Emerging Concepts in Pain Cancer Care

Scott Pritzlaff, MD

Division of Pain Medicine

Department of Anesthesia, Perioperative and Pain Medicine

Stanford University

https://stanfordhealthcare.org/pain

spritzla@stanford.edu

Disclosures:

There is no conflict of interest or personal *commercial interest* in any entity producing, marketing, re-selling, or distributing health care goods or service consumed by, or used on, patients in the last 12 months for all the following speakers AND planners in relation to this activity

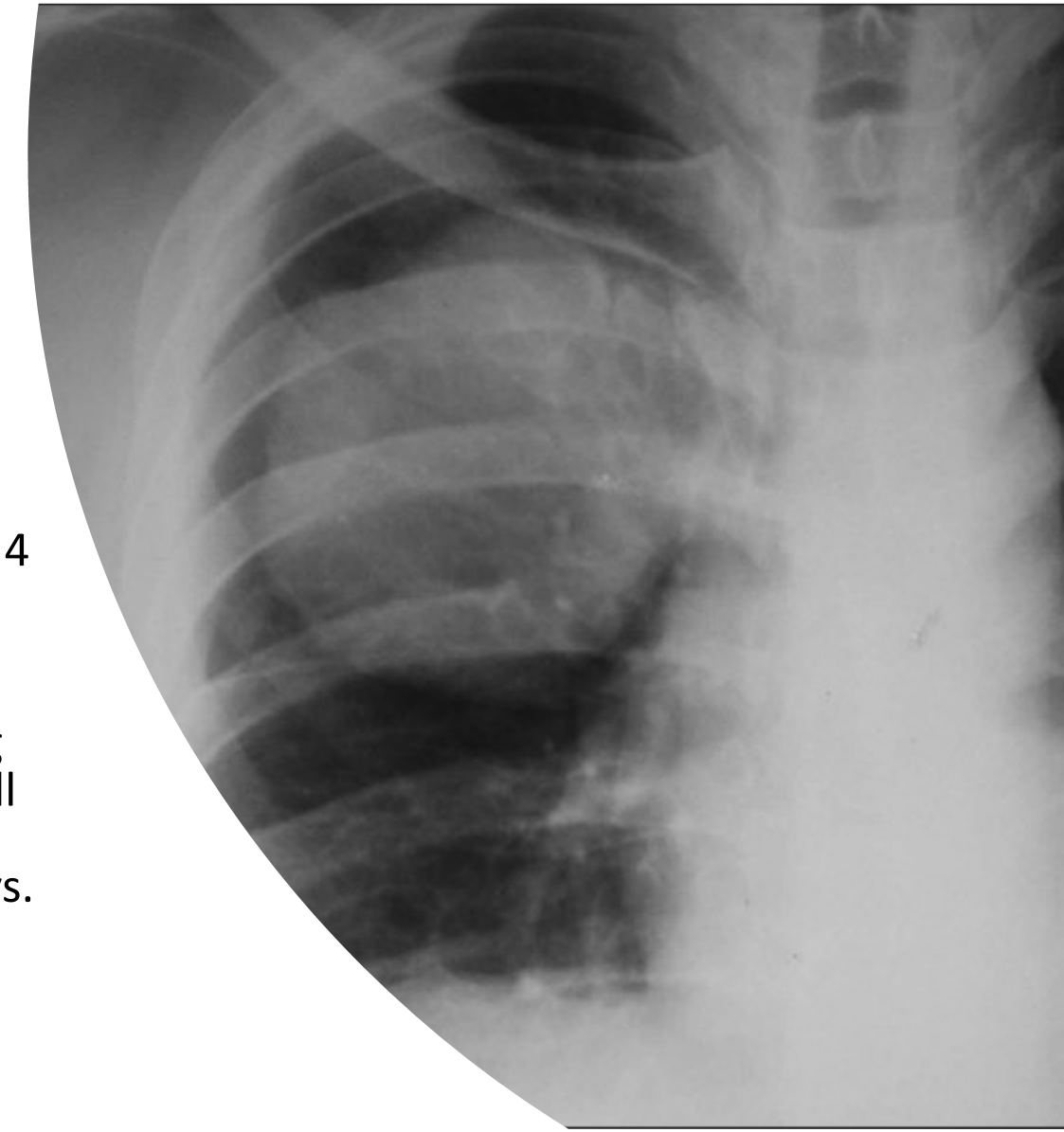
Speakers: Scott Pritzlaff, MD

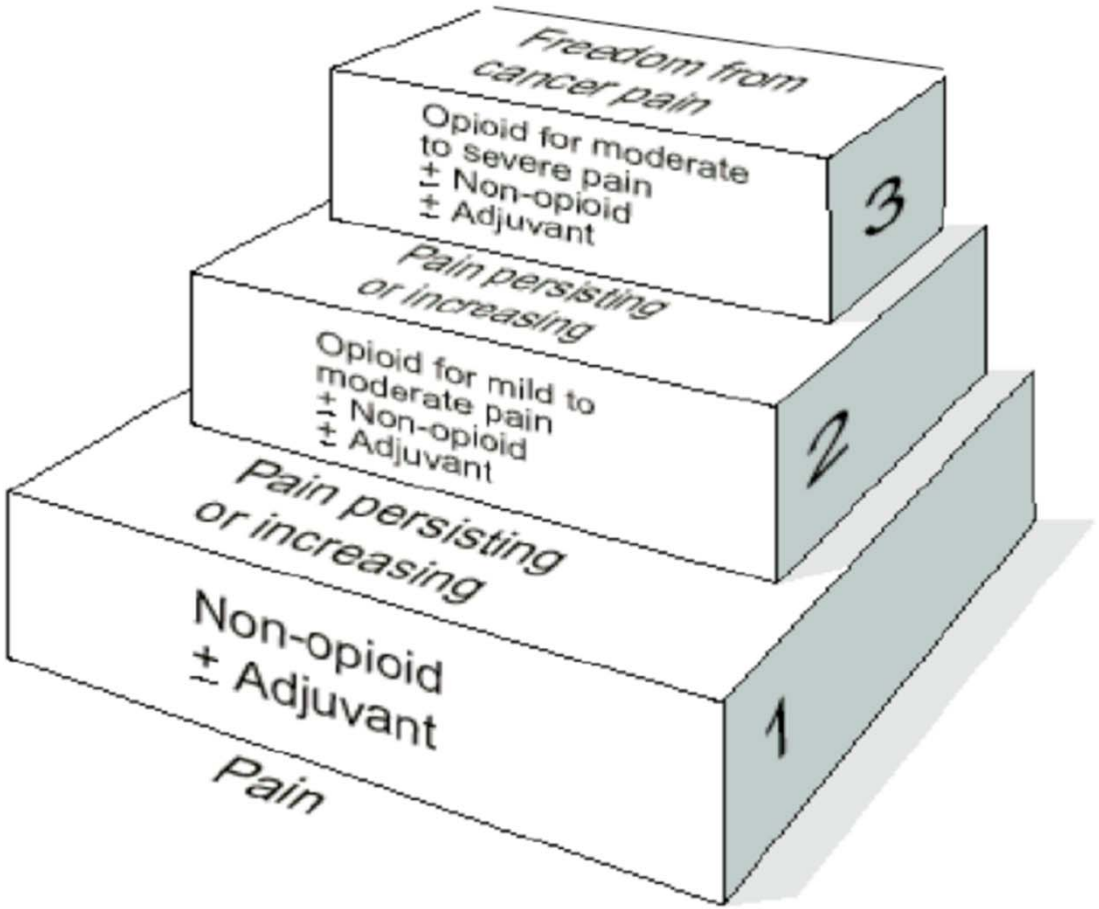
OBJECTIVES

- Identify new methods of assessing and understanding the pain experience
- Develop a basic toolbox for treatment of mild and moderate cancer pain
- Recognize evolving interventional treatments for cancer pain: neurolytic techniques, peripheral stimulation, high intensity focused ultrasound (HIFU), and intrathecal therapy

Clinical Vignette

A 64 year old retired tech CEO presents with shortness of breath and persistent chest pain. A CT scan reveals a large, 4 x 4 right lung mass. There is evidence of metastatic disease to the right 9th and 10th ribs and chest wall. His pain is uncontrolled despite oxycodone 5-10mg every 4 hours. Biopsy confirms non-small cell adenocarcinoma. He is scheduled to begin chemotherapy in the next few days. What options do you have for pain control?




Freedom from cancer pain
Opioid for moderate to severe pain
± Non-opioid
± Adjuvant
3
Pain persisting or increasing
Opioid for mild to moderate pain
± Non-opioid
± Adjuvant
2
Pain persisting or increasing
Non-opioid
± Adjuvant
Pain
1

www.who.int

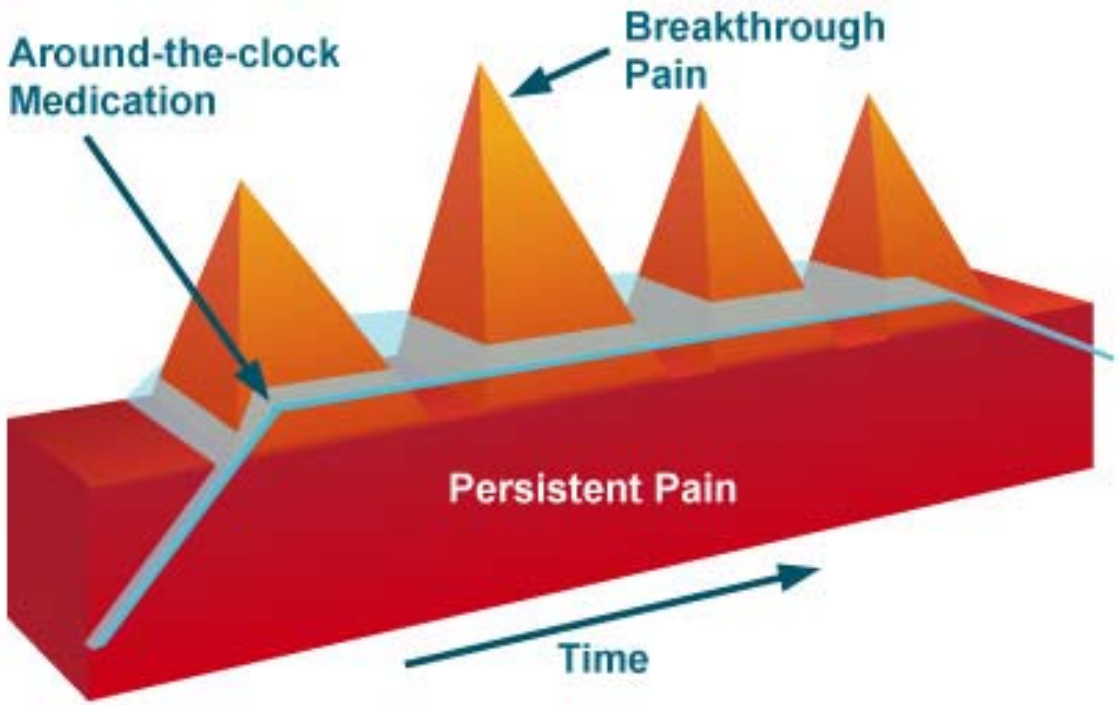
What is Cancer Pain?

Traditionally considered the archetype of “mixed pain”

- Experts estimate 31.2-43% of patients with cancer pain experience neuropathic pain

Breakthrough cancer pain (BTPc)

- Defined as a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain
- Pooled prevalence 59.2%

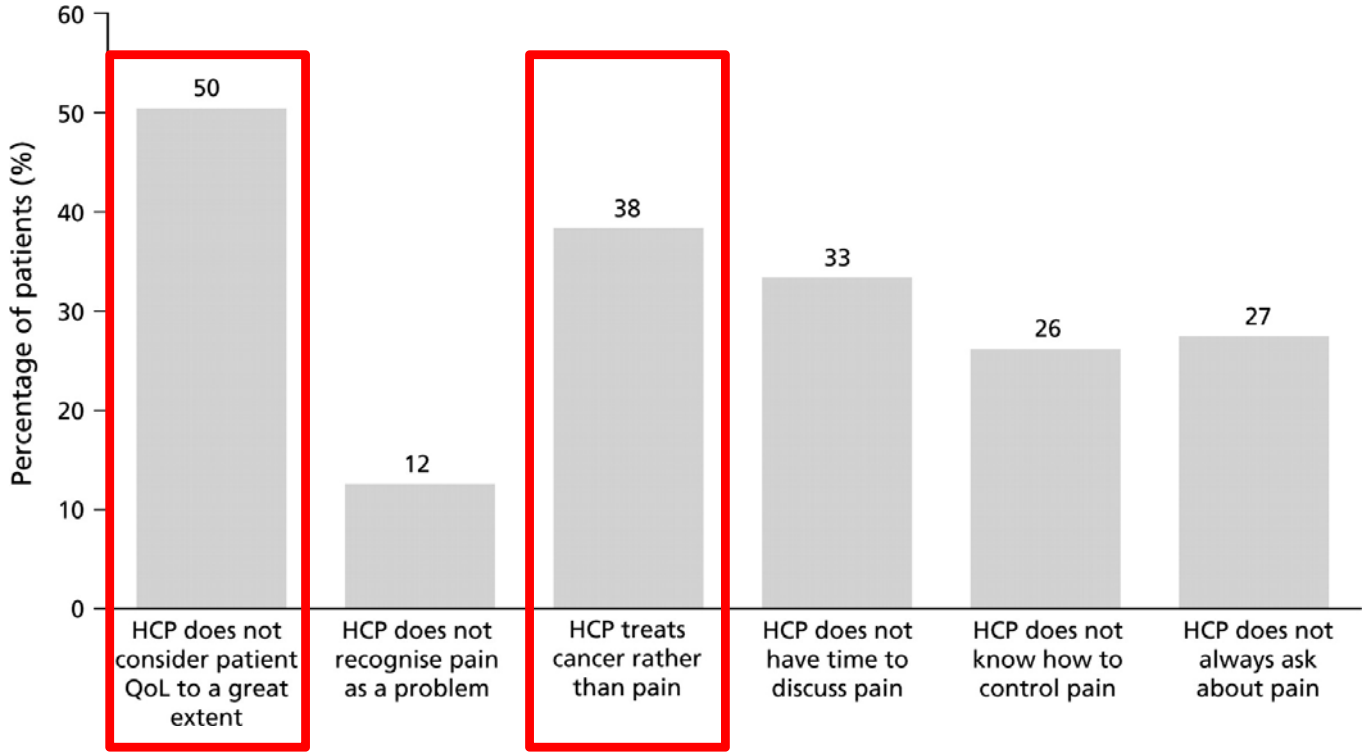

Around-the-clock
Medication
Breakthrough
Pain
Persistent Pain
Time

Basics of Cancer Pain

- Most recent meta-analysis (2016), 122 studies, 95,794 patients
  - 66.4% of patients with advanced, metastatic or terminal disease experience pain
  - 55% experience pain during treatment
  - 39.3% experience pain after curative treatment (i.e. chronic)

- **38% of all cancer patients experience moderate – severe pain (>/=5)**

Patient beliefs about their pain treatment from their health care provider (HCP)—global survey results (n = 573).



