Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Cephalon's effervescent fentanyl appears to work quicker than its Actiq for breakthrough pain, but doctors raised a number of questions about the outlook for the product.

♦ The outlook for FDA approval of Endo Pharmaceuticals' oxymorphone ER is clouded by alcohol interaction in humans at high doses, though this was described as not clinically significant. If it gets approved, it will be another option for opioid rotation but could gain first-line status over time.

♦ Adolor/GlaxoSmithKline's alvimopan appears effective in reducing the opioid-induced constipation, and about 25% of opioid patients are expected to get a prescription for it when it is approved.

♦ Doctors predicted that Pain Therapeutics/ King's Remoxy will be a niche product because payors are unlikely to pay extra for it. ♦ Doctors were not enthusiastic about combination products like Forest Lab's Combunox and Pain Therapeutics' Oxytrex.

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AMERICAN PAIN SOCIETY (APS)

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Chronic pain affects a large number of Americans. Experts estimated that 9%-20% of the general population, 25%-73% of community-dwelling older adults, and 45%-80% of people in long-term care facilities and nursing homes have chronic pain. Transdermal fentanyl (e.g., Johnson & Johnson's Duragesic) is the only drug which currently has labeling for chronic pain.

Pain affects **the brain**. Normally, as people age they lose some gray matter in the brain, on average 0.5% per year starting at about age 30. However, one estimate put the gray matter loss of chronic low back pain patients at 5.4%/year. A speaker said, "The impact of chronic low back pain is an additional 10 years of brain atrophy…The duration of low back pain is a strong predictor of gray matter changes…There is no pain center in the brain. Pain is a conscious connection of different regions of the brain community with each other."

There also seems to be a correlation between type of pain therapy and **life expectancy**. A speaker referred to a study of 661 cancer patients.

Daily Opioid Requirements for Home-Based Hospice Patients with Cancer

Opioid dose	Correlations	Mean survival
No opioid (34.2%)	Older patients less likely to receive opioids	22 days
5-299 mg/day (59.9%)	Same adverse effects reported as in higher dose groups	18 days
300-599 mg/day (4.8%)	Males required higher doses than females	27 days
>599 mg/day (1.1%)	Associated with primary GI, lung, ovarian, and brain cancer and metastatic bone disease	37 days

BREAKTHROUGH PAIN

Breakthrough pain also is a big problem, affecting an estimated 52%-64% of in-patient cancer patients, 65% of outpatient cancer patients, and 60%-80% of hospice patients. The intensity of breakthrough pain was described as "severe" or "excruciating," occurring from one to four times a day and reaching peak intensity within 30 minutes (mean 3.2 minutes). Most commonly, breakthrough pain is treated with short-acting oral opioids taken as needed, but they take 30-40 minutes to start working.

Cephalon's Actiq (transmucosal fentanyl) is the only drug with labeling for breakthrough pain. Cephalon also has an oravescent (effervescent) fentanyl in development, and Endo Pharmaceuticals has applied for FDA approval for oxymorphone IR.

CEPHALON'S fentanyl effervescent buccal tablet (FEBT), also known as oravescent fentanyl (OVF)

This is a tablet that is placed above a molar between the upper cheek and the gum and allowed to dissolve for ~15 minutes. A speaker pointed out that OVF works in 15 minutes or less, compared to an onset of action of 40-45 minutes for hydrocodone or oxycodone. Asked if the onset of action is quicker than 15 minutes, he said, "We only looked at the onset of action at 15 minutes. My clinical impression is that some patients start to see an effect at five minutes, but there is no clinical data on that…Ongoing studies are looking at 5-10 minutes." Asked about the role of effervescence in the onset of action, he said, "A poster here shows that FEBT gets higher and faster levels than Actiq, and the difference is effervescence, so it really does seem that the effervescence makes a difference in the speed of onset."

In the efficacy trial, OVF met the primary endpoint, but it did not reach a statistically significant difference from placebo at 15 minutes on the endpoint of 50% reduction in pain intensity, but that was the only endpoint missed.

Asked how generic Actiq will affect use of both brand Actiq and OVF, doctors were cautious about generic Actiq. They said they have been "burned" on generic products in the past and approach any new generic cautiously. However, they indicated that a lower priced Actiq would be strong competition for OVF. A Louisiana doctor said, "OVF uptake will depend on formularies. If it is 10 times the cost of the generic and there are no head-to-head studies, it will have trouble. It may be useful in spinal cord injury and in patients who need something that can be administered by someone else – where you can't depend on the patient to deliver it adequately – for example in dementia or quadriplegics."

Doctors also raised several questions about OVF and the data presented on it, including:

- ***Could or would patients actually keep the tablet against the gum for that long without chewing it?*** Many people can't resist the urge to chew a lifesaver after a couple of minutes, so would the same hold true for OVF outside of a clinical trial? However, an expert pointed out that Actiq also has problems: "Actiq still doesn't have a sugarless version, and teeth rot continues to be a problem. It also falls off the stick sometimes, so there are quality issues."
- ***Is the faster onset of action with OVF vs. Actiq clinically significant?*** OVF is faster, but is the benefit really sufficient? An Ohio doctor said, "Faster is not necessarily better. In patients who have a history of addiction or are very sensitive, you can get a high you don't want. I'll move most Actiq patients to generic Actiq, but not all of them. Generics are not necessarily the same."
- ***Is the faster action of OVF more important to patients than the ability they have to control titration with Actiq?***
- ***What does the high dropout rate in the trials mean in interpreting the results?***
- ***Are the incidences of mouth irritation (site reactions, including ulcers) with OVF a concern?*** Only two patients dropped out of the efficacy trial because of this, but 13% experienced the problem.
- ***Is OVF more abusable than Actiq?***
- ***Will it be cost prohibitive?***

Four posters were presented on OVF:

1. A poster presented an open-label, crossover study in 32 healthy volunteers of the comparative bioavailability of FEBT. Each person received a single dose of each of these: FEBT 400 µg transmucosally, IV fentanyl 400 µg, Actiq 800 µg, and FEBT 800 µg orally. The absolute bioavailability was greater with transmucosal FEBT than Actiq, and T_{max} was earlier. Researchers concluded that an ~30% smaller dose of FEBT transmucosal would achieve equivalent systemic levels of fentanyl as with Actiq.

2. Another study presented the results of a randomized, double-blind, placebo-controlled study in opioid-treated adult cancer patients with chronic pain. Patients first identified an effective dose of FEBT for breakthrough pain in an open-label titration period, and then they were enrolled in the double-blind period and randomized to one of 18 pre-defined dose sequences of 10 tablets (3 placebo, 7 FEBT at the initially-effective dose).

