70%) reduction in pain interference with quality of life during the first month of maintenance treatment – and comparable and significant reductions in pain interference were maintained throughout the study.

Oxymorphone ER

Measurement	Oxymorphone ER n=126
Titration period	
Successfully titrated to an effective stable dose	74.6%
Discontinuations due to adverse events	15.9%
Maintenance period	
Completed maintenance period	63.8%
Discontinuations due to adverse events	22.3%
Discontinuations due to adverse events considered related to oxymorphone ER	17%
Mean change from baseline in interference rating for BPI quality of life parameters at Month 5	
General activity	-3.4
Mood	-3.1
Walking ability	-2.8
Normal work	-3.2
Relations with others	-2.6
Sleep	-3.9
Enjoyment of life	-3.9
Dosing	
Mean maintenance dose	27.8 - 30.8 mg
Use of oxymorphone IR rescue medication	68.1%
Safety	
Constipation	17%
Nausea	9.6%
Nasopharyngitis	8.5%
Dizziness	6.4%
Somnolence	6.4%
Appetite decreased	4.3%
Insomnia	4.3%
Peripheral edema	4.3%

NEUROPATHIC PAIN

The clinical features of neuropathic pain include:

- Pain that occurs in the absence of a detectable, ongoing, tissue-damaging process.
- Often delay in onset after a precipitating injury.
- Pain is felt in a region of sensory deficit.
- A shooting or stabbing component.
- Normally non-noxious stimuli are painful.

Symptoms of neuropathic pain include:

- Spontaneous burning pain – mediated by C- and A-delta fibers.
- Tactile allodynia – mediated by A-beta fibers.
- Cold allodynia – likely mediated by C- and A-delta fibers.

Side Effects of Drugs Used for Neuropathic Pain

Drug	Side effects
Pfizer's Neurontin (gabapentin)	Somnolence, dizziness, and peripheral edema
Pfizer's Lyrica (pregabalin)	Somnolence, dizziness, peripheral edema, and euphoria
Wyeth's Effexor (venlafaxine)	Nausea, dyspepsia, sweating, somnolence, and insomnia
GlaxoSmithKline's Lamictal (lamotrigine)	Rash, nausea, and diarrhea
Johnson & Johnson's Topamax (topiramate)	Diarrhea, loss of appetite, somnolence, and nausea
Novartis's Trileptal (oxcarbazepine)	Dizziness, headache, nausea, and somnolence

FDA-approved drugs for neuropathic pain include:

➢ **Carbamazepine** – for epilepsy and trigeminal neuralgia – not first-line and doubt even second-line now.

➢ **Mexilitine** (conjuger of lidocaine).

➢ **PFIZER'S Neurontin (gabapentin)** – for post-herpetic neuralgia.

➢ **ENDO PHARMACEUTICALS' Lidoderm (lidocaine patch)** – for post-herpetic neuralgia.

➢ **LILLY'S Cymbalta (duloxetine).** This SNRI has already been approved by the FDA for the treatment of depression and neuropathic pain. Lilly got an approvable letter for duloxetine in stress urinary incontinence (SUI) in August 2004, and it has not been clear what the FDA's concerns are in SUI. Duloxetine, which will be sold as Yentreve for SUI, already is approved and marketed in Europe. Sources suggested two reasons for the FDA's SUI approval delay:

1. Safety. A higher dose may be needed in SUI. In Europe the Yentreve dose is 40 mg BID (compared to 60 mg QD for depression and DPN). Perhaps there is a dose- or exposure-related cardiovascular signal.
2. Efficacy. The FDA may want additional efficacy data in U.S. patients.

➢ **ELAN'S Prialt (intrathecal ziconitide)** – for severe refractory chronic pain, not neuropathic pain, but a substantial number of patients in the clinical trials had neuropathic pain.

➢ **PFIZER'S Lyrica (pregabalin)** – for post-herpetic neuralgia and painful diabetic neuropathy. Lyrica was described as having "a pretty consistent record of beating placebo," but there have also been two negative trials. The FDA did not grant approval for the adjunctive treatment of epilepsy in adults, and it has turned down an application for the treatment of generalized anxiety disorder (GAD).