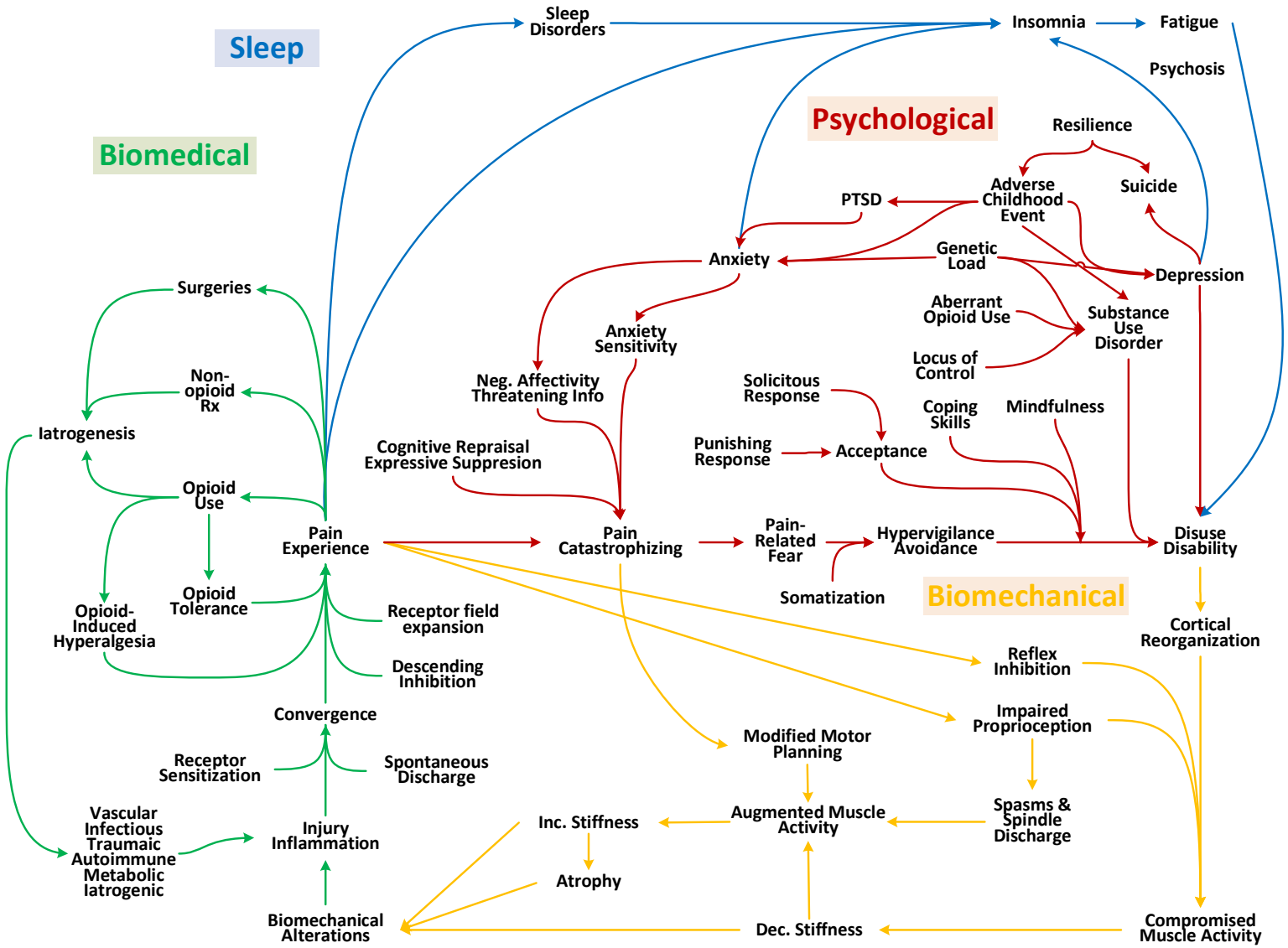
H. Breivik et al. Ann Oncol 2009;20:1420-1433

Cancer Pain Challenges

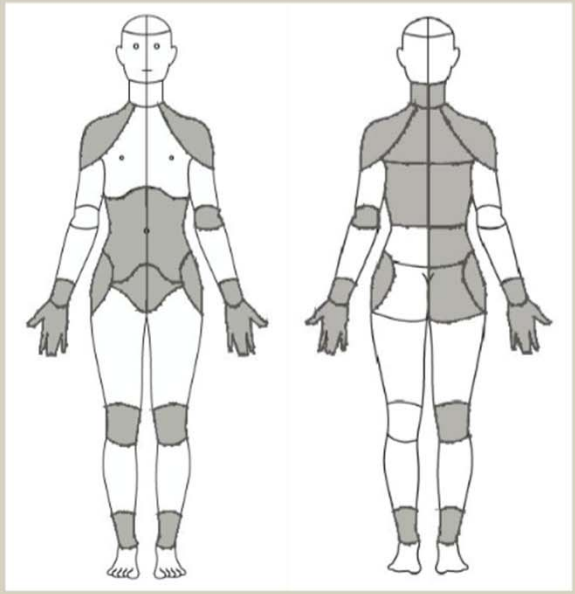
- Related to tumor involvement
  - Accounts for 78% of pain problems in inpatient cancer population and 62% of outpatient cancer population
  - Metastatic bone disease, hollow viscous involvement and nerve compression or infiltration are most common causes
- Pain associated with cancer therapy
  - 19% of pain problems in inpatient population and 25% in outpatient population
- Pain unrelated to cancer or therapy
  - Approx. 3% of inpatients have pain unrelated to their cancer and 10% in outpatient population
- Generalized pain in a dying cancer patient

Foley KM. Acta Anaesthesiol Scand 1982;74:91-6. Twycross RG. Pain 1982;14:303-10.


0
No pain
10
Worst possible pain



Courtesy of Ming Kao, MD, PhD

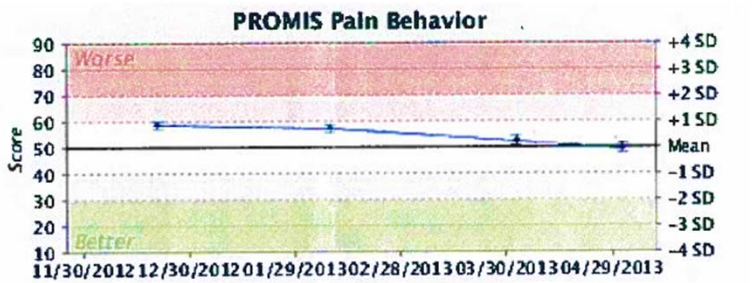


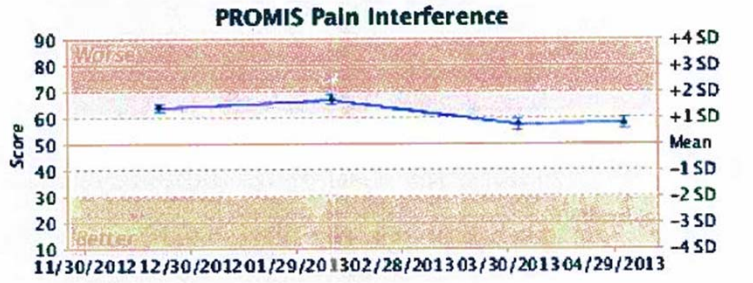
37 areas selected on the most recent body map

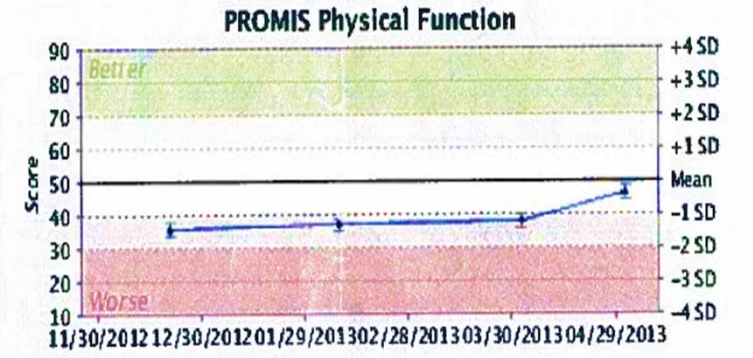
CHOIR

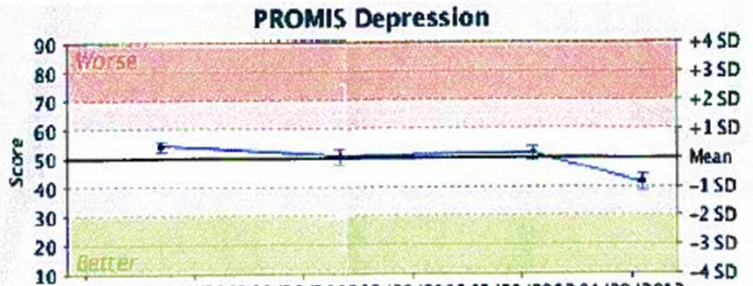
PROMIS Outcomes Measures	Score	%ile	Category
Depression	66	95	Moderate
Anxiety	54	66	Mild
Anger	48	42	
Upper Extremity *	65	93	
Mobility *	68	96	
Pain Interference	70	98	
Pain Behavior	62	88	
Fatigue	59	82	
Sleep-Related Impairment	56	73	
Sleep Disturbance	56	73	Mild
Emotional Support *	46	34	
Satisfaction Roles Activities *	70	98	
Global Health - Physical *	68	96	
Global Health - Mental *	69	97	
Social Isolation	52	58	

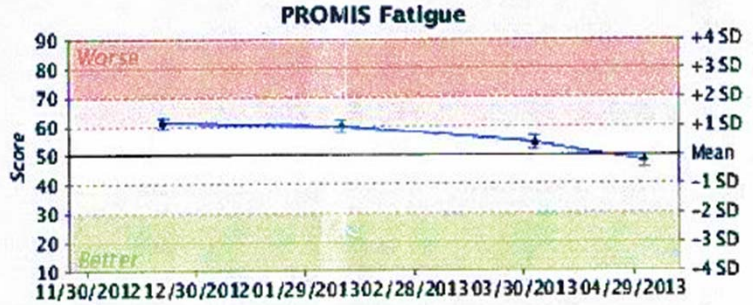
** Scores and percentiles have been inverted*

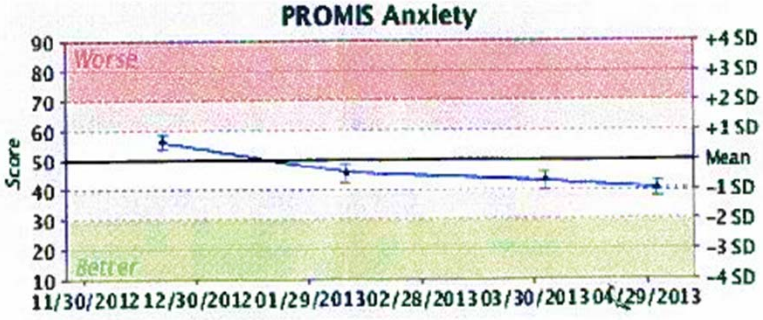

PROMIS Pain Behavior
Worse
Better
Score
90
80
70
60
50
40
30
20
10
+4 SD
+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
-4 SD
11/30/2012 12/30/2012 01/29/2013 02/28/2013 03/30/2013 04/29/2013


PROMIS Pain Interference
Worse
Better
Score
90
80
70
60
50
40
30
20
10
+4 SD
+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
-4 SD
11/30/2012 12/30/2012 01/29/2013 02/28/2013 03/30/2013 04/29/2013


PROMIS Physical Function
Better
Worse
Score
90
80
70
60
50
40
30
20
10
+4 SD
+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
-4 SD
11/30/2012 12/30/2012 01/29/2013 02/28/2013 03/30/2013 04/29/2013


PROMIS Depression
Worse
Better
Score
90
80
70
60
50
40
30
20
10
+4 SD
+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
-4 SD
11/30/2012 12/30/2012 01/29/2013 02/28/2013 03/30/2013 04/29/2013


PROMIS Fatigue
Worse
Better
Score
90
80
70
60
50
40
30
20
10
+4 SD
+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
-4 SD
11/30/2012 12/30/2012 01/29/2013 02/28/2013 03/30/2013 04/29/2013


PROMIS Anxiety
Worse
Better
Score
90
80
70
60
50
40
30
20
10
+4 SD
+3 SD
+2 SD
+1 SD
Mean
-1 SD
-2 SD
-3 SD
-4 SD
11/30/2012 12/30/2012 01/29/2013 02/28/2013 03/30/2013 04/29/2013

Therapeutic Strategy for Cancer Pain

Pharmacotherapy

- Non-opioid analgesics
  - NSAIDs
  - Acetaminophen
- Opioid analgesics
  - Codeine
  - Morphine
  - Hydrocodone
  - Oxycodone
  - Fentanyl
  - Hydromorphone
  - Methadone

Pharmacotherapy

- Adjuvant analgesics
  - Anticonvulsants
  - Antidepressants
  - Local anesthetic agents: Lidocaine
  - GABA agonists
  - NMDA antagonists: Ketamine
  - **Others: Cannabinoids**

Non-pharmacological Modalities

- Cognitive behavioral interventions
- Massage, Physical Therapy
- Acupuncture
- Radiation Therapy
- **HIFU**
- Surgery
- **Interventional procedures**

14% of Cancer patients do not achieve good pain relief with acceptable side-effects even when treated by experts.