FEBT Bioavailability Study

Measurement	FEBT 400 µg transmucosal	FEBT 800 µg oral	Actiq 800 µg	IV fentanyl 400 µg
T_{max}	46.8 minutes	90.1 minutes	90.8 minutes	---
$T_{1/2}$	14.4 hours	15.4 hours	18.3 hours	17.6 hours
C_{max}	1.02 ng/mL	0.98 ng/mL	1.26 ng/mL	3.00 ng/mL
$AUC_{0\text{-}Tmax}$ (early systemic exposure)	0.40 ng·hr/mL	---	0.14 ng·hr/mL	---
Absorption through the buccal mucosa	48%	---	22%	---
Absorption through the GI tract	52%	---	78%	---
Absolute bioavailability	0.65	0.31	0.47	---

FEBT Efficacy Study

Measurement	FEBT	Placebo
Breakthrough episodes	493	208
Use of supplemental opioid	23%	50%
Primary endpoint: summed pain intensity difference at 30 minutes ($SPID_{30}$)	3.0 ($p<.0001$)	1.8
Clinically significant reduction in pain intensity (score ≥33%)		
15 minutes	13%	9%
30 minutes	48%	29%
45 minutes	71%	44%
60 minutes	75%	48%
Reduction in pain intensity score ≥50%		
15 minutes	8% *	6%
30 minutes	24%	16%
45 minutes	51%	25%
60 minutes	64%	35%
Patient-rated global assessment of drug performance (mean performance score)		
30 minutes	1.4	0.9
60 minutes	2.1	1.3

* Only time point not statistically significant vs. placebo

3. The interim results on tolerability were presented from an ongoing long-term (1-year) safety and tolerability study in cancer patients whose breakthrough pain was adequately controlled with a short-acting opioid. Of the 87 patients who entered the titration period, 68% (59) identified an effective dose, and 57 entered the long-term study; another 77 patients entered this study after finding an effective dose of FEBT during a previous study (total 134 patients). The study found the dose of FEBT remained relatively stable during long-term treatment – whatever dose initially worked, generally continued to work.

FEBT Long-Term Tolerability Study

Measurement	Patients
Patients enrolling	134
Patients receiving FEBT	129
Total discontinues	55
Discontinuations due to adverse events	28
Adverse events (n=109)	
Nausea	32%
Vomiting	25%
Dizziness	14%
Fatigue	19%
Anemia	14%
Dehydration	14%
Headache	12%
Somnolence	6%
Discontinuations for oral mucosal adverse events	2 patients
Effective dose at interim cutoff	
Initial dose 100 µg	73% at 100 µg
Initial dose 200 µg	77% at 200 µg
Initial dose 400 µg	75% at 400 µg
Initial dose 600 µg	87% at 600 µg
Initial dose 800 µg	97% at 800 µg

4. Data from a pooled analysis of open-label dose-titration periods of three studies in 271 cancer patients with chronic pain were presented. Patients all received a test dose of FEBT, and those who tolerated the test dose proceeded with titrated from 100 up to 800 µg until adequate pain relief was achieved within 30 minutes for 2 consecutive episodes of breakthrough pain. There was no correlation between baseline opioid dose and the effective dose of FEBT, and researchers concluded that clinically, patients should be started on a relatively low dose and titrated up as needed. About one-third of patients did not identify any effective dose, and studies of higher doses will be needed.

FEBT Dose-Titration Pooled Analysis

Measurement	100 µg FEBT	200 µg FEBT	400 µg FEBT	600 µg FEBT	800 µg FEBT
Patients achieving efficacy	~ 7%	~ 11%	~ 14%	~ 15%	~ 19%
Discontinuations due to adverse events	18 patients (15 drug-related, including dizziness, nausea, site reactions, vomiting, and diarrhea)				
Dizziness	19%				
Nausea	17%				
Headache	9%				
Vomiting	6%				

CONSTIPATION

Constipation is an almost universal side effect with opioid use, with up to 50% of cancer patients experiencing constipation. Current treatment options for opioid-related constipation are:

- Check for appropriate opioid dosage.
- Change opioid.
- Change route of opioid administration.
- Initiate laxative regimen with the start of opioid therapy. Up to 75% of patients respond well to a laxative. However, patients can become laxative-dependent.

Constipation in U.S. Patients Taking Opioids

Measurement	All patients	
	General population n=10,018	Opioid users n=76
<3 complete bowel movements per week	7.6%	40.3%
Time bowel movements complete	9.2%	36.1%
Straining	9.1%	39.6%
Hard, lumpy stools	17.3%	45.5%
	Patients with constipation	
	General population n=10,018	Opioid users n=76
Treatment for constipation	55%	80%
>50% treatment success	84%	46%

Off-Label or Investigational Agents for Opioid-Induced Constipation

Drug	Type	Indication	Issues
Approved			
Colchicine	Alkaloid prepared from dried corns and seeds of autumn crocus	Gout	Diarrhea
Erythromycin	Motilin receptor stimulant	Antibiotic	---
Misoprostol	Synthetic prostaglandin	GI ulcers	---
Neurotropin-3	Protein growth factor	N/A	---
Novartis's Zelnorm (tegaserod)	5HT4 agonist	Constipation with irritable bowel syndrome	Diarrhea, ischemic colitis
Roche's Xenical (orlistat)	Lipase inhibitor	Weight loss	Oily anal leakage
Investigational			
Adolor/GlaxoSmithKline's alvimopan	Peripherally-acting μ-opioid receptor antagonist	Opioid-induced constipation	---
Alizyme's renzapride	5HT4 agonist	Irritable bowel syndrome	---
Naloxone	Tertiary μ-opioid receptor antagonist	Opioid toxicity	Effective but can reverse analgesia
Progenics' methylnaltrexone	Quaternary ammonium μ-opioid receptor antagonist	Opioid-induced constipation	Effective in studies for POI
Rottapharm's loxiglumide	CCK-1 antagonist	Pancreatitis	IBS development discontinued
Rottapharm's dexloxglumide	CCK-1 antagonist	Constipation-predominant irritable bowel syndrome	---

Methylnaltrexone and Naloxone for Opioid-Induced Constipation

Measurement	Placebo	Drug
Methylnaltrexone		
Oral-cecal transit time (change from baseline) with IV dosing	Down ~ 2 minutes	Down ~ 63 minutes ($p<.001$)
Percent laxation at 4 hours	~ 12%	~ 62% at 0.15 mg/kg ~ 57% at 0.3 mg/kg
Percent laxation at 24 hours	~ 32%	~ 67% at 0.15 mg/kg ~ 64% at 0.3 mg/kg
Naloxone		
Efficacy	---	Dose-dependent
Side effects	---	Dose-related loss of morphine efficacy and withdrawal symptoms

ADOLOR/GLAXOSMITHKLINE'S alvimopan (ADL-8-2698)

This oral opioid antagonist looks very promising to treat the constipation associated with opioid use as well as post-operative ileus (POI). It has low systemic absorption and a high affinity for μ-opioid receptors. It appears to reverse opioid bowel dysfunction without compromising opioid analgesia or inducing CNS withdrawal. An investigator said Adolor is pursuing the POI indication, and GlaxoSmithKline is running the trials in constipation, where the next stage reportedly is a titration study.

Efficacy doesn't appear to be an issue; the drug definitely works. Moving from a 3- or 6-week trial to a 12-week trial did not concern any doctors asked about it. Rather, they thought that a longer trial would give them a better picture of the clinical utility, and investigators did not think the longer trial would diminish the efficacy in any way. They pointed out that the benefits appear early (within one week) and then are generally maintained. They did not believe there would be any drop off in effect over time. One expert said, "Longer studies are a good idea; 12-18 weeks is what resonates with doctors."

One question that has been raised is whether there is any significant GI withdrawal with alvimopan – pain, cramps, diarrhea, and discomfort that can occur when a bowel that has slowed down due to opioid use encounters a drug like alvimopan. However, investigators insisted the GI side effects with alvimopan are dose-dependent, are seen in the first week, and then dissipate.

POI studies were in naïve patients; chronic pain studies were in opioid-experienced patients. There have been no studies in naïve chronic pain patients (i.e., patients just starting long-term opioid treatment).