At the American Society of Pain meeting in 2004, speakers expressed frustration with the long time it was taking to get pregabalin – a follow-on to Pfizer's Neurontin (gabapentin) approved by the FDA. This year, experts were frustrated with Pfizer's delay in launching the drug. The FDA approved Lyrica in December 2004 for the management of neuropathic pain associated with diabetic peripheral neuropathy and for post-herpetic neuralgia. However, Pfizer still has not launched Lyrica, and a source indicated it will not be launched until at least May 2005 and probably much later in the year. What's the delay? Sources said Pfizer is not talking about it. A member of Pfizer's own Speakers Bureau for pregabalin said, "Pfizer has gotten really, really quiet on pregabalin...We (speakers) were told we will be notified a month in advance (of the launch), and we haven't heard anything."

The FDA has classified Lyrica as a controlled substance, though reportedly in a low-risk category. This still means that Lyrica must undergo review by the Drug Enforcement Agency (DEA) prior to marketing. It also may make it harder for Pfizer to convert patients to Lyrica from Neurontin, which is not a controlled substance. A speaker said the reason Lyrica was classified as a controlled substance is that it causes euphoria in some patients, "I suppose (the scheduling) must be because in pivotal clinical trials of gabapentin, there must not have been an excess of reports of euphoria in PHN patients vs. elderly patients treated with placebo. In the pregabalin clinical trials, the difference in euphoria in PHN patients treated with pregabalin vs. placebo is really much smaller than in some of the other conditions in which pregabalin was studied, so the signal might not have been there with gabapentin – or not sufficient to cause a great concern at the FDA and DEA."

Another source suggested the delay in launching Lyrica is due to negotiations between Pfizer and the DEA over the level of the schedule for Lyrica. He explained, "The launch is not imminent. My expectation is that it will be later this year…What is holding it up is the DEA has to decide if it should be a Schedule 4 [e.g., benzodiazepines or Sanofi-Aventis's Ambien (zolpidem)] or a Schedule 5 [e.g., Wyeth's Robitussin (guaifenecin with codeine) or Lomotil (atropine+diphenoxylate)]. That is the hold-up now."

The only discussion at APS of the weight gain with Lyrica that was reported at the New Clinical Drug Evaluation Unit (NCDEU) meeting in 2004 came up during a question and answer period. A speaker said, "Patients gain 10-15 pounds the first year, then stabilize. It is not something we've discussed with patients."

Pfizer sponsored a seminar on ion channel drugs – which includes Lyrica, Prialt, and Neurontin – but there was little overt focus on Lyrica.

Pfizer researchers presented several posters on pregabalin at APS, including:

- A study of long-term (≥1 year) treatment of neuropathic pain and fibromyalgia in patients refractory to tricyclic antidepressants, Neurontin, and third-line analgesics (e.g., anti-epileptics, opioids, SNRIs, NSAIDs, Cox-2s, SSRIs, tramadol, lidocaine, or mexilitine). This study found that patients achieved clinically meaningful and sustained pain relief with Lyrica, including a reduction in VAS scores, and few subjects withdrew for lack of efficacy. After 15 months, there was a 51% decrease in concomitant use of Neurontin and a 27% decrease in concomitant use of tricyclic antidepressants.

- A meta-analysis by Pfizer of 2,164 patients in 11 randomized, double-blind, placebo-controlled clinical trials of Lyrica in diabetic peripheral neuropathy (DPN) and post-herpatic neuropathy (PHN). Researchers concluded that all tested doses of Lyrica significantly reduced DPN and PHN pain, and more than half of all Lyrica patients had ≥30% improvement in pain.

- A Lyrica trial in chronic central neuropathic pain after spinal cord injury. Researchers reported a clinically meaningful response to treatment, with 42% of Lyrica patients having a ≥30% response, and >55% of Lyrica patients reporting improved PGIC.