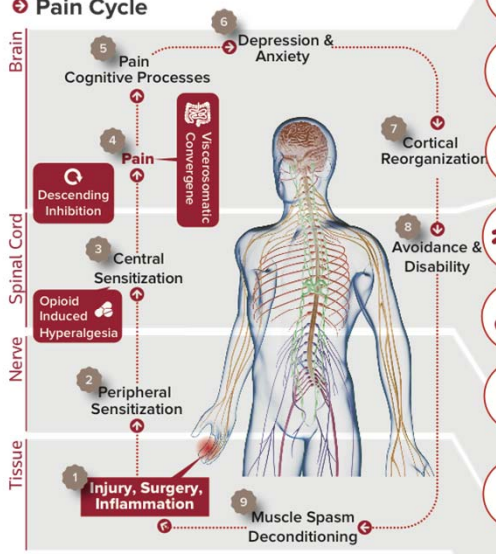
Meuser T. et al., Pain, 2001

Multi-Modal Pain Medicine

Stanford HEALTH CARE
STANFORD MEDICINE

Pain is complex. It is a cycle of medical, physical & psychological factors. Optimal pain management targets all of these factors, so you can stop worrying about pain, and spend time on what matters to you.

Pain Cycle



Treatments

Brain

- Serotonin
- Norepinephrine
- Dopamine
- Neuropathic
- Coping skills
- Cognitive Behavior Therapy
- Meditation
- Biofeedback

Spinal Cord

- Acupuncture
- Glial-cell modulators
- Neuromodulation

Nerve

- Nerve block
- Radiofrequency
- Cryoablation

Tissue

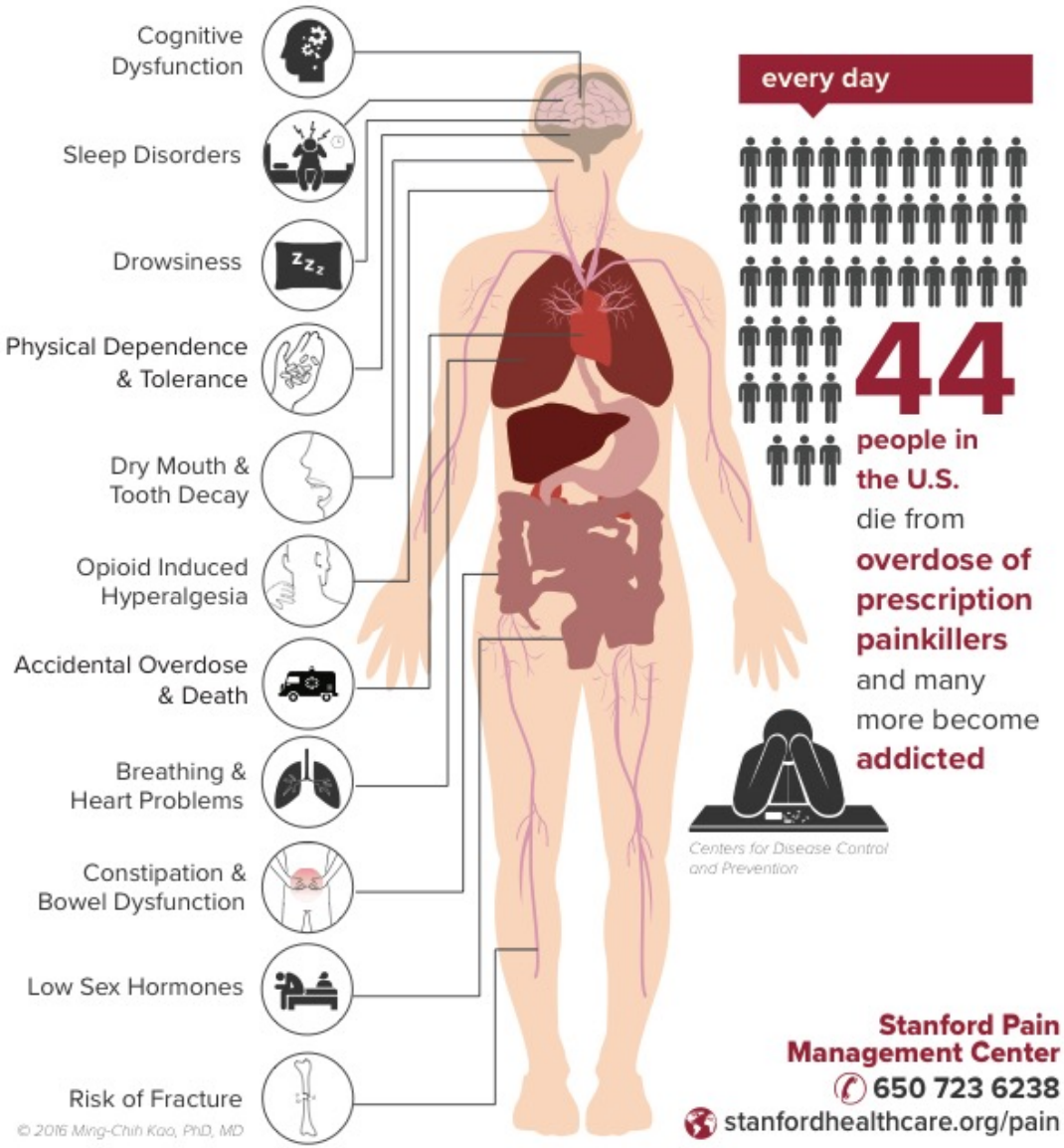
- Trigger point injection
- Botox injection
- Active physical therapy
- Modalities
- Muscle relaxants
- Anti-inflammatories

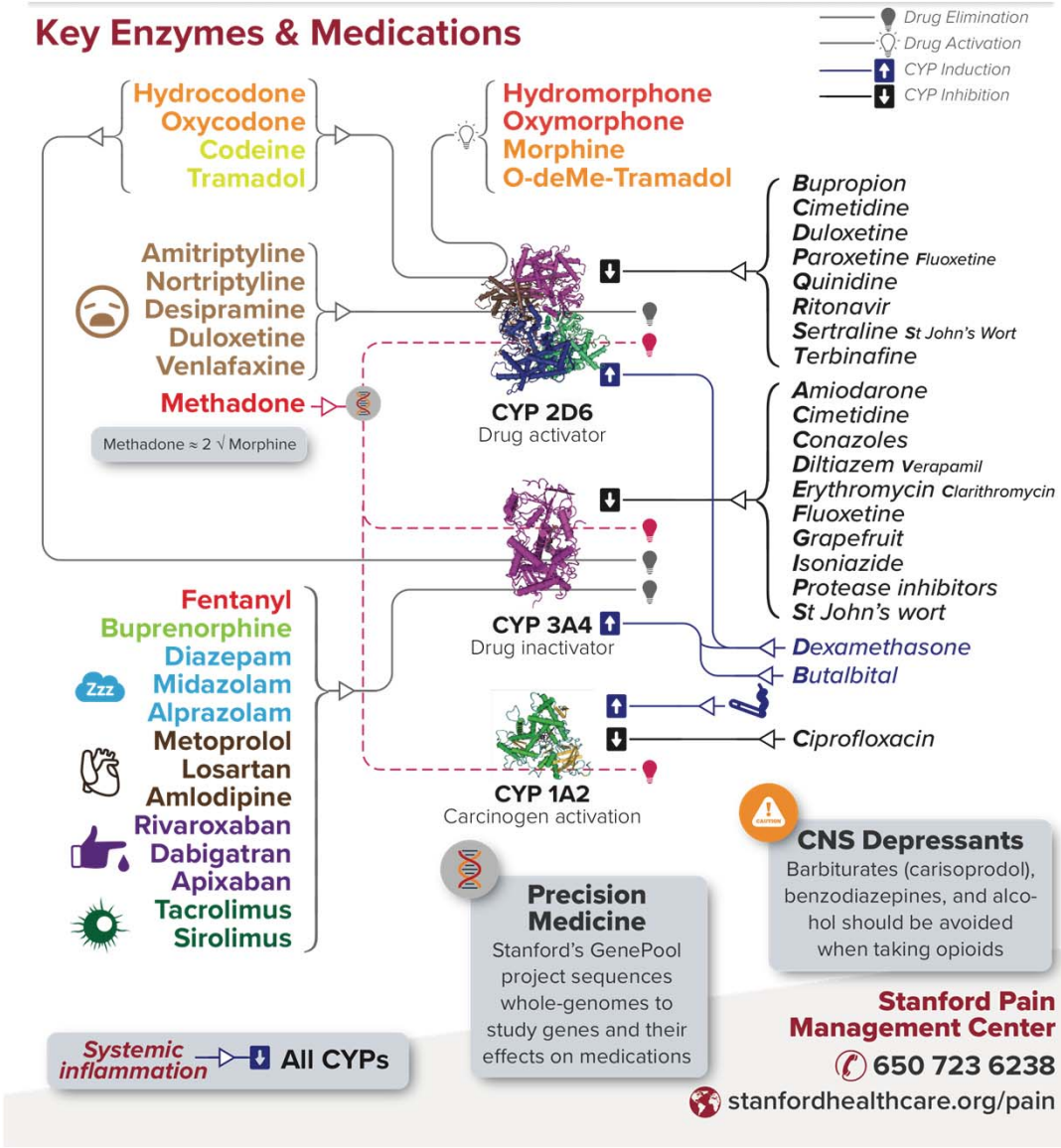
To Make an Appointment with Stanford Pain Management Center

650-723-6238 https://stanfordhealthcare.org

The Stanford Pain Management Center **requires completion of inter-disciplinary evaluation** before consideration of prescription of opioid medications. For patients struggling with **substance abuse**, on-going treatment with board-certified addictionologist is a requirement before Pain Clinic evaluation.

Pharmacologic Considerations


Cognitive Dysfunction
Sleep Disorders
Drowsiness
Physical Dependence & Tolerance
Dry Mouth & Tooth Decay
Opioid Induced Hyperalgesia
Accidental Overdose & Death
Breathing & Heart Problems
Constipation & Bowel Dysfunction
Low Sex Hormones
Risk of Fracture
© 2016 Ming-Chih Kao, PhD, MD
every day
44
people in the U.S.
die from
overdose of prescription painkillers
and many more become addicted
Centers for Disease Control and Prevention
Stanford Pain Management Center
650 723 6238
stanfordhealthcare.org/pain


Key Enzymes & Medications
Drug Elimination
Drug Activation
CYP Induction
CYP Inhibition
Hydrocodone
Oxycodone
Codeine
Tramadol
Hydromorphone
Oxymorphone
Morphine
O-deMe-Tramadol
Amitriptyline
Nortriptyline
Desipramine
Duloxetine
Venlafaxine
Methadone
Methadone ≈ 2 √ Morphine
Bupropion
Cimetidine
Duloxetine
Paroxetine Fluoxetine
Quinidine
Ritonavir
Sertraline St John's Wort
Terbinafine
CYP 2D6
Drug activator
Amiodarone
Cimetidine
Conazoles
Diltiazem Verapamil
Erythromycin Clarithromycin
Fluoxetine
Grapefruit
Isoniazide
Protease inhibitors
St John's wort
CYP 3A4
Drug inactivator
Dexamethasone
Butalbital
Ciprofloxacin
CYP 1A2
Carcinogen activation
Fentanyl
Buprenorphine
Diazepam
Midazolam
Alprazolam
Metoprolol
Losartan
Amlodipine
Rivaroxaban
Dabigatran
Apixaban
Tacrolimus
Sirolimus
Systemic inflammation
All CYPs
Precision Medicine
Stanford's GenePool project sequences whole-genomes to study genes and their effects on medications
CNS Depressants
Barbiturates (carisoprodol), benzodiazepines, and alcohol should be avoided when taking opioids
Stanford Pain Management Center
650 723 6238
stanfordhealthcare.org/pain


SPECIAL DOUBLE ISSUE
NOVEMBER 22, 2010
Inside: The 50 Best Inventions of the Year
*not including this one
Plus: Joe Klein on the Bush book
How to shrink a city / The Sheconomy
Mark Twain's memoir / Marriage apps
TIME
The United States of
Amerijuana
Legalization went up in smoke, but "medicinal" pot has gone mainstream
BY ANDREW FERGUSON

Cannabinoids in cancer pain

- There is low-quality evidence indicating THC is not a useful analgesic for cancer pain.
- There is low-quality evidence indicating synthetic THCs are not useful analgesics for cancer pain.
- There is low-quality evidence suggesting that other cannabinoids are effective analgesics for cancer pain
  - Specifically nabiximols (CBD:THC, Sativex) and only in patients already on opioids

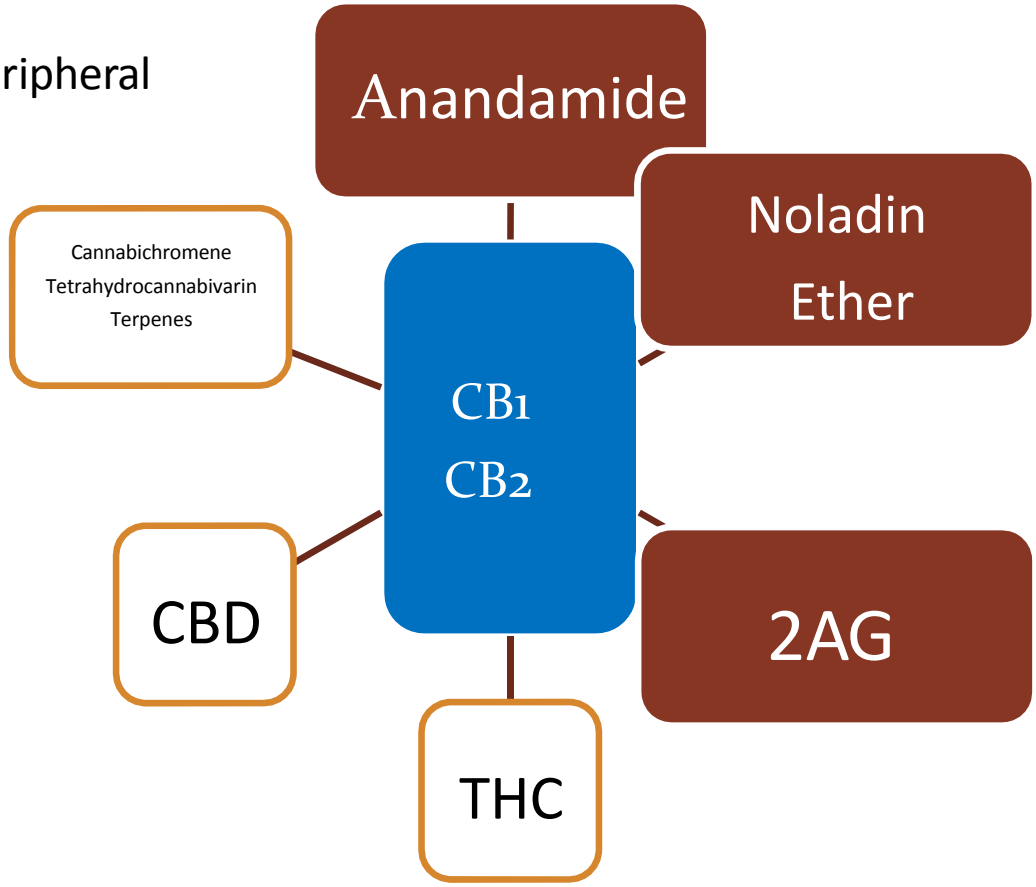
Site of action

CB1 receptors
Expressed by central & peripheral neurons.