An investigator put the likely appropriate patient population at 10%-15% of all opioid patients. Another put the number of patients who will need this medication at 30%-40% of chronic pain patients, but he said it would start with the 10% of chronic pain patients who are very refractory. Except for one

doctor who thought she would recommend it to 80% of her opioid patients, doctors not associated with the alvimopan trials estimated that, on average, 25% of their opioid patients might take it. They explained that 75%-80% of their patients have problems with constipation when taking an opioid, but most of them are able to deal with this through diet or over-the-counter laxatives, leaving 10% who definitely need a prescription aid, and another 15% that could benefit from one.

Among the comments on the outlook for alvimopan were:

- *Florida:* "From 25%-30% of patients get opioid-induced constipation, and about 10% might get a prescription for alvimopan when it is available."
- "Constipation recurs when alvimopan is withdrawn, but it isn't worse…Over-the-counter laxatives have a cost, too."
- "Fifty percent of my patients have significant bowel dysfunction (30%-70% in other practices have a problem with constipation). But not all of these patients need a medication. From 10%-15% of all opioid patients might need it."
- "Eighty percent of patients develop GI side effects with opioids, especially if they are on an opioid long-term. The problem with laxatives is the bowel becomes dependent."
- *Investigator:* "There is a big placebo response, but placebo responders are not happy. They are still uncomfortable. Alvimopan patients ***felt*** much better…Ten percent of patients have constipation and are very refractory (to what is currently available), and probably 30%-40% might take it. Seventy percent of my patients are on a laxative regimen and claim constipation is not a problem. Usage will depend on the cost. If it is not too expensive, I would like to try it in most patients to see if they feel better. The average patient spends about $60 a month on over-the-counter products…And alvimopan could be cost effective if it replaces proton pump inhibitors; 31% of symptomatic patients in one study had GERD…And we could look at opioid initiators and give alvimopan preventively. I don't know if that would be beneficial, but we are considering that study."
- *Investigator:* "There is no food effect with alvimopan. You can give it with or between meals."
- *California #1:* "Thirty percent of opioid patients might find it of value, but they will try less expensive options first. Cancer patients and patients with higher opioid doses will use it more."
- *Texas:* "With every opioid, I give patients a constipation sheet, and I tell them to prophylactically drink water, watch their diet, drink prune juice, take Senokot (Purdue Frederic, senna). I tell them not to reduce the opioid dose. From 10%-20% would need a drug like alvimopan – and I'm proactive about constipation."
- *Ohio:* "Fewer than 10% of my younger opioid patients (which is about 60% of my opioid patients) have a problem with constipation, but 40%-50% of patients over age 60 have a problem." (NOTE: Averages to 24%)
- *California #2:* "Constipation is a side effect that doesn't go away. It bothers more than 50% of opioid patients (who complain), but the majority can be helped with a laxative and diet. If a good drug were available, if it wasn't too expensive, and if insurance covered it, then 25% of patients would probably take it. The question is whether insurers will consider treating constipation a legitimate side effect as part of the (opioid) treatment regimen."

Five posters at APS offered information on alvimopan:

1. Dose-finding – A randomized, 6-week, double-blind, placebo-controlled, multicenter, Phase IIb study (SB767905/011) of multiple dosage regimens for the treatment of GI adverse events associated with opioid use in 522 patients with persistent non-cancer pain. All alvimopan doses significantly increased weekly spontaneous bowel movements (SBMs) vs. placebo. Researchers concluded that the 0.5 mg BID regimen has the best risk:benefit profile.

Alvimopan Phase IIb Dose-Finding Results

Measurement	Placebo n=129	Alvimopan 0.5 mg BID n=130	Alvimopan 1.0 mg QD n=133	Alvimopan 1.0 mg BID n=130
Spontaneous bowel movement				
≥SBMs/week	39%	63% -68% (p<.001)		
Straining	Down 18%	Down 35% *	Down 26% *	Down 31% *
Stool consistency	Down 21%	Down 30%	Down 26%	Down 35% *
Incomplete evacuation	Down 6%	Down 20% *	Down 15% *	Down 18% *
Abdominal bloating	Down 20%	Down 24% *	Down 33% *	Down 35% *
Abdominal pain	Down 19%	Down 27% *	Down 19% *	Down 30% *
Decreased appetite	Down 7%	Down 24% *	Down 13%	Down 18% *
Adverse events				
Any	66%	71%	65%	67%
GI-related	36%	30%	38%	43%
Abdominal pain	15%	17%	22%	28%
Diarrhea	5%	7%	11%	14%
Nausea	9%	7%	9%	10%
Discontinuations due to adverse events	9%	5%	11%	13%
Opioid use				
Average daily opioid use (change from baseline)	Up 4.5 mg	Up 7.0 mg	Up 3.0 mg	Down 5.6 mg

* p<.05 compared to placebo

2. No effect on opioid analgesia – A pooled analysis of three randomized, double-blind, placebo-controlled, parallel-group, U.S. Phase III efficacy trials in post-operative ileus. The study found alvimopan accelerated GI recovery without reducing opioid pain relief.

3. Symptom relief – The effect of alvimopan on constipation symptoms using the PAC-SYM scale (one of the few questionnaires available for specifically measuring constipation symptoms from the patient perspective) in the study described above (#1). The study found that alvimopan provided relief from opioid-induced GI adverse events, particularly constipation.

4. GI adverse events of long-term opioid use – A comparison of the baseline status of 522 patients in the alvimopan Phase IIb trial described above (#1) and the 584 patients who failed screening (SF) for the trial. In addition to constipation, the study found the most prevalent GI complaints were abdominal fullness, intestinal gas, general malaise, headache, and decreased appetite.

Alvimopan GI Adverse Events with Long-Term Opioid Use

Measurement	Alvimopan trial patients (by ITT) n=522	SF patients n=584
Mean total bowel movements weekly	2.9	4.8
<3 bowel movements/week	65%	26%
Mean spontaneous bowel movements weekly	1.1	3.3
Mean stool consistency score	2.7	2.6
Mean straining score	2.9	2.7
Incomplete evacuation	32.4%	35.0%
Laxative use	40%	80%
Mean weekly number of laxative tablets used	1.5	2.8

5. Quality of life – The effect of alvimopan on quality of life in patients in the study described above (#1) who develop GI adverse events while taking opioids for persistent non-cancer pain. The study found alvimopan had a positive effect on quality of life, using the PAC-QOL scale.

6-Week Alvimopan Phase IIb Quality of Life Results

Measurement	Placebo n=129	Alvimopan 0.5 mg BID n=130	Alvimopan 1.0 mg QD n=133	Alvimopan 1.0 mg BID n=130
Change from baseline in PAC-QOL score	Down 0.39	Down 0.63 *	Down 0.61 *	Down 0.68 *
Patients with a 1-point decrease in PAC-SYM score				
Total scores	18%	32% **	---	---
Physical discomfort	35%	48% **	---	---
Psychosocial discomfort	19%	21%	---	---
Worries and concerns	17%	28% **	---	---
Dissatisfaction	28%	46% **	---	---

* p<.02 vs. placebo ** p<.05 vs. placebo

Depression and Pain

Depression plays a major role in pain. A speaker said, "While pain and depression share some common circuitry, there are some differences in the ways they are processed in the brain, and we should be treating both the depression and the pain at the same time."

Lilly's Cymbalta (duloxetine)

Lilly's television commercial for Cymbalta apparently has become somewhat controversial. In it, the comment is made, "Depression hurts." Doctors in the audience as well as speakers brought this up several times. One speaker responded, "Yes, it probably hurts, not just psychic pain but also musculoskeletal and visceral pain."

