Trends-in-Medicine

March 2004

By Lynne Peterson

SUMMARY

Johnson & Johnson's Topamax and Allergan's Botox both appear promising for headache pain. ♦ There is substantial interest in Abbott's sustained release Dilaudid and Vicodin, though hydrocodone is moving to Schedule II, which will make it harder for doctors to prescribe. ♦ Sales of Cephalon's regular Actiq are expected to grow, but a new sugar-free formulation is viewed as a marketing gimmick. ♦ Endo Pharmaceuticals has a winner in LidoDerm; doctors like it, and it appears to work in some low back pain patients. Endo's generic oxycodone will have to overcome the negativity associated with OxyContin abuse and diversion. There is interest in Skye/Endo's depot morphine, but it may take time to catch on. ♦ New data on Elan's Prialt may satisfy the FDA, but it is not generating excitement among pain doctors who remain concerned about the side effects, even with lower doses and slower titration. ♦ Ligand's Avinza continues to gain popularity.

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AMERICAN ACADEMY OF PAIN MEDICINE

Orlando, Florida
March 3-7, 2004

The American Academy of Pain Medicine (AAPM) was a good meeting to talk with pain specialists about their use of various pain medications. Among the things doctors said they found exciting at this meeting were:

- **Allergan's Botox** for pain, particularly migraine headaches.
- **Adolor's alvimopan**. A source said, "I'm excited about this because it may speed recovery of the bowel after bowel surgery, so patients can get out of the hospital sooner."
- **Methadone**. Doctors repeatedly stressed the value of this agent, and most predicted use would increase. A Florida doctor commented, "Methadone is the cheapest narcotic."
- **Polypharmacy**.

ADJUVANT ANALGESICS IN CHRONIC PAIN

Atypical antipsychotics may have real value in pain patients:

- **LILLY'S Zyprexa (olanzapine).** A speaker called this "the most interesting (pain medication) for me as a psychiatrist." He suggested it may be useful in cancer pain, fibromyalgia, and refractory and chronic daily headaches. Pain data is expected in April 2004.
- **JOHNSON & JOHNSON'S Risperdal (risperidone).** A speaker said animal studies suggest this has a powerful antinociceptive effect: "In clinical practice, we use it for problem patients – not addictive patients but those with a prominent affective component (the catastrophizers, who tend to over-use opioids)."
- **ASTRAZENECA'S Seroquel (quetiapine).** A speaker said, "We are using low dose quetiapine for flare…We found very good results in six or seven patients, and we hope to push this as a case report."

COX-2 INHIBITORS

At a lunch session sponsored by Merck, off-label use of a Cox-2 inhibitor was described as a good "pre-emptive analgesia" for back pain. A speaker said, "If you can administer analgesic prior to a noxious stimulus, you may be able to mitigate the resulting pain…and perhaps get improved wound healing, etc."

Audience area of specialty	
Anesthesiology	43%
Internal Medicine/family practice	10%
Neurology	4%
Physical medicine/ rehabilitation	10%
Other	23%
Have you ever had back pain?	
Never	12%
Occasional, trivial	53%
Occasional, significant	27%
Persistent	8%
Back pain factoids	
Prevalence	15% - 20%
Lifetime incidence	70% - 85%
Patient who cannot be given an anatomical basis for their pain	Up to 85%
Volunteers >60 by MRI with herniated disk	36%
Volunteers >60 by MRI with degenerative disk	93%
Spinal mediators likely to be involved in pathogenesis of referred pain	
Prostaglandin	43%
Dopamine	5%
Substance P	38%
Nitric Oxide	14%

Another speaker said Cox-2 inhibitors can have an opioid-sparing effect in cancer patients. A speaker said, "Cancer patients are a high risk group…For some patients, the Cox-2s have replaced some of the opioid drugs for patients with mild-to-moderate pain…And there is an experimental model that suggests Cox-2s may affect osteoclast activity in bone mets."

Asked whether there is a difference between Merck's Vioxx (rofecoxib) and Pfizer's Celebrex (celecoxib) in terms of cardiovascular effects, a speaker said, "It is very controversial whether Celebrex is more cardioprotective than Vioxx…The pharmacology means there shouldn't be any difference between these agents…But there have been reports where certain coxibs (e.g., Vioxx) are reported to have less hypertensive effect than other coxibs, so you have to make up your own minds." Another speaker said, "The question is still open."

Asked what they would prescribe to a patient with mild/moderate pain who is on a chemotherapy regimen, 74% of the audience said Vioxx, 11% Percocet, 10% morphine, 2% naproxen, and 3% other.

However, the session was a little too promotional for many doctors in the audience. Several commented that they felt Vioxx was pushed too overtly.

TRANSDERMAL FENTANYL

At least two companies are planning a generic formulation of Johnson & Johnson's Duragesic patch, including:

- **MYLAN,** which is expected to launch in July 2004.
- **NOVEN/ENDO**, which are expected to launch in January 2005, at patent expiration. However, a doctor suggested J&J's patent on the patch technology (which it acquired with Alza) may extend the patent life beyond January 2005.
- **WATSON** may be working on a generic patch, but sources could not confirm this.