Meta-Analysis of Pregabalin for Neuropathic Pain

Measurement	Placebo	Pregabalin 150 mg/day	Pregabalin 300 mg/day	Pregabalin 600 mg/day
Safety (11 trials)				
Number of patients	**857**	**514**	**633**	**523**
Dizziness	6.8%	14.2%	27.1%	31.4%
Somnolence	39%	9.7%	15.5%	18.7%
Peripheral edema	2.9%	7.2%	12.5%	13.6%
Infection	4.9%	8.0%	7.4%	4.0%
Headache	7.1%	7.6%	5.4%	7.5%
Dry mouth	1.9%	4.9%	5.4%	9.0%
Withdrawals due to adverse events	5%	11%		
Efficacy (9 trials)				
Number of patients	**775**	**429**	**430**	**530**
Primary measures: Mean pain scores	Significant reductions vs. placebo in 4 of 5 painful DPN and 3 of 4 PHN trials (p≤.0077)			
Secondary measure #1: 50% responders	15%-30% in DPN 8%-20% in PHN	39%-48% in DPN studies (p≤.036) 26%-50% in PHN studies (p≤.006)		
Secondary measure #2: 30% responders	26%-45% in DPN 12%-28% in PHN	55%-65% in DPN studies (p≤.02) 37%-63% in PHN studies (p≤.007)		
Secondary measure #3: 50% responders DPN+PHN	~18%	~25%	~35%	~45%
Secondary measure #4: 30% responders	~30%	~40%	~50%	~60%

➢ A preclinical study that found Lyrica is three times more potent than Neurontin in attenuating anxiety-like behavior in a rat model of neuropathic pain, while tramadol and diazepam had no effect on anxiety. The company also is starting preclinical studies looking at cognition and sleep with Lyrica.

➢ A study in elderly patients with DPN or PHN. Researchers found Lyrica significantly reduced pain levels across all age groups. No significant differences in efficacy were found among the age groups – 18-64, 65-74, and ≥75. There was a suggestion that older patients tend to report larger pain decreases per unit dose, but researchers concluded that dose adjustments were not necessary on the basis of advanced age alone.

➢ A head-to-head study of Lyrica and Neurontin in DPN and PHN. Researchers concluded that Lyrica was a more effective analgesic than Neurontin.

12-Week Lyrica vs. Neurontin in DPN/PHN

Measurement	Lyrica 375 mg/day	Neurontin 1200 mg/day	Neurontin 1800 mg/day
Mean % change vs. baseline in pain intensity	54.1%	34.3%	36.2%
Mild average pain	64.1%	40.8%	44.3%
Moderate average pain	27.8%	43.7%	41.1%
Severe average pain	8.1%	15.5%	14.6%
Mean additional days with no or mild pain	37 days	25 days	26 days
Days with ≥30% reduction in pain intensity	50 days	41 days	42 days
Days with ≥50% reduction in pain intensity	37 days	23 days	26 days

➢ A study showing the Lyrica in PHN is not affected by concomitant medications. Researchers reported that Lyrica was not affected by concomitant administration of tricyclic and non-tricyclic antidepressants, anticonvulsants, opioids, or other analgesics.

➢ A meta-analysis of Lyrica's effect on quality of life in DPN patients in six randomized, double-blind, placebo-controlled clinical trials. Researchers reported that Lyrica – at doses of 150 mg/day, 300 mg/day, and 600 mg/day – produced significant improvements in six domains of health-related quality of life, measured by the SF-36 – bodily pain, vitality, mental health, social functioning, emotional role limitation, and general health perception.

Other medications that have been tried for neuropathic pain include:

➢ **Methadone.** For addiction, QD dosing is sufficient, but pain patients need 3-4 doses a day. A speaker said, "This is very popular because it is very cheap, long-acting, effective, and useful. I've converted some of my patients from long-acting opioids to this…In my area, it is the drug of choice, but it is difficult to manage, and in 20% of patients, cross-tolerance is difficult to establish, and we have to under-dose at first." Another expert said, "It should work, but we need to find the money to do the trials to prove it, and that is difficult with an off-label drug."

➢ **Tricyclic antidepressants.** Trials have been mixed and there is cardiac toxicity.

➢ **JOHNSON & JOHNSON'S Topamax (topiramate).**

➢ **WYETH'S Effexor (venlafaxine).** It has sodium channel activity, but it has not been well-researched in neuropathic pain.