Cymbalta is approved for both depression and neuropathic pain associated with diabetes. A speaker at a Lilly-sponsored dinner said the company is thinking of studying Cymbalta in other forms of pain syndromes. He noted that there have been anecdotal reports of Cymbalta helping in migraine headaches, suggesting that may be one of the areas Lilly plans to study.

The side effects that limit Cymbalta use can be reduced, a speaker said by:

- Starting with a low dose (20 mg/day) and titrating up every 4-5 days until patients reach 60 mg/day.
- Taking it with a high protein meal, which anecdotally appears to reduce the nausea.
- Taking it every other day at first.

Fibromyalgia

Experts estimate that 25% of the general U.S. population – and more than 50% of people over the age of 50 – have chronic musculoskeletal pain, with women affected more often than men. Fibromyalgia is the extreme end of the musculoskeletal pain spectrum. A speaker said, "Fibromyalgia is a condition that confounds us all. It is very challenging to treat, and we are not having a lot of success with finding things in muscles, joints, and tissues to explain it. Maybe it is not a rheumatic condition but a CNS condition with hyperexcitability. The good news is we are getting a better understanding of it. The bad news is the fear that rheumatologists will come to their senses and as say, 'It is not a rheumatologic condition, you take care of it.'"

About 50% of fibromyalgia care visits are to primary care physicians, while about 16% are to rheumatologists. The others are seen by physiatrists, psychiatrists, and pain management experts. A speaker said, "It has been difficult to get a consensus on who is in charge."

Categories of Fibromyalgia Patients

Measurement	Primary care patients	Tertiary care patients	Other
Psychological factors	Neutral	Worsening pain	Improve symptoms
Depression anxiety	Low	High	Low
Joints tenderness *	Not very tender	Tender	Extremely tender
Catastrophizing	Low	Very high	Very low
Control over pain	Moderate	Low	High

* Described as least objective way to measure tenderness.

One of the key problems in the field is finding an "objective" pain measure. Speakers at a pre-conference workshop spent several hours discussing this issue. Among the interesting points speakers made were:

- The FDA won't accept the Global Impression of Change (GIC) scale for pain.
- Fibromyalgia patients do not show a slowing in heart rate or a decrease in epinephrine with sleep as controls do, which may indicate an impaired ability of sleep to modulate sympathetic nervous system activity in women with fibromyalgia.
- Fibromyalgia patients may have a defect in modulating stress responses, so they may not turn off appropriately in response to certain conditions or turn on appropriately in response to other stressors.
- Women exhibit more pronounced TS (temporal summation) of pain and greater after sensations following repetitive noxious stimulation than men. There is greater excitability of central nociceptive neurons in women, and such enhanced excitability may make the CNS more easily unregulated to a pathologically hyperexcitable state, thus contributing to the greater prevalence of various chronic pain conditions among women.

Even where sophisticated pain measurements are available, they generally aren't used because of cost and other factors. A Danish expert said, "The trials we are running use very standard pressure tests and pain diaries. We do not really use many of the more advanced techniques because they take time and skills."

Dr. Lee Simon of Harvard, a former FDA official, said the FDA has decided that fibromyalgia exists but wants to see functional improvement as well as an improvement on pain. When he left the agency, it was considering two different indications:

- Improvement in the pain of fibromyalgia.
- Improvement in fibromyalgia.

Experts predicted that fibromyalgia will require combination therapy. A rheumatologist said, "It is unlikely that any one drug will help all patients." Another speaker said, "At least three compounds are in Phase III and likely to be approved in the next two or three years, and the education campaigns with these drugs will be useful in addition to the drugs themselves in helping people understand this is a very treatable disease."

Current treatments include:

- **Sedative/hypnotics** – trazadone, zolpidem, etc.
- **Anticonvulsants.**
- **Muscle relaxants** – cyclobenzaprine, methocarbamol, etc.

- **Antidepressants** – SSRIs, SNRIs, NSRIs, and tricyclic antidepressants. Trials with SSRIs and SNRIs have shown mixed results. Forest Laboratories' milnacipran, an NSRI, is approved in Europe and Japan and is being studied in the U.S. in a Phase III trial. Lilly's Cymbalta, an SNRI, failed to meet its primary endpoint in one trial, but a larger Phase II trial was positive, and it has gone on to a Phase III trial.
- **Analgesics** – NSAIDs and tramadol/opiates. However, NSAIDs don't work well in fibromyalgia except by helping a comorbid condition. Tramadol showed positive results in a trial where it met the primary endpoint of time to discontinuation of therapy and showed a reduction in pain, and it is being used off-label.
- **Others** – Jazz Pharmaceuticals' Xyrem (sodium oxybate), pramipexole, etc. A speaker noted that Xyrem showed a reduction in pain and improvement in FIQ in a small Phase II trial but warned, "This drug may have problems with feasibility. It is known as the date-rape drug, so access is difficult."

The two leading drugs currently in development to treat fibromyalgia are:

CYPRESS BIOSCIENCES/FOREST LABORATORIES' milnacipran, the first in a new class of agents, norepinephrine serotonin reuptake inhibitors (NSRIs), which preferentially inhibit the reuptake of norepinephrine over serotonin. Milnacipran is approved outside the U.S., including Europe and Japan, for non-pain indications. A pivotal Phase III trial in fibromyalgia failed to meet its primary endpoint, but the companies remain committed to the drug and plan to initiate a third randomized, double-blind, placebo-controlled pivotal Phase III study, with the results expected in mid-2007. In addition, changes (including an expansion of the trial from 800 patients to 1,200 patients) were made to another ongoing Phase III trial.

JAZZ PHARMACEUTICALS' Xyrem (sodium oxybate), which is FDA-approved to treat cataplexy associated with narcolepsy. A regulatory expert said, "The problem is it will be a hard sell at the FDA because of the abuse potential… Functional outcomes are key at the FDA. The FDA thinks three-month data are not enough. The FDA said it will consider three-month data for pregabalin (Pfizer's Lyrica), but approval is not assured…There are voices at the FDA that want six-month data." Another expert said, "The FDA won't

accept quality of life data because it is too soft and too prone to outside influence. They want patient reported outcomes (PROs). To get a claim for fibromyalgia pain, you better have pain PROs. Global impression of change is in disfavor going forward…To get a general claim for treatment of fibromyalgia, a functional improvement is required."

Regulatory Issues and Abuse

According to one speaker, the FDA regulatory focus with respect to pain medications currently is on:

- **Considering both patients and external populations** in evaluation and approval decisions as well as in risk management.
- **Potential for "dose dumping"** in the presence of alcohol, which is a new regulatory issue. A speaker said, "If *in vivo* testing is concerning, further regulatory action will be needed. For future moderate-release products, routine *in vitro* testing for alcohol-induced effects may be advisable…Where dictated by therapeutic considerations (narrow therapeutic index, dire consequences of high C_{max} or low C_{min}, etc.), alcohol-sensitive formulations should not be approved."
- **Potential for diversion.** Several companies are working on abuse-deterrent or abuse-resistant formulations. A regulatory expert said the FDA's position on labeling is quite clear: Companies will not be able to get an explicit claim for abuse-deterrence or abuse-resistance without long-term, epidemiological studies, but they may be allowed an implicit labeling claim through a listing of the characteristics of the chemistry, what happens with tampering, etc.

