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from the desk of
Bhaval Shah
610.883.5508

Approved 11/14/07. BSB

GRANT #401

Cephalon, Inc.
41 Moores Road
PO Box 4011
Frazer, PA 19355

EXHIBIT
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PLAINTIFFS TRIAL EXHIBIT
P-29943_00001

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Approved 11/14/09 BSB

Cephalon, Inc.
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DANNEMILLER
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Kimber Titus
Operations Coordinator
Medical Affairs
Cephalon, Inc.
41 Moores Road
Frazier, PA 19355

Subject: Support of Pain.com and the Breakthrough Pain Category from October 2006 - September 2007. Grant number 401.

In October 2006, Cephalon, Inc. awarded an educational grant to Dannemiller in the amount of $64,000 for the support of the website Pain.com and the Breakthrough Pain category. During the twelve month duration of this grant, Pain.com issued 33,629 educational certificates. The Breakthrough Pain CME activity issued 860 certificates. By the end of the grant period, the website logged 1,393,263 visitor sessions.

The awarded amount of $64,000 was used in its entirety during the approved time period to support not only webhosting, maintenance, and content development on Pain.com, but also the Breakthrough Pain directory. Each month, an e-letter highlighting the Breakthrough Pain category was sent to more than 34,000 registered users. Articles in the e-letter focused on the most recent Breakthrough Pain modules (educational activities) published on the site. The grant also provided for four expert interviews with clinicians who specialize in treating breakthrough pain, and these interviews were read by 6,977 users. Cephalon was acknowledged as the supporter of the Breakthrough Pain directory and educational activities.

With the help of this educational grant Pain.com continues to grow, not only with new and innovative educational content, but also by more registered healthcare professionals joining the site. The site currently has 54,600 members.

Dannemiller thanks Cephalon for its support of Pain.com and the Breakthrough Pain category and looks forward to strengthening our relationship for the benefit of clinicians and their patients.

Attached, please find:

1. Evaluation data
2. Outcomes data
3. Metrics report
4. Detailed budget reconciliation
5. Expert interviews

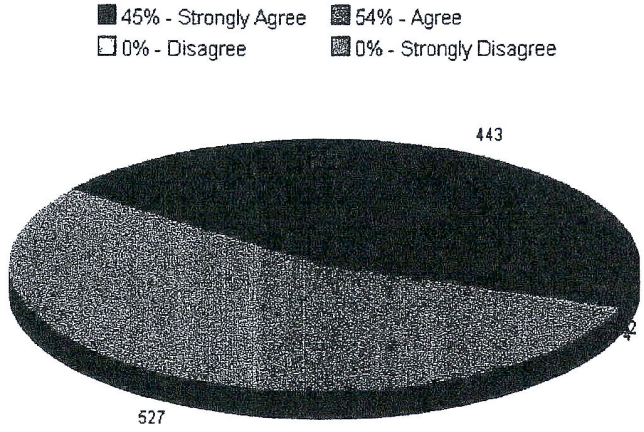
Breakthrough Pain 2007		
Pain.com (24) (ID 281)		
DMEF/Cephalon	AMA, CBRN	1.00 Credit
Release Date: March 2007	Expiration Date: 12/31/2008	

Credential Percentages

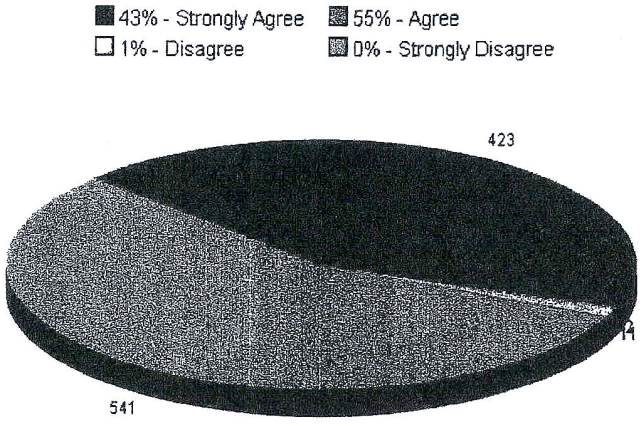
CRNA	DO	MD	NP	Other	PA	Pharm. D.	R.Ph.	RN	RRNA	Total
197	15	152	15	114	21	5	12	444	1	976
20%	2%	16%	2%	12%	2%	1%	1%	45%	0%	

Evaluation Report

1. The program objectives were fully met.

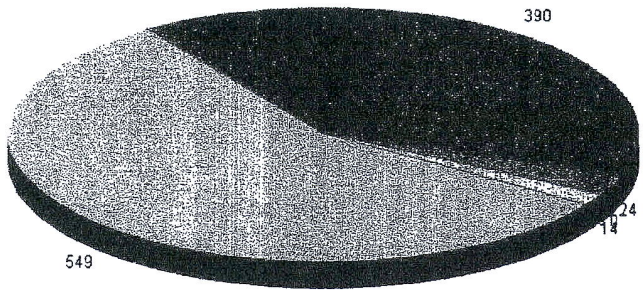


2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.



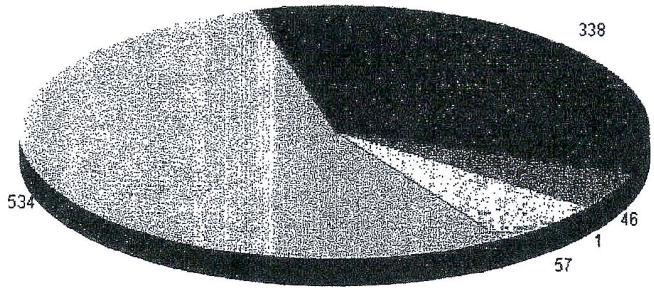
3. The educational activity has enhanced my professional effectiveness in treating patients.

40% - Strongly Agree 56% - Agree 1% - Disagree
0% - Strongly Disagree 2% - Not Applicable



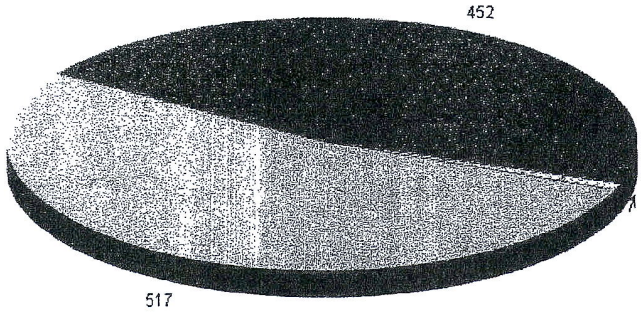
4. The educational activity will result in a change in my practice behavior.

35% - Strongly Agree 55% - Agree 6% - Disagree
0% - Strongly Disagree 5% - Not Applicable

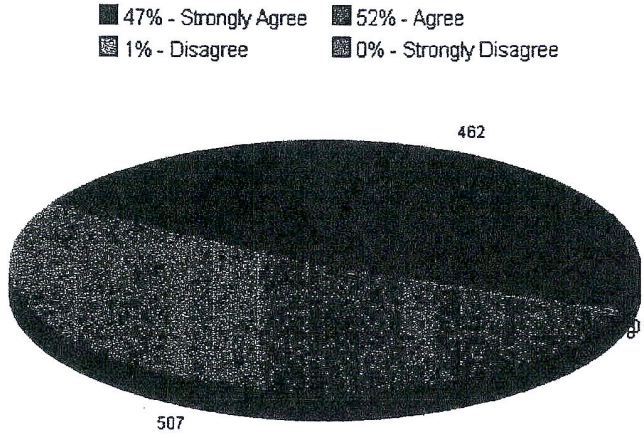


5. The information presented was without promotional or commercial bias.

46% - Strongly Agree 53% - Agree
1% - Disagree 0% - Strongly Disagree



6. I learned new information during this program.



7. What new information did you learn during this program?

- We truely know very little about pain and the individual response from our patients.
- Nanotechnology is on the rise.
- the use of ketamine in chronic pain
- different delivery methods available
- INTERESTING TOPIC
- The use of ketamine for pain control and that it can be taken intranasally. I also wasn't aware of OTFC.
- treatment of breakthrough pain for chronic pain
- very informative
- Temporary information for a person's memory if they do not directly deal with these patients day after day.
- THAT PAIN IS REAL AND TOLERANCE TO PAIN VARIES. WE NEED TO CONTINUE RESEARCH TO UNFOLD THE MASSIVE AMOUNT OF INFORMATION, DRUGS,AND TECHNOLOGY OUT THERE TO HELP OUR PATIENTS.
- role of intranasal ketamine in BTP
- precise diffusion kinetics
- many things, too large to name
- My personal anesthesia practice does not include pain management, not even epidurals. This was a true learning experience in that I had no knowledge of these treatments.

