Cancer : Beyond the Ladder

- **Peter S Staats MD MBA FIPP ABIPP**
- **Past President WIP, NANS, ASIPP, NJSIPP, SPS**
- **Chair and President Vagus Nerve Society**

Conflicts of Interest

- Consulting and/or research grants:
  - AIS Healthcare, Biotronik, Nalu, Saluda Medical Medtronic
  - SPR Therapeutics
- Co-Founder and CMO: electroCore, Inc.
- National Spine and Pain Centers
- Shareholder
  - National Spine and Pain Centers
  - electroCore, Inc.
  - SPR Therapeutics
  - Nalu
  - Saluda

Scope of the Problem

- Patients with pain:
  - at least 50% of all cancer patients
  - more than 70% of patients with advanced cancer
- Pain intensity:
  - moderate to severe in approximately 50% of patients with pain
  - excruciating in 30% of patients with pain

50-80% of cancer patients do not obtain satisfactory pain relief

Bonica, 1985; WHO, 1986

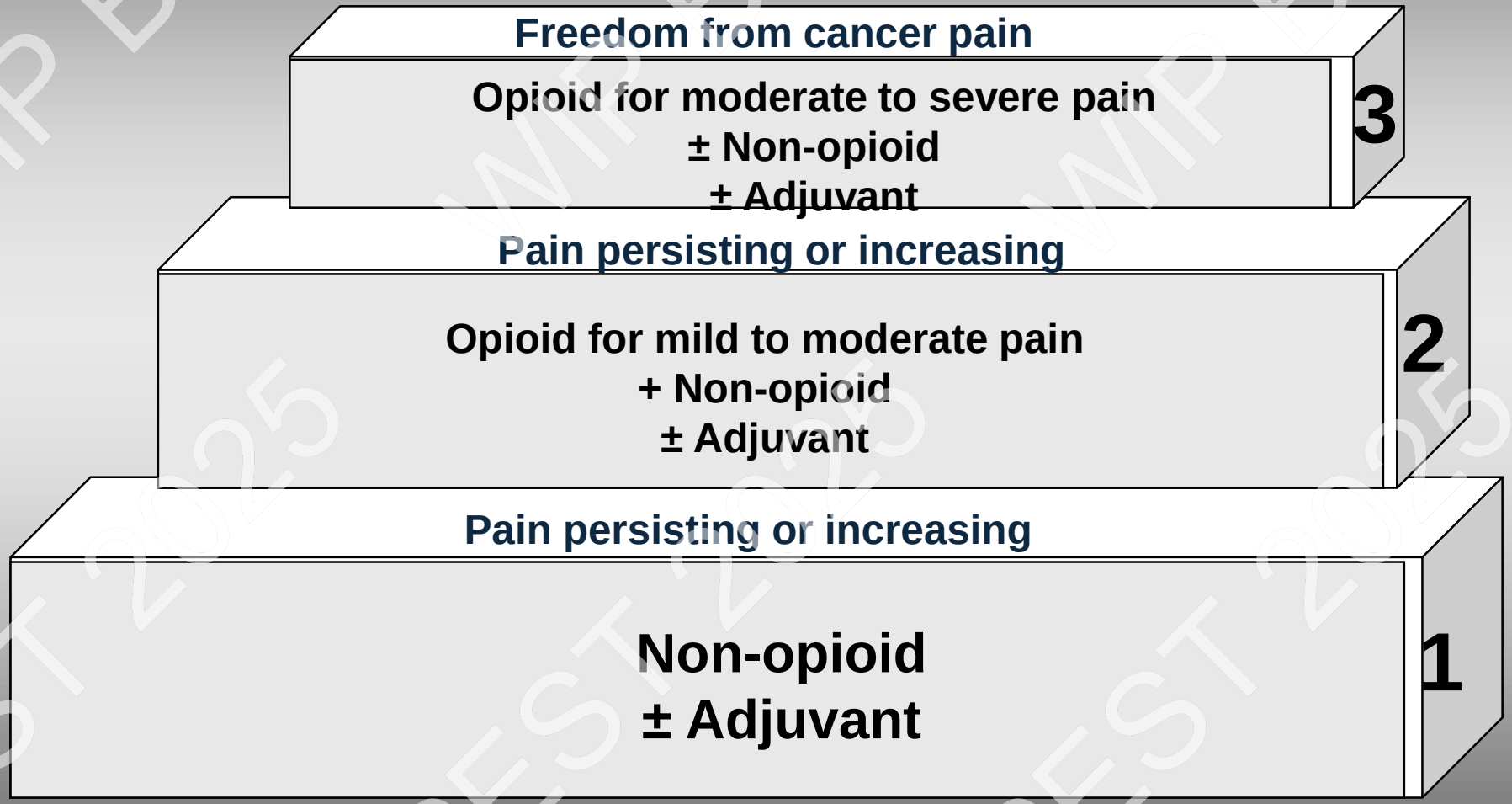
Etiology of Cancer Pain

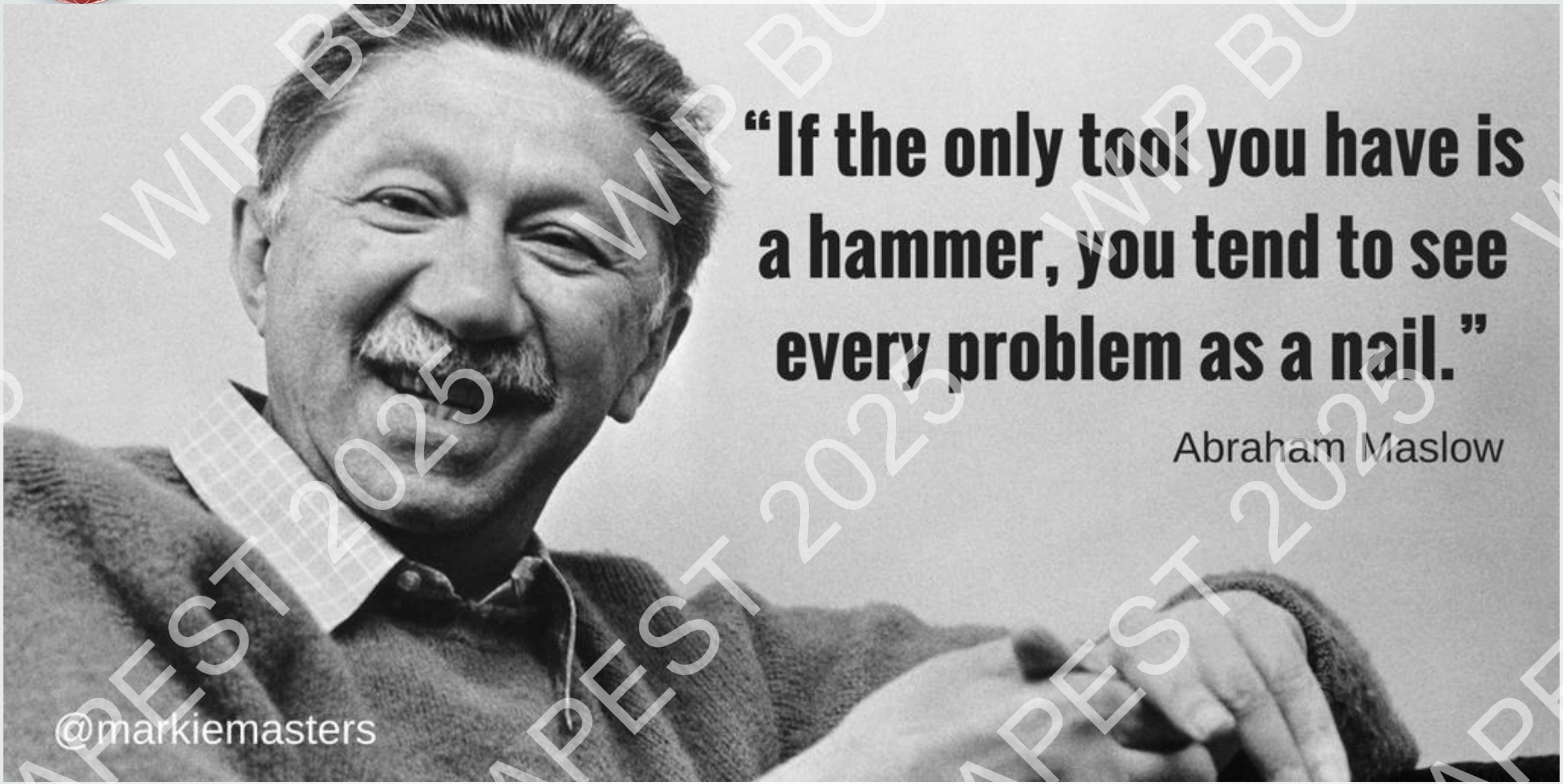
Up to 70% of patients with advanced or terminal cancer report pain. This can be caused by:

- Direct tumor involvement
- Complications of treatment
- Physical changes associated with chronic illness
- Concomitant disorders unrelated to cancer

Bonica J. The management of pain. Vol 1, 1990.

Medical Therapies Remain the Mainstay of Chronic Cancer Pain Management





Prevalence of Cancer Pain

- 8 million patients have cancer (1996)
- If 50% have pain (WHO estimates). 4 million cancer patients suffer with pain
- If 90% of these patients could be adequately treated with opiates, we would be left with 4 hundred thousand patients suffering with cancer pain each year.

Staats PS 1998 J Back Musc Rehab

Intractable Cancer Pain

"It is postulated that 25% of all patients with cancer throughout the world die without relief from severe pain."

Foley K. The treatment of cancer pain. NEJM 1995.

Increased Attention?

- Physician assisted suicide
- Palliative care
- Interventional pain Medicine

Depressed? Don't Go See Dr. Kevorkian

By Wesley J. Smith

OAKLAND, Calif.

"If a patient with multiple sclerosis has bed sores, it means by definition that, for whatever reason, he or she is not receiving adequate medical care," Dr. Randolph B. Schiffer, an adviser to the National Multiple Sclerosis Society, told me when I asked whether that condition could be generally considered normal for such a patient.

Last month, Esther Cohan, who was 46 years old, committed suicide with the help of Jack Kevorkian. Ms. Cohan, who had multiple sclerosis, was disabled but not terminally ill. Esther's sister told reporters that her sister's body was covered with bed sores. Yet, according to Jack Kevorkian's lawyer, Geoffrey Feiger, Dr. Kevorkian had been "counseling" Ms. Cohan since March. Didn't he know that he was participating in the suicide of someone who, by Dr. Schiffer's standards, appears to have received inadequate care?

There are some equally disturbing facts about other deaths assisted by Dr. Kevorkian, who is facing trial in Michigan for participating in four such suicides. At least half of the people whom Dr. Kevorkian helped to die, for example, were not terminally ill. And a number of those driven to seek his help probably could have had their suffering eased.

> Half of his patients were not terminally ill.