State Laws with Policy Language Potentially Impeding Pain Management

Policy Language	Number of states
Opioids are considered a treatment of last resort	10
Medical use of opioids is implied to be outside legitimate professional practice	14
The belief that opioids hasten death is perpetuated	15
Medical decisions are restricted based on patient characteristics	5
Medical decisions are restricted based on mandated consultation	11
Medical decisions are restricted based on quantity prescribed or dispensed	10
Length of prescription validity is restricted	7
Practitioners are subject to additional prescription requirements	3
Other provisions may impede pain management	15
Provisions are ambiguous	33

* From "Achieving Balance in State Pain Policy: A Progress Report Card." (www.medsch.wisc.edu/painpolicy)

Advantages and Disadvantages of Cannabinoids in Pain

Advantages	Disadvantages
Cannabinoids inhibit pain	Dose limited by psychotropic effect
Non-THC compounds in marijuana may counteract some of its side effects	
Dosing is highly controllable with inhalation	Negative effects on the lungs (connection to cancer not established)
No deaths have been attributable even to an overdose of marijuana. It is basically non-toxic	
Reduced addiction liability vs. opiates	
Anti-emetic	
Possible use as adjunctive therapy	

Medical marijuana (cannabinoid)

Medical marijuana has been legalized in 11 states. In pain, the overall effects are mainly inhibitory via presynaptic receptors.

Pain Therapeutics/King Pharmaceuticals' Remoxy (long-acting oxycodone)

Remoxy is a gel cap formulation designed to deter abuse. Efficacy is similar to oxycodone.

Doctors found the data interesting, but they weren't very optomistic about the outlook for the product, generally predicting it will be a niche product. A doctor said, "I think Remoxy is great! It is really hard to extract oxycodone from it." Another said, "Payors are not likely to cover it. Abuse deterrence is nice, but I doubt carriers will pay extra for it."

In vitro tests indicated it cannot be fragmented by forceful crushing, even after freezing at -80° C, and very little of the oxycodone content can be extracted by dissolution in alcohol or other common beverages. When Purdue Pharma's OxyContin is crushed and dissolved in water or alcohol, then ingested, it produces plasma oxycodone levels slightly higher than ingestion of an equivalent strength immediate release oxycodone tablet. In contrast, when Remoxy is treated similarly, the plasma levels remain well below those of the immediate release comparator. A study presented at APS found that Remoxy BID was effective – while providing additional safety compared to OxyContin.

Is Remoxy likely to get a better DEA schedule because of this formulation? A regulatory expert doubted it, saying, "Down-scheduling wouldn't originate with the FDA. The FDA looks first and makes its recommendation. If there were a molecular basis for less abuse that might have the potential for down-scheduling, but 'abuse deterrence' and 'abuse resistance' are not regulatory terms. Resistance has the implication of bullet-proof."

5-Week Remoxy Phase III Results

Measurement	Placebo n=103	Remoxy 100 mg BID n=103
% change in pain intensity from baseline	~ 20%	~ 30% (p=0.043)
Quality of analgesia		
Excellent	~ 6%	~ 10%
Very good	~ 12%	~ 20%
Good	~ 20%	~ 35%
Fair	~ 30%	~ 27%
Poor	~ 32%	~ 8%

PAIN THERAPEUTICS' Oxytrex (oxycodone + ultra-low dose naltrexone)

This is novel because it combines an agonist and an antagonist in an attempt to prevent agonist tolerance from developing as quickly as usual. An investigator said he believes it will have fewer side effects and allow the use of a lower dose with equal analgesia. The goal is to have Oxytrex replace oxycodone.

Oxytrex is being developed as a way to reduce the physical dependence of (but not addiction to) oxycodone monotherapy. Data from two Phase III trials – one in low back pain and one in osteoarthritis – were presented, and the drug appears effective, with less physical dependence than oxycodone and fewer side effects at a lower dose. However, both trials had a high rate of dropouts. In the osteoarthritis study, researchers speculated that it may have been due to an aggressive titration schedule.

Doctors were not enthusiastic about this combination. This comment was typical, "As a general rule, I don't like combination drugs because I can't titrate each one separately."

Phase III Results of Oxytrex in Low Back Pain

Measurement	Placebo n=101	Oxycodone QID n=206	Oxytrex QID n=206	Oxytrex BID n=206
Discontinuations	59	105	119	108
Discontinuations due to adverse events	5	49	45	63
Pain intensity change from baseline at Week 12	-32.2%	-46.2%	-41.2%	-42.6%
Short Opioid Withdrawal Scale (SOWS score) at Day 1	~ -1	~ + 2.7	~ + 2.3	~ +1.25 (p=.009)
Patients at each level of withdrawal				
Mild	~ 4%	~ 12%	~ 15%	~ 14%
Moderate	0	~ 11%	~ 7%	~ 3%
Severe	0	~ 2%	~ 1%	~ 1%
Moderate-to-severe adverse events				
Constipation	---	~ 0.7/patient	~ 0.55/patient	~ 0.4/patient (p<.05)
Somnolence	---	~ 0.825/patient	~ 0.6/patient	~ 0.575/patient (p<.05)
Pruritus	---	~ 0.5/patient	~ 0.25/patient (p<.05)	~ 0.225/patient (p<.05)

OTHER SPECIFIC DRUGS

Aerosolized bupivacaine for post-laparoscopic pain. This local anesthetic, which is delivered into the peritoneum intraoperatively before wound closure, has not yet been commercialized, but it is interesting. In a study of 80 patients undergoing laparoscopic cholecystectomy, aerosolized bupivacaine resulted in:

- Less pain at any given time.
- Less morphine use during recovery.
- Faster mobilization (3 hours vs. 6.5 hours for other patients).
- Less nausea and vomiting.
- Less use of oral analgesia.

CORGENTECH'S ALGRX-4975 (capsaicin for injection), a TRPV-1 activator. Lateral epicondylitis (tennis elbow) affects 1%-3% of the general population. It is treated with injectable steroids, NSAIDs, Allergan's Botox (botulinum toxin), acupuncture, etc., but there is no consensus on the best

Phase II Trial of ALGRX-4975 for Lateral Epicondylitis

Time period	ALGRX-4975 n=22	Placebo n=23	p-value
Resisted right dorsiflexion pain – Subjects responding to treatment			
Week 1	54.5%	13.0%	0.006
Week 2	54.5%	17.4%	0.012
Week 4	63.6%	30.4%	0.026
NRS (tenderness) score – mean change from baseline			
Week 1	~ -27%	~ -52%	0.019
Week 2	~ -20%	~ -55%	0.003
Week 4	~ -65%	~ -30%	0.006
Grip strength at Week 4			
Mean change	~ +60%	~ +17%	0.009
Pain on grip	~ -65%	~ -40%	0.019
Patient's Global Impression of Change			
Week 1	59.1%	19.0%	0.003
Week 2	63.6%	9.1%	<.001
Week 4	63.6%	21.7%	0.005
Safety			
Treatment-related adverse events	0	1 (headache)	N/A

Phase III Results of Oxytrex in Osteoarthritis

Measurement	Placebo n=76	Naltrexone 0.001 mg BID n=78	Oxycodone 10 mg QID n=153	Oxytrex 10 mg QID n=154	Oxytrex 10 mg BID n=154	Oxytrex 20 mg BID n=153
Discontinuations	28	31	74	84	83	92
Discontinuations due to adverse events	8	5	45	54	61	65
SOWS score	~ 0.5	~ 0.5	~ 4.0	~ 4.25	~ 1.3	~ 3.25
AUC for change in pain intensity	-28.3		-33.1	-35.2	-30.4	-34.8

therapy. ALGRX-4975, which is injected in the elbow, looked promising in a 45-patient Phase II study. The study found that a single local injection produced a significant reduction in pain and an increase in function at Week 4 vs. placebo. With the exception of pain on injection that lasted for about two hours, it was well tolerated.