JOHNSON & JOHNSON also has two new fentanyl patches of its own in development.

- **E-Trans**, for acute pain. This is expected to be on the market sometime in 2005. This patch uses iontophoresis to release 4 µg over 10 minutes. Patients can self-administer up to 80 doses over a 24-hour period by simply pressing on the patch. An investigator said, "I don't think patients can go home with this. Hospice and cancer patients will get it. It's not good for chronic pain."
- **A-48**, a matrix technology patch. A J&J official said, "We need to do more studies, but we haven't dropped this. It uses a matrix technology instead of reservoir technology."

As with other generics, sources are taking a cautious approach to these generic patches. A source said, "I hate the Duragesic patch. Patients become very tolerant to it, and it is highly addictive. You can't control it, and getting patients off is a problem. So I'm not interested in a generic version." A Georgia doctor said, "I won't change quickly, but I'll try it. However, if I write 'fentanyl patch' and the patient calls and says the pharmacy is not stocking it or it is not working, we'll go back to brand. Patient phone calls will determine generic use." Another expert said, "My concern is whether the bioavailability and efficacy are the same as the brand. Generic patches will not increase use."

How quickly substitution occurs is likely to depend on managed care. A New Jersey doctor said, "I'll probably keep using the brand because I'm used to writing Duragesic. It depends on how easy it is to write the generic. If I need to write 'transdermal fentanyl,' I probably won't do it. If the pharmacists let us write 'TD,' I may do it. If the efficacy is the same, I'll look at cost, which is always a factor." A South Carolina doctor said, "I will try it, mostly for cost, but it has to stick and work...If the patient tolerates it, there is no reason not to give it – if it is cheaper…But generic Lortab (UCB Pharma, hydrocodone) causes itch." A Virginia doctor said, "If it is less expensive, then people will switch quickly. The decision will be cost-driven."

DIABETIC NEUROPATHY

Soon-to-be published data will report on the efficacy of tramadol (Johnson & Johnson's Ultram) in diabetic neuropathy. A speaker said, "All tramadol studies found it effective, so this is a real option in the treatment of diabetic neuropathy."

There have been few head-to-head trials to help doctors determine which agents are best. In one trial Pfizer's Neurontin (gabapentin) proved superior to amitriptyline, but in another trial, they were equivalent.

Effective NMDA-receptor antagonists include:
- Dextromethorphan
- Amantadine IV

Anticonvulsants include:
- Pfizer's Dilantin (phenytoin) – not utilized because of variable responses.
- Novartis's Tegretol (carbamazepine) – effective and an option.
- GlaxoSmithKline's Lamictal (lamotrigine) – effective and an option.
- Novartis's Trileptal (oxcarbazepine) – shown effective in one study, but that is just one study.
- Johnson & Johnson's Topamax (topiramate) – described as "a real option."
- Pfizer's Neurontin (gabapentin) – a possibility but a negative study was never published.
- Pfizer's pregabalin – described as "a very exciting drug."

Serotonergic antidepressants:
- Pfizer's Zoloft (sertraline) – variable results.
- Sandoz's Trazodone – variable results.

Effective noradrenergic/serotonergic antidepressants:
- Mallinckrodt's Tofranil (imipramine)
- AstraZeneca's Elavil (amitriptyline)
- Mallinckrodt's Anafranil (clomipramine)
- Lilly's Cymbalta (duloxetine)

Effective noradrenergic/dopaminergic antidepressant:
- GlaxoSmithKline's Wellbutrin (buproprion)

Antidepressants:
- Wyeth's Effexor (venlanfaxine) – effective only at large doses (>150 mg)
- GlaxoSmithKline's Paxil (paroxetine) – effective for neuropathy and irritable bowel syndrome (IBS)
- GlaxoSmithKline's Wellbutrin (buproprion) – little data, but an option. A speaker said, "We don't often think of this in pain…In 41 patients with mixed neuropathic pain, 73% were improved to much improved…There are also anecdotal reports in low back pain and headache. Patients who can't tolerate other efficacious drugs might try this."
- Organon's Remeron (mirtazapine) – works in mouse model but no studies in human pain. A speaker said, "In the cases where I tried it, I didn't find an analgesic effect."
- Lilly's Cymbalta (duloxetine) – similar to Effexor, effective at 60 mg QD or 60 mg BID

FIBROMYALGIA

Several treatments for fibromyalgia were reviewed, including:

LILLY'S Cymbalta (duloxetine), an SNRI. A speaker said, "This has a significant direct effect on fibromyalgia pain, but insomnia, dry mouth, and constipation are more common than placebo…Duloxetine shows a lot of promise for the treatment of fibromyalgia…(In trials) female subjects demonstrated significantly greater improvement on most efficacy measures vs. placebo, but male subjects failed to show a significantly greater improvement on any efficacy measure compared with placebo-treated males."