- regarding the use of Buccal fentanyl
- PTCA, where absorption of certain drugs occured.
- Use of samarium. Kinetics of fentanyl oral
- about buprenex
- The effectiveness of drug resulted in cancer patients comfort.
- CHANGE SOME OF MY IDEAS ON PAIN MAMAGEMENT
- The entire content was new info to me as I am new to oncology field
- nanotechnology
- all of it
- Radioisotopes as a means to reduce pain.
- A faster method of alleviating BP
- Use and effectiveness of OFTC; had not heard of levo-bupivacaine and was interested in that information.
- I hadn't realized the extensive amount of research that goes into these drugs
- the safety of treating breakthrough pain with additional opioids
- infusion
- I learned that the initial dose of oral Transmucosal fentanyl citrate should be 200 ug.
- New information
- Re: labor and delivery medication during labor.
- use of the meds
- I am a fairly new RN, therefore a lot of this material was new to me. I am glad that I was able to read all of these articles and find out the different studies on pain management.
- Adequate use of pharmacology for treating BTP
- Definition of differing methods of analgesia
- more study based vs practice based

- The use of medications in btp
- That the oral buccal tablets were so effective in the pain management
- deeper understanding of opiods
- ON SET TIME FOR ORAL FENTANYL.
- pain is the perception of the patient, there are many different ways to elliviate pain rather than just a handful that most physicians tend to follow
- newer methods for chronic pain control and future methods
- different methods of treating BTP
- The effectiveness of the buccal route
- new awareness about oravescent buccal fentanyl tabs
- reevaluated my opinion about patients need for pain medication and appropriate options
- about fentnyl
- USe of Fentanyl
- treatment options
- Fine tuning intrathecal anesthesia in labor can help to eliminate breakthrough pain
- multiple facts re btp
- New drug information, onset
- that there was a way to relieve pain bone pain in cancer patients
- btp
- new info on pain mangement
- pain control in cancer patieent
- The different methods being tested to treat breakthrough pain
- computer aided PCEA
- precise drug interactions

- about buccal pain meds about automatic adjustments on epidural pain management based on pcea usage
- tx of ca pain
- The direction that treatment of BTP is heading.
- OTFC more effective in neurogenic pain
- The use of radioisotopes and OTFC
- I was not aware of an OTFC.
- Pain control in cancer patients
- THe many different methods being used in pain control
- More info on BTP
- oral transmucosal fentanyl citrate dosing
- I learned i like articles compared to research info, i do no retain it as well.
- new meds, alternative therapies
- the use of short and long term use of narcotics
- new modalities for pain relief
- I learned that there was such a thing as intranasal ketamine.
- better insight into alternatives for breakthrough pain
- oral fentanyl effectiness
- intrathecal drug therapy has slow onset
- New understanding on pain therapy and treatment
- How cancer patients respond to medications.
- The use of different types meds that treat pain in a better way.
- breakthrough pain issues
- various meds to treat pain

- about different pain control measures
- new medications and ne w approaches to therapy
- mechanism of action of radiostopes for bones met tx in prostate ca
- case studies
- how the analgesics work and their effect on breakthrough pain
- goals and objectives for btp patients
- nanotechnology
- teamwork
- New methods of administration of opiods.
- drugs for cancer pain relief
- why isotopes are thought to decrease pain
- More on how to treat cancer pain!
- The results of studies and what they can mean to the patient with continueing pain.
- The onset of analgesia w/OTFC
- Research being done to develop new methods of opioid administration.
- new fast acting medications for breakthrough pain
- Fentanyl for a BT pain
- interesting comparisions of effectiveness of treatment modalities
- nanotechnology
- All of the studies were new information for me.
- efficacy of analgesia
- Different types of breakthrough pain
- about levo-bupivicaine and one other drug

- dosing and effectiveness between fentanyl and morphine was interesting
- nanotechnology as applied to pain
- Neuropathic pain responded better to pain treatment than Nociceptic pain
- The use of bupomorphine and spinal anesthesia during labor
- fentanyl oral labor dose
- recommended dosage for fentanyl
- pain relief patho and drugs
- information regarding the usage of transmucosal meds
- more about the oral release of fentanyl and the treatment of pain for bone cancer
- I learned about the meds that will help break thru pain
- Information on oral transmucosal meds
- pain is relieved in so many ways. For one who has the lowest of tolerance may need more than one who hs a high tolerance rated at the same level. Pain is highly individualized as is the treatment for each person.
- Transmucosal oral opioids
- That almost no one suffering from chronic pain had the relief they should have, and now there are so many ways to relieve breakthrough pain, and we should strive to make sure all patients are pain free.
- Radioisotopes were new to me
- New methodologies for treating various types of breakthrough pain.
- Review of prior info.
- exposure to knowledge of specific meds
- Practical clinical dosaging of OTFC
- new meds and dosing

8. What are your recommendations for topics of future presentations?

- A checklist of to include information for charting efficiently and effectively.
- More on advances in nanotechnology.

- post anesthesia related topics
- WILL RECOMMEND TO MY FRIENDS AND COLLEAGUES
- more emphasis on alternate pain aides
- tough test
- Feel that it was written too technically
- would not change a thing!
- More in pain management.
- LOCAL INJECTIONS PRE OP IN ORS
- pt addicted to pain medication
- Not so darn boring to read.
- I feel you already have everything covered
- Pain control for pelvic floor dysfunction/interstitial cystitis
- Prevention of spreading infection
- sedative affect of opiods
- pain managament in the occupational setting
- TRY TO GEAR THE ARTICLES FOR NURSING CE, WITH NURSES IN MIND.
- hospice
- Use of opioids for chronic inflammatory join disease
- cardiac meds
- obstetric analgesia
- continuation of offering
- nature of metabolization of opioids and comparison of metabolites
- Cancer types, symptom management

- medications used in surgery and anesthesia
- Emergency department management of breakthrough pain
- similiar clinical based
- pre-procedural medication evidence based practice which transmucosal medicine is best to use for outpatient setting
- CVD
- more topics for anesthesia techs.
- Anything on continuous epidural during labor
- studies regarding pacient controlled analgesia (PCA) use and PCA-pumps
- addiction potential for chronic pain
- drug seeking patients in pain
- Treating beginning cancer pain.
- pain management with death and dying
- insomnia treatments and their effectiveness
- Please be more careful when typing up your summaries of these articles. Article #9 Sia et al, the summary states that 15 mg of fentanyl were administered Intrathecally as well as a concentration of fentanyl 2 mg/ml as continuous epidural. These are gross typoes when compared to the original article. The actual amounts reported are micrograms (a factor of 1000)
- More information on dosing.
- Fibromyalgia
- Neuropathic pain
- The future of nanotechnology in medicine
- proper documentation for pain meds
- Management of Restless Leg Syndrome
- new research in pain management
- Meta-analysis reviews of new BTP treatment methods.

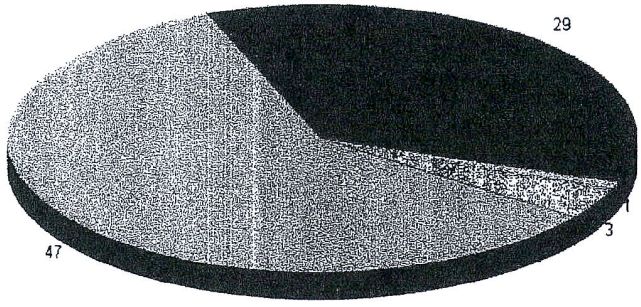
- Cervical radicular pain
- treating FMS pain.....effectively

Online Survey Report

80 of 709 (11%) completed surveys

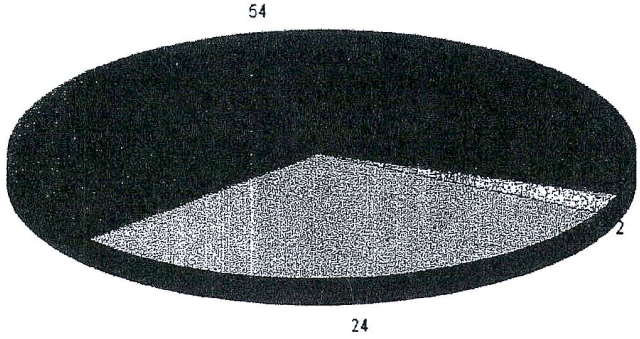
1. I learned new information from attending/completing this activity.

36% - Strongly Agree
59% - Agree
4% - Disagree
1% - Strongly disagree



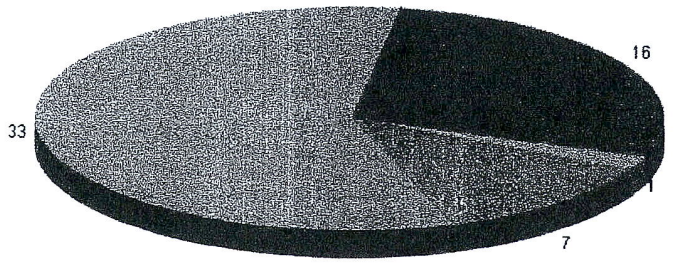
2. I treat patients in my current practice.

68% - Yes
30% - No (If you select this choice, please skip to question 6.)
2% - I am not currently practicing. (If you select this choice, please skip to question 6.)



3. I have incorporated the knowledge I gained from attending/completing this activity into my practice.

28% - Strongly Agree
58% - Agree
12% - Disagree
2% - I did not learn new information. (If you select this choice, please skip to question 6.)



4. If you answered "strongly agree" or "agree" to question 3, please tell us how you have incorporated the knowledge you gained into your practice.

- Have not seen patients that fit the profile.
- In the ever changing healthcare field, it is nice to have this resource to keep you up to date.
- While sitting at my computer and turning 70 years old yesterday it is difficult to recall some specific knowledge that I read a month ago. I will tell you this, I will be working and thinking about a specific question and you answer will pop into my head. These classes are very beneficial.
- better handling of breakthrough pain
- surgery patients...treating fresh post-op pt w/pain and then break through pain
- I work in a pain clinic and we have many patients that need b/t pain meds. Any info given is very useful.
- Enjoyed all the new information on current treatments. Have been out of the hospital setting for 5 years.
- better options for pain control for my terminally ill clients
- TO TRY TO DECREASE THE # OF BREAKTHROUGH PAINS MY PATIENTS HAVE
- Relating the type of medications that are known to addictive more than the others.
- working with athletes
- i try to look at patient expressions, comments, and vital signs more closely, i treat pain quickly so that they will be comfortable
- I make sure I use the various descriptions of pain. I research their past pain history.
- By being more aware of pain levels.
- Information was general, and the administration at my current employer is not conducive to adding

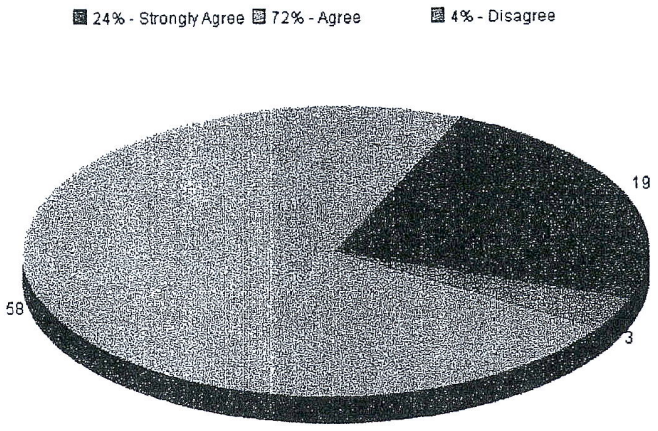
information into the practices.