➢ **GLAXOSMITHKLINE'S Lamictal (lamotrigine).** Six small trials have shown lamotrigine to be better than placebo in a variety of neuropathic pain models, but the FDA has not approved lamotrigine. The company's pivotal trial failed to meet its primary endpoint, and an official said this was due to a higher-than-expected dropout rate. About 20%-30% of patients were lost even before they reached the target dose. A Glaxo official said, "The dropouts were not due to drug effect. I think it is patients' expectations that were the problem… Patients can't be titrated faster because of the risk of rash." The company plans two new trials aimed at a neuropathic pain indication, and an official said investigators will "work hard to better manage patient expectations."

Four lamotrigine posters were presented at APS, but none of these is sufficient to get FDA approval in neuropathic pain.

- Three posters were presented on the results of a pooled analysis of two large, randomized, double-blind studies of lamotrigine. One looked at nerve conduction safety data, concluding that there was no evidence of neurotoxicity with any dose of lamotrigine. Another which found lamotrigine 300 mg and 400 mg may be effective and is

Pooled Analysis of Lamictal for DPN

Measurement	Placebo n=174	Lamictal 200 mg n=177	Lamictal 300 mg n=179	Lamictal 400 mg n=176
Withdrawals due to adverse events	12%	15%	16%	22%
Rash	6%	7%	5%	6%
Dizziness	<1%	2%	2%	6%
Adverse events				
Any adverse event	67%	72%	78%	74%
Headache	5%	12%	19%	18%
Rash	9%	12%	9%	14%
Dizziness	5%	4%	8%	11%
Serious adverse events				
Any adverse event	6%	8%	6%	7%
Coronary artery disease	0	1%	1%	<1%
Congestive heart failure	<1%	<1%	0	2%
MI	0	0	0	1%
Chest pain	1%	<1%	<1%	0
Anemia	<1%	<1%	0	<1%

generally well tolerated in the treatment of pain associated with diabetic neuropathy. A third which found Lamictal 200 mg – 400 mg was generally well-tolerated.

- A poster which examined the effect of oral contraceptives on the PK of lamotrigine. The study found that a lamotrigine dosage adjustment may be necessary when co-administered with a hormonal contraceptive. Serum concentrations of lamotrigine increased in a rapid and linear manner during the "pill-free week," with concentrations at the end of this week, on average, about two-fold higher than during the rest of the month when lamotrigine and oral contraceptives were both taken. However, no subject showed hormonal evidence of ovulation during the study.

➢ **NOVARTIS'S Trileptal (oxcarbazepine).** A positive trial in painful diabetic neuropathy is expected to be published soon. A speaker said, "It will be hard to know what to make of the results of this study until we see the results of three other trials in painful diabetic neuropathy, which have not been disclosed yet."

Sources asked how they choose among these drugs offered these comments:

- *Virginia:* "My bias is to Cymbalta because it is a smooth dual reuptake inhibitor. I'm not a big gabapentin user, but it is safe. I don't use pregabalin yet, but I'm interested in it. I use tricyclic antidepressants because of the (low) cost. I also like lamotrigine because it is a mood stabilizer, but it is best tolerated in bipolar depressive maintenance therapy."
- *Texas:* "The gold standard is gabapentin, but it has a lot of side effects in the elderly. I don't like lamotrigine because of the side effects; it can cause Stevens-Johnson Syndrome at higher doses, so it can be an extremely dangerous drug. Pregabalin and duloxetine may be better, and I heard pregabalin has better results, QD dosing, and fewer side effects (than gabapentin)…Methadone is also very good for diabetic neuropathy.

POST-OPERATIVE PAIN

The leading causes of hospital readmissions after surgery are: pain (36%), surgery (20%), medications (15%), and bleeding (5%). At a Johnson & Johnson-sponsored seminar on post-operative pain, a speaker said that a survey in 1995 found that ~55% of patients experienced extreme pain after major surgery, but a survey in 2003 conducted by Beth Israel Hospital found that 60% of patients reported pain after major surgery.