CYPRESS BIOSCIENCE'S Ixel (milnacipran), an SNRI. Phase II data has already been completed and presented on this BID agent, and that showed a significant improvement in weekly pain assessment, physical function, and the number of days patients reported feeling good. However, QD dosing did not show a statistically significant improvement over placebo. A speaker said, "We're not sure why, but this indicates the drug needs to be dosed BID." The improvement in females was described as "similar to duloxetine."

PFIZER'S pregabalin
Speakers expressed frustration with the long time it is taking to get this drug approved by the FDA. One expert commented, "Pregabalin, which is son of gabapentin, is supposed to be available soon – but it's had that status for about five years." Another expert said, "We may some day see pregabalin. That's another drug I've been waiting and waiting for." A third noted that the higher doses (300 mg/day and 450 mg/day) appear to be more effective than a lower dose (150 mg/day), saying, "There was a pretty significant reduction in mean pain score after one week at the 450 mg/day dose, which is about equivalent to 2400 mg of gabapentin (Pfizer's Neurontin)…Pregabalin behaves like gabapentin in many ways…It reduces pain at the study endpoints and improves fatigue and sleep quality."

WYETH'S Effexor (venlanfaxine)
Effexor has been shown to work in rats, and it is my drug of choice for fibromyalgia – by virtue of being the only one (SNRI) out there that works. The problem with it is that when the headaches stop, you get anorgasmia."

HEADACHE

The director of the Southern California Headache Center offered some interesting headache facts:

- 8% of females and 6% of males experience migraines.
- 5% of females and 2.8% of males have chronic daily headaches – which are the headaches most frequently seen in headache clinics.
- A transient ischemic attach (TIA) aura begins abruptly, but a migraine starts slowly and builds over a half hour.
- There is a lot of overlap between tension-type and migraine headaches.

Another speaker warned doctors that "neurotoxins are not alike." She said they have different side effect profiles and dosing ratios. She also advised doctors that if patients get Botox for cosmetic purposes, it is advisable to wait three months to administer it for headaches.

JOHNSON & JOHNSON'S Topamax (topiramate)

A recent article in the Journal of the American Medical Association reported on a 26-week, double-blind, placebo-controlled trial of topiramate in 468 migraine patients. Researchers found about twice as many patients had a ≥50% reduction in migraines with Topamax as with placebo. A speaker said, "Most data (about topiramate in migraine) has been anecdotal or retrospective…(But) this looks like pretty hard science to me."

ELAN'S Zonegran (zonisamide)

A speaker said this sodium channel blocker has moderate benefit in migraine.

Botulinum toxin-A (ALLERGAN'S Botox and INAMED'S Dysport)

A breakfast symposium focused on the use of botulinum toxin for headache and muscle pain. Doctors in the audience were attentive, but none who were interviewed plans to go home and start using Botox off-label for these purposes who were not already doing so. However, several doctors cited Botox use for pain as one of the more exciting things at the AAPM meeting. A Florida doctor said, "Botox may be a great leap forward for myofacial pain."

Doctors were concerned about reimbursement. A speaker said, "When I started using Botox (for migraines), I felt way out on a limb, but now I think there is enough information out there that the medical reviewers have generally heard of this…so what I tell them is that I can demonstrate where the patients have been, what they had done, what hasn't worked, and how much that cost. Then, I tell them what my plan is…And that's one reason the adjusters generally like Botox…There are four carriers that cover it. The biggest resistance is in Georgia by the Blues."

Following is information on specific companies and products:

AAIPHARMA'S Darvocet (propoxyphene mapsylate)

In early March 2004, AAIPharma said it was investigating "sales abnormalities" of Darvocet, and withdrew its first-quarter and full-year earnings estimates. The company said it had appointed an independent committee of directors to conduct an inquiry.

Doctors at the AAPM meeting were not surprised that Darvocet sales had not increased as much as AAIPharma had initially indicated. A Georgia doctor said, "Darvocet use is down. The word in the market is that it doesn't have a lot of analgesic effect, and it contains a lot of acetaminophen." A South Carolina doctor said, "I don't use Darvocet much. There are too many other options. It is perceived as very mild, a step above Tylenol, but I would hate to see it go away. Tramadol kicked Darvocet out because of the perception that Tramadol is not a narcotic. Tramadol is not controlled, so you can give patients samples…But Tramadol does have some dependence, and we are starting to see some abuses, so Tramadol probably will be made a Schedule III drug." A Virginia doctor said, "There is some use, but not a lot. My use is mostly patient-driven. Darvocet is a very inferior drug, and it has acetaminophen in it. I prefer oxycodone with no acetaminophen."

ABBOTT

Abbott has two sustained release drugs in development – Dilaudid SR and Vicodin SR. A Georgia doctor said, "Both are exciting. A lot of patients are on either Dilaudid or Vicodin for breakthrough pain, and they get good relief, which says the brain receptors are better targeted by these than by another long-acting medication." A Virginia doctor said, "SR is the name of the game for chronic pain." A Texas doctor said, "I'm very interested in these, especially the Dilaudid SR."