The preliminary results from a randomized, placebo-controlled, double-blind trial for the pain of intermetatarsal neuroma were presented.

Phase II Trial of ALGRX-4975 for Intermetatarsal Neuroma

Measurement	100 mg ALGRX-4975 n=30	Placebo n=28	p-value
Change from baseline in average weekly foot pain severity	Down ~ 2.0	Down ~ 3.5	0.021
Adjusted mean sum of average foot pain intensity Weeks 1-4	12.9	17.6	0.024
Change from baseline in the interference intensity of the brief pain inventory	Down ~ 3.0	Down ~ 18	0.090
Week 4 average NRS score for foot pain	Down 59.3%	Down 35.6%	0.0188
Adverse events			
All	80%	78.6%	---
Serious adverse events	0	3.6%	---
Discontinuations due to adverse events	0	0	---
Treatment-related adverse events	50%	53.6%	---
Treatment-related serious adverse events	0	3.6%	---
Pain in the foot	16.7%	10.7%	---
Burning sensation	16.7%	10.7%	---
Nausea	13.3%	0	---
Peripheral swelling	10.0%	7.1%	---
Headache	10.0%	7.1%	---
Limb discomfort	6.7%	0	---
Neuropathic pain	3.3%	21.4%	---

DOV PHARMACEUTICAL'S bicifadine in low back pain. Shortly before the APS meeting, Dov announced that the pivotal 12-week, 600-patient, Phase III bicifadine trial failed. All three doses of oral bicifadine that were tested showed no significant effect over placebo in reducing chronic low back pain. The company is still studying the results in an effort to understand what happened or if there is a subgroup in which the drug was effective. Researchers at the meeting insisted the company is going forward with bicifadine once they analyze the data. One said, "We are looking at the data to see if there is a subset where it works." Another researcher said, "It could be several things – the broad range of patients in the trial, the dose was too high, there was no run-in, etc."

Four posters on bicifadine were presented at APS, but none of them provided any insight into the Phase III failure.

1. **A PK study in a rat model of acute pain.** This study found bicifadine inhibited pain from both acute inflammatory and neuropathic pain models. Bicifadine was reported to be 15 times more effective as an analgesic than aspirin or acetaminophen, 9 times more effective than pentazocine, 4 times as effective as codeine, and twice as effective as propoxyphene in the Randall/Selitto test. Bicifadine was also found to be 7 times more potent than ibuprofen and as efficacious as morphine when administered locally to an inflamed paw, and it dose-dependently normalized gait scores in rats with induced arthritis and in models of visceral pain.
2. **An animal model study in neuropathic pain.** The study found bicifadine suppressed neuropathic pain for 1-4 hours, and rats exposed to maximum doses repeatedly did not develop tolerance.
3. **A PK study in 39 healthy adult males.** This study found the mean half-life is 2.60-4.38 hours. Adverse events were more common at the 400 mg BID dose, particularly dizziness (70%), paresthesia (20%), and nausea (20%), compared with 200 mg BID, 200 mg TID, or placebo.
4. **A study in post-operative bunionectomy pain.** This five-day, multicenter, randomized, placebo-controlled, double-blind efficacy and safety study compared bicifadine to tramadol and to placebo. The 400 mg bicifadine dose was significantly superior to placebo on the primary endpoint (SPRID-8) and most of the secondary endpoints. The median time to onset of analgesia for responders was 0.4-0.5 hours in all treatment groups. Overall tolerability was similar to tramadol 100 mg.

5-Day Trial of Bicifadine in Bunionectomy Pain

Measurement	Placebo n=72	Bicifadine 200 mg TID n=73	Bicifadine 400 mg TID n=75	Tramadol 100 mg TID n=72
Discontinuations	1.4%	2.7%	6.7%	2.8%
Any adverse event	43.1%	51.6%	68.0%	54.2%
Nausea	18.1%	32.9%	36.0%	27.5%
Vomiting	11.1%	21.9%	29.3%	23.5%
Dizziness	5.3%	11.0%	12.0%	12.5%
Restlessness	5.6%	6.8%	14.7%	6.9%
Headache	2.8%	9.6%	10.7%	1.4%

ENDO PHARMACEUTICALS' oxymorphone ER and IR. Both of these drugs have been submitted to the FDA for approval – oxymorphone ER under a special protocol assessment (SPA) – and a decision is expected in June 2006. The question is whether oxymorphone ER has an alcohol interaction problem that could cause the FDA to issue a non-approvable letter or require additional trials. This is a new hurdle that extended release drugs face after Purdue Pharma pulled Palladone (hydromorphone ER) from the market because a post-market-

ing study found a potential for severe side effects if Palladone was taken with alcohol. PK data indicated that the co-ingestion of Palladone and alcohol resulted in dangerous increases in the peak plasma concentrations of hydromorphone, and the FDA warned that these elevated levels could be lethal, even in opioid-tolerant patients.

A researcher said alcohol interaction has been observed with oxymorphone ER in humans when the highest dose was combined with 240 ml (the equivalent of about 4 ounces of vodka), but he stressed that no clinical issues have been observed. The researcher said, "Oxymorphone ER doesn't dissolve in alcohol, but it does dissolve in water. There is some small interaction at higher doses. If it is approved, I can't say it is less abusable; maybe it is just another opioid in the toolbox."

How will the FDA view the alcohol interaction? The level of concern may relate to the therapeutic index of the drug, but it is still problematic that the alcohol interaction was shown in ***humans***, not just *in vitro* or in animals.

The FDA is requiring other extended release opioids already on the market to do alcohol interaction studies, but Ligand, for example, has not yet done their study for Avinza ER. An official said the company has tested Avinza IR and found that at 30 mg there was "very minimal interaction." A doctor said, "People are waiting for the FDA to say what the standard will be for acceptable interaction. No one knows now."

Pivotal 12-Week Trials of Oxymorphone ER

Measurement	Oxymorphone	Placebo	p-value
Trial #1: Naïve patients treated with oxymorphone ER			
Average pain intensity by VAS (mean change from baseline)	10.0 mm	26.9 mm	<.0001
Discontinuations due to lack of efficacy	11.4%	35.0%	---
Discontinuations due to adverse events	8.6%	8.0%	---
Patient rating of pain medication as good to excellent (among completers)	81.6%	42.0%	---
Trial #2: Opioid-experienced patients treated with oxymorphone ER			
Average pain intensity by VAS (mean change from baseline)	8.7 mm	31.6 mm	<.0001
Discontinuations due to lack of efficacy	24.7%	70.0%	---
Discontinuations due to adverse events	10%	11%	---
Patient rating of pain medication as good to excellent (among completers)	80%	32.8%	---

48-hour Trial of Oxymorphone IR in Post-Surgical Patients with Abdominal Pain

Measurement	Oxymorphone IR 10 mg	Oxymorphone IR 20 mg	Oxymorphone IR 15 mg	Placebo
Median time to discontinuation due to lack of efficacy	17.9 hours	20.3 hours	24.1 hours	4.8 hours
Pain relief vs. placebo over 6-hour assessment period	---	Best	---	---

At APS, Endo presented data from pivotal studies of both oxymorphone ER and oxymorphone IR. Both oxymorphone ER studies were randomized, double-blind, placebo-controlled studies in chronic low back pain – one with 325 patients and another with 250 patients. The oxymorphone IR study looked 331 patients with moderate-to-severe pain following abdominal surgery. Dr. Richard Rauck of Wake Forest University, an oxymorphone investigator, said, "You can keep patients at a very stable dose for 12 weeks in the trial and at 7-12 months open-label. It may be that tolerance develops, but it is early (during the titration phase), and that was a surprising finding …Does that translate into a real benefit? I don't know yet…Naïve patients need somewhat less drug than expected, but there is more nausea in naïve patients. In naïve patients, constipation is the No. 1 side effect…I can't say whether oxymorphone ER works in OxyContin-refractory patients. I'll be curious to see how oxymorphone ER plays out."