Take the case of Margaret Garrish, 72 years old, who had a painful form of rheumatoid arthritis and had had to have her legs amputated. Several months before her death, in November 1994, Mr. Feiger issued a warning: Unless doctors came forward who would treat her pain, Dr. Kevorkian would agree to her request to help her die.

At least seven pain control specialists from around the country responded, yet neither Mr. Feiger or Dr. Kevorkian put these physicians in contact with the suffering woman, who died with the aid of Dr. Kevorkian. When asked why he had not put the specialists in touch with her, Mr. Feiger claimed that the doctors were publicity seekers. Yet pain control specialists can often alleviate pain that nonspecialists find intractable.

Marjorie Wantz is one of the people for whose death Dr. Kevorkian will stand trial. Ms. Wantz, 58 years old, complained of pelvic pain. Not only was she not terminally ill, her autopsy showed she wasn't even physically ill. According to press accounts, she had deep emotional problems and her family and doctor said that she had been abusing Halcion, a sleeping medication that some experts believe can cause suicidal impulses. Despite this, in October 1991 Dr. Kevorkian helped her kill herself.

The circumstances of these and other deaths assisted by Dr. Kevorkian demonstrate that legalizing doctor-induced death could encourage chronically ill people who are depressed or not receiving adequate treatment to choose suicide. Such was conclusion last year of the New York Task For on Life and the Law, which una mously recommended against legal ing assisted suicide.

In its 1994 report, the panel dete mined that legalization "would profoundly dangerous for many in viduals who are ill and vulnerable and that the risks were most seve "for those who are elderly, poo socially disadvantaged or witho access to good medical care."

The panel also shed light on scandal that receives far too lit attention. Doctors are doing a po job of alleviating the suffering a depression of their dying and chro cally ill patients. According to t report, perhaps half of all canc patients receive inadequate pa treatment, and depression in the d ing is routinely overlooked. Yet wh these patients receive appropria treatment, according to the Ne York panel, "they usually aband the wish to commit suicide."

If we want to alleviate suffering ill and dying people, then we shou not legalize assisted suicide. Aft all, if doctors are doing such an ina equate job of relieving suffering no how will they do if death becon merely another treatment option?

Wesley J. Smith, a lawyer and consumer advocate, is writing a book about euthanasia.

Journal of Back and Musculoskeletal Rehabilitation

IOS Press

Impact Factor: 1.4 / 5-Year Impact Factor: 1.7

Journa

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Cancer pain: Beyond the ladder

Peter S. Staats View all authors and affiliations

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Abstract

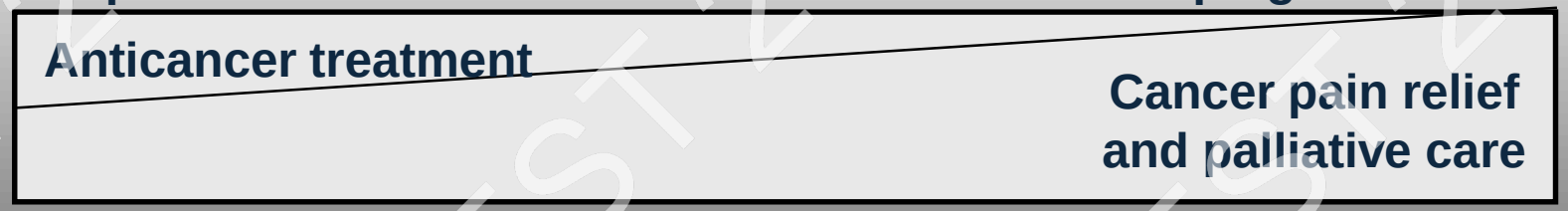
Current estimates indicate that between 50 and 90% of patients with cancer experience pain. The World Health Organization has outlined a three-step analgesic ladder, that, if followed will result in close to 90% pain relief. Opioids should not be withheld for fear of addiction or respiratory depression and are clearly the most effective systemic analgesic available for patients with cancer-related pain. Unfortunately, opioids can also cause side effects including, but not limited to, constipation and mental cloudiness. Interventional therapies and physical modalities can decrease pain without systemic side effects associated with opioids and should be considered a useful adjunct in the battle against pain. It is likely that by incorporating interventional and non-pharmacologic approaches, the success rate of pain control and the quality of life can be improved.

Source: WHO: Technical Report Series No. 804, 1990

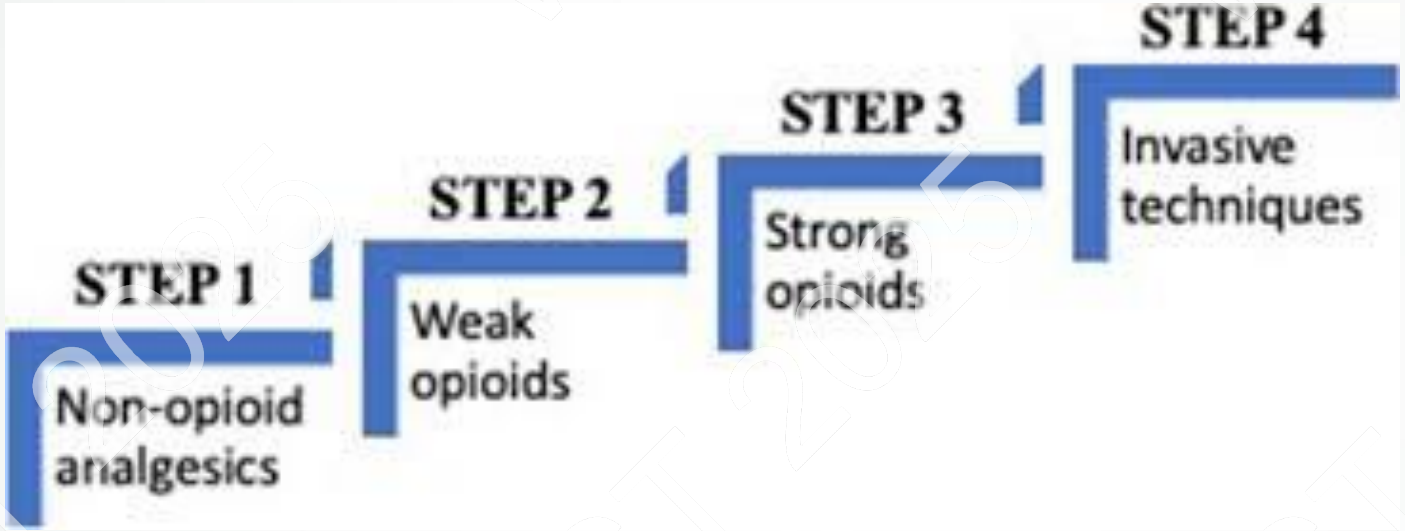
Present Allocation of Cancer Resources

Proposed allocation of cancer resources in developed countries

Proposed allocation of cancer resources in developing countries



Beyond the ladder

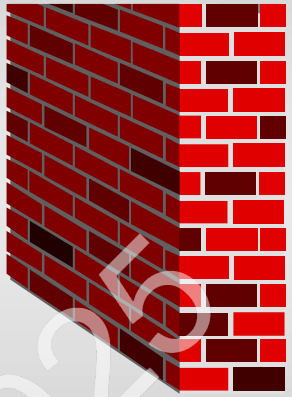


The reason for increase in palliative care

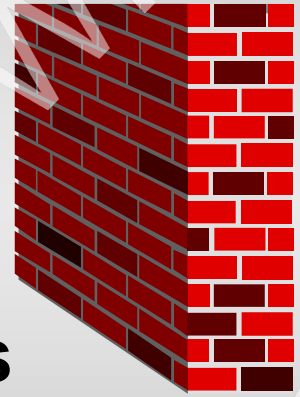
- Oncologists Don't know what we can do
- Interventional Pain Medicine Physicians have not adequately demonstrated what we can do
- Increase awareness of the appropriate role of opiates in cancer pain
- Patients and families demand comfort care

Barriers to Adequate Pain Control

Cancer Pain



Attitudes and beliefs
Knowledge deficits and clinical practice
Laws and regulations



Pain Relief

Therapies Directed at Decreasing Opioid Dosage

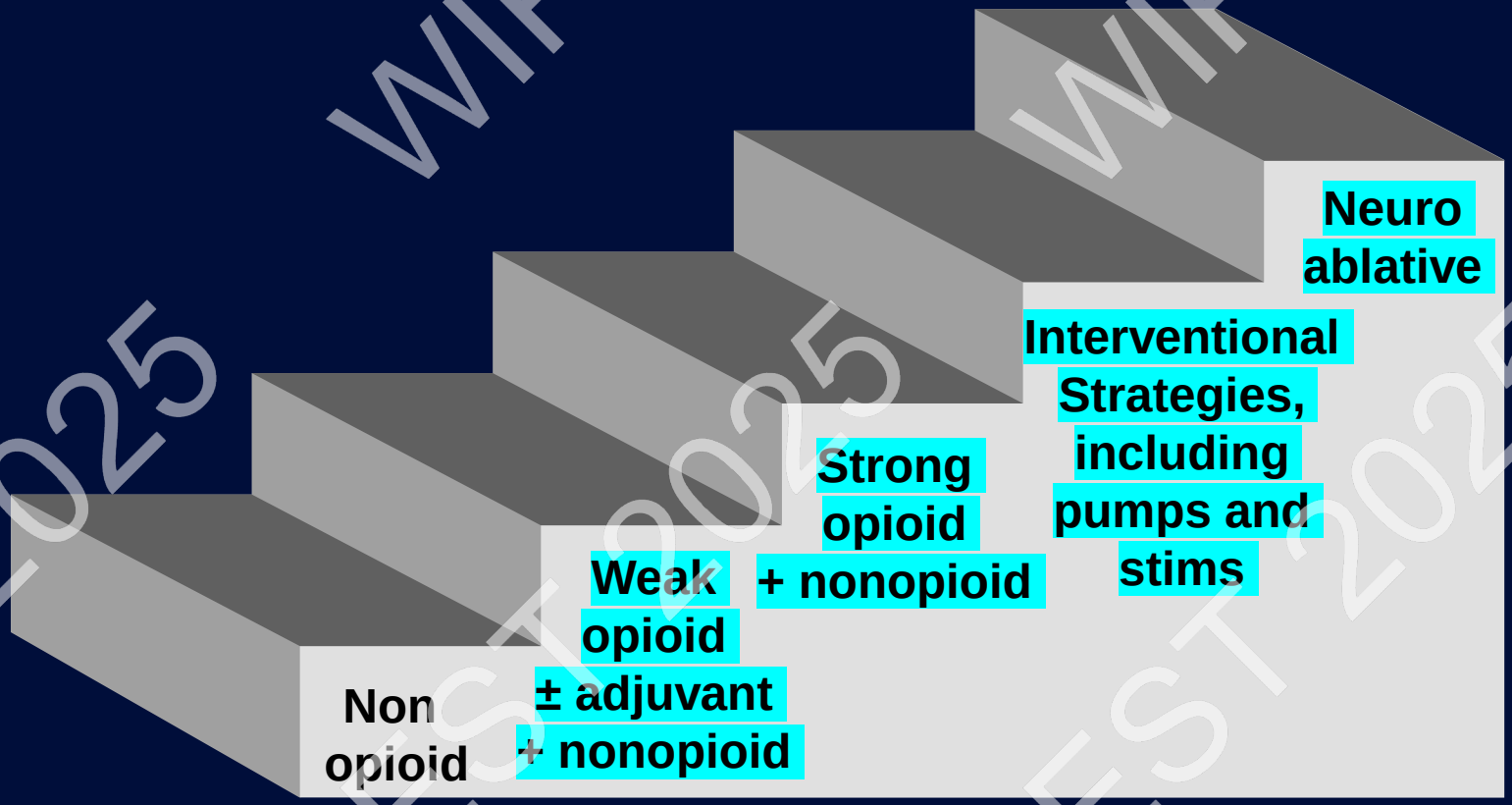
- Infusions
  - Epidural
    - Local
    - Other
    - Opioids (10-1)
  - Intrathecal
    - Non-Opioids
    - Opioids