Dilaudid SR (hydromorphone)

An FDA filing is expected in 2004. A source said, "Dilaudid SR has appeal." Another doctor said, "I like Dilaudid in some patients. It works better than anything else. I've been waiting three years for the SR formulation." Another doctor said, "It would be a potential option, a utility for opioid rotation. I have more interest in this than in Vicodin SR."

Vicodin SR (hydrocodone)

This is intended for moderate/acute pain, with an FDA filing expected in 2005. A doctor said, "Some patients do well on hydrocodone. We tried to compound a time-release formulation in our pharmacy, but it didn't work. Vicodin SR will be interesting…but SR is not for acute pain."

According to sources, the FDA plans to make Vicodin – and any other hydrocodone – a Schedule II drug later this year. This would mean that doctors could not call in a prescription; they would have to write a prescription and have the patient pick it up. Sources predicted this would put a serious damper on use of any form of Vicodin. A South Carolina doctor said, "The DEA (Drug Enforcement Agency) announced that hydrocodones are going Schedule II. I think that happens this summer. That will mean patients won't be able to get more than a 60-90 day supply, depending on the state they live in, and refills will not be allowed. That will make a lot of primary care doctors and others stop writing this – and that could increase use of Darvocet and tramadol." Another doctor said, "Most Vicodin patients do fine on morphine or fentanyl, and you run into the Tylenol wall with Vicodin, so we switch to something without Tylenol. The change of hydrocodone to Schedule II eliminates Vicodin's advantage, period."

CEPHALON'S Actiq (oral transmucosal fentanyl citrate)

Though Actiq is approved for cancer patients, sources said it is most commonly used for non-cancer pain. Sources generally expect usage to continue to increase. A North Carolina doctor said, "Actiq use will really grow." A South Carolina doctor said, "I rarely use it. I'm anxious with it. The concern is abuse and diversion. Actiq almost makes it too simple, and fentanyl is a potent, deadly agent. The speed of onset is good, but the problem is abuse where people want a quick, fast buzz. I would use Actiq in cancer pain, but not for more benign pain." A Virginia doctor said, "The formulation (of regular Actiq) was changed recently, and patients now complain about the taste."

Cephalon has a sugar-free formulation of Actiq in development. While sources see a role for a sugar-free formulation, most consider this primarily a marketing tactic. A doctor said, "Sugar-free Actiq is a big deal for diabetics and for preventing dental caries, but the new formulation of regular Actiq already has less sugar. There is a role for both regular and sugar-free Actiq because tastes vary. A sugar-free formulation will increase overall use of Actiq." A Florida doctor said, "It's a big deal. Dental caries are a real concern, and it would be good for diabetics." Another doctor said, "We're worried about cavities in patients with dentures?!"

ENDO PHARMACEUTICALS

LidoDerm (lidocaine patch)

Doctors were very enthusiastic about LidoDerm, and most said they are using it. A New Jersey doctor said, "It is effective for people with cutaneous hypersensitivity. I use it quite frequently." A North Carolina doctor said, "Drugs like this are almost ahead of their time."

Sources agreed there is still room for growth in sales of LidoDerm. A doctor said, "The whole patch field will grow. LidoDerm is a useful tool, and its role may expand as we learn more about cutaneous hypersensitivity." An emergency room doctor said, "We use LidoDerm for post-hepatic neuralgia. There is a great deal of potential if the studies are supportive." A Georgia doctor said, "I use it mostly for neuropathic pain – shingles. But I've also see some benefit in muscle pain…It is catching on." A Florida doctor said, "I do a lot of procedures in the office, and 12 hours before, I put a LidoDerm patch on the site of needle insertions, and that reduces the need for sedation. I also use it for patients with neuropathic pain – e.g., shingles." A physiologist said, "It works okay for low back pain, but it is very expensive, and geriatric patients can't afford it, so I won't use it for that, but I expect LidoDerm use to increase. The whole patch market will increase."

LidoDerm is starting to be used to treat lower back pain, and sources generally believe it has value in that condition. However, patient selection is important. One doctor said, "It only works for lower back pain if the patient has cutaneous hypersensitivity or allodynia." A past president of the AAPM said, "I know it works, but not for all patients. The challenge is defining which patients are most likely to benefit from topical analgesics. We need studies to determine who responds and which disorders are most likely to benefit." A Georgia doctor said, "I've used it for a few sacroiliac pain patients, but use depends on the size of the patient. Smaller is better – not fat patients. It is designed for skin sensitivity, but it can get down to the muscle." A Florida doctor said, "It works in some patients where there is neuropathic pain…but it works best on thinner patients with muscle spasticity…There is no significant muscle relaxation outside of the area of coverage."

Percocet (oxycodone plus acetominaphen)

There was no information on what Endo is working on – new dosage forms or timing – to compete with Watson's just-approved generic Percocet.