- I am a nurse educator, I incorporate new information I learn into my education for the staff
- i have changed some prescribing of medications due to the article
- how to dose and different medications
- adding knowledge to the knowledge bank
- I understand the use of long acting meds and breakthrough meds.

5. If you answered "disagree" or "strongly disagree" to question 3, please describe any barriers that prevented you from implementing the practice changes you would like to make as a result of this activity.

- Nice Refresher course for things we don't use on an everyday bases.
- I do not treat patients with chronic pain

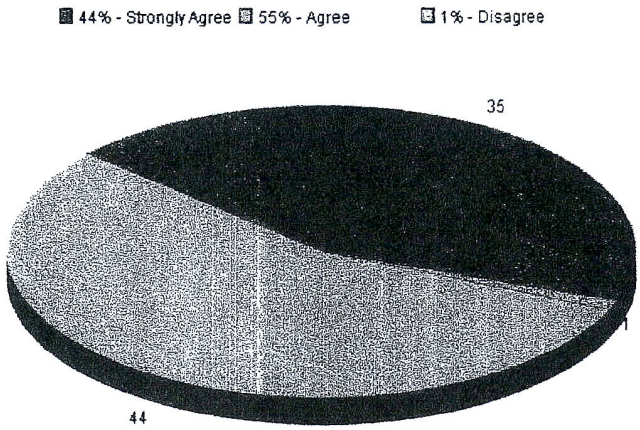
6. I learned all that I hoped or expected to learn from this activity.



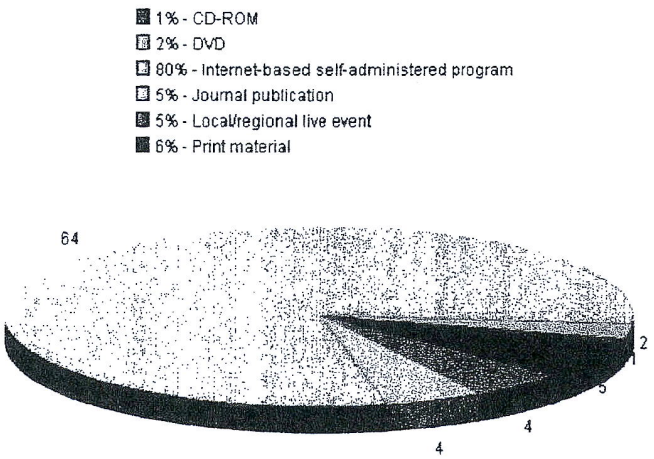
7. If you answered "disagree" or "strongly disagree" to question 6, please tell us what you hoped or expected to learn that you did not.

- Very informative modules. They cover the subject completely.
- it's not that I didn't learn what I had hope, but I know that there is so much more to learn and who knows what tomorrow brings.
- Very good articles and would like to study them again for my professional use.
- Some alternative treatments to controlling low back pain or headaches.

8. I would recommend this activity to a colleague.



9. Which format for CME programs do you prefer? (Please select up to three.)



10. Please provide us with suggested topics for future CME activities that would address your professional practice knowledge gaps. (The ACCME defines a practice gap as one *between what the professional is doing or accomplishing compared to what "is achievable on the basis of current professional knowledge.")*

- Pain management in peds and obstetrics.
- Maybe, more specific to the CRNA practice in the future and the ever changing role of the CRNAs.
- I am a certified anesthesia tech and would like more topics on anesthesia.
- pain management for General Surgery and surgical subspecialties
- pediatric or school nursing
- surgeries and patient expectation with quicker recuperating methods and practices

- pain management gaps from pacu to nursing unit, how to manage.
- *Fibromyalgia*

For On-Line Program											
CME Prov. or MEC	Program Start Date	Program End Date	Program Title	Means of Distribution	Total Cost of Tactic	Hits/Sessions*	Cost per Hits	Projected Certifications	Actual Certifications	Cost per Certification	Target Audience
Dannemiller Memorial Educational Foundation	Oct-06		Pain.com	online	20,000	1,393,263	0.0144	22,500	33,629	0.5947	Physicians, RNs, CRNAs, Pharmacists, NPs
Dannemiller Memorial Educational Foundation	Oct-06		Breakthrough pain page	online	30,000	141,157	0.2125	0	0	0.0000	Physicians, RNs, CRNAs, Pharmacists, NPs
Dannemiller Memorial Educational Foundation			Expert Interview - Lynn Webster MD	online	1,000	2,850	0.3509	0		0.0000	
Dannemiller Memorial Educational Foundation			Expert Interview - Gerald Aronoff MD	online	1,000	1,767	0.5659	0		0.0000	
Dannemiller Memorial Educational Foundation			Expert Interview - Charles Argoff MD	online	1,000	2,360	0.4237	0		0.0000	
Dannemiller Memorial Educational Foundation			Expert Interview - Perry Fine MD	online	1,000	819	1.2210	0		0.0000	
Dannemiller Memorial Educational Foundation	1-Oct		BTP CME activity	online	10,000	8,883	1.1257	500	860	11.6279	Physicians, RNs.
Expert Interviews shown are the last four (4) interviews posted on the BTP Directory											
Average Session Length for Pain.com - 15:53											
Average Session Length for Breakthrough Pain Directory - 11:10											
Average Session Length for BTP CME Module - 12:18											
Total Participants in CME Module from January 1 , 2006 through February 28, 2007 - 612											
Total Participants in CME Module from March 1, 2007 through June 30, 2007 - 235			through Oct 31, 2007 - 443								

2006-2007	Budget Fees	Reconciliation	Notes
www.Pain.com	**$ 20,000.00**		
Site Management Fee		$ 5,000.00	Management of system, programming, communications and client services, reporting
Content Development		$ 4,000.00	Ongoing research, writing, editing, data entry, quality control, purchase of original articles, abstracting
Accreditation		$ 3,500.00	Needs assessments, identification of objectives from identified educational gaps, objectives, certification for CE and ACPE, provision of online certificates, registration, participant transcripts, evaluations and outcomes studies
Hosting/Maintenance		$ 4,000.00	Server maintenance, backup, security
Acknowledgement of Commercial Support		$ 3,500.00	Commercial supporter logo placement on home-page and throughout the site on all non-CME pages. Link from Cephalon logo to commercial site identified by Cephalon. Cephalon logo prominently provided in monthly eletter to all registered users with information and link directly to the Breakthrough Pain Directory every other month
Total for Pain.com site support		**$ 20,000.00**	
Breakthrough Pain	**$ 40,000.00**		
Management Fee		$ 5,000.00	Management of system, programming, communications and client services, reporting
Content Development		$ 6,000.00	Research, writing, editing, formatting, data entry, quality control, purchase of articles, abstracting, final editing, maintenance of major categories and directories

Accreditation		$ 12,500.00	Needs assessments, identification of objectives from identified educational gaps, objectives, certification for CE and ACPE, provision of online certificates, registration, participant transcripts, evaluations and
Hosting/Maintenance		$ 4,000.00	Server maintenance, backup, security
Acknowledgement of Commercial Support		$ 12,500.00	Cephalon logo placed on the BTP Direcotry banner on homepage and on BTP Directory homepage
Total for BTP		**$ 40,000.00**	
Expert Interviews	**$ 4,000.00**	**$ 4,000.00**	4 expert interviews honorarium
Total Grant Amount	**$ 64,000.00**	**$ 64,000.00**	

Breakthrough Pain

Pain.com routinely interviews pain specialists on a variety of topics so that our healthcare professionals can receive up-to-date information on medications, therapies, procedures, and other medical news. Please note that the opinions expressed in these interviews are specific to the interviewees.

Opioid Risk Tool (ORT)
Interview with Lynn R. Webster, MD, FACPM, FASAM

Dr. Webster recently published in Pain Medicine journal preliminary results showing the Opioid Risk Tool (ORT) exhibited a high degree of sensitivity and specificity for determining which opioid-treated individuals are at risk for aberrant behavior.

Pain.com: Please explain what the ORT is and why it is needed.

Dr. Webster: The ORT is a five-question clinical interview or patient questionnaire to assess patients who may be at risk for opioid-related aberrant behaviors (Figure 1). It is administered to patients whose chronic pain is to be treated with opioids at the first clinical visit before treatment starts. Its aim is to predict the risk that behaviors will be exhibited once treatment is initiated.

The need is driven by the recent rise in prescription opioid abuse. According to the 2003 National Survey on Drug Use and Health, new nonmedical users of pain relievers more than quadrupled during the 10-year period of the 1990s. Many of these first-time users are young people. Substance abuse is a leading cause of preventable illness and death in the United States, and opioid analgesics are among the most frequently abused prescriptions. To keep opioids available to treat pain, as we must, doctors who treat pain are called on to help prevent abuse and addiction, too.

Pain.com: How is the ORT administered, and how does it work?

Dr. Webster: It is self administered by the patient in the office or waiting room and requires less than 5 minutes to complete. Patients are asked to identify their age; history of preadolescent sexual abuse; family and personal histories of alcohol, illegal drug or prescription drug abuse; and presence of certain mental diseases. These are the risk factors for abuse. The probability of opioid abuse increases with the number of positive responses.

Each risk factor is attributed a point value compared to other risk factors, and responses are weighted differently based on gender. Based on the total score, the patient is placed in one of three risk categories: Low risk with a score of 0 to 3 points total indicates individuals are unlikely to abuse; moderate risk with a total score of 4 to 7 points indicates individuals who are just as likely as not to abuse; and high risk with a total score of 8 or greater indicates individuals likely to abuse opioids.