American Society of Anesthesiologists 2004 Pain Survey

Anesthesia	Number of patients	Patients with pain score >5 on the first post-op day
All	2,248	31.2%
PRN	1,512	29.1%
Epidural	258	27.1%
CPNB	88	25.0%
APS	527	24.5%
Non-APS	1,721	33.3%

Patient-controlled analgesia (PCA) devices are commonly used post-operatively. In 2003-2004, the FDA's MAUDE (Manufacturer and User Facility Device Experience) database had 19 spontaneous user reports of adverse events involving PCA devices. PCAs were No. 3 in a list of the Top 10 Medical Errors by the Institute for Safe Medication Practices (ISMP) in Canada, a private organization, topped only by insulin and free flow IV pumps. The ISMP recommended:

- Being more finicky about who gets these high tech pain devices (PCAs).
- Programming safeguards (safe pumps), such as one with bar-coding of the cartridge that fits into the pump, which reads the bar code. This is currently only available for morphine and fentanyl but the company is considering getting a cartridge for oxycodone.
- Labeling "high alert" medications.
- Having two nurses program the pump.

Comparison of Analgesics

Patient-Controlled Anesthesia (PCA)	Johnson & Johnson's ionophoretic transdermal fentanyl	Pfizer's parecoxib (an IV Cox-2 inhibitor)
Advantages		
Each patient can control own pain relief	Easy for patients to use and offers patient activation	Greater versatility and safety than IV ketorolac in perioperative and emergent settings
High degree of patient acceptance and satisfaction (if they can understand it)	Credit-cared-sized device doesn't interfere with ambulation	
Reduces total opioid dose and related side effects	Easy for nurses to apply and activate, and requires less monitoring	
Disadvantages	Does not require IV access, pumps, or tubing	**Disadvantages**
Patients need the ability to understand the directions	Easy for pharmacists to stock	May increase post-op MI in patients recovering from CABG
Requires availability of specific infusion pumps	Advantages of PCA dosing paradigm without risk of phlebitis and drug incompatibility	
Pumps subject to programming errors	No programming errors	

New analgesics on the horizon that will compete with PCA include ionophoretic fentanyl patches and IV parecoxib.

➢ **JOHNSON & JOHNSON'S ionophoretic, patient-controlled, transdermal fentanyl delivery system (PCTS).** This is, at least initially, designed for in-hospital use. A poster presented a subgroup analysis of a random-ized, multicenter study comparing the safety and efficacy of PCTS vs. an IV patient-controlled morphine pump (IV PCA), looking at the treatment of acute post-operative pain after general surgery. Researchers concluded that fentanyl is comparable in efficacy to IV PCA morphine.

PCTS vs. IV PCA After General Surgery

Measurement	PCTS n=53	IV PCA n=58
Drug delivered	40 µg fentanyl, up to 6 doses/hour	1 mg morphine, up to 10 mg/hour
Primary endpoint: PGA rating of pain control excellent or good during the first 24 hours	83.0% (p=.618)	79.3%
Treatment-related adverse events		
Nausea	34.0%	44.8%
Pruritus	5.7%	12.1%
Vomiting	5.7%	6.9%
Abdominal pain	3.8%	0
Application site reactions	3.8%	0
Fever	3.8%	1.7%
Hypoxia	3.8%	3.4%
Dizziness	1.9%	5.2%
Headache	1.9%	8.6%
Hypotension	1.9%	3.4%
Discontinuations due to inadequate analgesia	8 patients (p=0.30)	5 patients

At a seminar sponsored by J&J, doctors were interested in ionophoretic PCTS, but many said they wanted to use it out-of-hospital. One commented, "It won't replace PCA, but it would be good for sending home tonsillectomy patients." A speaker responded, "This is not designed for tonsillectomies because it won't have a pediatric indication, but it is a nice, compact system. It would be good for hysterectomies, total joint replacements, and major abdominal surgery. You won't be allowed to use it to send patients home – that would require really high safety data – though eventually it may be used for that." Another doctor said, "Transdermal ionophoresis is exciting – especially if you could use it at home. It has great potential."

Cost may be an issue for hospitals, but the ambulation with J&J's ionophoretic PCTS will definitely have appeal, sources agreed. One source said, "I'm not sure hospitals will pay extra for this, but what is appealing to me is that there is no hook up to a pole." J&J currently is conducting a cost-effectiveness study of ionophoretic PCTS with a questionnaire to nurses.