Neurolytic Blocks

- Intercostal Blocks
- Visceral Blocks
- Rhizotomy/Neurectomy

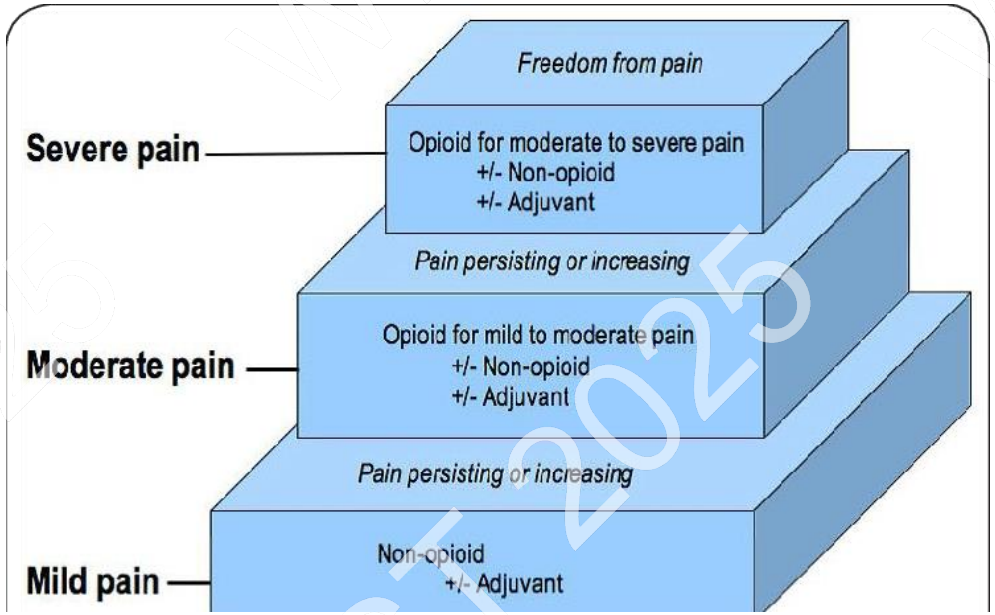
Treatment of Pain of Terminal Diseases

The WHO Ladder - *Revised*



Problems with the World Health Organization Ladder

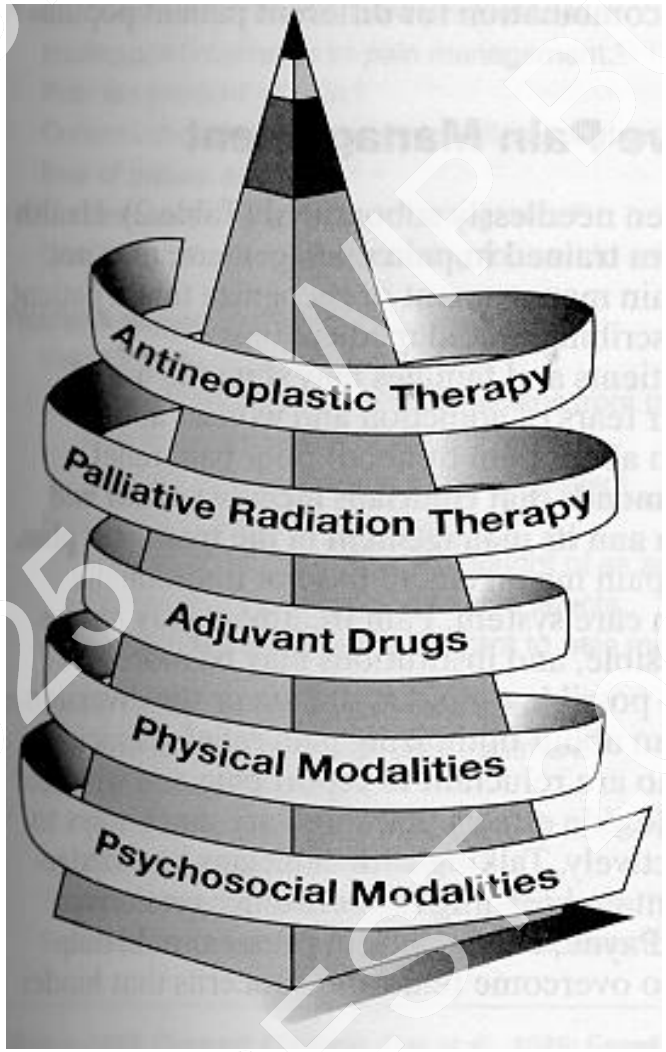
- 80-90% of patients could have their pain controlled by following this ladder
- Provides a framework for managing patients with intractable pain
- Does not indicate how to manage side effects or when interventional therapies are indicated



Examples of Interventional pain treatment strategies

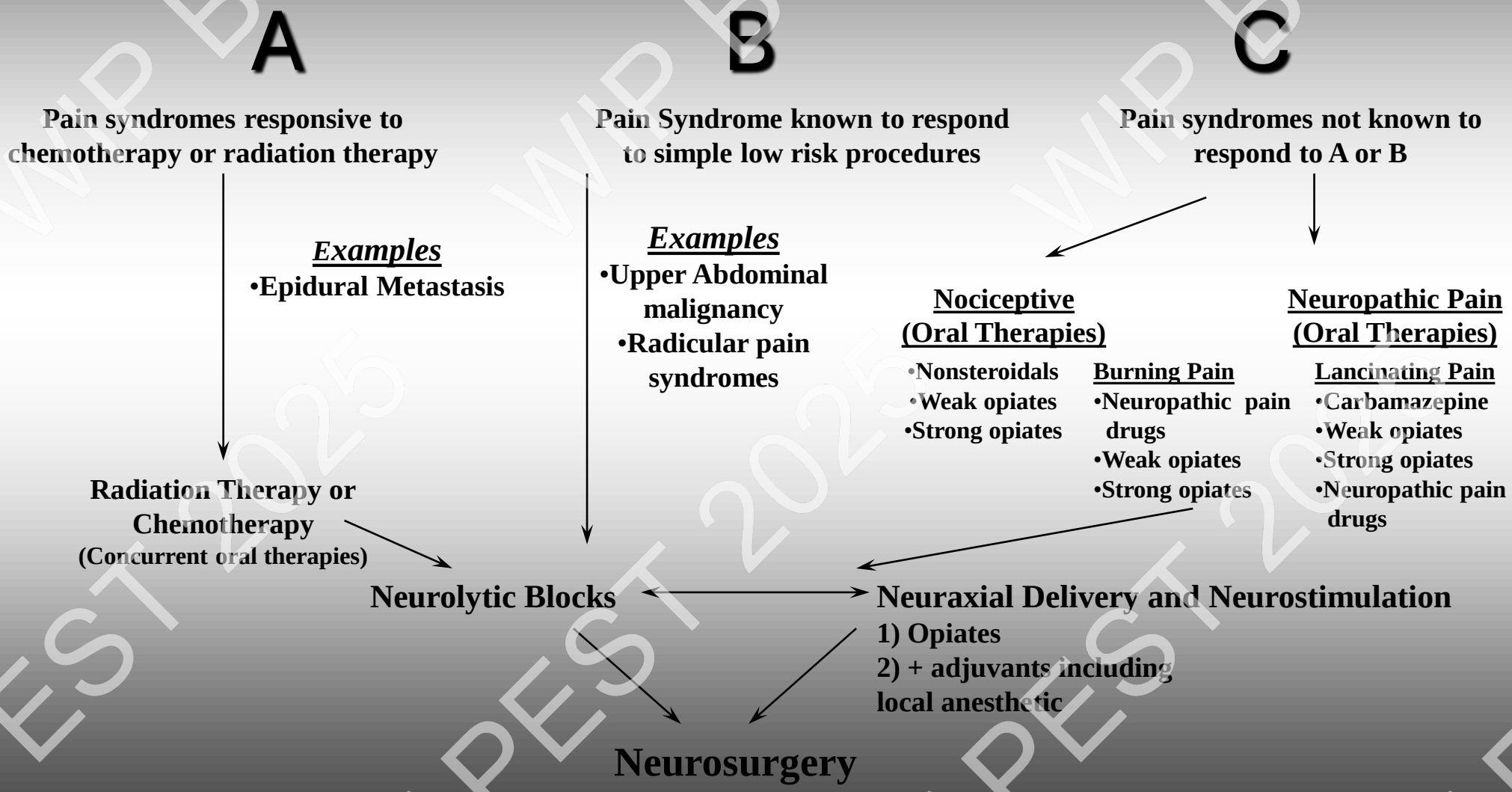
- Cervical cordotomy: Unilateral pain below C5 – shoulder
- Celiac plexus block/ Splanchnic Block: high visceral pain
- Hypogastric plexus block: lower visceral pain
- Intrathecal drug administration: any location
- Neurostimulation –Neuropathic pain (ie Radiation