Pain.com: Please talk a little about the risk factors contained in the questionnaire. Why are these considered the factors most predictive of abuse?

Dr. Webster: Many individual risk factors are linked to aberrant behaviors that might indicate abuse or addiction. These key factors were determined and substantiated through an investigation of the medical literature and my personal experience as a practicing pain and addiction specialist.

A family history of substance abuse can create both genetic and environmental risk factors for developing substance abuse or addiction. Numerous studies and clinical observation have shown that a personal history of substance abuse is a strong predictor of potential drug misuse.

Age is included as a risk factor because of the documented early onset of mental disorders and higher risk of drug abuse in young adults. Women who experience preadolescent sexual abuse have been shown to be at particular risk for mental disorders, (i.e., depression, anxiety and panic disorders and substance abuse disorders).

Mental disease is significantly correlated with substance abuse or addiction. One significant study showed that having a lifetime mental disorder can increase the risk of drug-abuse disorders by four times that of what is typically found in the general population. All of these studies are referenced in the Pain Medicine article.

Pain.com: Can you describe how the patient categories would be utilized and why this is necessary?

Dr. Webster: It is important to say, straight off, that in no way is this intended as a means to deny high-risk patients treatment for their pain. Rather, the purpose is to match the degree of clinical monitoring to the degree of risk based on the initial assessment. Monitoring measures include a number of interventions from routine to intense. All patients must understand and agree to certain treatment parameters: that all analgesics will be obtained from one physician and one pharmacy, that only enough drugs to last from visit to visit will be prescribed, and that the patient will be responsible if the drug supply is used before the next visit. The higher the risk, the more controls are put in place. For example, high-risk patients may need more urine drug screens, including some that are unannounced, shorter periods between visits and refills, counts of leftover medications and so forth.

Involving the patient's family is often essential and can help corroborate patient self report. Referral to an addiction specialist may be indicated if the patient has a history of addiction, and referrals to mental-health professionals can help manage psychiatric comorbidities. If violations of the opioid agreement persist, it may be necessary to discontinue opioid therapy. Documentation of every patient interaction is important to support the treatment plans recommended.

Pain.com: What statistical measures were used to judge the validity of the ORT?

Dr. Webster: To validate the ORT, the total score along with one or more observed aberrant behaviors, over the course of the study period, were used to compute the concordance index (c statistic) for each of the patients in the study sample. The c statistic is a measure of the predictive ability or diagnostic discrimination of the model and simultaneously assesses both sensitivity and specificity. The ORT displayed excellent discrimination for both the male (c = 0.82) and female (c = 0.85) prognostic models.

The paper published in Pain Medicine documents the results of a preliminary study showing the instrument was predictive in the setting in which it was administered. In the study, 185 new patients being treated with opioids for chronic pain took the ORT during their initial visits and then were monitored for 12 months. Of the low-risk patients, 17 out of 18 (94.4%) did not display an aberrant behavior. Of the high-risk patients, 40 out of 44 (90.9%) did display an aberrant behavior (Figure 2).

Pain.com: What are the strengths and weaknesses of the ORT, and how does it compare to other clinical measures of substance abuse?

Dr. Webster: In the sample tested, the ORT demonstrated validity and accuracy in predicting who is at high risk and low risk for opioid-related, aberrant behavior. It was less predictive for patients in the middle, moderate-risk category. This is the gray area. People in this category may abuse if they are exposed to enough stress with pain itself being a top stressor.

The advantages of a tool like the ORT lie in its opioid specificity and the fact that it is brief, easy to administer, nonconfrontational and predictive. The majority of now-available assessment tools diagnose current substance abuse rather than help predict it, are not specific to the use of opioids, tend to be long and cumbersome and are impractical for the average physician to use.

The ORT is part of new generation of tools that address the needs of opioid-treated pain patients. Other assessments having the same aim include the Screener and Opioid Assessment for Patients with Pain (SOAPP) and The Prescription Drug Use Questionnaire (PDUQ). All of these tools need further studies in a variety of pain settings to determine their wider applicability and to see if their results are consistent.

It would help the patient and the clinician to be able to tailor the monitoring of patients according to their risk profiles. Patients who are at high risk could be identified before opioid therapy starts and directed to appropriate treatment of the disorders that make them high risk. The goal is less abuse and better clinical outcomes.

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Persistent Pain in Older Patients
Interview with Perry G. Fine, MD

Dr. Perry Fine completed medical school in 1981 at the Medical College of *Virginia in Richmond*. He served an internship in 1982 at the Community Hospital of Sonoma County in California and completed his residency in 1984 at the University of Utah Medical Center. In addition, Dr. Fine completed a fellowship in 1985 at the Smythe Pain Clinic at the University of Toronto in Canada.

Dr. Fine is a Professor in the Department of Anesthesiology in the School of Medicine at the University of Utah, where he serves on the faculty in the Pain Research Center and is an attending physician in the Pain Management Center. He teaches the first and second year medical school courses in Social Medicine and the fourth year medical school course in Medical Ethics. Dr. Fine serves as Senior Fellow for Medical Leadership for the National Hospice and Palliative Care Organization, where he has served on the Board of Directors, and chaired both the Ethics Committee and Research Committee.

Dr. Fine was a founding member, and served on the Board of Directors, VistaCare Hospice Foundation (including as Chair), for ten years. He currently holds several Board of Directors positions, including: VistaCare, Inc., a national leader in hospice care, based in Scottsdale, Arizona; the American Academy of Pain Medicine (Treasurer); the Society for Arts in Healthcare. He is a consultant to the Center for Advanced Illness Coordinated Care, based in Albany, NY, developing and educationally supporting self-sustaining models of pre-hospice palliative care in community settings, as an integrative component of disease management and advanced illness coordinated care. He has served as the Chair of the National Initiative on Pain Control since 2003, an educational endeavor of CME offerings in pain management that has engaged several hundred thousand physicians during this time.

Dr. Fine is widely published in the fields of pain management and end of life care. He serves on the editorial boards of several peer review medical journals. As a medical avocation, he has worked as a team physician for the University of Utah football team for the last 16 years, and was a medical officer for the 2002 Winter Olympics in Salt Lake City. He was awarded The Josefina Magno Distinguished Hospice Physician Award by the American Academy of Hospice and Palliative Medicine in 2007.

Pain.com: How common is persistent pain in older patients?

Dr. Fine: The prevalence of persistent pain in older persons has been reported to be between 20 and 50% in community dwelling-adults, and up to 84% of nursing home patients report *daily pain. Despite the high incidence* of pain in older persons, studies have revealed that older patients are less likely to be adequately treated for pain compared with younger individuals.

Pain.com: What are the consequences of persistent pain in the geriatric age group?

Dr. Fine: Poor pain control in older persons has been shown to contribute to an overall diminished quality of life and impaired physical functioning. It also has been associated with impaired cognition and mood and sleep disorders, impaired ambulation and gait disturbances. Poorly controlled pain is associated with decreased self-rated overall health assessments which have been shown to be an independent predictor of age-matched life expectancy. Needless to say, the link between persistent pain, independent of its cause, and the risk of premature mortality to persistent pain as a public health issue needs to be taken seriously and addressed accordingly.

Pain.com: What are the common pain-producing conditions that affect older patients?

Dr. Fine: Similar to younger adult populations, low back pain is a leading cause of pain and debility in older patients, with combinations of nociceptive and neuropathic pain arising from degenerative changes in spinal structures, including intervetebral discs and facet joints with resultant spondylosis, neuroforaminal encroachment and spinal canal stenosis. Osteoarthritis and osteoporosis are very common with advanced age, and older individuals are at risk for developing polymyalgia rheumatica, peripheral neuropathies, post-stroke central pain, postherpetic and trigeminal neuralgia, as well as vascular diseases with concomitant ischemic pain. Therefore, because pain-producing conditions are increasingly common with aging, a brief screening assessment for pain should be considered a routine part of geriatric care.

Pain.com: How can physicians and other healthcare professionals *determine if patients are in pain* if they are unable to self-report due to cognitive impairment from a dementing illness such as Alzheimer's Disease or other causes? Link to PAINAD is http://www.coh.org/prc/Review%20of%20Tools%20for%20Pain%20Assessment/PAINAD.htm Link to DOLOPLUS-2 *is* http://www.doloplus.com/Versiongb/rubechelle/intro.htm

Dr. Fine: Pain assessment in patients who are not able to provide a verbal report themselves is an important issue in this patient population. Caregivers and clinicians must observe behaviors as "proxies" for verbal self-report. Changes in usual activity, facial expressions, vocalizations, lack of interest in previously pleasurable events such as eating or grooming, stiff or rigid body postures or guarding, restlessness and spontaneous movements, and so forth, represent the types of behavioral indicators that suggest pain may be present.

Pain.com: What are the affects of aging on drug disposition?

Dr. Fine: Reduced muscle mass, decreases in serum proteins, and decreased renal clearance are the most common changes that account for alterations in pharmacokinetics, such as volume of distribution and clearance. Drugs such as the opioids that are highly protein bound may lead to seemingly more potent effects due to more free drug available to cross the blood-brain barrier. Drugs with active metabolites, such as morphine, that depend upon renal clearance must be used with much greater caution in older patients with predictably elevated creatinine clearance.

Pain.com: What is new and different within the last year or two with regard to pharmacologic agents used to treat pain that may have applicability to older patients in particular?