Generic oxycodone (a generic version of Purdue Pharma's OxyContin)

Pain specialists generally take a cautious approach to generics. Several doctors pointed out that generics are not always equivalent to brand products. A North Carolina doctor said, "If the generic is the same as the brand, then I favor it, but often the quality control with generics is not as good or the efficacy is different."

Sources were not certain about the effect that generic oxycodone will have on other pain drugs, and none predicted a generic would expand the market. A New Jersey doctor said, "I'm not sure it does affect other pain drugs, but it may have an effect if the insurance carriers allow generic oxycodone and not brand products. This is more a managed care and a cost issue than a physician issue." A Texas doctor said, "It hasn't

had an impact on me, but it could on other doctors." Another doctor said, "There has been a significant backlash against OxyContin because of the negative publication and abuse. Doctors are afraid to prescribe it. When we do dispense it, it is as oxycodone LA instead of OxyContin, and that may make it hard for a generic." A Georgia doctor said, "Generic OxyContin will not affect my use of the morphines or patches."

Teva reportedly plans to launch an 80 mg generic OxyContin in July 2004. Endo is expected to launch generic 10 mg, 20 mg, and 40 mg generic OxyContin in January 2005 when the Purdue Pharma patent expires; Endo is not expected to launch earlier (at risk). Endo officials were not aware of any specific risk management program planned for their generic. However, the FDA, which approved both the Teva and the Endo products in March 2004, made that approval contingent on both companies having in place, prior to marketing, risk management plans that are "consistent with the innovator product's plan."

Thus, the FDA will be watching these products to try to avoid further diversion or abuse of oxycodone ER. The FDA suggested that one sign of diversion might be market expansion rather than simply market share shifts. As part of its announcement of the Teva and Endo generic approvals, the FDA noted: "…when the first generic versions of an innovator drug reach the market, the use of that drug does not increase. Rather, demand tends to remain steady, with an increasing proportion of the market share being held by the generic versions."

According to doctors at AAPM, use of the 80 mg dose of oxycodone is not likely to go up significantly with the entrance of the Teva drug. A North Carolina doctor said, "I mostly treat chronic pain, so it is exceptional for me to have patients on 80 mg OxyContin. I more commonly use 10 mg, 20 mg, or 40 mg, so an 80 mg generic is not likely to affect me much." A Connecticut doctor said, "80 mg would hurt the 20 mg and 40 mg doses, and people may not go back to the lower dose generics when they are available." A Texas doctor said, "I didn't reduce my OxyContin use after the news (about abuse). You can guard against abuse if you are careful…The cost (of OxyContin) is not an issue for most patients – except Medicare patients – so a generic 80 mg won't change my use of that dose." A New Jersey doctor said, "I try to get patients on a maximum dose and control the number of tablets. The problem with a lower dose is the number of tablets, which raises compliance and diversion issues."

ENDO/PENWEST'S oxymorphone ER (oral BID)

The FDA issued an approvable letter for this drug, but highlighted the high drop out rate in the pivotal trial. The company was supposed to be meeting with the FDA in March 2004 to discuss this. Sources were not sure, if the company has to do another trial, whether it will be a 30-day trial as provided by the old FDA rules or the 90-day trial now required, but one knowledgeable expert suspected it will be 90 days.

The fact that this is not an oxycodone is likely to help its use, at least somewhat. A New Jersey doctor said, "It may help. I see personality changes with oxycodone, and those are not as marked with oxymorphone compounds." A Georgia doctor said, "An ER formulation is good news, but I'll wait and see how it performs." A South Carolina doctor said, "It will help because it is not codeine, so there is less nausea." A Florida doctor said, "It will affect mostly OxyContin, not Percocet." A Virginia doctor said, "Given the OxyContin stigma, any alternative is helpful."

Doctors said they probably will use this instead of OxyContin. A doctor said, "It will be new, and people will want to try it." Another doctor took a more cautious approach, saying, "Oxymorphone is 1.5 times more potent than oxycodone, but the problem is the formulation. Oxymorphone can easily be extracted. It is very abusable, so it needs a deterrent in it." Endo sources were not aware of any deterrent expected to be in their formulation.

Skye Pharma/Endo's depot morphine

This is a gel matrix that is injected pre-operatively into the epidural space for post-operative pain. The effect reportedly lasts 48 hours. Initially, patients probably will have to stay in the hospital for at least 24 hours if not the full 48 hours while on this drug, but as doctors gain experience with depot morphine, the patients are likely to be released quicker from the hospital. A New Jersey doctor said, "It depends on whether they get respiratory depression. If the respiratory profile shows that 90% of any respiratory depression occurs early and not late, then patients could go home." A South Carolina doctor said, "A lot of people who use spinal morphine are cautious about sending opioid patients home because they don't know how they will respond." A Florida doctor said, "With our current modality, patients with centrally-administered narcotics are not allowed to go home." A Virginia doctor said, "Any patient with an epidural has to stay in the hospital for the first 12-24 hours." Another doctor said, "It will have to be used in the hospital because of the possibility of late respiratory depression. We never know who will stop breathing as late as 24 hours after one dose, and the effect is enhanced if the patient is taking Valium (diazepam), etc."