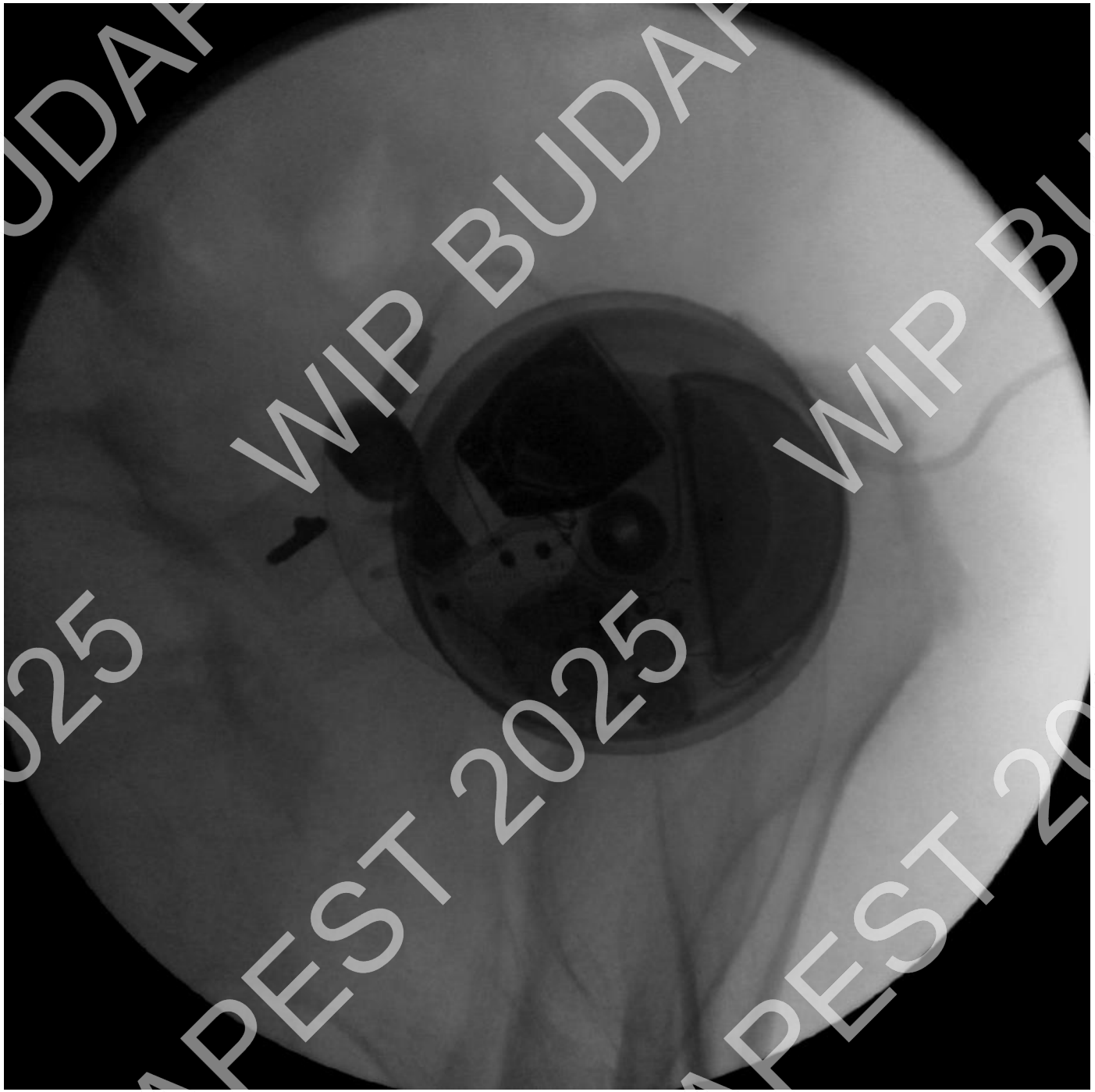
Pain Management Strategies: A Hierarchy



- **Nerve blocks, palliative surgery and ablative surgery, 1-5%**
- **Epidural and intrathecal analgesics, 2-6%**
- **Intravenous and subcutaneous drugs 5-20%**
- **Oral, transdermal, and rectal drugs, 75-85%**

Management of Cancer Pain





What is the data on intrathecal opioids in pain?

Before 2000's
Primarily prospective and retrospective review

Historical Literature Review

Reference	No. of Patients	Indication	Good-Excellent Pain Relief
Paice JA, et al. *J Pain Symptom Manage.* 1996;11:71-80.	429	1/3 Cancer 2/3 Nonmalignant	95%
Devulder J, et al. *J Pain Symptom Manage.* 1994;9:75-81.	33	Cancer	76%
Onofrio BM, Yaksh TL. *J Neurosurg.* 1990;72:200-209.	53	Cancer	64%
Penn RD, Paice JA. *J Neurosurg.* 1987;67:182-186.	43	35 Cancer 8 Nonmalignant	84%
Shetter AG, et al. *Neurosurgery.* 1986;18:740-747.	14	Cancer	79%
Krames ES, et al. *Cancer.* 1985;56:696-702.	17	16 Cancer 1 Meningomyelocele	88%

The Questions

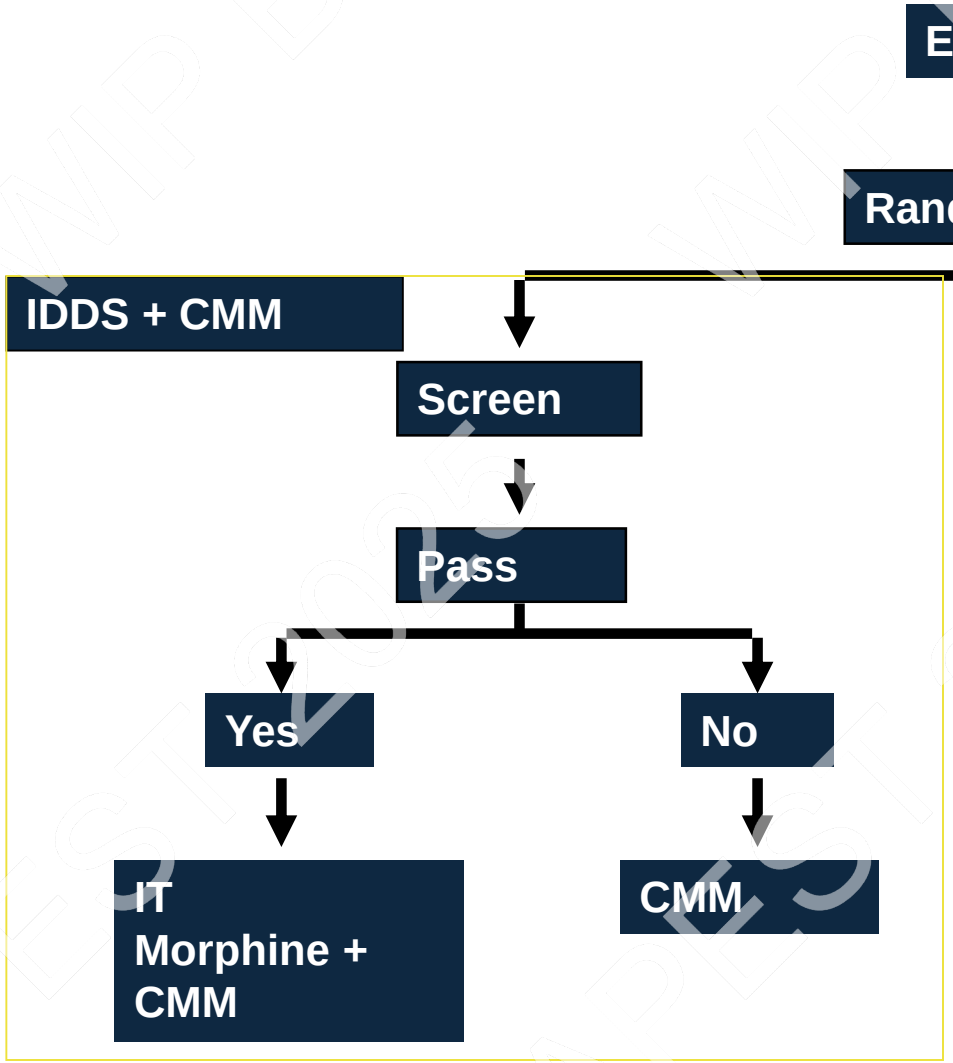
- Does intrathecal (IT) therapy work?
  - Without question
- Does IT therapy work better than maximal medical therapy?
- Do spinal opiates provide improved pain relief over medical therapies?
- What Drugs do we administer in the pumps?

IT Morphine Versus Maximal Medical Therapy

- Randomized controlled trial in patients with cancer
- Comprehensive medical management (CMM) versus implantable IT drug delivery systems (IDDS) plus CMM
- Primary objective
  - Clinical success
    - ≥20% improvement in Visual Analog Scale (VAS) pain score with equal or reduced National Cancer Institute (NCI) Common Toxicity Criteria (CTC) score
    - Equal VAS pain score with ≥20% improvement in NCI CTC score

Smith TJ Staats PS, et al. *J Clin Oncol.* 2002;20:4040-4049.

Study Design

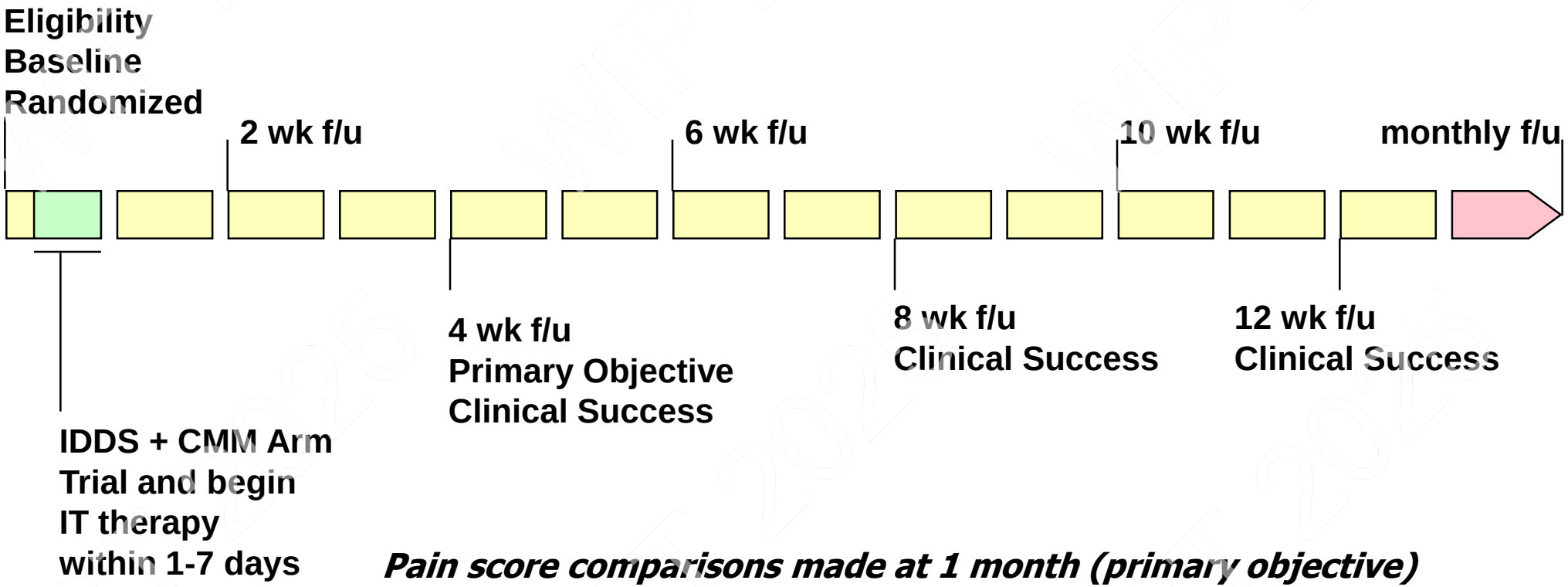


Crossover:
allowed 1 month after enrollment either arm

Intention to treat:
patients analyzed with group to which they were randomized

Smith TJ, et al. *J Clin Oncol.* 2002;20:4040-4049.