Dr. Fine: With the withdrawal of two of the three previously available COX-2 inhibitors from the analgesic formulary, and the most recent FDA advisory group recommendation not to approve etoricoxib for osteoarthritis due to concerns about cardiac and cerebrovascular risks, as well as the new warning labels for over-the-counter NSAIDs, clinicians are faced with the challenge of reduced treatment options for their older patients with chronic pain. There has been the addition of a low-dose transdermal fentanyl patch, that releases 12 mcg fentanyl per hour, which may be of benefit to older patients with continuous moderate-to-severe pain from a variety of causes, including cancer, Osteoarthritis (OA) or degenerative joint or spine disease and painful neuropathies not responsive to other treatment modalities. Similarly, tramadol is now available in an extended release formulation for around-the-clock coverage of continuous pain. Oxymorphone has recently been approved for oral administration and is available both as immediate release and extended release formulations, adding to the expanding pharmacopoiea of opioids available for the treatment of moderate or greater pain. One other opioid preparation, the fentanyl buccal tablet, is a rapid-onset agent approved by the FDA for the treatment of cancer-related breakthrough pain in opioid tolerant patients.
In the realm of neuropathic pain, duloxetine, a mixed norepinephrine and serotonin re-uptake inhibitor and pregabalin, an anti-convulsant drug, have been approved for the treatment of painful diabetic peripheral neuropathy. These drugs may be less likely to produce less adverse effects and be better tolerated in older patients than the tricyclic antidepressants, due to less anticholinergic effects. Although not quite as new, it is worth reminding readers that the lidocaine 5% patch is approved for the treatment of post-herpetic neuralgia, but clinical trials have also shown efficacy in a variety of other localized pain states. Since it is extremely safe, its use should be considered as a stand-alone agent or adjunct to systemic therapies.
Lastly, I would like to add that there has been an increased usage of methadone for the treatment of chronic pain conditions, probably due to anecdotally-reported heightened efficacy compared with other opioid analgesics coupled with its relatively low cost. However, there has also been an alarming rise in methadone-related morbidity and mortality in adults being treated for persistent pain. It needs to be emphasized that methadone has a highly variable elimination half-life, making dose accumulation a very real potential problem. As well, methadone has been shown to have a dose-dependent effect on the cardiac QT interval, which can lead to ventricular arrhythmias. Although it can be a very valuable agent, all due caution needs to be exercised in prescribing, titrating and monitoring its use, and those without ample experience should consult with clinicians who are highly experienced with this agent in order to minimize risks in their patients.

Pain.com: Other than the concerns you have raised about methadone, how does opioid therapy in elderly patients differ from younger adults?

Dr. Fine: It must be remembered that pharmacodynamic and pharmacokinetic alterations occur with aging. Most commonly, drug sensitivity is increased leading to more potential cognitive, balance and bowel-related side effects in the older patient. Although not inevitable, a more slow and cautious approach to initiating therapy, dose titration, and opioid rotation are required. Similarly, drug absorption, distribution, metabolism and clearance are likely to be altered, due to progressive changes in body tissue composition, cardiac function and consequent tissue perfusion, bowel motility, hepatic and renal function, and protein binding capacity. All told, this requires more awareness of each individual's physiologic state, potential for drug-drug and drug-disease interactions, and likely consequences of metabolite-related adverse effects. For example, morphine's metabolites, morphine-3 and morphine-6 glucuronide, depend upon renal excretion. In older patients with reduced creatinine clearance, these potentially toxic metabolites may accumulate and lead to excessive sedation or CNS irritability, depending upon the relative ratios of these metabolites. An alternative opioid might be preferred in patients with incipient renal insufficiency. Also, since opioid-related bowel dysfunction is so common, and older patients are especially vulnerable, instituting a bowel regimen that includes a motility agent such as senna or bisacodyl is advised when initiating opioid therapy. It may well be that in the future there will be peripherally-acting opioid antagonists that will counteract opioid-agonist bowel dysfunction, but until then, the more conventional prophylactic approaches need to be remembered and reinforced continually.
Other than this, when opioids are indicated for the control of moderate or greater intensity pain, assessment and subsequent treatment for both components of persistent pain, continuous and breakthrough pain, is required in order to optimize functional outcomes. A risk assessment and management plan should be part and parcel of routine care in order to ensure that therapeutic intent is realized, while toxicity, untoward side effects, misuse, abuse and purposeful or unintended diversion are minimized and rapidly detected. Since older patients, and especially those with cognitive impairment, may be dependent on caregivers, the risk management plan must take this into account. Treatment goals such as reduced pain intensity, reduced pain behaviors, improved functional capacities, improved sleep and mood, or improved social interactions should be documented in order to justify ongoing pharmacologic therapy.

Pain.com: Is breakthrough pain more or less of a problem in older patients?

Dr. Fine: This is a rather new area of inquiry, but surveys to date suggest that breakthrough pain is very common in all patients with advanced cancer. Patients with a variety of non-cancer chronic pain disorders appear to have increasingly frequent episodes of breakthrough pain as their chronic condition progresses to end-stage. Since breakthrough pain erodes quality of life, this is an important component of persistent pain to assess and treat, especially when comfort is a chief objective in end-of-life care.

Pain.com: Are there any additional or concluding comments you would like to share?

Dr. Fine: Additional treatment challenges in the provision of effective pharmacological pain management for older patients include an increased risk of drug-drug and drug-disease interactions due to the commonality of multiple comorbidities and medications in this population. Pharmacokinetic and pharmacodynamic differences in older persons can contribute to increased sensitivity to adverse drug reactions and noncompliance due to concerns about adverse drug reactions and fears of addiction, side effects, or dependence with opioids. With this segment of our population growing quite rapidly, it is increasingly incumbent upon clinicians who are involved in adult medicine to continually update their core knowledge, assessment and management skills in this clinical area. This discussion is a good beginning and on behalf of this vulnerable group of patients, I am grateful for the readers' interest in pursuing this area of inquiry.

References

1. Hartikainen SA, Mantyselka PT, Louhivouri-Laako KA, Sulkava RO. Balancing pain and anlgesic treatment in the home-dwelling elderly. *Ann Pharmacother.* 2005;39:11-16.
2. Won AB, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing homme residents. *J Am Geriatr Soc.* 2004;52:867-874.
3. Teno JM, Weitzen S, Wetle T, Mor V. Persistent pain in nursing home residents. *JAMA.* 2001;285:2081.

4. Landi F, Onder G, Cesari M, Russo A, Barillaro C, Bernabei R, on behalf of the SILVERNET-HC Study Group. Pain and its relation to depressive symptoms in frail older people living in the community: an observational study. *J Pain Symptom Manage.* 2005;29:255-262.
5. Reyes-Gibby CC, Aday L, Cleeland C. Impact of pain on self-rated health in the community-dwelling older adults. *Pain.* 2002;95:75-82.
6. Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. *Drugs Aging.* 2003;20:23-57.
7. Hadjistavropoulos T, Herr K, Turk D, Fine PG, et al. An interdisciplinary expert consensus statement on assessment of pain in older persons. *Clin J Pain.* 2007; 23: S1-S43.
8. Argoff CE, et al. *Mayo Clin Proc.* 2006;81(suppl):S12-S25
9. Gazelle G, Fine PG. Methadone for pain. *J Palliative Med.* 2004; 7 (2):303-304.
10. Fine PG. Pharmacological management of persistent pain in older patients. *Clinical Journal of Pain.* 2004; 20(4):220-226.

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Use of opioids in chronic pain.
Interview with Charles E. Argoff, MD

Charles E. Argoff, MD, is director of the North Shore University Hospital, Cohn Pain Management Center, located on Long Island, New York, and is an assistant professor of neurology at New York University School of Medicine, New York, New York.

Dr Argoff is a member of the American Academy of Neurology, American Association for the Study of Headache, the International Association for the Study of Pain, the National Headache Foundation, and the American Pain Society. His clinical and research interests include the evaluation and treatment of pain, and headache and stroke rehabilitation.

He has contributed to articles in peer-reviewed publications and has been the author or coauthor of book chapters on metabolic and neurologic diseases. A graduate of Northwestern University Medical School, Chicago, Illinois, he completed a residency in neurology at the State University of New York at Stony Brook Medical School and a fellowship in developmental and metabolic neurology at the National Institute of Neurological Disorders and Stroke of the National Institutes of Health, Bethesda, Maryland.

Pain.com: WHAT IS BREAKTHROUGH PAIN AND HOW DOES IT RELATE TO CHRONIC PAIN?

Dr. Argoff: Chronic pain consists of two components: stable, persistent baseline pain and a transient exacerbation of pain, or breakthrough pain (Portenoy, Hagen 1990; Fine, Busch 1998). Although the duration of baseline pain varies among patients and pain types, it typically lasts months or years (Portenoy 2006c). Breakthrough pain, found in patients with chronic baseline pain who are undergoing analgesic drug therapy on most days, is transitory pain that lasts seconds to hours, is more severe than the background pain, and has a negative effect on function or quality of life (Consensus definition 2006). Both components of chronic pain—baseline persistent and breakthrough pain— need to be independently assessed and treated.

Pain.com: HOW DO OPIOIDS WORK?

Dr. Argoff: Several major classes of opioid receptors in both the peripheral and central nervous system have been identified. These include the mu opioid receptor (typical agonist-morphine), the kappa receptor (typical agonist- butorphanol) and the delta opioid receptor. Endogenous opioids such as endorphins, enkephalins and dynorphins as well as exogenous opioids have multiple sites of action including within the peripheral nerve, the dorsal horn of the spinal cord as well as at higher levels of the central nervous system. Multiple subtypes of these opioid receptors exist and these polymorphisms may be important in ultimately understanding why some patients respond better to opioids than others as well as why some patients respond better to particular opioids and not others.

Pain.com: IS THERE ANY EVIDENCE THAT OPIOIDS ARE EFFECTIVE IN CHRONIC PAIN?

Dr. Argoff: Numerous randomized controlled studies have been completed which demonstrate that compared to placebo the studied opioid offered greater pain relief for patients with osteoarthritis, post-herpetic neuralgia, painful diabetic neuropathy, chronic low back pain, and cancer related pain. A non-controlled study has suggested that a subset of patients with chronic headache may respond favorably long term when treated with opioids. The important point made by this study was that only a relatively small subset of patients (less than 25%) continued to do well on opioids for the three-year period. Most of the other reported studies were of a much shorter duration. While opioids have been shown to provide analgesic benefits, which are superior to placebo treated patients, there are insufficient data to predict how durable this response will be for a given patient. The opioid medications, which were studied included codeine, oxycodone, morphine, fentanyl, methadone, and levorphanol among others.