Central neural processes through expression on astrocytes
& microglia

CB2 receptors
Expressed mostly by cells of the immune system.

Modulates immune cell Migration & cytokine release



Clinical Endocannabinoid Deficiency Syndrome
(Russo, E. 2008)

Forms & Preparations

Herb 3-22% THC

Hashish/Hash Oil 40-90% THC

Nabiximols (Sativex/Epidiolex)

Synthetic:

- Dronabinol (Marinol) CIII
- Nabilone (Cesamet) CII

Dronabinol : 2.5 mg, 5 mg, 10 mg
Nausea/vomiting, chemo-related
5 mg oral q2-4hr x4-6 doses/day

Nabilone: 1 mg Nausea/vomiting, chemo-related 1-2 mg oral bid

Do Cannabinoids have a role in pain management?

Intervention	Quality of evidence	Strength of recommendation	Additional comments
Neuropathic Pain	High	Strong	Consensus statement and guidelines from the Canadian Pain Society: First-line treatments = gabapentinoids TCA & SNRI. Second-line = Tramadol & controlled-release opioid analgesics. Third-line = Cannabinoids.
Inflammatory Pain	Low	Inconclusive	In the first ever controlled trial of a CBD in RA, a significant analgesic effect was observed and disease activity was significantly suppressed following Sativex treatment.
Chronic Pain	High	Strong	38 published RCTs = 71% (27) concluded that cannabinoids had empirically demonstrable and statistically significant pain relieving effects, whereas 29% (11) did not. Systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain.

American Pain Society

RESEARCH
EDUCATION
TREATMENT
ADVOCACY

PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 6 (June), 2016: pp 654-668

Clinical practice recommendations include:

- Know the federal and state laws governing use of medical cannabis.
- Be clear with patients about goals for therapeutic cannabis.
- Counsel patients about routes of administration and potential benefits and risks, based on scientific evidence and individual symptoms, conditions and comorbidities.
- Advise patients on cannabis strains, cannabinoid medications or extracts, explaining limitations due to lack of herbal/substance uniformity and regulatory oversight.
- Monitor patients the same as for treatment with opioids or other controlled substances.
- Patient follow up should assess progress toward achieving treatment goals, incidence of side effects, and evidence of psycho-behavioral changes.

Medical Marijuana Program

WRITTEN DOCUMENTATION OF PATIENT'S MEDICAL RECORDS

(Please Print)

Note to Attending Physician: This is not a mandatory form. If used, this form will serve as written documentation from the attending physician, stating that the patient has been diagnosed with a serious medical condition and that the medical use of marijuana is appropriate. A copy of this form must be filed in the attending physician's medical records for the patient. If the patient chooses to apply for a Medical Marijuana Identification card through the county health department or its designee, the agency will call the attending physician to verify the information contained on this form, in accordance with Health & Safety Code, Section11362.72 (a)(3).

Attending physician name			California medical license number
Service mailing address (number, street)			Office telephone number ( )
City	State	ZIP code	Office fax number ( )

Licensed by *(check one)*:

☐ Medical Board of California ☐ Osteopathic Medical Board of California

_____ is a patient under the medical care and supervision of the above
Patient's name

named physician who has diagnosed the patient with one or more of the following medical conditions:

1. Acquired Immune Deficiency Syndrome (AIDS)
2. Anorexia
3. Arthritis
4. Cachexia
5. Cancer
6. Chronic pain
7. Glaucoma
8. Migraine
9. Persistent muscle spasms, including, but not limited to, spasms associated with multiple sclerosis
10. Seizures, including, but not limited to, seizures associated with epilepsy
11. Severe nausea
12. Any other chronic or persistent medical symptom that either:
    a. Substantially limits the ability of the person to conduct one or more major life activities as defined in the Americans with Disabilities Act of 1990.

Interventional Considerations

Common Concerns with Interventions in cancer patients

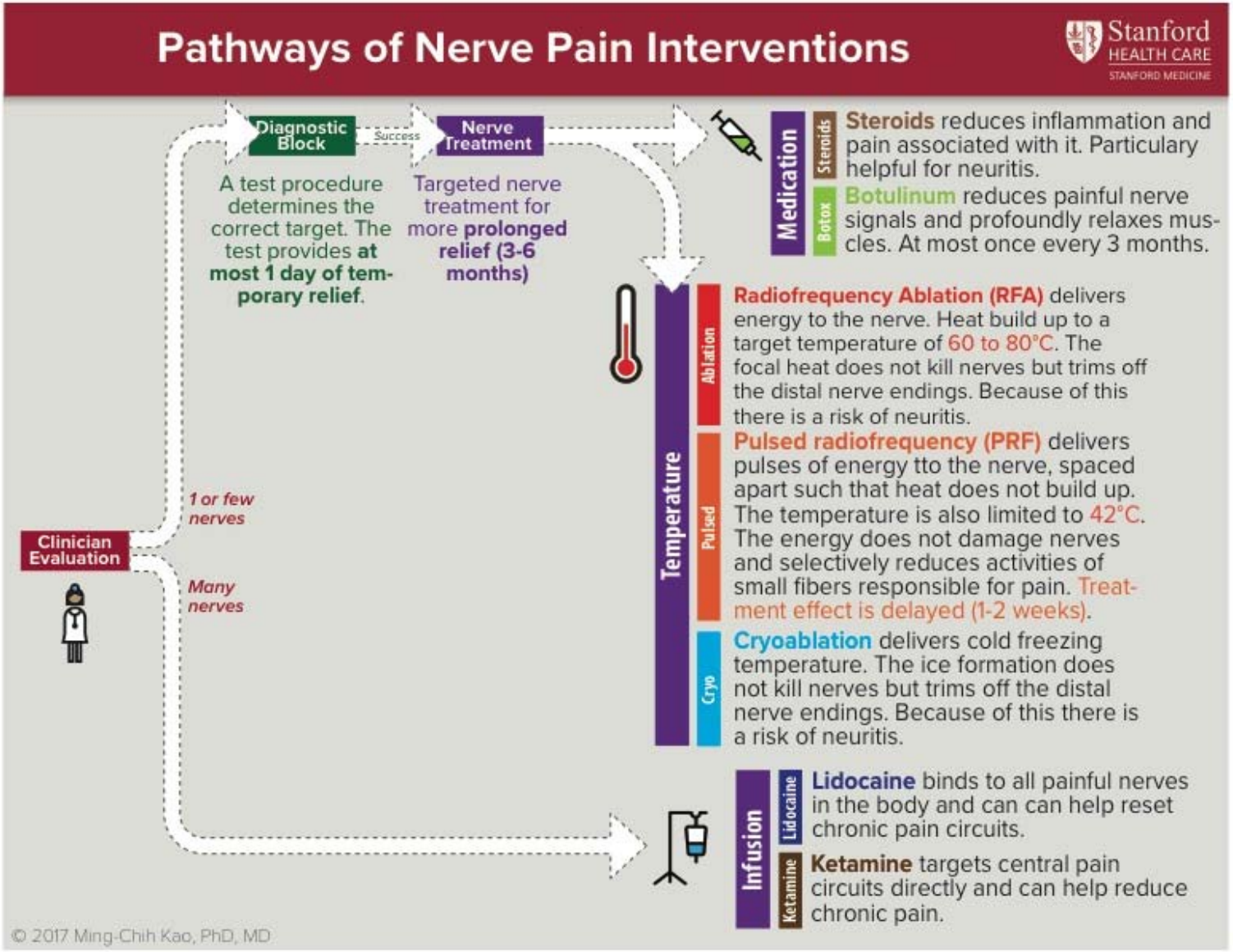
- Should we put patients through an "intervention"?
- "Too early" or "too sick" phenomena
- Sick patient population: immunosuppressed, coagulopathic, concerns with positioning
- Access and follow up with interventionalists

Nerve Ablation

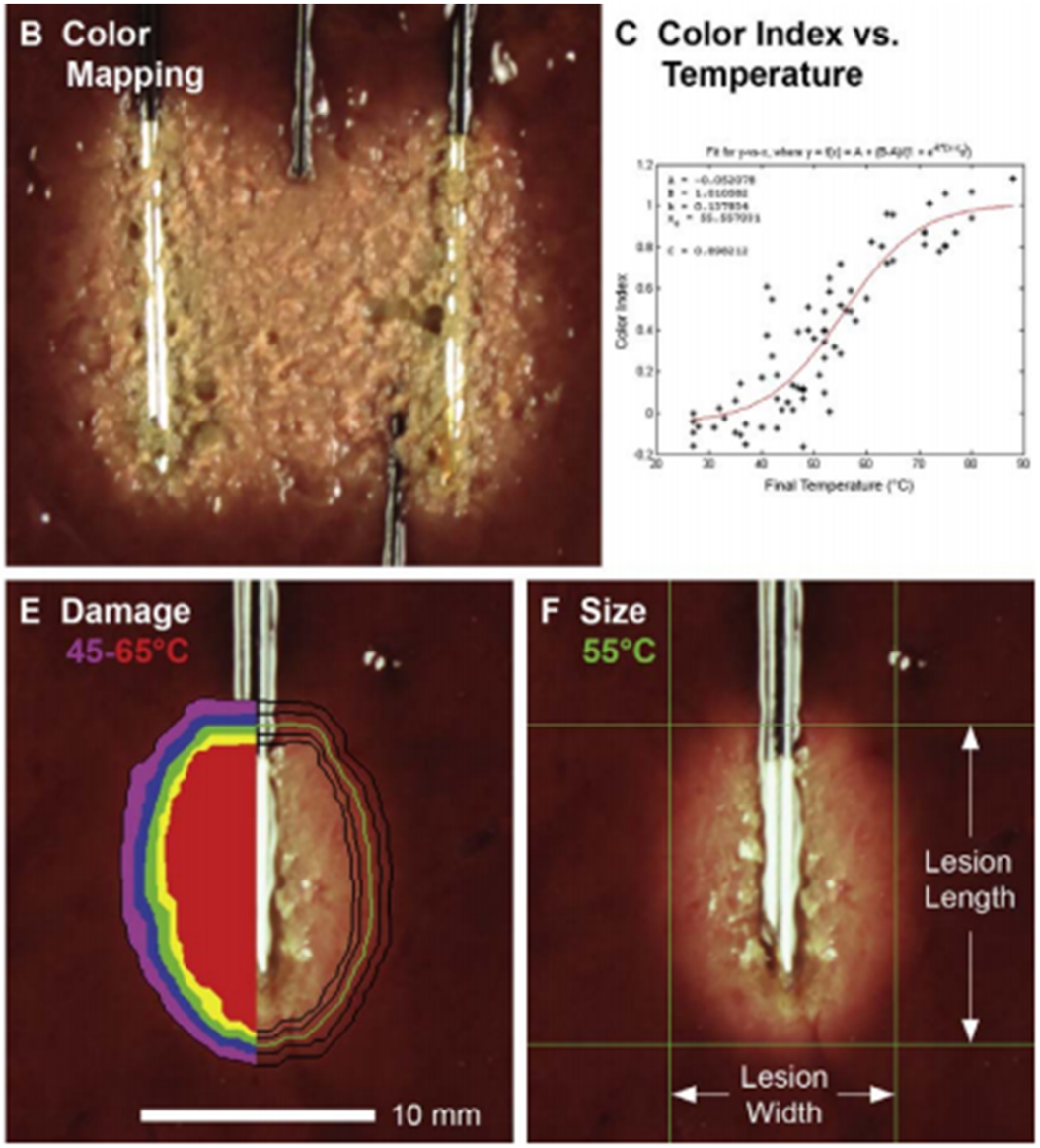
Types of Ablation

- Thermal radiofrequency ablation
- Pulsed radiofrequency neuromodulation
- Cryoablation