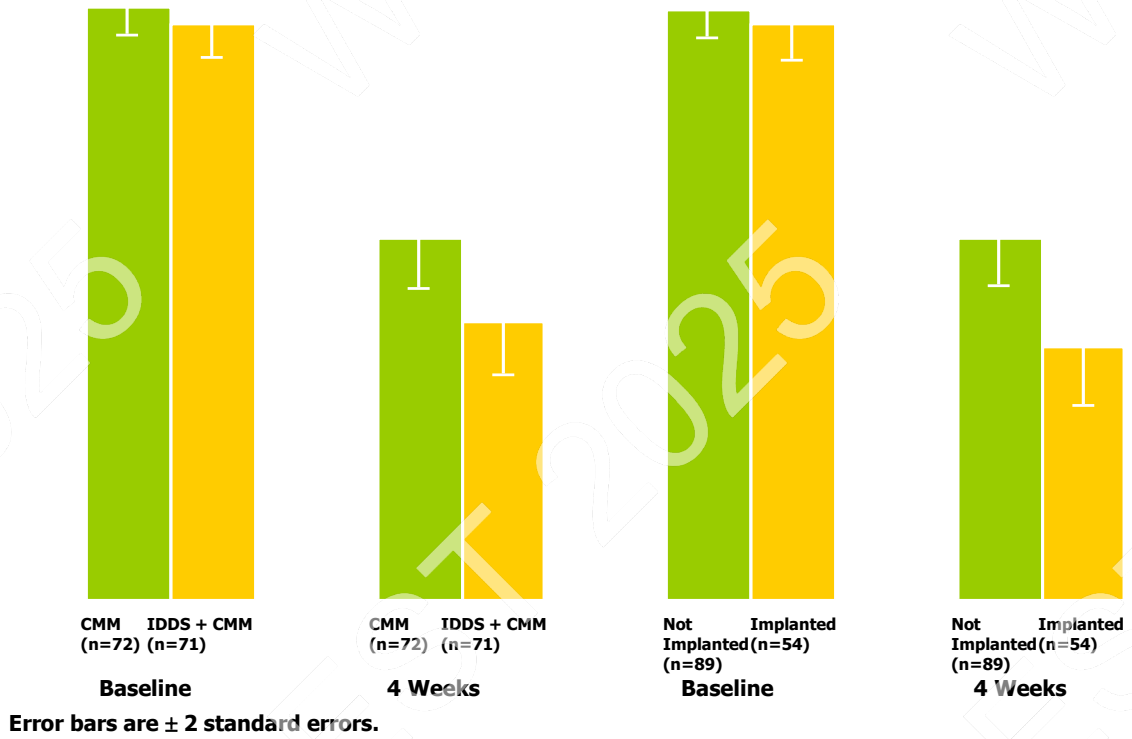
Schedule: Primary End Point



Pain score comparisons made at 1 month (primary objective) and at 2, 3, and 6 months. Monthly follow-up continued until all patients withdrew from the study or were lost to follow-up

Smith TJ, et al. *J Clin Oncol.* 2002;20:4040-4049.

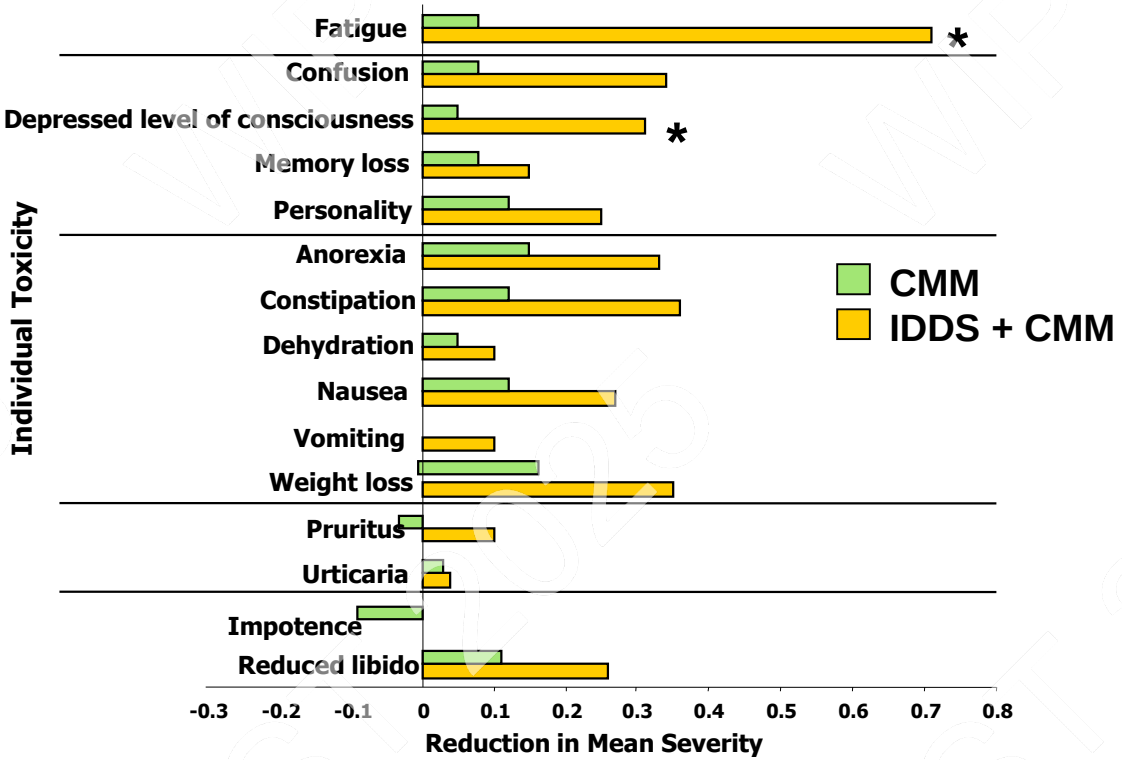
Reduction in Pain



Error bars are ± 2 standard errors.

Significantly improved pain control with IDDS + CMM (p=0.055 as randomized; p=0.007 as treated).

Reduction in Specific Side Effects



From baseline to Week 4, all opioid side effects reduced with IDDS + CMM, fatigue and sedation (depressed level of consciousness) significantly (*p<0.05).

Smith TJ, and Staats et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol.* 2002;20(19):4040-4049. Reprinted with permission from the American Society of Clinical Oncology.

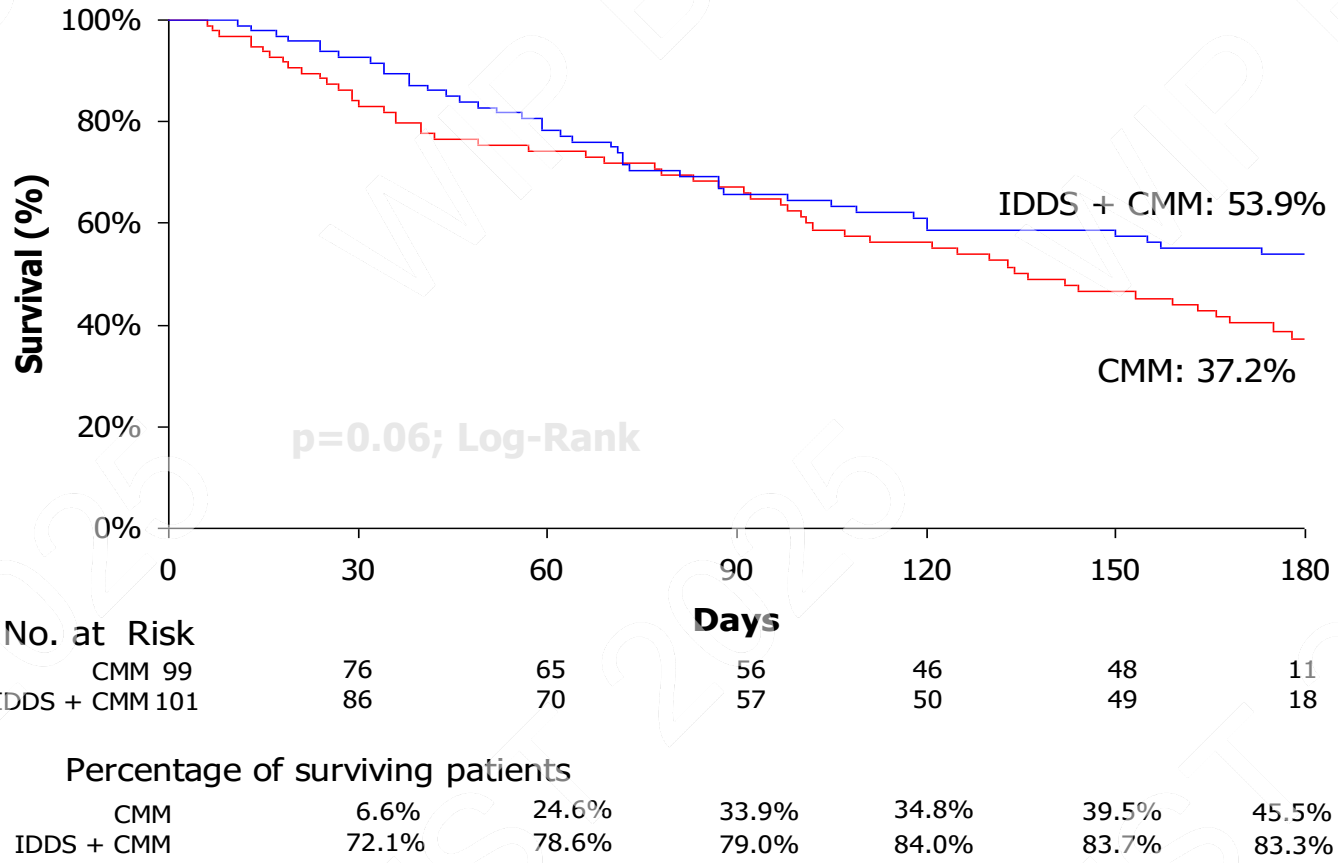
Clinical Success

	IDDS + CMM	CMM	p Value
Pain reduced ≥20% regardless of toxicity ***or*** equal pain with ≥20% reduced toxicity	60/71 84.5%	51/72 70.8%	0.05
Both pain and toxicity reduced ≥20%	41/71 57.7%	27/72 37.5%	0.02
Neither pain nor toxicity reduced ≥20%	8/71 11.3%	17/72 23.6%	0.05

Superior clinical success with IDDS + CMM pain management

Smith TJ Staats PS, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol.* 2002;20(19):4040-4049. Reprinted with permission from the American Society of Clinical Oncology.