A source estimated that 85%-90% of abdominal surgery patients and ~50% of total joint replacement patients get PCA. He said, "After 24 hours, I would put all of these on ionophoretic PCTS."

➢ **PFIZER'S Dynastat (parecoxib),** an IV Cox-2 inhibitor. A speaker said, "Whether we will see this drug or whether it will be restricted to patients without cardiac disease is unclear. But if it comes along, it will be useful in a multimodal paradigm."

➢ **BRISTOL-MYERS SQUIBB'S injectable acetaminophen.** This is widely used in Europe. A speaker said, "The potency is remarkable because it is injectable. It is comparable to toradol and, possibly, to parecoxib, without effects on platelet function or renal function, so it may have use in the future. I think it is about two years from the U.S. market."

➢ **ENDO PHARMACEUTICALS' extended-release epidural morphine (EREM).** EREM is designed to provide the benefits of continuous epidural analgesia with a single peri-operative dose that may obviate many of the risks associated with indwelling catheters. Researchers presented a meta-analysis of three Phase II/III trials in hip arthroplasty patients. Their conclusions were:

- A single peri-operative dose of EREM consistently delayed the median time to the first dose of supplemental fentanyl, with significantly fewer patients requiring supplemental fentanyl in the 24 hours following EREM administration.
- The benefit was extended beyond 24 hours in many patients.
- EREM may require no IV PCA in the post-operative period and may be able to be transitioned directly to oral medications.
- The fentanyl-sparing effects appeared to be dose-depending, with a plateau at the EREM 20 mg dose.

EREM Meta-analysis

Measurement	Placebo	EREM 10 mg	EREM 20 mg	EREM 30 mg
Average median time to first post-operative fentanyl usage	<5 hours	~15 hours	~30 hours	~27 hours
Patients using no fentanyl during the 24-hour post-surgical period	~7%	~21%	~48%	~45%
Adverse events				
Constipation	12.2%	15.4%	10.1%	17.6%
Dizziness	5.4%	10.3%	15.7%	8.8%
Headache	36.5%	48.7%	29.2%	50.0%
Hypotension	33.8%	17.9%	43.8%	23.5%
Nausea	47.3%	56.4%	73.0%	76.5%
Pruritus	17.6%	66.7%	49.4%	70.1%
Somnolence	4.1%	12.8%	13.5%	23.5%
Urinary retention	5.4%	17.9%	15.7%	26.5%
Vomiting	17.6%	53.8%	49.4%	50.0%

PATCHES

ENDO PHARMACEUTICALS' Lidoderm (lidocaine patch 5%). An Endo official said Lidoderm is "a known equity," and the company is looking for ways to maintain its franchise. To this end, four posters on Lidoderm were presented:

➢ A randomized, open-label, active-control, parallel-group study comparing Lidoderm to Pfizer's Cox-2, Celebrex (celecoxib) 200 mg, for pain associated with osteoarthritis, was halted prematurely in the fall of 2004 when the withdrawal of Merck's Vioxx (rofecoxib) raised safety concerns about all Cox-2 inhibitors. The trial was not fully enrolled when it was terminated, but Endo still performed an analysis, which found Lidoderm superior to Celebrex.

6-Week Results of Study of Lidoderm vs. Celebrex

Measurement	Lidoderm n=56	Celebrex n=63
≥30% improvement in daily pain intensity	54%	62%

➢ An Endo-sponsored cost analysis of Lidoderm vs. gabapentin, based on employee health claims from MEDSTAT's MarketScan Commercial Claims and Encounter Database, which has health information on more than eight million patients. The study matched 821 Lidoderm patients with 20,125 gabapentin patients. The Lidoderm patients were statistically significantly: older, more likely to be female, urban dwellers, had indemnity coverage, resided in the North Central region, and had fewer co-morbidities. Post-treatment, the Lidoderm patients averaged:

- More opioid and total pain pharmaceutical-related expenditures ($p<.001$).
- More pain-related spending ($p<.001$).
- Less mental health-related spending ($p<.05$).
- 21.9% of Lidoderm patients switched to – or added – gabapentin vs. 3.8% of gabapentin patients who added or switched to Lidoderm ($p<.01$).
- Spent an average of $1,780 less on annual healthcare expenditures vs. brand gabapentin (Neurontin), which would be an average of $1,330 less than generic gabapentin.