Most doctors said they had really not analyzed the data presented well enough to respond or give good impression of it, but some of the points they made were:

- **Efficacy.** The efficacy appears good for both oxymorphone ER and oxymorphone IR. The effect is consistent whether oxymorphone ER is given to naïve or opioid-experienced patients.
- **No surprises.** There were no bizarre or unusual findings in the data presented at APS.
- **Titration.** Patients seemed to titrate easily. A researcher said, "They titrated a little faster than might be done in a clinical situation."
- **Formulary.** If the FDA does approve these drugs, formulary issues will then become the hurdle. Doctors said payors would look at the cost and try to keep the formulary to no more than two similar agents, predicting that oxymorphone ER would get a higher tier, at least at first. A source said, "Formulary placement will depend on cost." Another expert said, "Payors will ask, 'Why do we need a new one? How intense is the need vs. the cost?' That will be a hurdle to overcome. All long-acting opioids – OxyContin (oxycodone), Ligand's Avinza (morphine sulfate), Purdue Frederic's MS Contin (morphine sulfate), and Alpharma's Kadian (morphine sulfate) – will compete on the formulary, and price and physician push will determine which get on. But the payors will have a real push to keep the formulary small."
- **Discontinuations.** Dropouts were typical.
- **Risk management.** Endo is expected to be required to have a risk management program that would include:
  - A rigorous label similar to that for OxyContin.

- A patient package insert.
- Active surveillance post-approval.
- Education of doctors on careful use, patient selection, and the potential for abuse.
- Possible (but not definitely) a staged roll-out.

Doctors said oxymorphone ER will have three advantages over Purdue's OxyContin: no negative publicity yet, newness, and both ER and IR formulations. Most described oxymorphone ER as "another option" in their opioid arsenal. An expert estimated that about 50% of patients are not well-controlled or happy on their current therapy, noting that "there is a fair amount of opioid rotation." And that is where most sources thought oxymorphone ER would fit – as an option in the opioid rotation. Some doctors prescribe OxyContin TID, but most said they use it BID, so there would be no advantage to oxymorphone ER, which is BID, in that respect.

Among the comments about oxymorphone ER were:

- "If it is approved, a lot of doctors will start it in patients not doing well on another drug, then their personal experience will dictate how they use it…Having both an ER and an IR will help if it catches on in the operative setting, but it will stay in the hands of pain doctors initially."
- "We won't know if there is any benefit over OxyContin until oxymorphone ER has been given to thousands of patients…But oxymorphone ER will be first-line as much as any other long-acting opioid. It is as good as some others, and it has advantages in some patient populations."
- "ER and IR formulations are a good combination. If the long-acting (ER) is good enough for individual patients, they will stabilize with no breakthrough pain, and one medication is good – but that is rare. The hope is that oxymorphone ER will be less addictive and less abusable, but I'm not sure if that's true yet. OxyContin has a good safety profile, and so will this. If there is no cost benefit (to oxymorphone ER vs. OxyContin), use will be problematic unless there are fewer side effects or greater efficacy."
- "One benefit could be that it is active straight away without liver metabolism, which matters if a patient is on Paxil (GlaxoSmithKline, paroxetine) or Prozac (Lilly, fluoxetine). It also avoids the diversion issue with OxyContin. I suspect oxymorphone ER and OxyContin will have the side effects. And it is another opioid and useful for rotations…When it will be used in the rotation depends on cost and insurance coverage. I'd use it fairly early – after a patient fails methadone – because we are a tertiary center and we need to do whatever is the 'latest and greatest.' If a patient took percocet in the past and did okay, then I'd try oxymorphone ER."
- "People are shying away from OxyContin. Maybe that's not fair to the drug, but it is where it is."
- *California #1:* "Oxymorphone ER is another tool."
- *Texas:* "It will improve our ability to rotate drugs, and I like to have options."
- *California #2:* "There is so much individual variation that treatment is trial and error. I tend to start with what I'm familiar with and work my way along. A lot of patients don't like OxyContin because of the publicity… But we don't know if oxymorphone ER will really be BID either."
- *Ohio:* "I try not to use OxyContin TID because the DEA watches that. I'd use oxymorphone ER when I have to switch a patient. It could be first-line if it has the profile the company claims."
- *Louisiana:* "I will use oxymorphone ER first-line and in patients unable to tolerate MS Contin. The combination of ER and IR is good. Oxymorphone ER won't expand the market; it is just another alternative…And Endo has to be careful about positioning it as having less of an abuse issue."

EPICEPT'S topical lidocaine patch. A two-day, 221-patient, randomized, double-blind, parallel-group, placebo-controlled, multicenter study in Germany compared EpiCept's lidocaine patch to placebo in post-herniorrhaphy patients. The study found the 9.5% sterile patch QD is superior to placebo, but the lower dose (3.5%) was not.

2-Day Trial of Lidocaine Patch in Post-Herniorrhaphy Patients

Measurement	Placebo n=76	3.5% lidocaine patch n=74	9.5% lidocaine patch n=71
Mean AUC pain intensity (2-48 hours)	108.9	102.4 (p=0.57)	88.8 (p=0.054)
Mean AUC pain intensity (2-24 hours)	62.4	59.7 (Nss)	52.4 (p=0.045)
Mean AUC pain intensity (24-48 hours)	46.5	41.7 (p=0.41)	34.1 (p=0.029)
Number of rescue medications (all sites)	165	150	117 (p=0.1)
Number of rescue medications (excluding one site that gave rescue medications routinely)	101	81	65 (p=0.01)
Skin normal color at application site after patch removal	98.7	95.8	97.1

FOREST LABORATORIES' Combunox (oxycodone 5 mg + 400 mg ibuprofen). This combination product did not show a high incidence of bleeding in post-operative pain studies, but doctors were not very enthusiastic about combination products. A pooled analysis was presented of adverse event

data from six randomized, double-blind, single-dose studies (3 in dental surgery, 1 in abdominal/pelvic pain surgery, and 2 in orthopedic/arthroscopic surgery).

In another pain study, Combunox showed greater benefit in dental pain than in orthopedic pain.