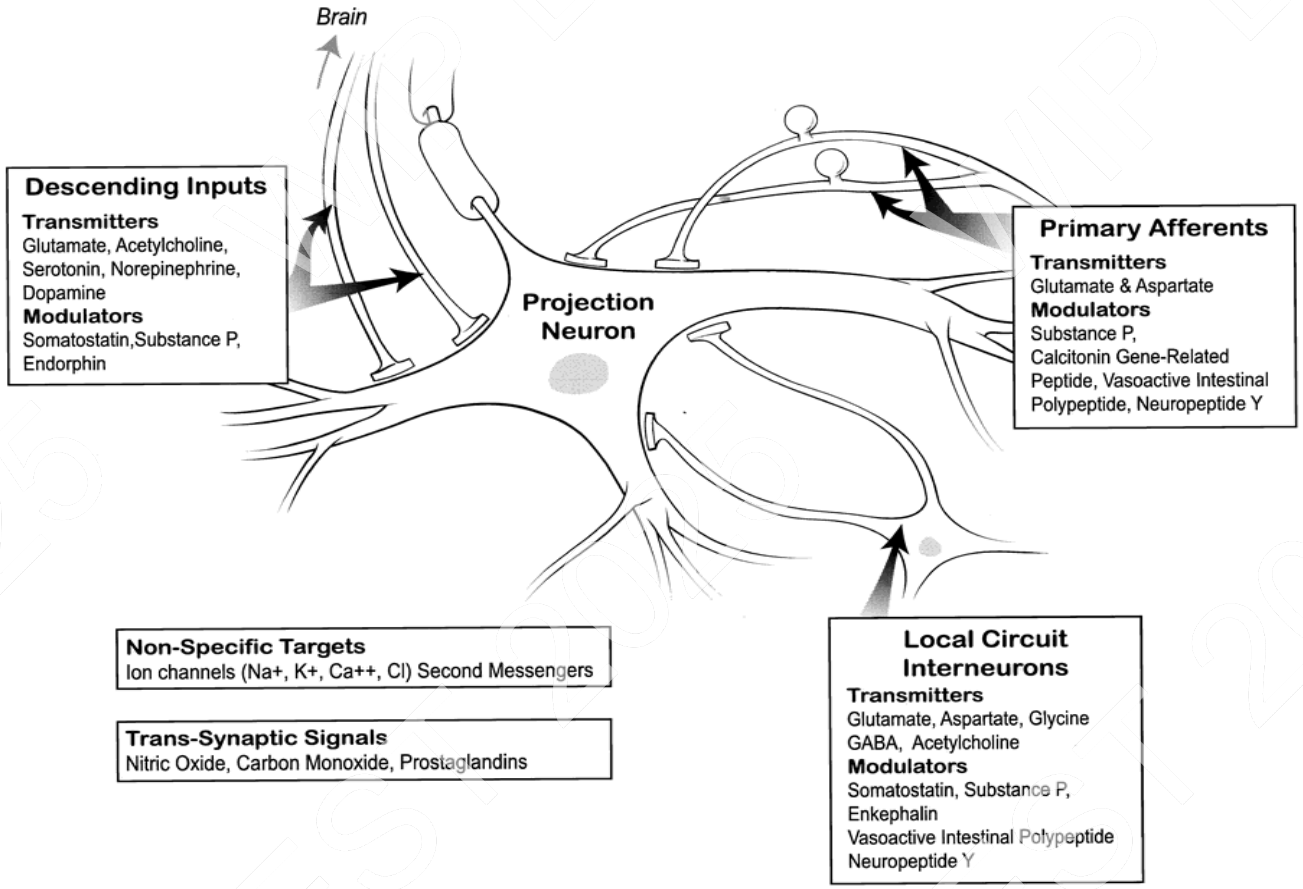
Survival – as Randomized



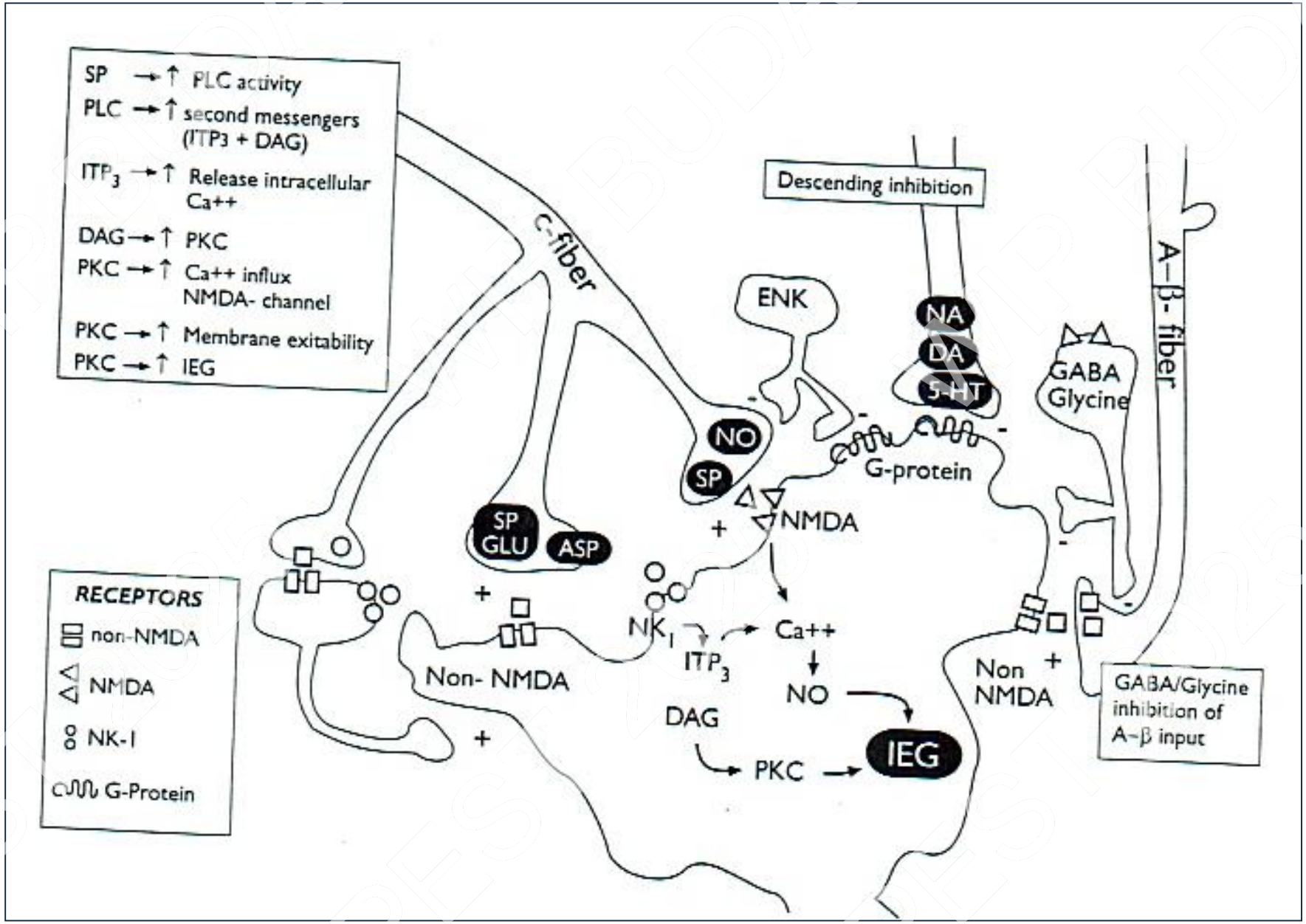
Estimated cumulative survival was 53.9% for the IDDS + CMM group and 37.2% for the CMM group.

Smith TJ, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol.* 2002;20(19):4040-4049. Reprinted with permission from the American Society of Clinical Oncology.

Dorsal Horn Circuitry



Dougherty and Staats 1999



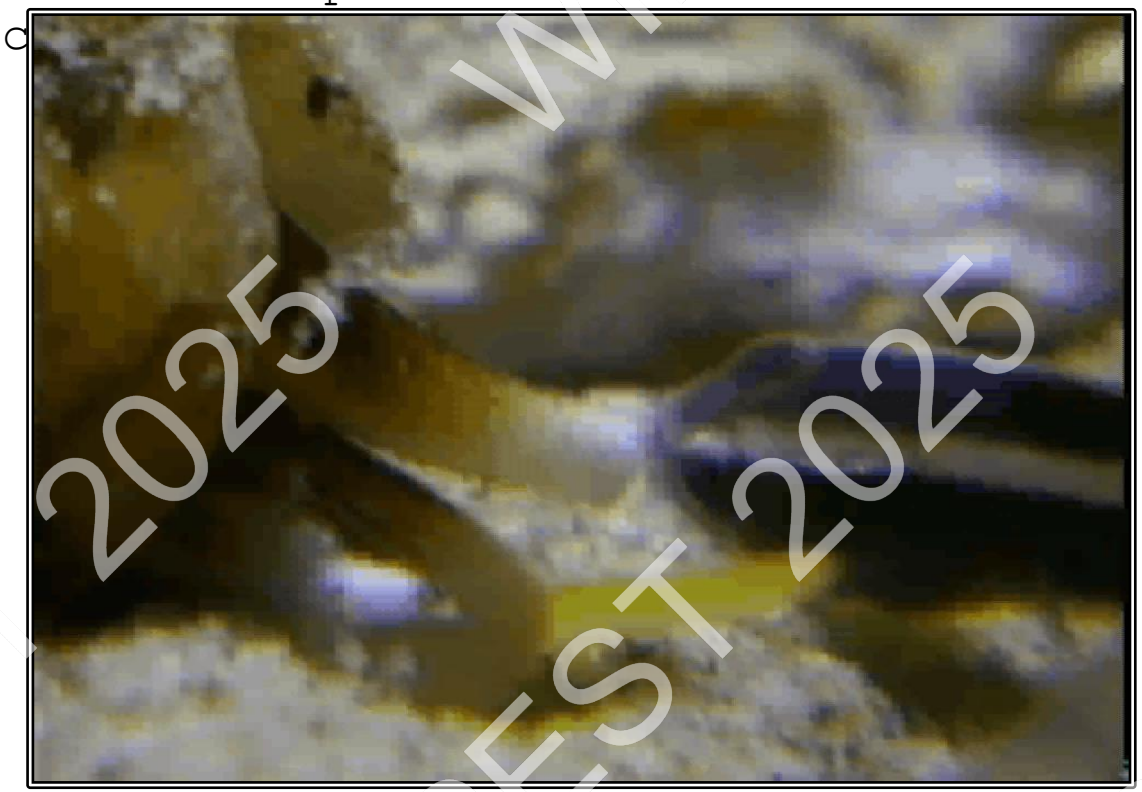
Dougherty and Staats 1999

Classes of Experimental Intrathecal Infusion Therapies Being Explored

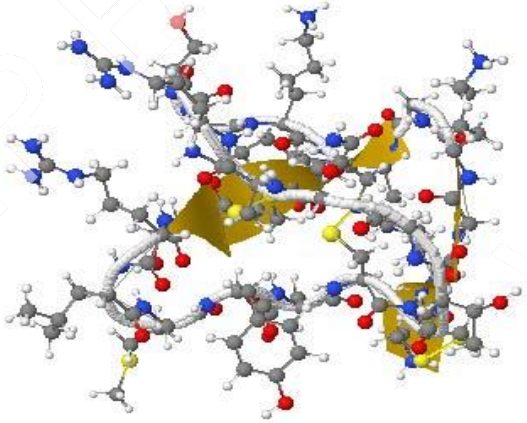
- Opioids
- Local anesthetics
- $\alpha 2$ agonists
- NMDA receptor antagonists
- GABA agonists
- Prostaglandin synthesis inhibitors
- Neuron specific calcium channel blockers
- Excitatory amino acid inhibitors
- Acetylcholinesterase inhibitors
- Tricyclic Antidepressants
- Labetalol