Pain.com: WHO SHOULD BE TREATED WITH OPIOIDS?

Dr. Argoff: Patients with chronic pain who continue to suffer despite treatment with non-pharmacotherpeutic approaches, or a reasonable number of trials of non- opioid analgesics including neuromodulating agents as well as patients whose unique situation would contraindicate their use of other analgesics may be considered candidates for a TRIAL of opioid therapy. The key at this point is to emphasize the word, TRIAL- while many people may ultimately benefit from and tolerate treatment with an opioid, many others do not and the patient to be treated must hear emphatically from the treating health care provider that the use of opioids will be continued only if the patient experiences meaningful pain relief with acceptable side effects and without any other issues occurring that would contraindicate their continued use (such as misuse or abuse of the medication). Opioids, of course, are used in acute painful states including acute exacerbations of chronic pain when the severity of the pain warrants rapid relief.

Pain.com: WHAT TYPE OF ASSESSMENT IS REQUIRED BEFORE INITIATING OPIOID THERAPY?

Dr. Argoff: The treatment provider must be able to document the pain syndrome that is being treated with opioid therapy. This may require further diagnostic testing in some instances. Do not confuse WNL for within normal limits as this often may mean we never looked! The specific characteristics of the pain, provocative as well as palliative factors and the variability of the pain must be noted. Various assessment tools are available to help to document the intensity of the pain (numerical pain intensity scale) as well as the interference of the pain on the patient's activities (brief pain inventory). The results of prior treatments and their results, the patient's history of addiction (if any) and psychosocial history needs to be explored and documented as well. A number of tools including SOAPP (Screener and Opioid Assessment for Patient s with Pain) are now available to help predict the likelihood that a given patient will use opioids long term without any aberrant behaviors. These should be considered during the initial evaluation, not after a problem has arisen. Unless the treatment provider is

appropriately trained to do so, patients who may be considered otherwise as appropriate candidates for opioid therapy but who have a history of substance abuse or significant psychosocial issues may be referred to a specialized pain treatment facility which may have more experience with and may be more comfortable with treating such patients. Any relevant family history of substance abuse or addictions should be noted and the treatment provider should document that upon considering the benefits and risks of an opioid trial that the benefits appear to outweigh the risks. The rationale for opioid therapy must be clearly documented. This assessment is subject however to ongoing reassessment of the patient and the need and appropriateness of continuing opioid therapy.

Pain.com: WHAT OTHER TYPES OF TREATMENT MIGHT BE CONSIDERED CONCURRENTLY WITH OPIOID THERAPY?

Dr. Argoff: The use of opioids in the management of chronic pain should be considered as one tool in the overall management of the patient. Appropriate use of other medications, interventional pain management, physical rehabilitation alternative medical approaches and behavioral pain management strategies must be considered and implemented to the fullest extent possible.

Pain.com: WHAT IS A TRIAL OF OPIOID THERAPY?

Dr. Argoff: A trial of opioid therapy involves the documentation of realistic treatment goals. These may include sufficient pain reduction, improvement in function and possibly if relevant return to work. The patient must be informed of the potential benefits and risks of opioid therapy and any other relevant information you deem to be important related to their use of opioids. This can be accomplished in part by having the patient review and sign a treatment agreement prior to the initiation of the trial. Your policy regarding refills and medication dose adjustments as well as your policies regarding emergency issues can be discussed in such an agreement. Side effects must be discussed as well as the need for regular follow up for ongoing assessment and reassessment off this therapy. Guidelines for continuing treatment as well as for discontinuing treatment, eg. often called, "exit strategy," needs to be discussed with the patient at the initiation of the opioid treatment trial. Patients need to be aware that it may be necessary to titrate the opioid dose to the desired analgesic effect, and that no pharmacologic agent is likely to completely relieve chronic pain. An exit strategy, eg. failure of the therapy and discontinuation of such may occur if there is a lack of significant pain reduction, lack of functional improvement, intolerable side effects or patient non-compliance with the treatment.

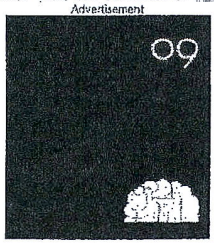
Pain.com: WHAT OPIOID SHOULD YOU USE?

Dr. Argoff: Numerous short-acting and longer-acting opioids are currently available. The treatment provider's choice of a particular opioid may be based upon the patient's past experiences, the patient's diagnosis and current evidence regarding treatment of such with specific opioids (if available) as well as the treatment provider's own personal experience with and comfort with the various agents currently available. Most pain specialists would advocate the use of a longer acting opioid for patients with chronic pain (around-the clock). Short acting opioids may be used to help titrate to an effective dose of a long acting agent as well as for breakthrough pain. Not all longer acting agents are equal with respect to their duration of action. For example, extended release oxycodone has a release mechanism which allows for approximately 40% of the dose to be immediately released and only 60% of it released over a more extended period of time (12 hours); contrast that with the fentanyl patch which may provide analgesia to a patient for up to72 hours. One must be familiar with the various agents and their relative strengths and limitations before prescribing. Certain opioids such as methadone have unique pharmacokinetic issues and/or drug-drug interactions, which the prescriber must be aware of when prescribing these!

Pain.com: WHAT SHOULD BE CONSIDERED AT PATIENT REASSESSMENT?

Dr. Argoff: Patient reassessment involves noting the presence or absence of analgesia, noting functional improvement or lack of such, noting the presence or absence of adverse effects (and treating them) as well as noting the presence or absence of aberrant drug-taking behaviors. If there is insufficient pain relief, then the opioid dose can be increased or the opioid itself rotated to a different one due to incomplete cross-tolerance among various opioids. Adverse effects must be aggressively managed. The treatment provider must be aware of the difference among physical dependence, tolerance, pseudotolerance, addiction and pseudoaddiction when screening the patient for aberrant behaviors.

Urine drug testing must be considered as well. Ultimately, the treatment provider needs to determine at the end of the reassessment visit whether the opioid therapy should be continued or if an exit strategy should be implemented.



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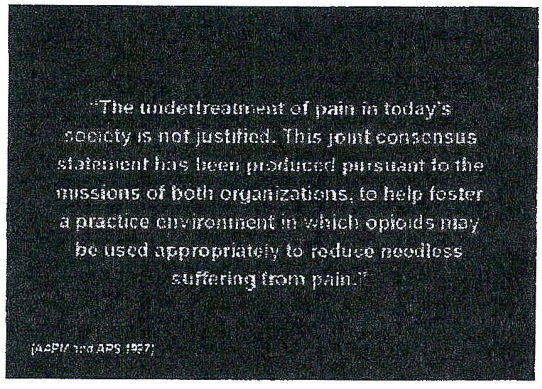
Advances in the Management of Breakthrough Pain
Interview with Gerald M. Aronoff, M.D.

Gerald M. Aronoff, M.D. is Board Certified by the American Board of Pain Medicine and in Psychiatry by the American Board of Psychiatry and Neurology. He has been practicing in the field of pain medicine for more than 25 years and is one of the founding members of the American Academy of Pain Medicine. Throughout his career, Dr. Aronoff has emphasized the importance of interdisciplinary pain management with the goal of functional restoration. Dr. Aronoff is a graduate of the New Jersey College of Medicine and did his residency training at the Harvard Medical School's, McLean Hospital. He did fellowship training at the Boston University School of Medicine and spent the first part of his career as Medical Director of the Boston Pain Center before relocating to Charlotte, North Carolina to become the Medical Director of the Presbyterian Center for Pain Medicine. From 2001 to 2005, he was Chairman of the Department of Pain Medicine at Presbyterian Hospital and Presbyterian Orthopedic Hospital in Charlotte, North Carolina. He continues in the full-time practice of pain medicine and is involved in patient care as well as clinical research on the pharmacological management of chronic pain as well as preventing disability from chronic pain. He is the author of *The Evaluation and Treatment of Chronic Pain* (3rd Ed, 1999) and his most recent book is *The Handbook on The Pharmacological Management of Chronic Pain* (2005). Dr. Aronoff is currently Adjunct Associate Professor, Department of Psychiatry, Duke University School of Medicine. Dr. Aronoff is the Consultant Editor for the Pain.com category, Breakthrough Pain

Pain.com: Good morning Dr. Aronoff, and welcome to the continuing series of expert interviews on breakthrough pain. You wrote the 1st Edition of your text *Evaluation and Treatment of Chronic Pain* in 1985, and you did not advocate the use of maintenance opioids for the treatment of non-cancer pain except in rare circumstances. I understand that your position on this topic has changed dramatically over the years. Could you please discuss why your position changed and tell us about your current views on the use of opioids for severe non-cancer pain management?

Dr. Aronoff: Much of my career has been spent working in the context of a multidisciplinary pain management center (MPC). In the 1970s and 1980s, one of the outcome measures for a successful MPC was the percentage of patients "successfully" tapered from opioids during the treatment program and maintained off of opioids during follow-up. Studies from MPCs often provided conflicting data. Much of this was uncontrolled data, anecdotal and inadequate to reach any definitive conclusions. For example, patients were queried about their opioid use. Most often, this involved short-acting opioids with an analgesic half-life of 3 to 4 hr. Yet often they were being prescribed every 6 to 8 hr. Patients were asked whether they had sustained benefit, significant functional improvement or a greater ability to cope with pain. Generally the responses were not affirmative, and it was concluded that opioids were ineffective for chronic pain. I now suggest that the conclusions were unfounded and misleading. They often reflected inadequate or inappropriate opioid prescribing without enough attention to pharmacodynamics or pharmacokinetics. As many of the patients responded to an MPC treatment approach, this further reinforced the conclusion that opioids should not be used in chronic pain. In retrospect, I can say that many of these patients had not done well prior to their admission to the MPC when they were on opioids and, therefore, justification of the medication taper was not difficult. But with 2006 knowledge and hindsight, I suspect that many of us inadvertently did a disservice to a group of patients who were "detoxified" or treated for "drug dependence." These patients might have benefited from long-term opioid treatment, but we dogmatically refused to prescribe opioids. Some of the patients lost to follow up might have changed physicians and were treated more aggressively elsewhere for ongoing pain. Over the years, I have been grateful to multiple colleagues who urged me to revisit this issue. Much has been learned about opioid use in chronic non-cancer pain, especially from clinical studies and treatment of cancer pain. Insights from the cancer population include the following: · Unrelieved pain is associated with increased morbidity and psychosocial distress. · Effective analgesia can reverse these and improve quality of life. · Management problems related to tolerance or physical dependency are rare. · Addiction is rare without a prior history of substance abuse. Multiple studies over the last 20 years, suggest that these same findings apply to the non-cancer pain population. We now know that in appropriately selected non-cancer pain patients, opioids have a low morbidity (often less than NSAIDs), and a low addiction potential. Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects (other than constipation) more so than to analgesic effects. In 1997, the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) issued a joint consensus statement (figure 1)



Pain.com: In view of these comments, why do some medical practitioners still feel uncomfortable treating non-cancer pain more aggressively, since many studies suggest that the problem is often quite disabling.