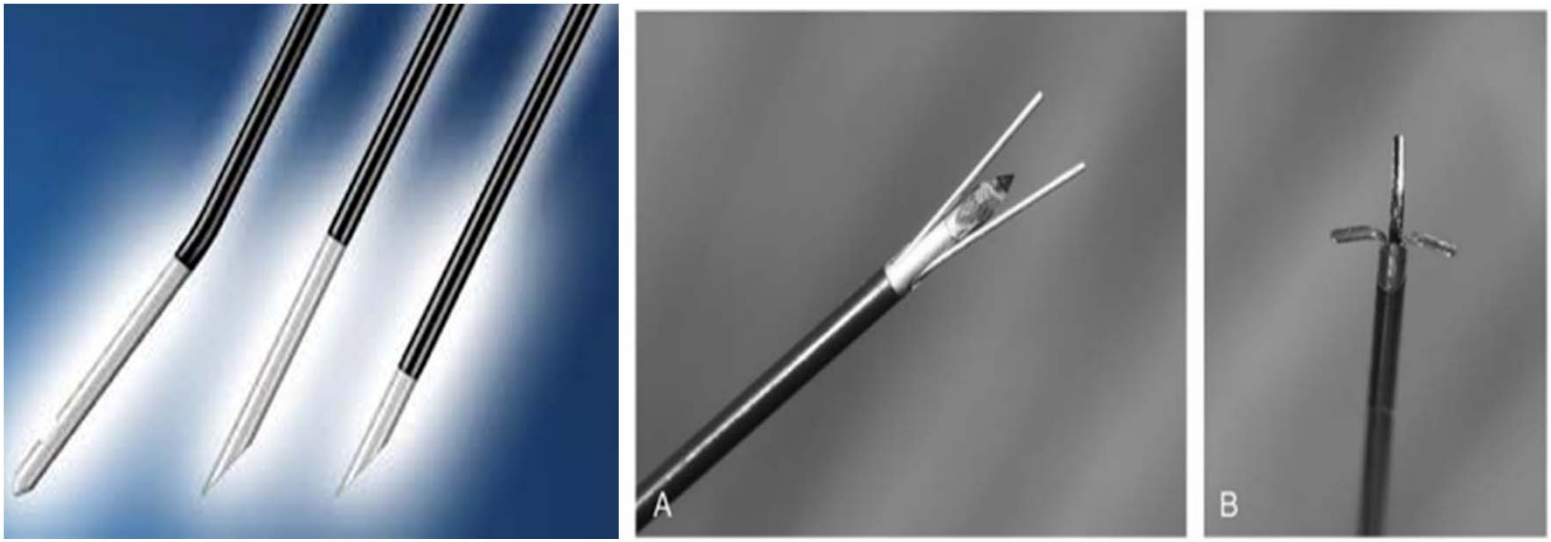
So many choices…

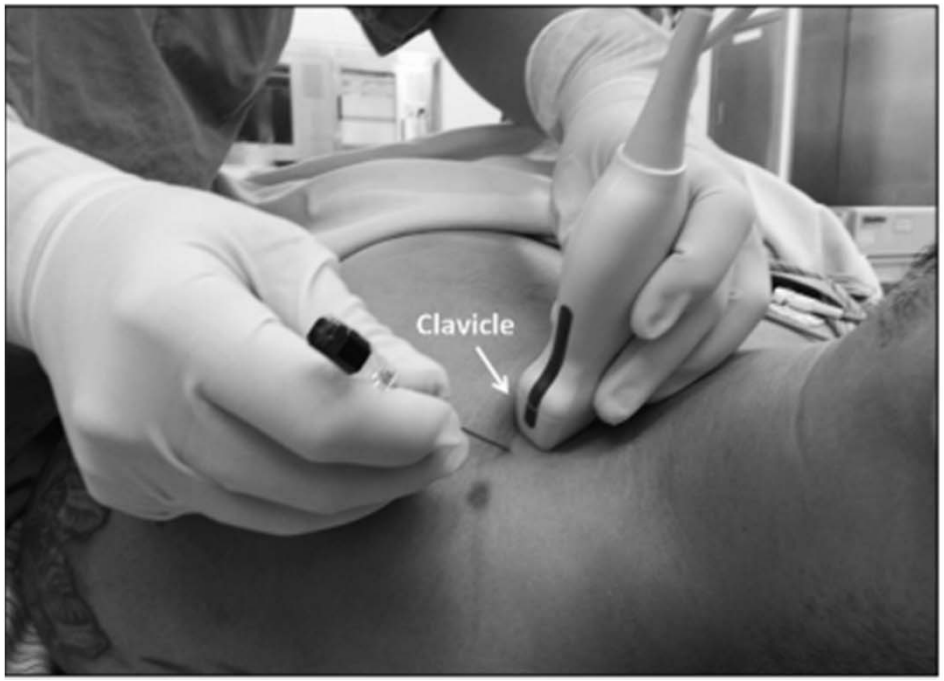


Courtesy of Ming Kao, MD, PhD



Cosman. Pain Medicine 2014


A
B



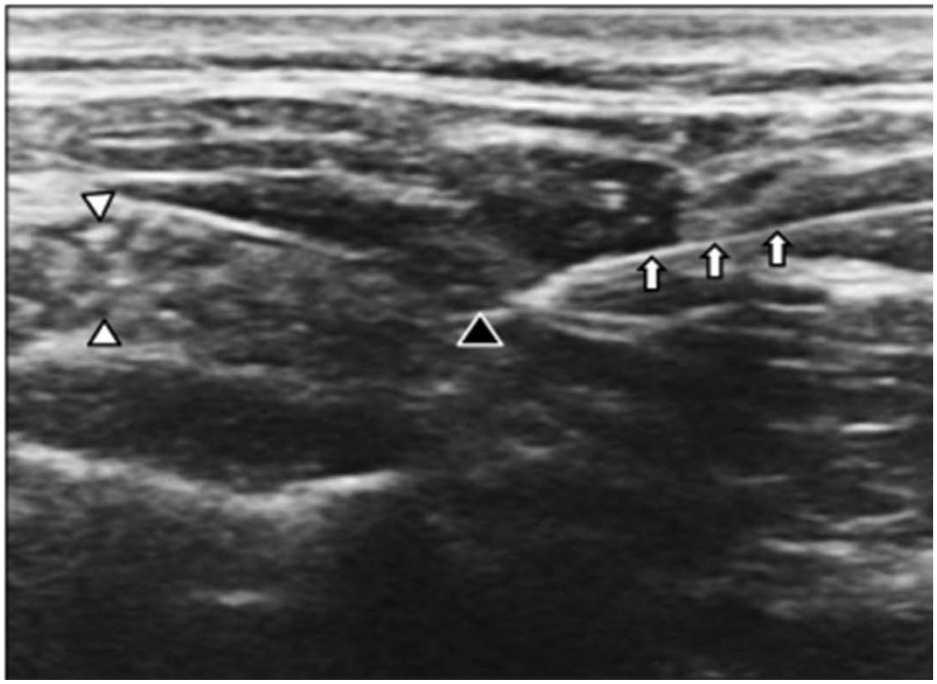


Table 2. Sonographic Measurements Derived From Images Taken During RF Lesioning and Comparisons of Symptoms Before and After the Intervention

Patient	SSN-Brachial Plexus Distance, mm	SSN Diameter, mm	SSN Depth, mm	Injection Angle, °	Pre-treatment VAS	Post-treatment VAS	Pretreatment ROM Limitation	Posttreatment ROM Limitation	Duration of Pain Relief, d
1	9.0	0.9	6.6	8.6	7	3	+	+	61, until death
2	7.5	2.5	10.4	24.0	8	2	+	–	6, until death
3	8.5	1.2	10.1	23.3	7	2	+	+	113, until latest follow-up
4	6.7	1.2	9.5	16.5	8	1	+	+	121, until latest follow-up
5	9.2	1.3	12.8	27.1	7	3	+	+	85, until death
6	7.4	1.0	11.1	24.1	7	1	+	–	42, until death

ROM indicates range of motion; SSN, suprascapular nerve; and VAS, visual analog scale.

Chang. J Ultrasound Med 2015; 34:2099–2105

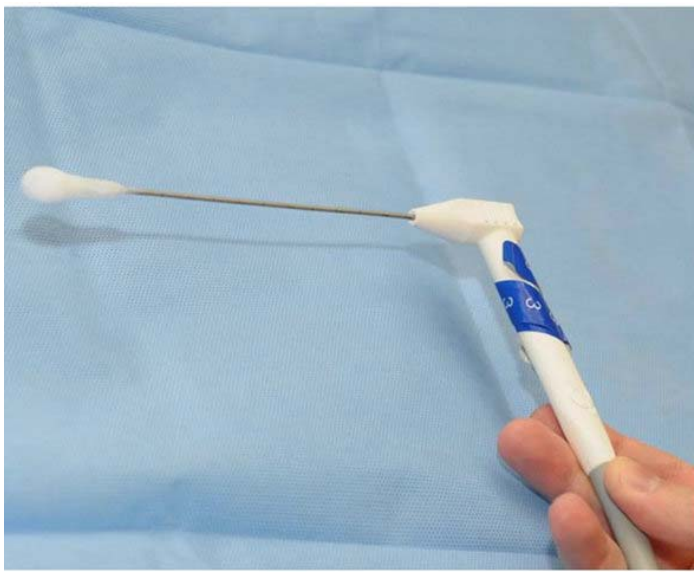
Ultrasound-Guided Radiofrequency Treatment of Intercostal Nerves for the Prevention of Incidental Pain Arising Due to Rib Metastasis: A Prospective Study

American Journal of Hospice & Palliative Medicine®
1-10

DOI: 10.1177/1049909115617933
ajhpm.sagepub.com
SAGE

Arif Ahmed, MD[1], Sushma Bhatnagar, MD[1], Deepa khurana, MD[1], Saurabh Joshi, DNB[1], and Sanjay Thulkar, MD[2]

- 25 patients with pain from rib mets
- More than 50% decrease in pain and BTP opioid use in more than 50% of patients at 3 months
- Significant improvement in background pain, functional status and QOL
- 80’C for 90 sec x 2 after stim confirmation <0.5v


Cryotherapy

ELSEVIER

European Journal of Cardio-thoracic Surgery 20 (2001) 502–507

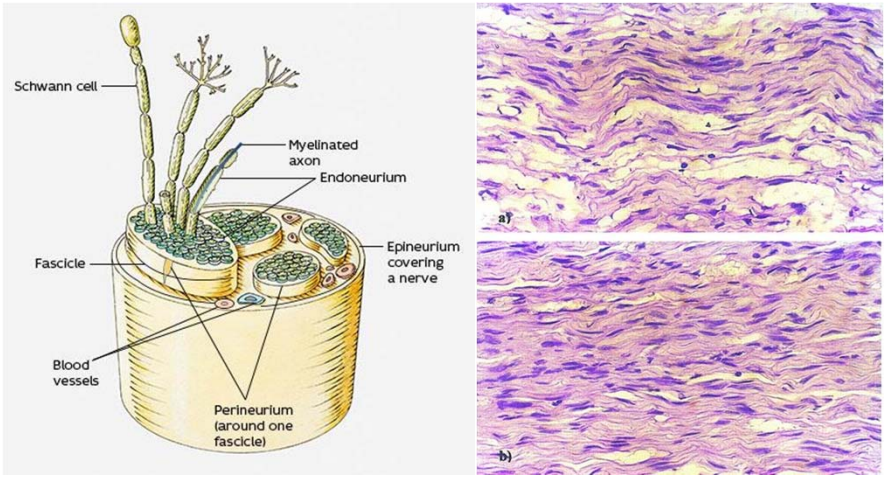
www.elsevier.com/locate/ejcts

Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: a human prospective randomized trial and a histological study☆

Narain Moorjani[a], Fengrui Zhao[b], Yanchu Tian[b], Chaoyang Liang[b], Joseph Kaluba[c], M. Omar Maiwand[a,*]

[a]*Department of Cryoresearch, Harefield Hospital, Harefield, Middlesex UB9 6JH, UK*
[b]*Department of Thoracic Surgery, China-Japan Friendship Hospital, Beijing, China*
[c]*Department of Histopathology, Barnet General Hospital, London, UK*

Received 11 October 2000; received in revised form 4 May 2001; accepted 18 May 2001



- After 1 min cryo immediate changes show axonal degeneration, accumulation of edema fluid, and capillary stasis. **Endoneurium remained intact**.
- After 1 week axonal swelling began to resolve gradually; Schwann cells proliferate, lymphocytic and histiocytic infiltrate.
- Axonal segments recover progressively and are complete by 1 month.
- With longer periods of cryo, the time for complete axonal recovery was “proportionately increased”

Ultrasound-Guided Intercostal Nerve Cryoablation

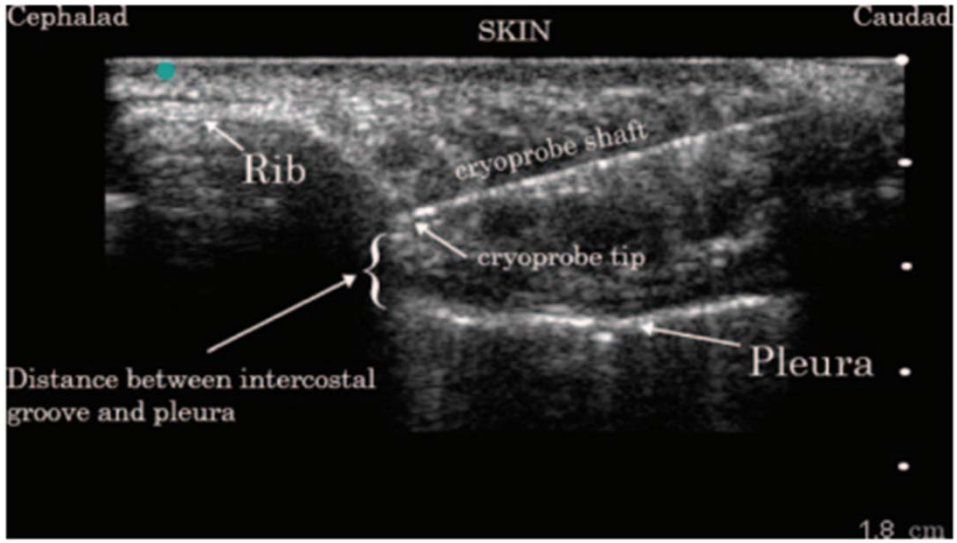
Michael G. Byas-Smith, MD*

Amitabh Gulati, MD†

Ultrasound technology has advanced regional anesthesia and pain management, by improving accuracy and reducing complication rates. We have successfully performed cryoablation of intercostal nerves with ultrasound guidance with no complications. Four patients with postthoracotomy pain syndrome had pain relief for at least 1 mo after selective cryoablation of intercostal nerves at the mid-axillary line. Visualizing the pleura during the procedure is the greatest benefit of using ultrasonography, especially in thin patients whose intercostal groove to pleural distance may be <0.5 cm. Although further studies are needed, we feel that this new technique should reduce the risk of pneumothorax as well as improve the success of cryoablation.