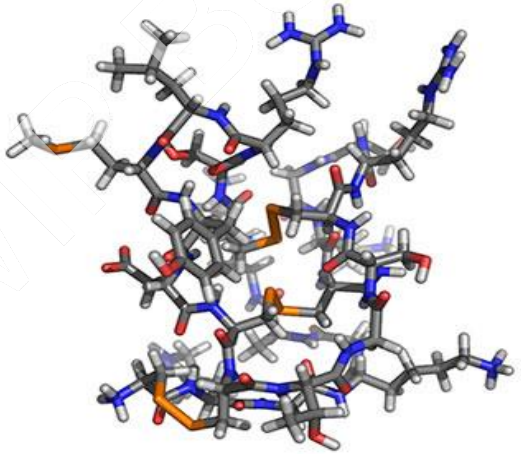
Only Non-opioid IT Therapy Approved for Severe Chronic Pain

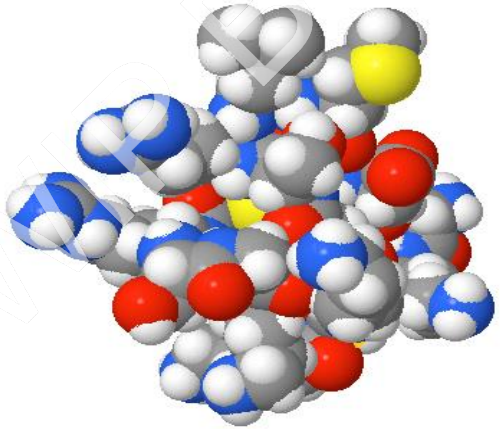
- 500+ species of cone snails populate the world's oceans
- Synthetic equivalent of omega conopeptide MVIIA found in the cone snail *Conus magus* (magician's cone snail)
- First intrathecal (IT) analgesic approved (December 2004) for the management of severe chronic pain in the United States in more than two dec



25-amino-acid sequence







H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-

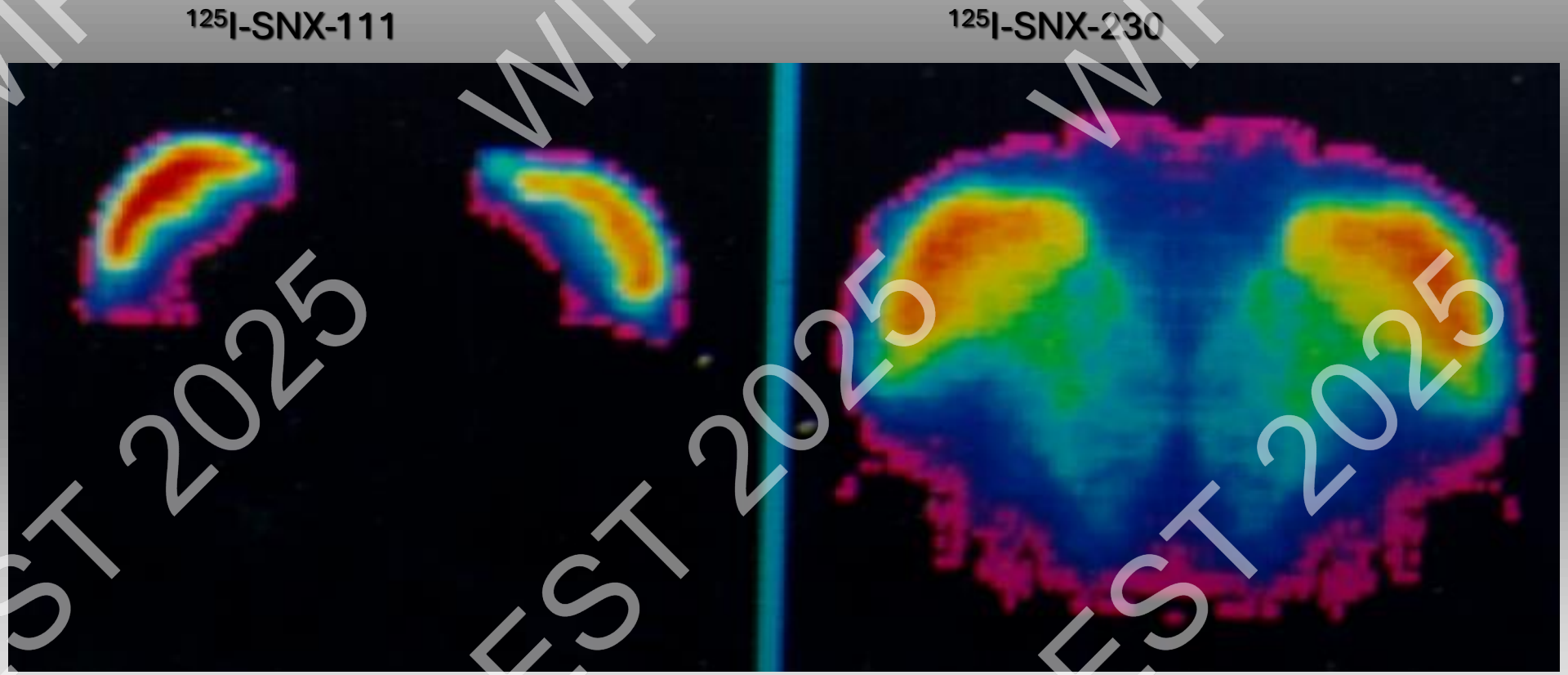
Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH_2

Mather V, et al. *Pharmaceutical News.* 1998;5:25-29.
Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/.

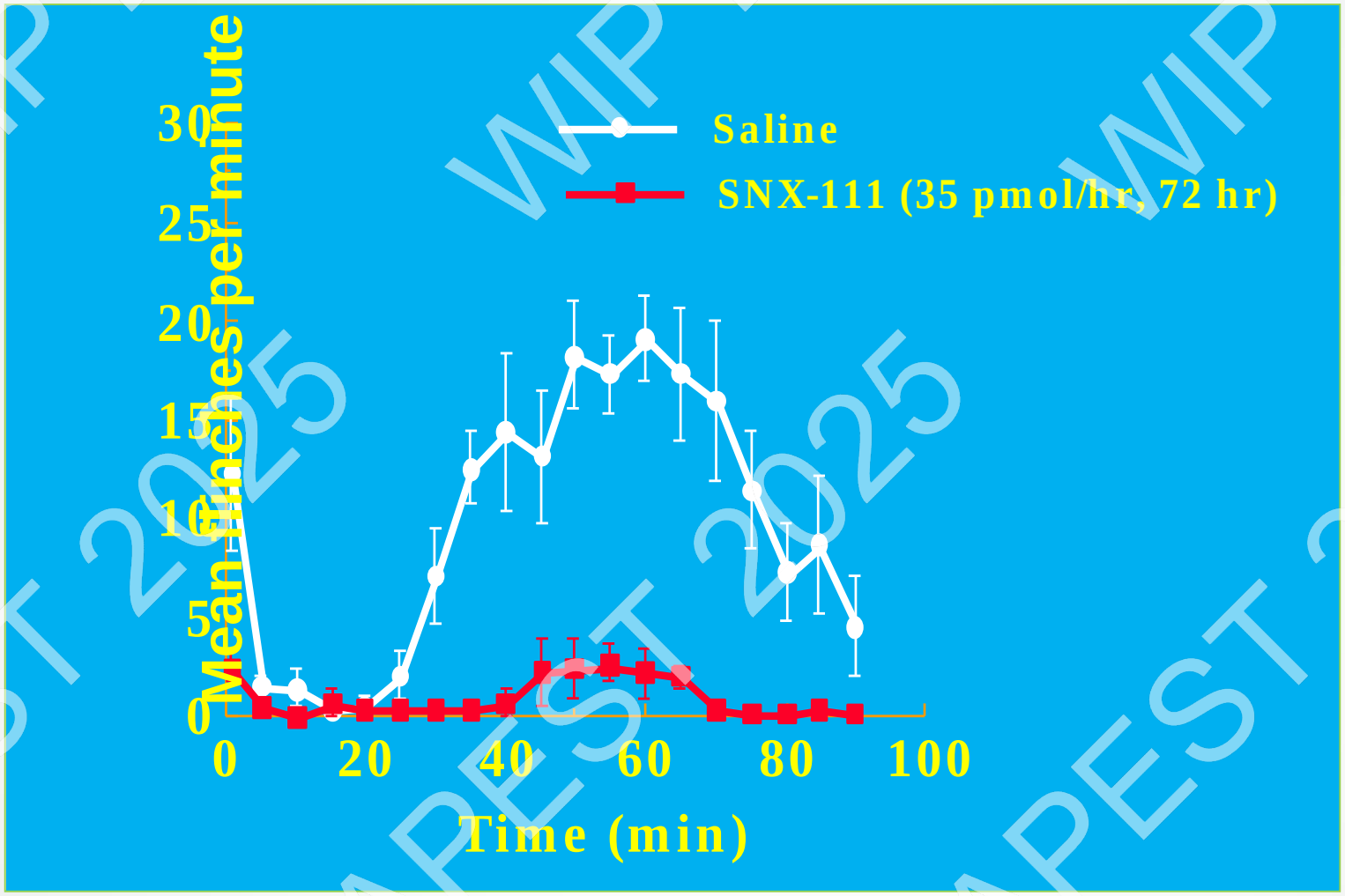
Ziconotide Discovery and Development Timeline

1980	Scientists discovered venom in *Magician's Cone*
1984	Calcium channel-blocking activity
1989	Anti-nociceptive activity in animals
1993	First in humans
1995	Analgesic activity in humans
1998	Pivotal phase III clinical studies
1999	New Drug Application submitted
2000	FDA: "Approvable"
2004	Re-submission of NDA
2004	Approval by the FDA