➢ A post-hoc pooled analysis of two multiple-dose, open-label, non-randomized, multicenter studies, looking at the efficacy of Lidoderm in 118 PHN patients with insufficient pain relief from Cox-2 inhibitors, NSAIDs, opioids, anti-epileptics, or tricyclic antidepressants. Researchers reported Lidoderm significantly improved pain intensity and pain interference with quality of life in these patients.

➢ A post-hoc analysis of two prospective, open-label, non-randomized clinical trials, looking at the safety and efficacy of Lidoderm as combination therapy for low back pain and OA in 119 patients with a partial response to a Cox-2 inhibitor or a traditional NSAID. The study found Lidoderm significantly improved pain intensity and pain interference with quality of life.

Endo also is working on:

- LidoPain, a lidocaine (19%) patch for acute low back pain that Endo licensed from EpiCept. When this patch is applied, it produces an area of numbness short-term. A source said, "This could be very good. It would probably work very well on outpatients."
- A low back pain indication for Lidoderm (5%). A Phase II trial in chronic back pain is still enrolling patients. It will have about 100 Lidoderm patients vs. ~100 placebo patients.
- A ketoprofen patch, acquired from ProEthic Pharmaceuticals. Ketoprofen is an oral NSAID, but Endo hopes that locally high tissue levels (with very low blood levels) will be good for sports injuries, sprains and strains, and tendonitis. An official said, "We are close to approval in Europe."
- A transdermal sufentanil patch. Endo recently licensed this from Durect. It is a seven-day patch about 20% the size of Johnson & Johnson's Duragesic (fentanyl patch).

Fentanyl patches

Several generic fentanyl patches are in development to compete with Johnson & Johnson's Duragesic, which uses a reservoir delivery system. So far, only Mylan's generic matrix patch and Novartis's reservoir patch have been approved. What's the delay with the others? A source suggested the FDA is "giving Mylan time on the market alone to make up for a snafu that kept Mylan from getting the 180-exclusivity usually granted to the first generic."

Most of the other generics in development use a matrix delivery system, but Endo reportedly has a reservoir patch in development. An Endo official said the company would expect to sell this patch based on price and relationships; it won't promote it.

Johnson & Johnson reportedly was looking at developing its own matrix fentanyl patch but, following an abusability study by its researchers, has now given up that idea. The study looked at the ease of extraction of fentanyl from different transdermal systems vs. Duragesic using a variety of ordinary household equipment and solvents at different temperatures. Researchers found methanol was the most effective solvent for extraction of fentanyl from matrix patches, and that fentanyl is more easily and more rapidly extracted from a matrix patch than from Duragesic.

Duragesic vs. Matrix Fentanyl Patches

Measurement	Duragesic	Matrix patch
Maximum theoretical yield of fentanyl	10 mg	18.4 mg
Extraction % after 3-hour room temperature soak		
Methanol	9.7%	87%
Ethanol 75.5%	9.9%	88%
Ethanol 40%	5.2%	51%
Extraction % after 3-hour percolation		
Methanol	56%	55%
Ethanol 75.5%	45%	40%
Ethanol 40%	29%	77%
Isopropanol	22%	85%
Acetic acid 6%	91%	81%
Water	57%	62%

Spinal Cord Stimulators

An estimated 50 million Americans have chronic pain. The typical candidate for a spinal cord stimulation device:

- Is age 25-55.
- Has severe chronic pain of the trunk or limbs that has persisted or recurred for more than six months.
- Has difficulty walking and is out of work.
- Likely has had at least two back surgeries that have failed to control the pain.
- Is probably taking opiates or other narcotics to control the pain, but with little success.

Three rechargeable stimulators have FDA approval and are on the market, and the fourth will be launched soon. A source estimated that 30% of stimulator patients will get a rechargeable version.