(Anesth Analg 2006;103:1033-5)

- 4 patients with postthoracotomy pain
- Cryoablation to -50'C for 60s + 30s
- Analgesia for at least 2 months



A&A. Vol. 103, No. 4, October 2006

Neurolytic Blocks for Cancer Pain

Overview of Neurolytic Blockade

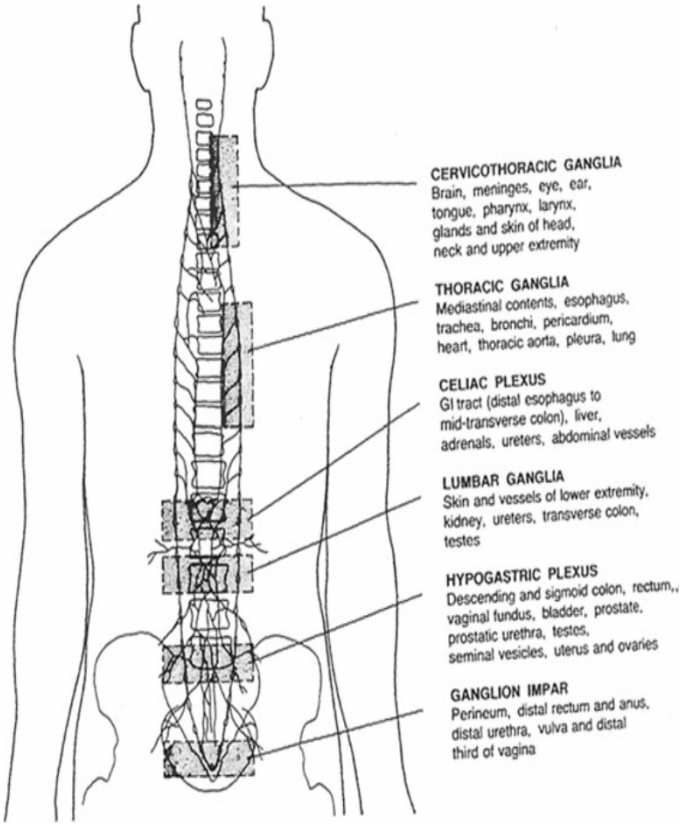
~8% cancer pain patients may need peripheral nerve block

Intentional injury to a nerve/plexus:

- Chemical* (alcohol or phenol)
- Surgical

Two Types:

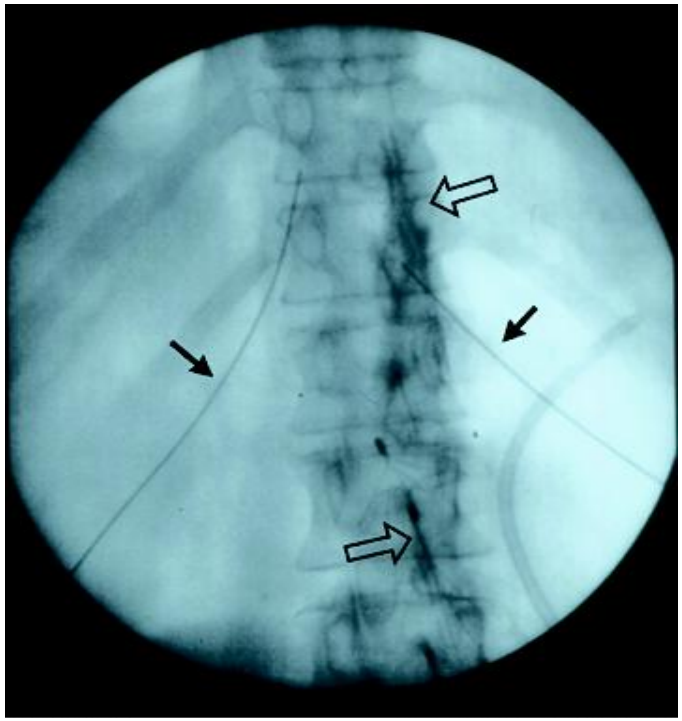
- Peripheral (intercostal, extremity)
- Autonomic (celiac, superior hypogastric plexus)



Zech et al. Validation of World Health Organization Guidelines for Cancer Pain Relief: a 10 year prospective study. Pain 1995; 63:65-76.

Overview of Neurolytic Blockade

- "Block" vs "Neurolysis"
- Neurolytic effects typically last 3-6 months
- Effects fade:
  - Progression of tumor
  - Nerve regeneration

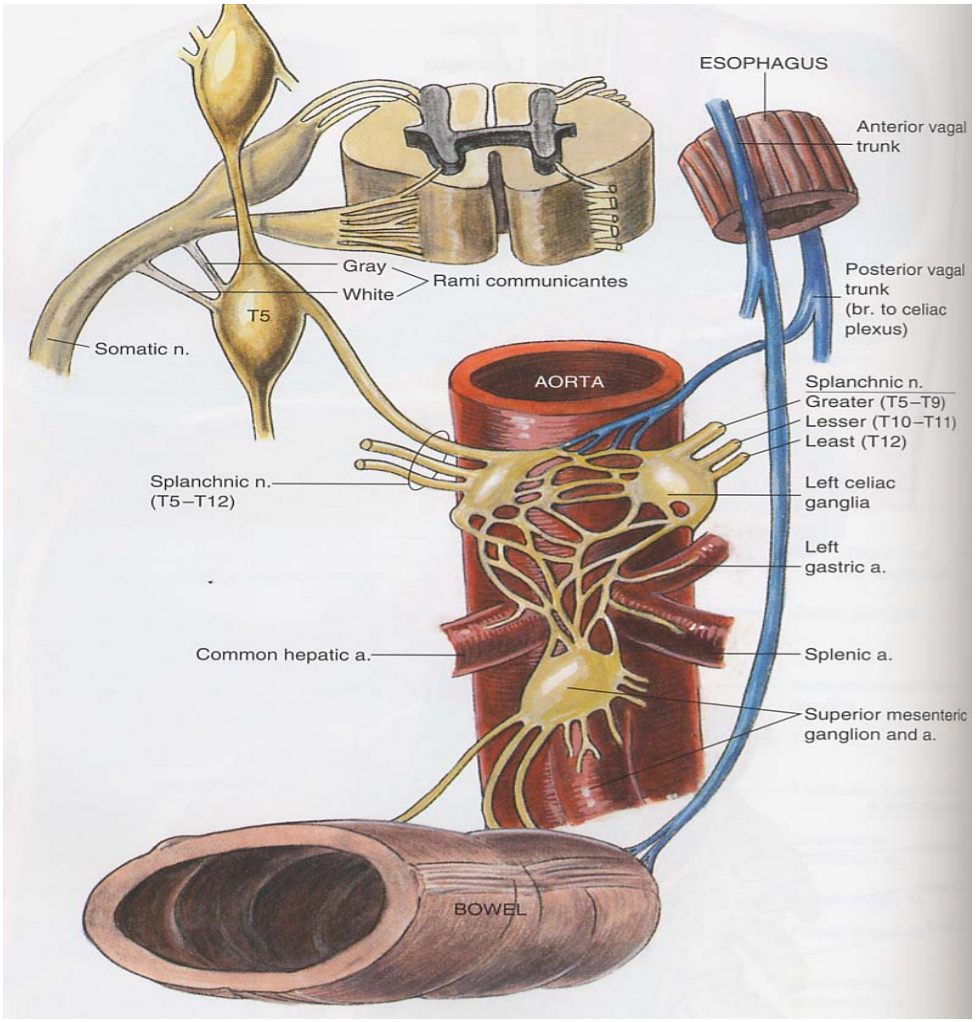


Pancreatic Pain and Survival

- Up to 85% of pancreatic patients report severe pain with advancement of disease despite medical therapy.

- Increased pain predicts **poorer survival** independent of resectability status in patients with pancreatic cancer.

Celiac Plexus: Anatomy



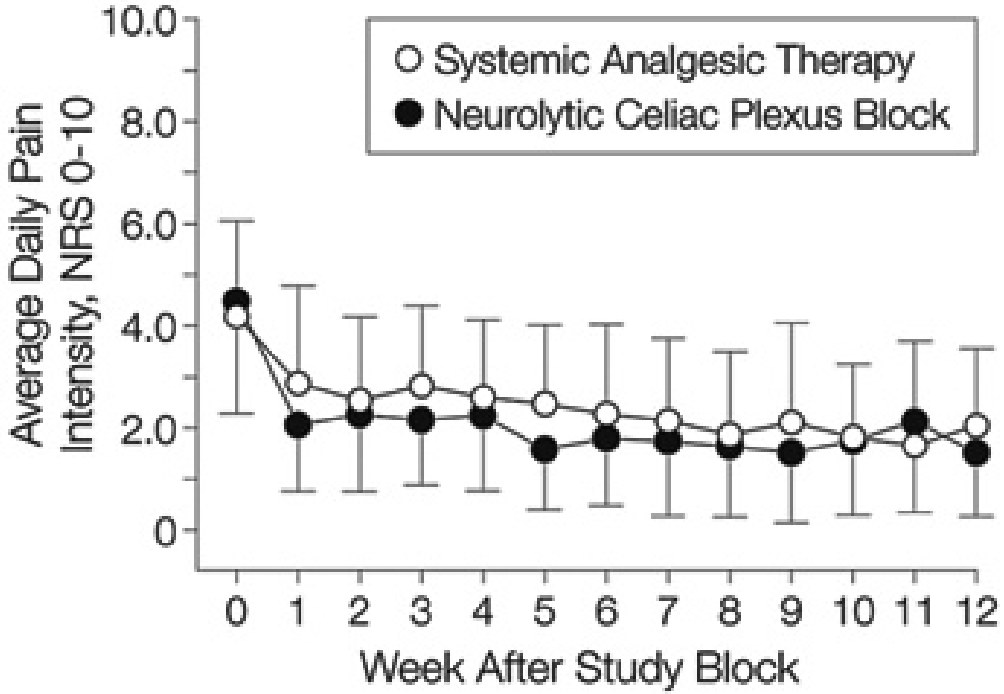
Recent Advances:

- In 2004 Wong et al. report in JAMA: prospective, randomized, double blind trial comparing NCPB with optimized systemic analgesic therapy in 101 patients with pancreatic cancer.

- Randomization was stratified by disease stage and patients randomized to systemic analgesic therapy were given **sham procedure.**

- Wong, G.Y., et al., *Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial.* Jama, 2004. **291**(9): p. 1092-9.

Pain Relief from NCPB



No. of Patients													
SAT	50	41	41	42	37	41	36	34	32	30	30	26	25
NCPB	50	45	44	42	40	36	34	34	36	32	29	25	27

Recent Advances:

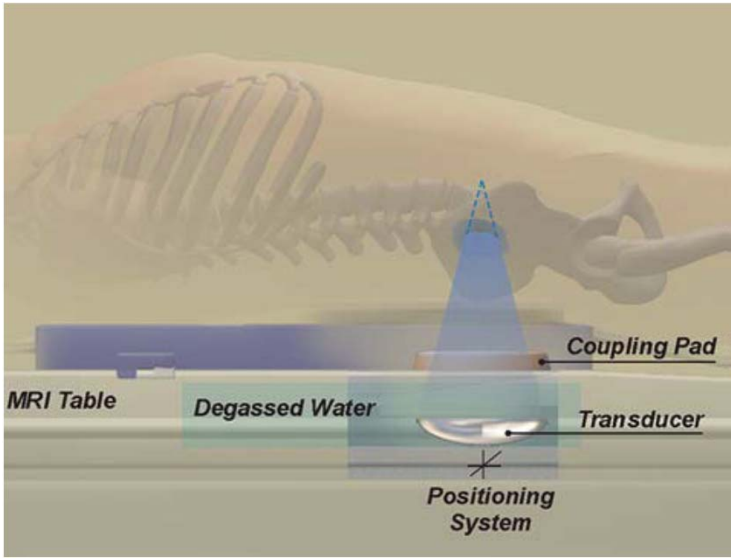
- Immediate significant pain reductions occurred in both groups, but relief was significantly greater with NCPB (P=.01).
- Time until analgesic rescue was required was significantly longer in patients receiving NCPB (P=.01).
- Percent with pain greater than 5/10 was significantly lower in those who received NCPB than in the SAT group (14% VS 40%)

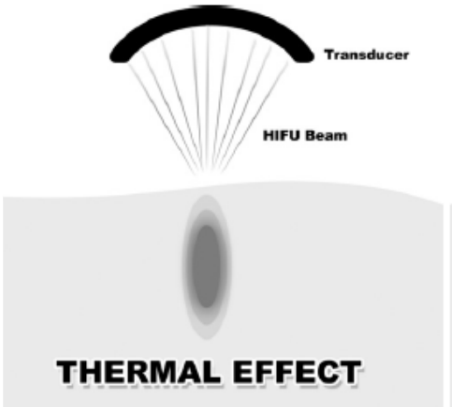
High-Intensity Focused Ultrasound

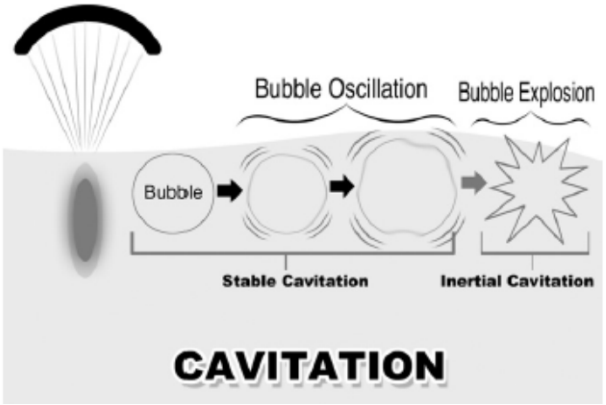
HIFU

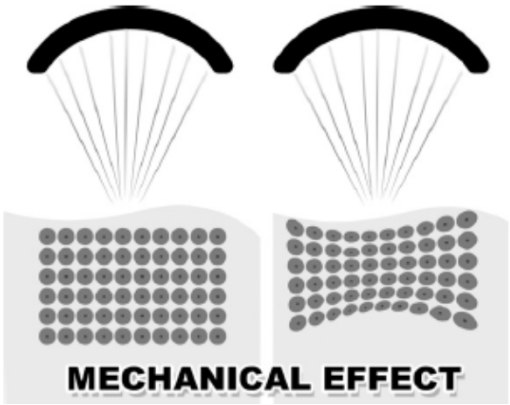
- Focused Ultrasound Waves
- MRI or Ultrasound guided
- 1 to 5 MHz
- Acoustic intensity