Sources also aren't certain depot morphine is an advantage for patients on Coumadin or LMWH. They noted that there is no data yet on this. A source said, "Not necessarily. There is no significant advantage to epidural over peripheral administration except perhaps side effects, but epidural administration doesn't necessarily reduce the bleeding risk. Once you violate the epidural space, the risk is there." Another doctor said, "If it is given during the procedure –

before Coumadin or LMWH is started – then there may be an advantage."

ELAN'S Prialt (ziconitide)

Experts disagree on how many patients are using intrathecal pumps. An industry source put the number at 80,000 Americans. An intrathecal pain expert thinks it is closer to 50,000. Another intrathecal pump expert estimated that only about 30,000 people are currently on intrathecal pumps. Increasingly, non-cancer patients are getting intrathecal pumps, but convincing oncologists to refer cancer patients has proven a challenge. A pump is considered by experts to have had a clinically significant effect if the pain is reduced 30%-50%.

Intrathecal pain therapy should be considered in patients with:

- A failure to achieve adequate results from oral opioid therapy.
- The inability to tolerate the side effects of oral opioids.
- A documented non-cancer pain condition.
- A pain syndrome secondary to cancer.
- Potentially compliance with the requirements of intrathecal pain therapy.
- Pain from an organic cause.
- No significant psychiatric dysfunction.
- Life expectancy >3 months.

Two companies sell pumps:

- **Medtronic**, which offers a programmable pump.
- **Johnson & Johnson/Codman**, which purchased Arrow International's line of continuous infusion pumps. There were two sales reps at the Codman booth but few devices on display and little traffic. The sales reps were upbeat about the future of Codman pumps. One said, "Doctors know now that we are in it for the long-haul with J&J behind us, and they know that innovation will come…It's been a smooth transition from Arrow."

Common Opioids	Experimental Agents
Morphine	Local anesthetics
Hydromorphone	Alpha agonists
Methadone	NMDA receptor antagonists
Fentanyl	GAGA agonists
Sufentanyl	Prostaglandin synthesis inhibitors
Meperidine *	Neuron specific CCBs (e.g., ziconitide)
	Excitatory amino acid inhibitors
	Acetylcholinesterase inhibitors
	Tricyclic antidepressants
	Clonidine
	Ziconitide

*The use of meperidine is controversial because it may alter pump function.

There is a growing concern with the alteration in testosterone production and granuloma formation in people on higher doses of intrathecal morphine, which is fueling a search for other drugs that can be delivered via implantable pumps.

In this environment, doctors are looking for intrathecal drug alternatives, and Elan's Prialt, a toxin from the conus magus snail, has promise. It is administered intrathecally with a Medtronic pump. The FDA issued an approvable letter for Prialt but requested additional data. Elan plans to submit an amendment with new data in the second quarter of this year. Prialt is not expected on the market until 2005.

Doctors who were familiar with Prialt (formerly Neurex's SNX-111) were cautious about its outlook. They heard about – or saw first-hand – the side effects, and that convinced them that Prialt either is not approvable or will be restricted to a very niche population. A Florida doctor who participated in clinical trials of Prialt said, "What you are hearing about this drug is all hype. It won't go. It causes oral hallucinations. Patients see words coming out of their mouths (like cartoon characters) at even the lowest dose." An oncologist said, "There is a lot of nausea with ziconitide. People don't tolerate it well, but it would be good for patients refractory to intrathecal morphine."

Elan sponsored a lunch at which Prialt was discussed. Speakers reviewed the randomized, double-blind, prospective, Phase III data in refractory pain patients with metastatic cancer, in which the drug was titrated up at 12 hours.

Pooled Analysis of Pivotal Prialt Trials (rapid titration)

Measurement	Ziconitide in cancer patients n=112	Control	Ziconitide in non-cancer patients n=257	Control
Primary endpoint: % improvement in Visual Analog Scale of Pain Intensity (VASPI) at Week 3	53.1% (p=.0002)	18.1%	30.7%	6.2%
Complete pain relief	9%	0	9%	0
VASPI improvement in responders	50%	18%	33%	14%

A speaker then reviewed new dosing regimen in the trial to be submitted to the FDA in the amendment. This dosing appears to reduce the side effects of Prialt. The key dosing difference was much slower titration. Instead of up-titration at 12 hours, Prialt doses were increased only once every few days. A speaker said, "New studies show less side effects…Oral hallucinations are a side effect…but there are side effects with intrathecal morphine as well." Another speaker said, "The side effects came with rapid titration…We did things quickly,

we got more side effects…I don't treat ziconitide like morphine any more. Now, we are not titrating up more frequently than every three or four days, and the side effect profile is dropping…That is not to say there still aren't side effects over time, but most come on early, and the way to handle it is not to push the patient through but to retract the dose until they go away."