Boston Scientific/Advanced Bionics' Precision

The company announced the "nationwide release" of Precision at APS – but the device actually has been available since April 2004. An official said the slow rollout was due to the patient learning curve and the company wanting to avoid producing too many "before we learned how to use it and make it reliably." A doctor said he plans to try Precision, "The company has to go to the hospital and get the device approved, then I will try it – because patients have asked for a rechargeable stimulator. The programming is very easy, and that's what appeals to me. It seems much easier (to program) than the Medtronic or ANS devices."

An Advanced Bionics official claimed the company is taking market share from competitors and expanding the market. He said, "We have our own sales force, which has to confront physician-supplier relationships, so we get last ditch patients, and we are very successful with those. That is helping us take market share."

An expert said the key patients for Precision have nerve-related injuries, most commonly spine surgery with post-operative pain. He said, "Precision treats the same conditions all other spinal cord stimulators treat. We are also investigating low back pain. My lab data suggest we can treat low back pain with Precision, and low back pain has not been able to be treated very successfully so far with stimulators." He claimed patients are beginning to ask for Precision, adding, "Any patient who gets a stimulator is someone who monitors new advances in the field."

Rechargeable Spinal Cord Stimulators

Feature	Boston Scientific/Advanced Bionics' Precision	Medtronic's Restore	Advanced Neuromodulation Systems' Eon	Advanced Neuromodulation Systems' Genesis
Frequency of recharge	Weekly to daily depending on settings	Every 3-4 weeks	Every 4-6 weeks	Every 4-6 weeks
Rechargeable	Yes	Yes	Yes	Yes
Size	Small	Medium	Large	Large
Cost	$7,500-$11,000	$12,000-$16,000	N/A	N/A
Time to recharge a dead battery	15 hours	6 hours	N/A	2 hours
Temperature control during recharge	No	Yes, temperature sensor cuts device off to prevent skin burns.	No heat generated; source is away from the body.	No heat generated; source is away from the body.
Recharger must be charged	Yes	No	No	No
Number of leads	2 with 8 electrodes each	2 with 8 electrodes each	1 with 8 electrodes	2 with 8 electrodes each
Battery life	5 year warranty	9 years	7 years at high settings	7+ years
Key advantages	Size, patient programming, rechargeable	Medtronic longevity and experience	N/A	N/A
Rechargeable while in use	No	Yes	N/A	N/A
Programming	Patient-controlled	Patients choose from settings established by physician.	N/A	N/A

Future studies of Precision include different applications and configurations. These include:

- Low back pain. A 300-patient prospective study in low back pain is ongoing. So far about 100 patients have been enrolled, and enrollment is expected to be complete by the end of 2005. The trial will have both one-year and two-year follow-up.
- Subcuticular placement for hip grafts. No formal study has been started for this yet.
- Back pain due to scarred muscles or ligaments.
- Transformed (non-aura) migraine. A preliminary study is ongoing looking at using Precision to abort migraines.

MEDTRONIC'S Restore. Shortly after APS, Medtronic announced FDA approval of its rechargeable stimulator, Restore. A Medtronic source said, "Precision may be more attractive, but the technology is not really proven…We have the experience and the data. I don't think patients who don't need frequent recharges will want these devices...Advanced Bionics' service level has been good, but they don't have the clinical data behind their product that we do."

ADVANCED NEUROMODULATON SYSTEMS' (ANS) Genesis and Eon. Genesis has been on the market, and two weeks before the APS meeting, ANS received FDA approval for its newest generation rechargeable stimulator, Eon. An ANS official said there will be a limited launch of Eon in 2Q05, with a full launch in 2H05. ANS claims it is the only company to offer a full array of spinal cord stimulation devices, including two radio-frequency powered stimulators, four conventionally-powered IPGs, and three rechargeable IPGs. An official said, "We firmly believe that each kind of system has its place in the treatment armamentarium."

MISCELLANEOUS

ALGORX PHARMACEUTICALS' ALGRX-4975 (capsaicin for injection). Researchers reported on a 12-patient randomized, double-blind, placebo-controlled, six-week Phase II safety, tolerability, and efficacy study of ALGRX-4975 local injections for OA of the knee. They found a single injection of 1000 µg ALGRX-4975 significantly reduced the mean, three-week, post-treatment NRS score. ALGRX-4975 is in Phase II development, and the company is looking for a partner.

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