  1000-10,000 W/cm²





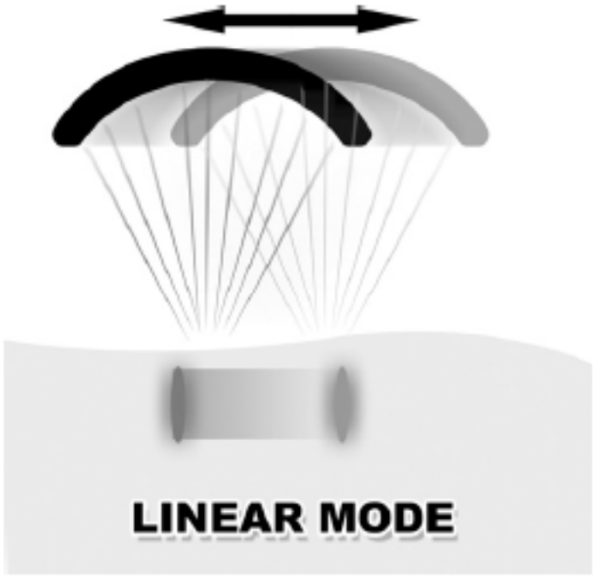




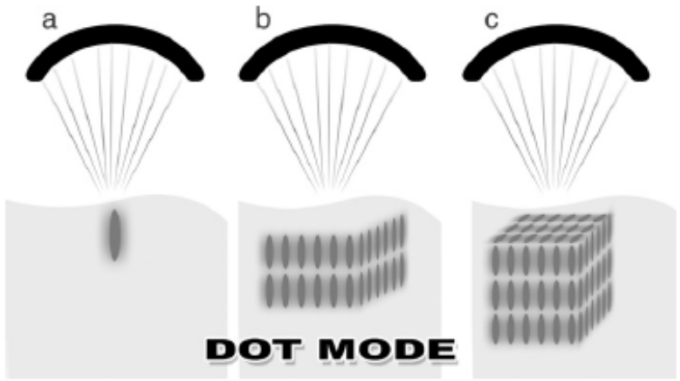
Shehata et al. Eur J Rad 2012

The Lesion

- Lesions in seconds
- Volumes as small as 20 mm^3
- Up to 160 mm depth



- Targets
  - Uterine Fibroids
  - Prostate
  - Liver
  - Breast
  - Pancreas
  - CNS transcranial
- Benefits
  - Non-ionizing
  - Non-Invasive
  - Decreased blood perfusion effects



Al-Batanieh O Can Treeat RV 2012

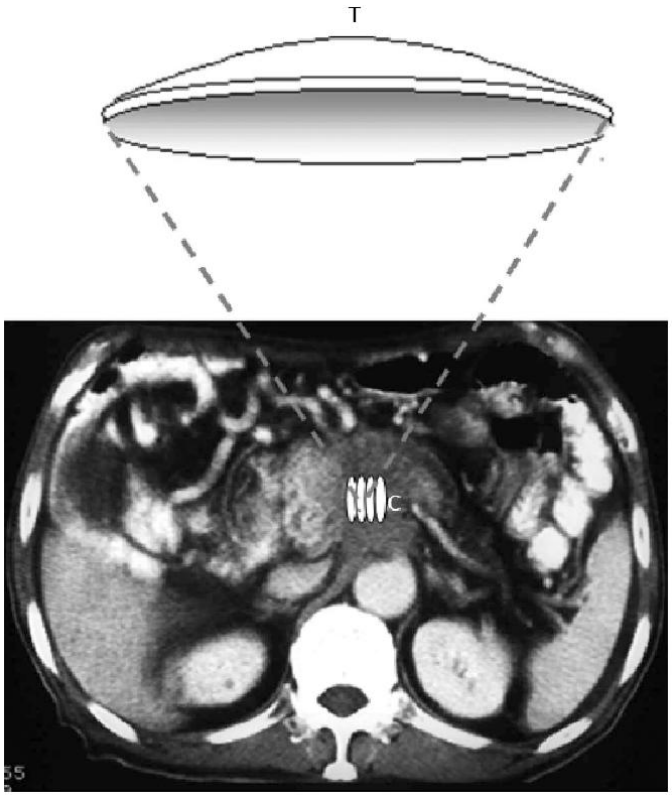
Pancreatic Cancer as an example

Table 1 Studies of continuous-wave high intensity focused ultrasound treatment for patients with advanced pancreatic cancer

Study	*n*	Patients	Treatment method	HIFU Device	Outcome and survival	Complications
Wu *et al*[21]	8	A phase Ⅰ-Ⅱ study of HIFU for advanced pancreatic cancer, unresectable. Average tumor size 5.89 cm (4.5-8 cm)	One-session HIFU monotherapy	Continuous HIFU irradiation, Model-JC HIFU System	Pain relief: 8/8 (100%); Median survival: 11.25 mo (2-17 mo)	None
Orsi *et al*[22]	6	Late-stage pancreatic cancer, unresectable. Average tumor size 4.6 ± 1.4 cm	One-session HIFU monotherapy	Continuous HIFU irradiation, Model-JC HIFU System	Pain relief: 6/6 (100%); Median survival: 7 mo; Overall survival: 42.9% at 12 mo and 21.4% at 24 mo	Portal vein thrombosis: 1/6 (16%)
Wang *et al*[24]	40	Advanced pancreatic cancer, unresectable. Average tumor size 4.3 cm (2-10 cm)	One-session HIFU monotherapy	Continuous HIFU irradiation, Model-JC HIFU System	Pain relief: 35/40 (87.5%) Median survival: 8 mo (stage Ⅲ: 10 mo; stage Ⅳ: 6 mo); Overall survival: 58.8% at 6 mo and 30.1% at 12 mo	None
Sung *et al*[25]	46	Advanced pancreatic cancer, unresectable. Average tumor size 4.2 ± 1.4 cm (1.6-9.3 cm)	One-session HIFU monotherapy	Continuous HIFU irradiation, Model-JC HIFU System	A significant reduction of pain score ($P < 0.001$); Median survival: 12.4 mo; Overall survival: 52.2% at 6 mo, 30.4% at 12 mo, and 21.79% at 18 mo	Mild abdominal pain: 16/46 (34%); severe abdominal pain with vomiting: 2/46 (4%); transient fever: 3/46 (6%); 2nd-3rd skin burns: 2/46 (4%); pancreaticoduodenal fistula: 1/46 (2%).; gastric bleeding due to ulcer: 1/46 (2%)
Wang *et al*[26]	224	Advanced Pancreatic cancer	One-session HIFU monotherapy	Continuous HIFU irradiation, Model-JC HIFU System	Pain relief and survival data not reported	Abdominal distension, anorexia and nausea: 10/224 (4%); asymptomatic vertebral injury: 2/224 (1%); obstructive jaundice: 1/224 (1%)
Gao *et al*[27]	39	Locally advanced pancreatic cancer, unresectable. Tumor size unclear	One-session HIFU alone: 14 pts; HIFU + gemcitabine: 25 pts	Continuous HIFU irradiation, Model-JC HIFU System	Pain relief: 31/39 (79.5%) Median survival: 11 mo; Overall survival: 82.1% at 6 mo, and 39.5% at 12 mo	None
Zhao *et al*[28]	37	A phase Ⅱ study of HIFU + gemcitabine for locally advanced pancreatic cancer, average tumor size 3.4 cm (1.7-8.5 cm).	Gemcitabine on days 1, 8 and 15, and multiple HIFU sessions on days 1, 3 and 5. The combined treatment repeated every 28 d	Continuous HIFU irradiation, HIFUNIT-9000 HIFU System	Overall survival: 12.6 mo (95%CI: 10.2-15.0); Pain relief: 29/37 (78%)	Fever: 26/37(70%); neutropenia: 6/37 (16%); thrombocytopenia 2/37 (5%); nausea and vomiting 3/37 (8%); diarrhea 2/37 (5%)

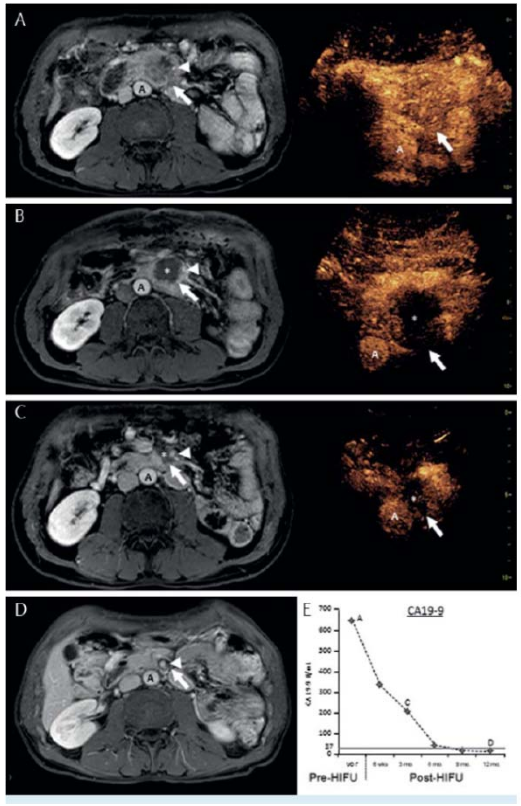
Technique

- Benefits
  - Any shape or volume can be lesioned
  - Thermal effect
    - Direct destruction
    - At 60°C vascular compromise
- Done primarily with ultrasound guided HIFU
- Pulse technique
    - Multiple sessions
    - Improved drug delivery?
- Combination with gemcitabine (chemotherapy)



Wu F World J of Gastro 2014

US HIFU lesioning for pancreatic CA related pain



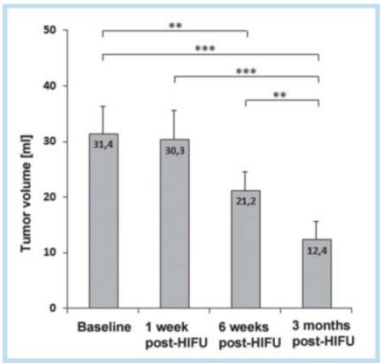


Fig. 4 Change in tumor volume post-HIFU. Tumor volumes (in ml) are shown with mean and standard deviation. Over time there was an average volume reduction (n = 15) of 26 % after 6 weeks and 64 % after 3 months.

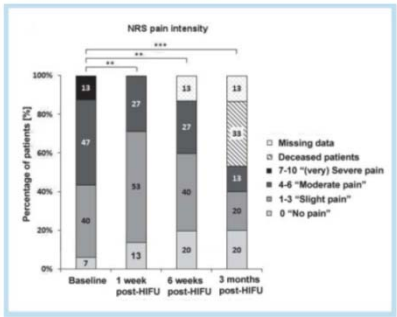


Fig. 5 Pain reduction post-HIFU; evaluation with NRS (Numerical Rating Score). Percentage of patients in the different NRS categories (0: no pain; 7 – 10 (very) severe pain) before HIFU and 1 week, 6 weeks and 3 months after HIFU. Missing data as well as the percentage of deceased patients are also shown.

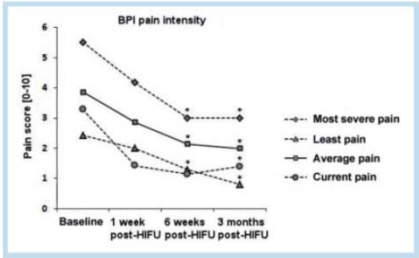
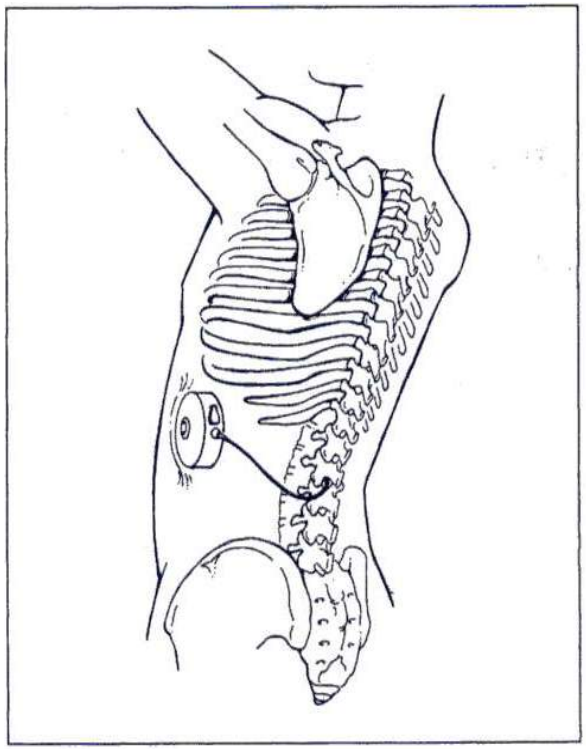


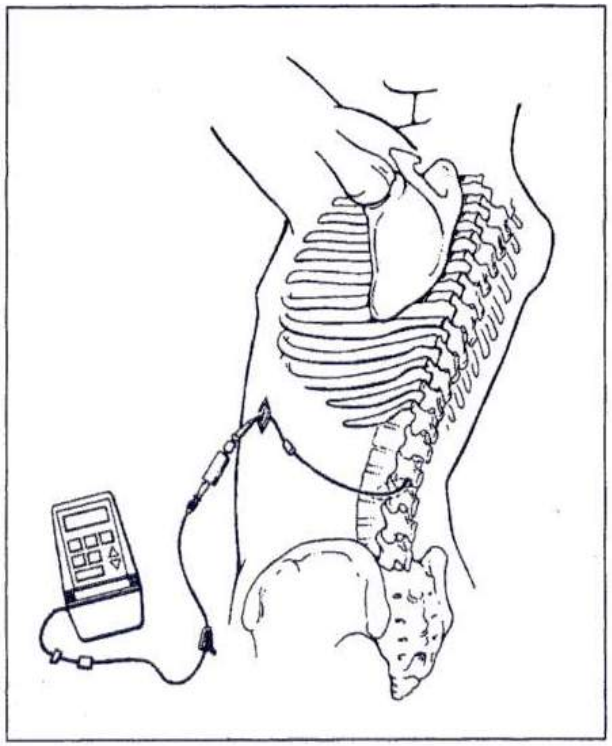
Fig. 6 Change in pain intensity post-HIFU; evaluation with BPI (Brief Pain Inventory).