Experts suggested that ziconitide is most likely to be useful in combination with other drugs – but it has not yet been studied that way. A speaker said, "The FDA has said we can't study it in combination (before it is approved)…Maybe it is not fair the drug has had to stand alone…clearly, it has efficacy in all the studies published. There is no question that it is an efficacious agent and a non-opioid. The rub has always been the side effects, which are greater with rapid titration but which happen in other patients even with slow titration…You need to be a little more cautious with this than with some other drugs…Ziconitide is a very powerful drug, and if we can keep people using it appropriately, it is a drug with much potential and upside use." Another expert said, "The risks are reversible. I would use it, and it will expand the market, but I'm not convinced of the safety yet."

Prialt Adverse Events by Titration

Side effect	Prialt fast titration	Prialt slow titration
Dizziness	~50%	N/A
Nausea	~45%	N/A
Nystagnus	~42%	N/A
Abnormal gait	~25%	N/A
Urinary retention	~20%	N/A
Constipation	~18%	N/A
Headache	~18%	N/A
Confusion	N/A	2.5%
Mental slowing	N/A	1.1%
Stupor	N/A	0.9%
Delirium	N/A	0.8%
Hallucinations	N/A	0.5%
Dehydration	N/A	0.3%

FOREST LABORATORIES' Namenda (memantine)

One Forest-sponsored trial of Namenda in pain came out negative, but the company reportedly has decided to continue investigating this use of the drug. Sources speculated that memantine may work in pain, and they supported further study of it in pain. One expert said, "Memantine could work. It has a lot of potential, and it makes sense to continue to develop it."

JOHNSON & JOHNSON'S Ultram (tramadol)

Neither Biovail nor Labopharm had a booth at the AAPM meeting, but both are working on a long-acting tramadol to compete with Ultram. A Texas doctor said, "That would be really good. I'd use that." Another doctor said, "Tramadol has some pharmacologic advantages in chronic pain, but LA tramadol would be good in cancer." Another doctor said, "I'm dubious about long-acting tramadol, but I shy away from tramadol anyway because of pharmacogenomic issues. It is metabolized by 2D6, and 10% of patients have that polymorphism."

A J&J sales rep said J&J is not working on its own long-acting tramadol – and is not looking at buying one of the competitors – because those formulations require the addition of acetaminophen, and the side effects of doing that outweigh the benefits. She said, "I'm not sure why Biovail and Labopharm are doing it."

Ligand's Avinza (morphine sulfate BID)

Avinza, formerly Morphelan, was licensed from Elan and is being co-promoted by Ligand and Akso Nobel's Organon. A South Carolina doctor said, "I love it…I'm not afraid of OxyContin, but MS Contin, Kadian (Alpharma, morphine sulfate), and Avinza are all gaining market share because people are scared of OxyContin." Another doctor said, "It is hard to switch patients from oxycodone to morphine. Patients do well once they are switched, but it is hard to do the switch."

Sales of Avinza have been surprisingly strong, and sources expect that to continue. A New Jersey doctor said, "There are not a lot of statistics out on the diversion of Avinza and MS Contin, so I feel better that the narcs won't be looking at every prescription I write." A Virginia doctor said, "I use morphine exclusively, and I use more Avinza than MS Contin, and no Kadian…I like the once-daily ability of Avinza."

One of the reasons for the popularity of Avinza is, quite simply, it allows doctors to avoid the problems associated with OxyContin. A Florida doctor said, "Morphine use is up to avoid OxyContin." A Virginia doctor said, "People are a little reluctant to go to OxyContin first. I try to be very selective. I need to know the patient before I give OxyContin." A New

Kadian Elderly Subgroup Analysis in Non-Cancer Pain

Measurement	Kadian	Placebo
Patient-evaluated Visual Numeric Pain Scale	Down 2.4 points	Down 1.7 points
Patients adjusting dose from QD to BID	28.6%	44.4%
Improvement in Global Assessment as assessed by patient	Up 2.4 points	N/A
Improvement in Global Assessment as assessed by physician	Up 2.9 points	N/A
Constipation	19.6%	N/A
Nausea	9.5%	N/A
Dizziness	7.4%	N/A
Somnolence	6.1%	N/A

Jersey doctor said, "There is some subconscious effort to avoid writing OxyContin because of the negative publicity…I used to write MS Contin, then OxyContin, but now I'm back to MS Contin and other drugs…I specifically don't write an OxyContin prescription if the patient asks for it."

Avinza competes primarily with once-daily Kadian. Data was presented at AAPM on Kadian for chronic, non-cancer related pain in the elderly. The study was a four-week, subgroup analysis of 103 elderly, refractory patients from the KRONUS-MSP trial.