Dr. Aronoff: It has become clear that chronic non-cancer pain is a major public health problem causing enormous suffering as well as being a major economic drain on society as a result of direct and indirect medical costs and associated lost productivity. The three most prevalent, nonmalignant diseases associated with significant pain include back pain with a prevalence of more than 50 million, arthritis 43 million and chronic headache with more than 40 million sufferers in the United States alone. Estimates indicate that on any given day in America, up to 30% of our population can be suffering from chronic pain. When the physician considers the use of opioids in chronic pain patients with moderate-to-severe pain, the use of sustained-acting (or long-acting) opioid preparations has improved the likelihood of getting good analgesia for around-the-clock pain. The side-effect profile of these medications is significantly lower than repeated dosing with short-acting opioids. Chronic pain is generally subdivided into persistent (e.g., around-the-clock) pain and breakthrough pain. Most pain practitioners think of persistent pain as the baseline pain that chronic pain patients experience. As noted above, when this pain is severe it is generally managed with the use of sustained-action, time-released opioids, at times in conjunction with peripherally acting non-opioid analgesics and adjuvant analgesics. In 1990, Portenoy and Hagen (1) described breakthrough pain in cancer patients as a flare up or acute exacerbation of moderate-to-severe pain in otherwise controlled baseline pain. They distinguished breakthrough pain from poorly controlled persistent pain, as well as from acute episodic pain. Breakthrough pain is further subdivided into *incident pain*, associated with movement or activities (that may be predictable, or unpredictable such as pain related to coughing or sneezing, or bladder spasms); *idiopathic or spontaneous pain*, not having a definable pattern; and *end-of-dose failure* that occurs because the analgesic action of the around-the-clock medication is inadequate to contain the pain until the next scheduled dose. End-of-dose failure generally is not considered actual breakthrough pain and often is best managed by an adjustment in the dose of around-the-clock medication. Multiple surveys and studies have documented that more than half of chronic cancer pain patients experience significant breakthrough pain (2), with some studies indicating a prevalence of breakthrough pain as high as 89% (3). It is generally of rapid onset, brief and in > 40 % of cancer patients begins in less than 4 minutes (2). It is now well established that uncontrolled breakthrough pain often predicts a poor patient outcome associated with patient dissatisfaction with treatment, decreased levels of function and increased levels of anxiety and depression. Unrelieved breakthrough pain increases the economic burden placed on patients and the healthcare system because of increased hospitalizations and more medical and emergency room visits (4). Most patients who have persistent pain and breakthrough pain are able to acknowledge that there are multiple factors influencing their pain, and these range from the disease itself to their activity level or other physical and psychological factors. Clinicians are advised to take a very detailed history in an attempt to define the factors that influence the baseline persistent pain, as well as the episodes of breakthrough pain. There is no justification for withholding treatment for patients with severe, non-cancer breakthrough pain if they meet the criteria for treatment. Despite concerns regarding scrutiny from regulatory agencies, pain management within the guidelines of the various regulatory agencies is appropriate and should be viewed as the standard of care.

Pain.com: Conventional management of breakthrough pain involves the use of immediate release opioids or short-acting opioids and most physicians have developed a certain level of comfort prescribing these. Why is there a need for new agents to manage breakthrough pain?

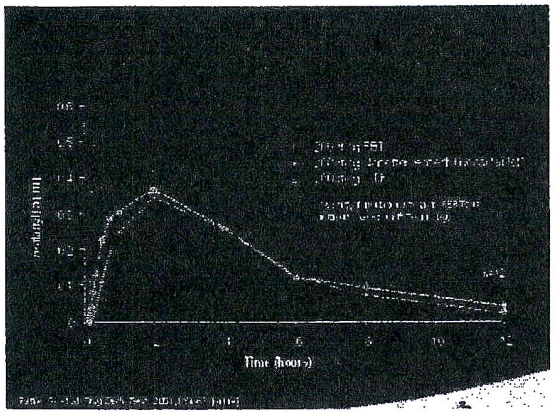
Dr. Aronoff: In a recent article, *Prevalence and Characteristics of Breakthrough Pain in Opioid Treated Patients with Chronic Non-Cancer Pain*, Portenoy et al. (5) surveyed 228 patients with diverse types of chronic non-cancer pain all of whom had controlled baseline pain. They noted that 74% experienced severe to excruciating breakthrough pain, (exceeding the prevalence of 64% and 51% in some cancer surveys) although they found that the median number of episodes per day was less (2 for the non-cancer pain group versus 4-6 for the cancer population). They also found that in the non-cancer pain population, the time to peak pain intensity was 10 minutes or less and the median duration was one hour. Although oral agents are most commonly used to treat breakthrough pain, GI absorption prevents rapid absorption for most agents and therefore is often inadequate for rapid-onset breakthrough pain. Other possibilities include rectal and transdermal routes, as well as multiple invasive techniques such as intramuscular, subcutaneous, intravenous, epidural, and spinal. Invasive techniques such as IV administration and patient-controlled analgesia (PCA) provide rapid onset of action but are expensive and require technical expertise.

Pain.com: In a 2005 article, you and several colleagues discuss some of the advantages of using oral transmucosal fentanyl citrate (OTFC, Actiq®) for rapid onset breakthrough pain. Can you discuss some of your conclusions with our readers?

Dr. Aronoff: Oral transmucosal fentanyl OTFC (Actiq®) was developed to provide rapid-onset and relatively short duration of action via a convenient and noninvasive delivery system (6-9). It is FDA approved for the treatment of breakthrough pain in opioid tolerant cancer patients, but because it is so well tolerated, increasingly has been used for severe rapid-onset breakthrough pain in noncancer patients. Advantages of the oral transmucosal route relate to the physiology of the oral mucosa and pharmacology of fentanyl. The oral mucosa is highly permeable, well vascularized, and lipophilic allowing for rapid drug delivery through the mucosa into the bloodstream. The oral cavity has a relatively uniform temperature and a large surface area, further optimizing this delivery route. The pharmacodynamics of OTFC are comparable to intravenous administration of hydrophilic opioids such as morphine (10,11) but because intravenous access is not necessary, OTFC has the advantages of convenience in terms of portability and ease-of-use that are similar to pills and liquids. Many drugs are not suitable for oral transmucosal administration. Overall, lipophilic drugs are better absorbed in hydrophilic drugs Morphine, hydrocodone, and oxycodone are poorly absorbed across the oral mucosa due to their low lipid solubility and extensive ionization at the pH of the mouth. Each OTFC unit consists of a fentanyl-containing lozenge attached to a handle. As the lozenge dissolves during the OTFC administration, approximately 25% of the total fentanyl dose is rapidly absorbed across the oral mucosa and become systemically available. The remaining 75% of the total dose is swallowed, and approximately one-third of that amount (25% of the total dose) escapes hepatic and intestinal first pass metabolism and is absorbed more slowly in the intestine. The rapid oral transmucosal absorption of fentanyl combined with fast diffusion across the blood-brain barrier contributes to its swift onset of effect. In our study (12), we noted that the most serious adverse effects associated with all opioids are respiratory depression, circulatory depression, hypotension, and shock. These are extremely rare in appropriately selected patients who take their medication as directed. Patients who are regularly receiving opioid analgesic drugs are typically less susceptible to the serious adverse effects then opioid-naive patients. In particular, caution should be used when titrating OTFC in patients with medical conditions that predispose them to respiratory depression. We specifically indicated that patients at highest risk for adverse side effects include: · The elderly · Patients with significant pulmonary disease · Patients who indicate that even low doses of most medications cause considerable adverse side effects. We advised increased caution in the titration of these higher risk individuals. We concluded that the unique pharmacodynamic properties of OTFC combined with its non-invasive delivery form offered advantages over current medications then available for the treatment of rapid onset breakthrough pain and that in appropriately selected patients, OTFC was safe and effective.

Pain.com: I understand that there is a next-generation fentanyl product that has recently been FDA-approved for cancer breakthrough pain. Can you discuss this and its advantages over existing breakthrough pain medication.

Dr. Aronoff: The newest transmucosal delivery system utilizes OraVescent® technology that relies on an effervescent reaction to improve the efficiency of the buccal fentanyl absorption. The effervescent reaction causes the production and dissipation of carbon dioxide, causing a dynamic shift in pH as the tablet dissolves. The initial low pH favors dissolution of fentanyl citrate in saliva. The subsequent increase in pH favors the buccal absorption of non-ionized fentanyl across the buccal mucosa and increases the permeation of fentanyl into and through the buccal mucosa. Pharmacokinetic data suggest that the effervescence reaction employed in the fentanyl effervescent buccal tablet (FBT, Fentora®) increases the total amount of fentanyl absorbed, increases peak blood concentration, and decreases the time it takes to achieve peak blood concentration when compared with buccal delivery systems without effervescence (13, 14) Research data is compelling at indicating that the rate and extent of fentanyl absorption is greater with FBT Fentora when compared to non-effervescent fentanyl formulations. (Fig 2) as a result of the effervescent reaction.