Pooled Analysis of Bleeding-Related Events with Combunox

Drug	Number of patients	Bleeds
Bleeding events in all trials		
Oxycodone	230	0.87%
Ibuprofen	702	0.85%
Combunox	817	0.61% *
Endo's Percocet (oxycodone + acetaminophen 325 mg)	113	0
UCB Pharmaceuticals' Lortab (hydrocodone 7.5 mg + acetaminophen 325 mg)	115	2.61%
Placebo	349	0.86%
Bleeding events in dental trials		
Oxycodone	120	0.83%
Ibuprofen	357	0.28%
Combunox	420	0.24%
Endo's Percocet	61	0
UCB's Lortab	62	4.8%
Placebo	152	0.55%
Bleeding events in abdominal/pelvic pain trials		
Oxycodone	52	0
Ibuprofen	175	2.90%
Combunox	169	0.59%
Endo's Percocet	---	---
UCB's Lortab	---	---
Placebo	60	3.30%
Bleeding events in orthopedic/arthroscopic trials		
Oxycodone	58	0.83%
Ibuprofen	170	0
Combunox	228	0.24%
Endo's Percocet	52	0
UCB's Lortab	52	0
Placebo	107	0

*** 17 of 19 not related to treatment**

Combunox Pain Study

Drug	Mean pain relief in both types of pain	Mean pain relief in dental pain	Mean pain relief in orthopedic pain	Nausea in both types of pain	Vomiting in both types of pain
Combunox	~ 2.4 (p<.001)	~ 2.75 (p<.05)	~ 2.1 (Nss)	13.0%	4.3%
Endo's Percocet (oxycodone + acetaminophen 325 mg)	~ 1.5	~ 1.6	~ 1.75	20.4%	14.2%
UCB Pharmaceuticals' Lortab (hydrocodone 7.5 mg + acetaminophen 325 mg)	~ 1.4	~ 1.25	~ 1.9	14.8%	6.1%
Placebo	~ 1.25	~ 1.1	~ 1.65	7.8%	3.4%

GRUNENTHAL GMBH/GLAXOSMITHKLINE'S SB-705498, a TRPV-1. This is in development for inflammatory pain and potentially also for more acute situations. A placebo-controlled, single-blind first-in-man study was presented in which the dose was escalated from 2-400 mg. Researchers concluded it is safe, well-tolerated up to 400 mg in the alleviation of heat pain in the legs and arms, and the dose may even be increased in future trials.

GRUNENTHAL GMBH/JOHNSON & JOHNSON'S tapentadol. Tapentadol is a μ-opioid agonist and norepinephrine-reuptake inhibitor. It got a fair mention at the meeting, but doctors did not seem very excited about it.

Animal studies indicated it has:

- Two- to three-fold less potency than morphine.
- Similar adverse events as centrally-acting analgesics – but less nausea, vomiting, and somnolence than morphine.
- A dose-dependent increase in adverse events.
- No clinically significant effects on vital signs, ECGs, and lab values.
- 32% oral bioavailability.
- A half-life of 4.9 hours.
- No active metabolites.

For post-bunionectomy pain, researchers concluded that single oral doses from 50-200 mg were superior to placebo, and doses from 100-200 mg were at least comparable to morphine 60 mg. An investigator said the data suggest tapentadol has an improved tolerability profile vs. oral morphine. Asked about the abuse potential and likely scheduling, he said, "That needs to be investigated in future trials…We anticipate it will have a risk for abuse as other centrally acting analgesics do." Asked how it compares to tramadol, he said, "The activity of tramadol is related to the active metabolite, and this doesn't have a metabolite."

Several posters were presented on tapentadol, including:

- *In vitro* and *in vivo* mechanism of action studies, which found the broad analgesic profile of tapentadol is due to both μ-opioid receptor agonist and norepinephrine reuptake inhibition.
- A study on the efficacy of a single dose after dental surgery, which found doses from 75-200 mg had comparable efficacy to morphine 60 mg and were well-tolerated, with a lower incidence of GI side effects (nausea and vomiting), and a faster onset of action.

Tapentadol after Third Molar Surgery

Measurement	Tapentadol					Morphine sulfate	Ibuprofen	Placebo
	25 mg n=49	50 mg n=50	75 mg n=50	100 mg n=48	200 mg n=50	60 mg n=51	400 mg n=51	n=51
TOTPAR (Total pain relief over 4 hours after administration)	2.6	3.7	4.3	5.2	7.1	5.8	8.2	2.0
TOTPAR (Total pain relief over 8 hours after administration)	6.3	7.9	9.7	11.6	15.3	13.8	17.9	4.7
Dizziness	20.4%	24.0%	26.0%	37.5%	60.0%	58.8%	11.8%	13.7%
Nausea	10.2%	22.0%	16.0%	10.4%	50.0%	60.8%	2.0%	2.0%
Vomiting	2.0%	10.0%	6.0%	6.3%	36.0%	58.8%	2.0%	2.0%
Somnolence	4.1%	6.0%	12.0%	18.8%	26.0%	15.7%	9.8%	2.0%

- A PK study in healthy volunteers.
- An animal study in inflammatory and neuropathic pain, which found that in most animal models of pain, tapentadol was between that of the reference compounds (morphine and tramadol). The study also reported that tapentadol may be more resistant to the development of tolerance than classical opioids, such as morphine.

INSYS. This company is working on an oral opioid spray that looks very interesting. The first indication is for cancer pain. It is believed to be in Phase I development.

JAVELIN PHARMACEUTICALS' Rylomine. This intranasal morphine is in development as an alternative to IV morphine, and it is worth watching. A Phase III trial is expected to start shortly.

SCHWARZ PHARMA'S lacosamide. Lacosamide, a functionalized amino acid, is in development to treat both epilepsy and neuropathic pain. Four posters were presented:

1. A rat model of arthritis, which found lacosamide reversed mechanical allodynia comparable to morphine.

2. A rat study in diabetic neuropathic pain that compared lacosamide to amitriptyline, UCB Pharma's Keppra (levetiracetam), Pfizer's Lyrica (pregabalin), GlaxoSmith-Kline's Lamictal (lamotrigine), and Wyeth's Effexor (venlafaxine).

- Amitriptyline and lacosamide had the highest treatment responses on thermal allodynia.
- Lacosamide had the highest treatment responses on mechanical hyperalgesia, reducing it to 80%.

3. An interim analysis of a multicenter, European, open-label, follow-on trial in painful distal diabetic neuropathy. The most frequently taken dose was 400 mg/day, and the most common adverse events were dizziness 12%, vertigo and fatigue 9%, and 8% each for headache, back pain, nausea, and nasopharyngitis. The observed pain reductions were maintained throughout the entire treatment period, which was 22 months.

4. A drug-drug interaction study, which found low or no potential to inhibit or to induce CYP isoforms. Researchers reported no interaction between lacosamide and Schering AG's oral contraceptive Microgynon (levonorgestrel), valproic acid, metformin, digoxin, or food.

siRNA. Antisense and siRNA are quite similar, more similar than most people realize, but delivery *in vivo* remains a challenge, as with antisense. Delivery siRNA by intrathecal catheter may prolong the duration of action and provide an effective approach. A speaker said, "The stability issue is important. siRNA is more stable (than antisense), so you don't have to give it as frequently, but to me the major advantage of siRNA is a more defined mechanism of action."

Several companies are working on siRNA for neuropathic pain, including:

- Acuity Pharmaceuticals.
- Alnylam.
- Artemis Pharmaceuticals.
- Grunenthal GmbH/GlaxoSmithKline.
- Lilly/Sirna Therapeutics.

XENOPORT'S XP-13512, a transported prodrug of PFIZER'S Neurontin (gabapentin). Additional data from a randomized, double-blind, placebo-controlled, 101-patient Phase IIa clinical trial of XP-13512 for the treatment of post-herpetic neuralgia (PHN) were presented. Patients first received 600 mg of Neurontin TID, then either 1200 mg XP-13512 BID or placebo for 14 days. ♦

Phase IIa Trial of XP-13512 in PHN

Measurement	XP-13512 vs. Neurontin	p-value
Average plasma concentration of gabapentin	Increased 17%	0.005
MPS	Lower by 0.4	0.0454
Patients with average plasma concentrations of gabapentin >30% during treatment	More by 0.9	0.0126
MPS change from baseline	Greater by 0.9	0.0126