Comparison of Kadian and Avinza

Measurement	Kadian	Avinza
Dose	20 mg QD or BID	30 mg QD
Strengths	5	4
Amount immediately released	None	10%
Administration	Oral, G-tube of sprinkle	Oral or sprinkle

LILLY'S Cymbalta (duloxetine)

Lilly sponsored a session where duloxetine data was reviewed. Speakers and doctors interviewed all hold out hope for this agent to have value – though not a dramatic effect – in pain reduction. An expert concluded, "Duloxetine really does work for pain. The dose needs to be 120 mg for fibromyalgia and diabetic neuropathy."

TYCO/MALLINCKRODT'S generic MS Contin (morphine sulfate)

Sales of Mallinckrodt's generic morphine sulfate (to compete with Purdue's MS Contin) have been slower than some experts predicted. Sources believe the issue is two-fold: (1) a lack of sales reps out there pushing it, and (2) no managed care push. However, some doctors also believe neither generic nor brand MS Contin is as good as Avinza or Kadian. A New England doctor said, "I haven't been detailed on it yet." A Georgia doctor said, "I write 'MS Contin,' but substitution is permitted. If a generic is not being substituted, it is a cost and pharmacy detailing issue. There may not be a big enough price difference to encourage substitution." A Florida doctor said, "It's up to the third-party payers…I write morphine ER and leave it to the pharmacist to decide which." Another doctor said, "Use of Mallinckrodt's generic MS Contin will increase. There has been a lack of marketing, no pipeline, and so not enough feet on the ground, but usage will pick up."

REGULATORY ISSUES

Hypnotics, including all the insomnia drugs, have been switched by the FDA from the jurisdiction of the Neuropharmcology Advisory Committee to the Anesthesia/Critical Care Advisory Committee. Several experts described what it is like to work with the Anesthesia/Critical Care Advisory Committee. Among their comments:

- The hypnotics move probably was an effort to shift work from a busy division to one with a lighter workload.
- They don't understand why hypnotics belong under anesthesia.
- Organon's Raplon (rapacuronium) was approved in 1999 – and withdrawn in 2001.
- Anesthesiologists care less about indications than some other specialties because they use a lot of drugs widely off-label.
- The panel traditionally was slow, had a narrow focus, and was difficult to work with. One source commented, "They are especially cautious with diversion issues."
- This committee generally asks for a specific indication, a narrow condition – e.g., for fibromyalgia – not just a broad indication such as neuropathic pain.

Drug	Warnings/Cautions
Anti-epileptics	10% of adverse events in the elderly come from these 4th leading cause of adverse events in nursing homes Don't combine even the newer agents with MAOIs because of serotonin syndrome Don't combine with alcohol
Cephalon's Gabatril (tiagabine)	Use low dose and titrate slowly Effective dose is much lower for pain than as anticonvulsant
Dextromethorphan	Combining with Paxil or Prozac can cause serotonin syndrome
Endo Pharmaceuticals' LidoDerm patch	With mexiletine, tocainide, and other local anesthetics
Forest Laboratories' Lexapro (escitalopram)	Don't combine with Celexa (citalopram)
GlaxoSmithKline's Lamictal (lamotrigine)	Rash limits use Reduce dose by half with Abbott's Depakote (valproate) Increase dose with gabatril
GlaxoSmithKline's Paxil (paroxetine)	Don't mix with Novartis's Mellaril (thoradiazine), an MAOI, or tryptophan Monitor INR with warfarin Inhibits TCA metabolism Can be activating and can cause seizures at high doses
GlaxoSmithKline's Wellbutrin (buproprion)	Contraindicated in patients at risk of seizure (benzodiazepine withdrawal, bulemia, anorexia, etc.)
Johnson & Johnson's Topamax (topiramate)	Reduced levels of some birth control pills Increases levels of metformin
Johnson & Johnson's Ultram (tramadol)	Prozac, Paxil and Elavil may inhibit efficacy Seizure risk when prescribed with TCAs, SSRIs, opioids, nalozine, Flexeril Serotonin syndrome possible when combined with SSRIs Interaction with acetaminophen
Lilly's Prozac (flextime)	Wait 5+ weeks before giving MAOI Caution with warfarin Increases plasma level of: diazepam, alprazolam, phytoin, haliperidol, lithium, carbamazepine, TCA
Methadone	Can raise levels of Solvay's Luvox (fluvoxamine) by 40%, and stopping can cause withdrawal
Mexitil (mexiletine)	Caffeine reduces clearance by 50%
Pfizer's Neurontin (gabapentin)	Morphine may increase Neurontin levels by 44%
Pfizer's Zoloft (sertraline)	Caution with warfarin Oral concentrate has alcohol in it
Sanofi-Synthelabo's Demerol (meperidine)	Combination with MAOI can cause serotonin syndrome
UCB Pharma's Keppra (levetiracetam)	May be a little weaker than gabapentin
Wyeth's Effexor (serzone)	Don't co-administer with triazolam May increase busprione levels by 20-fold

*** Serotonin syndrome: cognition changes, agitation, fever, sweats, diarrhea, hyper-reflexia, myoclonus. Therapy is usually supportive only.**

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