Perhaps the most important clinical advantage in the use of the fentanyl effervescent buccal tablet is the significant increase in fentanyl bioavailability. The enhanced bioavailability via the oral transmucosal route allows for more of the fentanyl to be rapidly absorbed into the systemic circulation and CNS (48% vs 22% for OTFC), and less absorbed via GI metabolism. The absolute bioavailability for FBT Fentora® is about 65% (vs 47% for OTFC). This has favorable implications for the significant population of chronic pain patients with rapid onset breakthrough pain. In my clinical experience, many such patients limit their activity level and are far more sedentary than they need to be because of a fear of breakthrough pain. As noted above in this article, although some of breakthrough pain is predictable, frequently it is not and comes on very rapidly without warning. Some patients are fearful that if they are out alone, or with family or friends, they will have an episode of breakthrough pain severe enough that they will need to be taken to an emergency room or be taken home. This fear contributes to many patients remaining homebound. For them, the reassurance of getting more rapid analgesia allows them to increase their functional daily activities and helps them improve their quality-of-life. FBT's Fentora® clinical indication is similar to that of OTFC Actiq® that is, the management of breakthrough pain in patients with cancer who are opioid tolerant. This degree of tolerance is described as patients who are taking · At least 60 mg of oral morphine a day · At least 25 µg transdermal fentanyl per hour · At least 30 mg of oxycodone a day · At least 8 mg oral Hydro morphine a day · An equianalgesic dose of another opioid for a week or longer. Guidelines from Cephalon, Inc. (package insert) indicate that Fentora® FBT should not be used in opioid non-tolerant patients. Multi-center cancer pain studies (15) document the clinical efficacy and safety of using FBT Fentora® for rapid onset chronic breakthrough pain and conclude that most patients (91%) found an effective dose of FBT Fentora® or were managed at the 800 µg dose with a low incidence of treatment-related adverse side effects and without any reports of respiratory depression.

Pain.com: You emphasized earlier that FBT Fentora® is FDA-approved only for breakthrough pain in cancer patients who are opioid tolerant. You also indicated that OTFC Actiq® had a similar indication. We understand from the clinical experience with OTFC Actiq® that many of the pain physicians who use OTFC Actiq® do so in patients who have moderate to severe non-cancer breakthrough pain. Can you comment on this and the implications for FBT Fentora®?

Dr. Aronoff: I believe that my clinical experience is similar to many of my pain medicine colleagues in that much of what we do in pharmacological management with chronic pain patients is "off label" for non-FDA-approved indications. Common examples include the use of tricyclic antidepressants for neuropathic pain. This class of medication is FDA-approved for the management of depression and is not FDA approved for any specific pain process. However, it has been used over the last 30 years for the management of many types of neuropathic pain and other pain states because it has been found to be clinically effective. Other examples of common off label prescribing include the use of gabapentin (Neurontin®) and many other antiepileptics drugs for many types of neuropathic pain. Until recent years, gabapentin was not FDA approved for any pain condition. Prior to its approval for postherpetic neuralgia, In recent years, it became FDA-approved for postherpetic neuralgia gabapentin For years it had been used off label because it was found to be safe and clinically effective. Pregabalin (Lyrica®) has more recently been developed released as an anti-epileptic drug that is FDA-approved for postherpetic neuralgia and for painful diabetic neuropathy. However, many studies are emerging to suggest clinical efficacy in other neuropathic and non-neuropathic pain conditions justifying, in my opinion off label usage. The Lidoderm 5% Patch® is FDA-approved for postherpetic neuralgia and in recent years has been used off label successfully in many neuropathic and nociceptive pain conditions. These are just a few of the many examples of appropriate off label prescribing in the field of pain medicine. Physicians who limit their pharmacological choices to only FDA-approved clinical indications are putting themselves and their patients at a serious disadvantage by not considering treatment options supported by evidence based medicine and good clinical studies to support off label usage. Having said that, I strongly believe that as a physician it is my responsibility to inform my patients when I am using a medication off label. I discuss with them the FDA-approved indications and also share with them my belief that there is adequate clinical evidence to support trying the proposed medication to assist them in their pain management. I document this discussion in my progress note. I have had a great deal of experience using OTFC Actiq® for rapid onset breakthrough pain in non-cancer patients as well as cancer patients. Available data suggests that the overwhelming use of OTFC Actiq® is off label for non-cancer breakthrough pain. Clinical reports support its efficacy and safety in appropriate carefully selected patients. A recent open-label multicenter study of fentanyl effervescent buccal tablets in opioid tolerant patients with chronic non-cancer pain and breakthrough pain (16) evaluated patient's preference regarding use of FBT FEBT® compared with previous supplemental opioids after approximately 4 weeks of use. The primary pain condition treated most often was chronic low back pain (65%) and the pathophysiology of the breakthrough pain was predominantly nociceptive (40%), mixed (37%) and predominantly neuropathic (22%). The most common previous supplemental opioids prior to entering the study were oxycodone (23%), hydrocodone/APAP (22%), and oxycodone/APAP (14%). The study concluded that: · The majority of patients (91%) with chronic non-cancer pain conditions were able to identify an effective dose of FBT FEBT to adequately treat their breakthrough pain. · The results of the interim analysis suggested that a majority of patients with chronic non-cancer pain and breakthrough pain prefer FBT FEBT (100 µg to 800 µg) over previous supplemental opioids.

Pain.com: Dr. Aronoff, do you have any concluding comments you would like to share with our readers?

Dr. Aronoff: In my book, *Handbook on the Pharmacological Management of Chronic Pain*, I emphasize what I believe to be basic principles in the management of all chronic pain patients. These include a treatment approach that addresses the patient's: · Pain · Suffering (emotional distress) · Functional activity level (ADL) · Quality-of-life Chronic pain is woefully under treated and as I noted above, is now recognized as being a major public health problem. Those of us involved in treating this population need to recognize that clinically effective pharmacotherapeutics may play a major role in the care of many patients who might otherwise be incapacitated by their pain. Patients should be carefully evaluated with a comprehensive history and physical examination. Every treatment offered to a patient should be selected only after consideration of the risks and potential benefits of the treatment. I strongly believe that pharmacotherapy is but one aspect of a more comprehensive treatment approach that many patients require. However, effective treatment of breakthrough pain episodes may improve physical and emotional well-being, as well as vocational and recreational functionality for many patients. Additionally, it may decrease patient's reliance upon and use of the healthcare system, particularly the emergency room. The rapid onset of analgesia from the latest effervescent fentanyl buccal tablets acts as oral from new formulations of fentanyl may act as oral PCA and gives outpatients the same type of control that parenteral PCA gives hospital patients.

References

1. Portenoy RK, Hagen NA. Breakthrough pain: Definition, prevalence and characteristics. Pain 41:273-281, 1990.

2. Portenoy RK. Symposium on Breakthrough Pain at the 15th Annual Scientific Meeting of the American Pain Society, 1996 Nov 14-15, Wash DC.

3. Fine PG, Busch MA. Characteristics of breakthrough pain by hospice patients and their care givers. J. Pain Sympt Manage 1998; 16: 179-183

4. Fortner BV, et al. A survey of pain-related hospitalizations, emergency department visits, and physician visits by cancer patients with and without breakthrough pain. J. Pain. 2002; 3:38-44.

5. Portenoy RK, Bennett DS, Rauck R, Simon S, Taylor D, Brennan M, Shoemaker S. The Journal of Pain, Vol 7, #8 (August) 2006: pp 583-591.

6. Lichtor JL, et al. The relative potency of oral transmucosal fentanyl citrate compared with IV morphine in the treatment of moderated to severe postoperative pain. Anesth Analg. 1999; 89:732-736.

7. Simmonds MA. Oral transmucosal fentanyl citrate produces pain relief faster than medication typically used for breakthrough pain in cancer pain in cancer patients (abst 180) Proc Am Soc Clin Oncol 1998; 16:3238-3245.

8. Christie JM et al. Dose titration, multicentre study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. J Clin Oncol 1998; 16:3238-3245.

9. Portenoy RK, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 1999; 79:303-312.

10. Lichtor JL, Sevarino FB, Joshi GP, et al. The relative potency of oral transmucosal fentanyl citrate compared with intravenous morphine in the treatment of moderate to severe postoperative pain. Anesth Analg 1999;89:732-8.

11. Lu JK, Bailey PL. Dose-related respiratory pharmacology of oral transmucosal fentanyl citrate (OTFC®) versus intravenous morphine: A randomized, double-blind, double company study. Anesthesiology [abstract] 2003; 99: A967.

12. Aronoff GM, Brennan MJ, Pritchard DD, and Ginsberg B. Evidence-based oral transmucosal fentanyl citrate (OTFC®) dosing guidelines. Pain Medicine 2005;Vol 6,#4: 305-314.

13. Durfee S, Messina J, Khankari R. Fentanyl Effervescent Buccal Tablets: Enhanced Buccal Absorption. Am J Drug Deliv 2006; 4(1): 1-5.

14. Pather SI, Siebert JM, Hontz J, et al. Enhanced buccal delivery of fentanyl using the OraVescent drug delivery system. Drug Delivery Tech 2001 (1):54-57.

15. Hale M, Webster L, Peppin J, Messina J. Open-Label Study of Fentanyl Effervescent Buccal Tablets in Patients with Chronic Pain and Breakthrough Pain: Interim Safety and Tolerability Results. Presented at the American Academy of Pain Medicine Annual Meeting, February 22-25, 2006, San Diego, CA.

16. Webster Lynn, Taylor Donald, Peppin John, Niebler Gwendolyn. Patient's Experience with Fentanyl Effervescent Buccal Tablets: Interim Analysis of a Long-Term, Multicenter, Open-Label Study in Cancer-Related Breakthrough Pain. Presented at the American Pain Society's Annual Meeting, May 3-6, 2006, San Antonio, TX.