Strunk HM Gastro Tract (German) 2016

Intrathecal Medications for Cancer Pain

Implantable infusion pump





Received: December 12, 2011 Revised: April 4, 2012 Accepted: May 16, 2012

(onlinelibrary.wiley.com) DOI: 10.1111/j.1525-1403.2012.00476.x

Polyanalgesic Consensus Conference 2012: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel

Timothy R. Deer, MD[1], Joshua Prager, MD[2], Robert Levy, MD, PhD[3], James Rathmell, MD[4], Eric Buchser, MD[5], Allen Burton, MD[6], David Caraway, MD, PhD[7], Michael Cousins, MD[8], José De Andrés, MD, PhD[9], Sudhir Diwan, MD[10], Michael Erdek, MD[11], Eric Grigsby, MD[12], Marc Huntoon, MD, PhD[13], Marilyn S. Jacobs, PhD[2], Philip Kim, MD[14], Krishna Kumar, MD[15], Michael Leong, MD[16], Liong Liem, MD[17], Gladstone C. McDowell II, MD[18], Sunil Panchal, MD[19], Richard Rauck, MD[20], Michael Saulino, MD, PhD[21], B. Todd Sitzman, MD, MPH[22], Peter Staats, MD[23], Michael Stanton-Hicks, MD, PhD[24], Lisa Stearns, MD[25], Mark Wallace, MD[26], K. Dean Willis, MD[27], William Witt, MD[28], Tony Yaksh, PhD[26], Nagy Mekhail, MD, PhD[24]

Table 2. 2012 Polyanalgesic Algorithm for Intrathecal (IT) Therapies in Nociceptive Pain.

Line 1	Morphine	Hydromorphone	Ziconotide	Fentanyl
Line 2	Morphine + bupivacaine	Ziconotide + opioid	Hydromorphone + bupivacaine	Fentanyl + bupivacaine
Line 3	Opioid (morphine, hydromorphone, or fentanyl) + clonidine			Sufentanil
Line 4	Opioid + clonidine + bupivacaine		Sufentanil + bupivacaine or clonidine	
Line 5	Sufentanil + bupivacaine + clonidine			

Line 1: Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first-line therapy for nociceptive pain. Hydromorphone is recommended on the basis of widespread clinical use and apparent safety. Fentanyl has been upgraded to first-line use by the consensus conference. **Line 2:** Bupivacaine in combination with morphine, hydromorphone, or fentanyl is recommended. Alternatively, the combination of ziconotide and an opioid drug can be employed. **Line 3:** Recommendations include clonidine plus an opioid (i.e., morphine, hydromorphone, or fentanyl) or sufentanil monotherapy. **Line 4:** The triple combination of an opioid, clonidine, and bupivacaine is recommended. An alternate recommendation is sufentanil in combination with either bupivacaine or clonidine. **Line 5:** The triple combination of sufentanil, bupivacaine, and clonidine is suggested.

Results and Conclusion

- Results
  - 85% IDDS vs 70% CMM (p=.05) achieved clinical success
  - IDDS pts more often achieved >20% reduction in VAS and toxicity
  - Mean VAS reduction 52% IDDS vs 39% CMM (p=.055)
  - Mean Toxicity reduction 50% IDDS vs 17% CMM (p=.04)
  - Survival IDDS 54% alive at 6m vs 37% CMM (p=.06)
- Conclusion
  - "IDDSs improved clinical success in pain control, reduced pain, significantly relieved common drug toxicities, and improved survival in patients with refractory cancer pain"

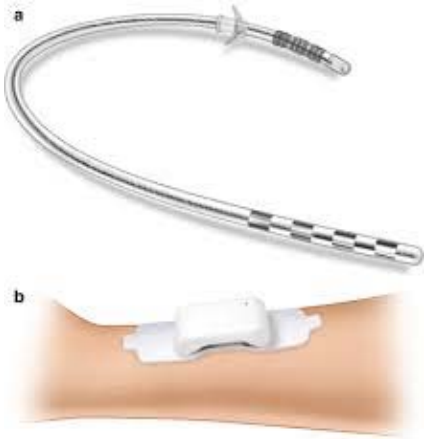
Side effects

- Urinary retention
- Lower extremity edema
- Urinary retention
- Pruritus
- Myoclonic activity
- Sweating

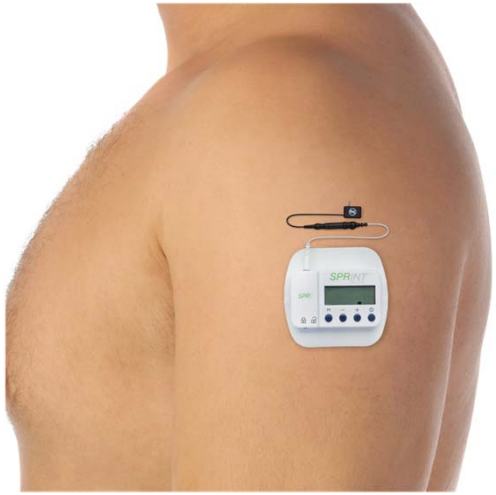
Emerging Technology: Peripheral Stimulation

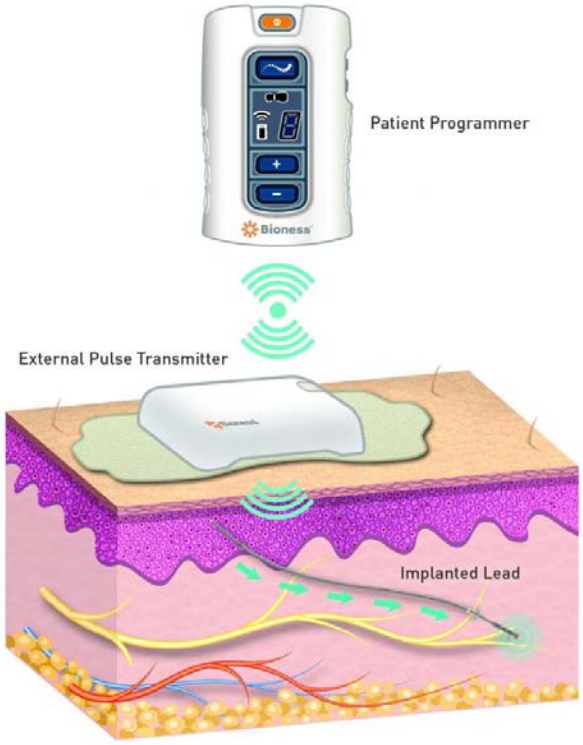
FDA-cleared PNS Options

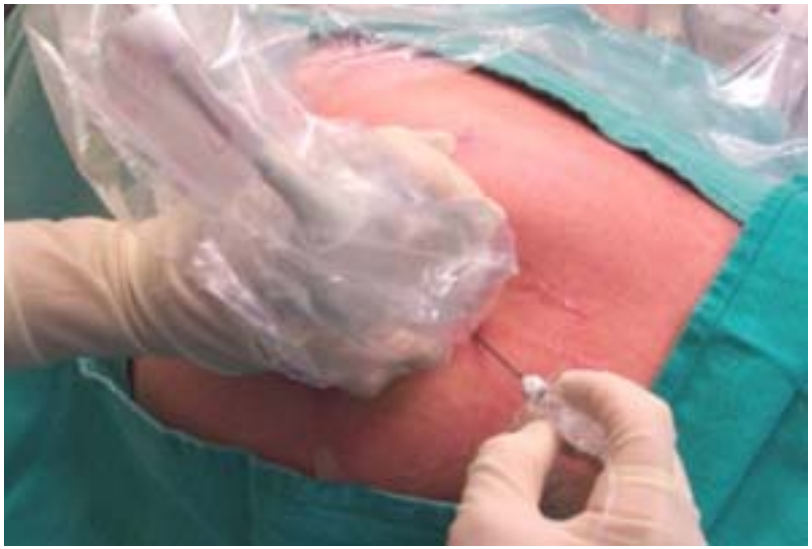
FDA-cleared for relief of chronic and acute pain, including post-operative and post-traumatic pain



FDA-cleared for pain management in adults who have severe intractable chronic pain of peripheral nerve origin, as an adjunct to other modes of therapy (e.g., medications)


SPRINT


Patient Programmer
Bioness
External Pulse Transmitter
Implanted Lead



Referring Physician Information

PHYSICIAN HELPLINE

Phone: 1-866-742-4811
Fax: 650-320-9443
Monday – Friday, 8:30 a.m. – 5 p.m.

For help with all referral needs and questions visit Referring Physicians.

HOW TO REFER

Mail or fax a completed consultation request form with relevant clinic notes and diagnostic study results to:

Stanford University Pain Management Center
450 Broadway Street (MC 5340)
Redwood City, CA 94063

Fax: 650-323-9443

Stanford Pain Management Center

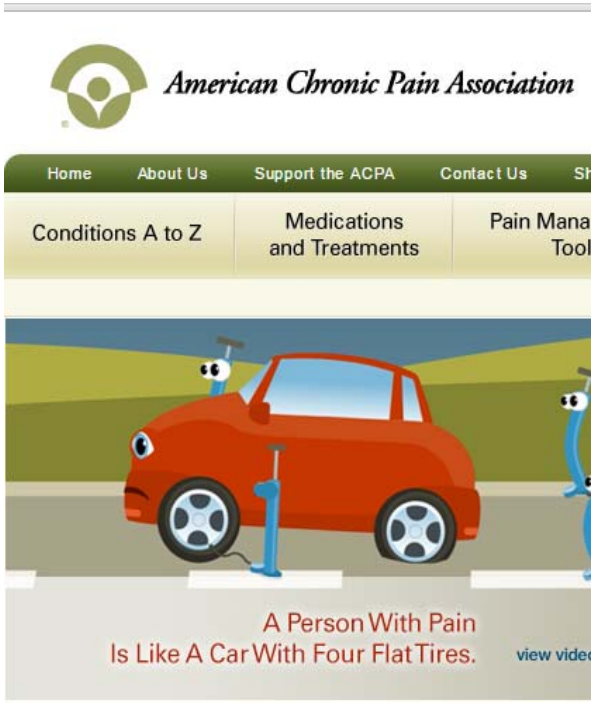
Redwood City *450 Broadway*
Emeryville *3800 Hollis*
San Jose *2589 Samaritan*
Santa Clara *2518 Mission College*

All sites *Mondays to Fridays*
Redwood City *Evenings & Saturdays*
650 723 6238
stanfordhealthcare.org/pain

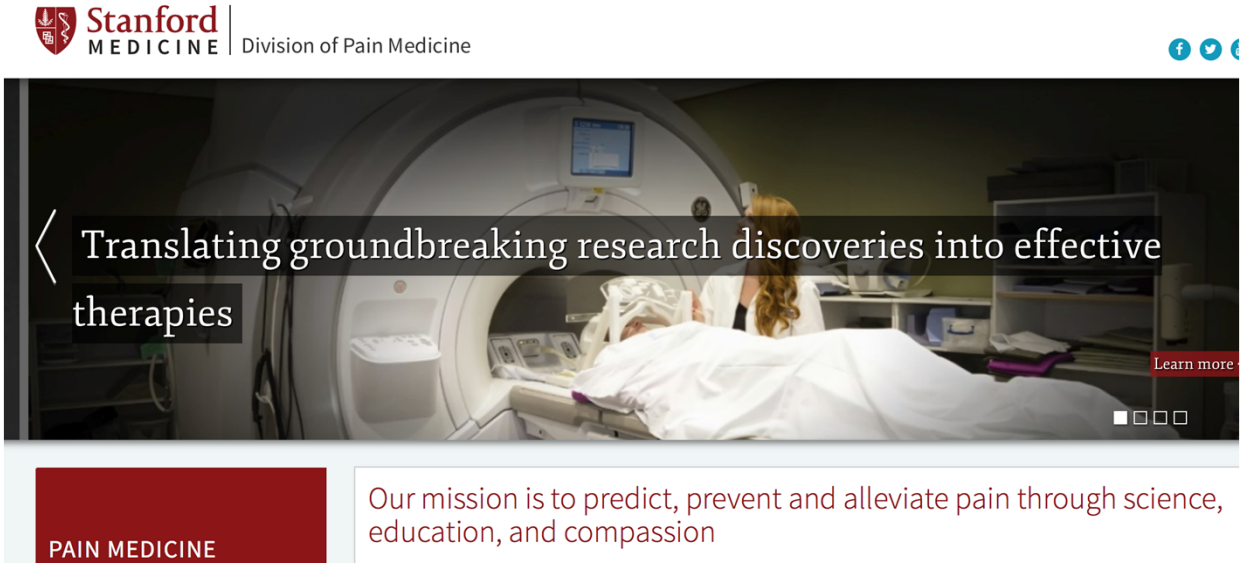
All sites
MD evaluation, interventions

Redwood City
Psychology, PT, acupuncture, nutrition, classes

Patient & Provider Resources



theacpa.org



https://stanfordhealthcare.org/pain

the AMERICAN ACADEMY of PAIN MEDICINE

www.painmed.org