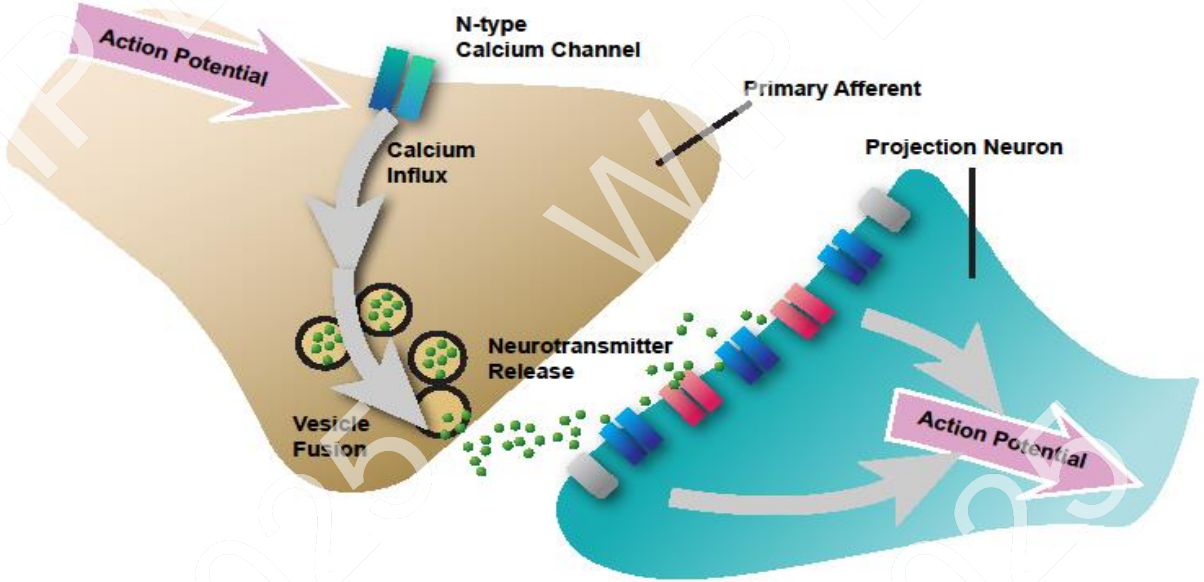
N-type Channels are Localized to the Outer Layers of the Dorsal Horn: P/Q Channels are More Broadly Distributed in the Spinal Cord.



Continuous Spinal Infusion of SNX-111 Blocks Acute Tonic Nociceptive Responses in Rat Formalin Test



- Presynaptic calcium channels trigger calcium-dependent transmitter release
- Ziconotide directly blocks presynaptic N-type calcium channels*[1]
- Opioids, such as morphine, also inhibit N-type channels through G-protein coupling, but this inhibition is indirect[2]

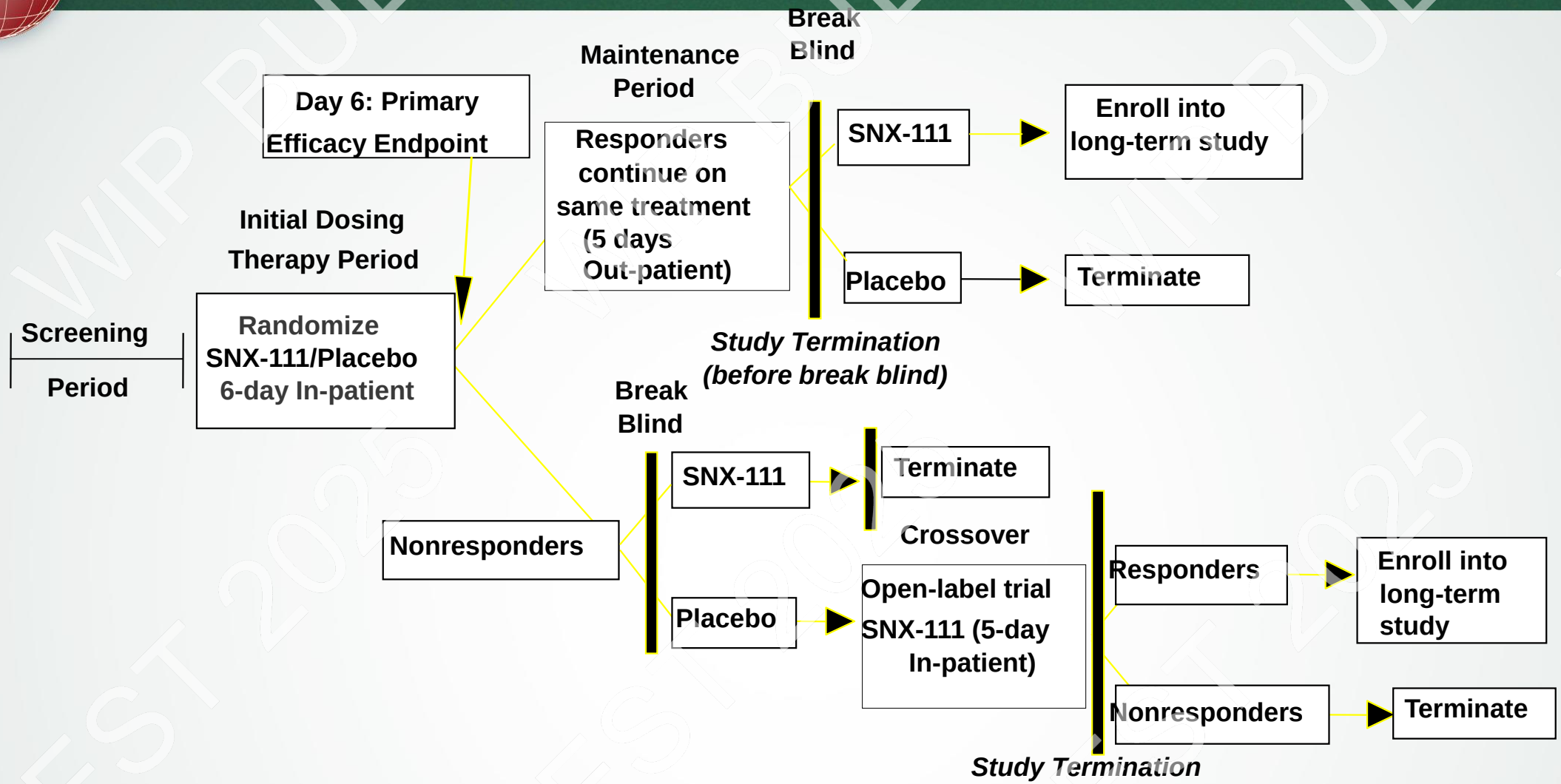


*Ziconotide's antinociceptive mechanism of action in animals is inhibition of primary nociceptive afferent neurons through blockade of N-type calcium channels. Ziconotide blocks human N-type calcium channels, but its analgesic MOA in humans has not been established.

1. Miljanich GP. *Current Medicinal Chemistry.* 2004; 11:3029-3040.
2. DuPen A, et al. *Pain Management Nursing.* 2007; 8(3);113-121.

Pivotal IT Ziconotide Trials

- **Randomized, double-blind, parallel comparison to placebo**
  - **Nonresponders switch to alternate treatment**
  - **Study centers in US, Europe, Australia**
- **Chronic pain patient populations**
  - **Cancer or AIDS (malignant pain study)**
  - **Nonmalignant conditions or injuries (nonmalignant pain study)**
- **Long-term, open-label follow-up for responders**


Screening Period
Initial Dosing Therapy Period
Randomize SNX-111/Placebo 6-day In-patient
Day 6: Primary Efficacy Endpoint
Maintenance Period
Responders continue on same treatment (5 days Out-patient)
Break Blind
SNX-111
Enroll into long-term study
Placebo
Terminate
Study Termination (before break blind)
Nonresponders
Break Blind
SNX-111
Terminate
Placebo
Crossover
Open-label trial SNX-111 (5-day In-patient)
Responders
Enroll into long-term study
Nonresponders
Terminate
Study Termination

Intrathecal Ziconotide in the Treatment of Refractory Pain in Patients With Cancer or AIDS

A Randomized Controlled Trial

Peter S. Staats, MD
Thomas Yearwood, MD, PhD
Steven G. Charapata, MD
Robert W. Presley, MD
Mark S. Wallace, MD
Michael Byas-Smith, MD
Robert Fisher, MD
David A. Bryce, MD
Eugene A. Mangieri, MD
Robert R. Luther, MD
Martha Mayo, PharmD
Dawn McGuire, MD
David Ellis, MD, PhD

Context Ziconotide (formerly SNX-111) selectively blocks N-type voltage-sensitive calcium channels and may be effective in patients with pain that is refractory to opioid therapy or those with intolerable opioid-related adverse effects.

Objective To assess the safety and efficacy of intrathecal ziconotide in patients with pain that is refractory to conventional treatment.

Design, Setting, and Patients Double-blind, placebo-controlled, randomized trial conducted from March 12, 1996, to July 11, 1998, at 32 study centers in the United States, Australia, and the Netherlands. Patients were 111 individuals ages 24 to 85 years with cancer or AIDS and a mean Visual Analog Scale of Pain Intensity (VASPI) score of 50 mm or greater. Patients were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment.

Interventions Intrathecal ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of nonresponders to the opposite treatment group.

Main Outcome Measure Mean percentage change in VASPI score from baseline to the end of the initial titration period.

Results Of the evaluable population, 67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/d for the ziconotide group and 600 mg/d for the placebo group; $P=.63$, based on mean values), and 36 had used intrathecal morphine. Mean (SD) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group ($P=.18$). Mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($P<.001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group ($P<.001$). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo ($P=.001$).

Conclusion Intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS.

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ZICONOTIDE (FORMERLY SNX-111, Neurex Pharmaceuticals, Menlo Park, Calif) is the synthetic equivalent of ω-conopeptide MVIIA, a 25–amino-acid polybasic peptide present in the venom of *Conus magus*, a marine snail.[1] Ziconotide produces potent antinociceptive effects[2] by selectively binding to N-type voltage-sensitive calcium channels[3,4] on neuronal somata, dendrites, dendritic shafts, and axon terminals, thus blocking neurotransmission from primary nociceptive afferents.

Ziconotide is the first selective N-type voltage-sensitive calcium channel blocking agent to be tested in clinical trials. There is no evidence of tolerance to ziconotide[5] or of addictive behavior in animals (Elan Pharmaceuticals Inc, unpublished data), and the drug must be administered intrathecally to maximize antinociceptive effectiveness and minimize sympatholysis.[6]

Author Affiliations: Division of Pain Medicine, Johns Hopkins University School of Medicine, Baltimore, Md (Dr Staats); Integrated Spine Clinic, Daphne, Ala (Dr Yearwood); Pain Management Associates, Research Medical Center, Pain Institute, Kansas City, Mo (Dr Charapata); Pain Care Specialists, Colorado Springs, Colo (Dr Presley); Center for Pain and Palliative Medicine, University of California, San Diego, La Jolla (Dr Wallace); Department of Anesthesia, Emory University School of Medicine, Atlanta, Ga (Dr Byas-Smith); R. C. Goodman Institute for Pain Management, Sparks Regional Medical Center, Fort Smith, Ark (Dr Fisher); Marshfield Clinic, Marshfield, Wis (Dr Bryce); Anodyne Research Services, Northport, Ala (Dr Mangieri); Rhino Pias Consulting LLC, Reno, Nev (Dr Luther); Eunoe Inc, Redwood City, Calif (Drs Mayo and McGuire); Elan Pharmaceuticals Inc, San Diego, Calif (Dr Ellis).

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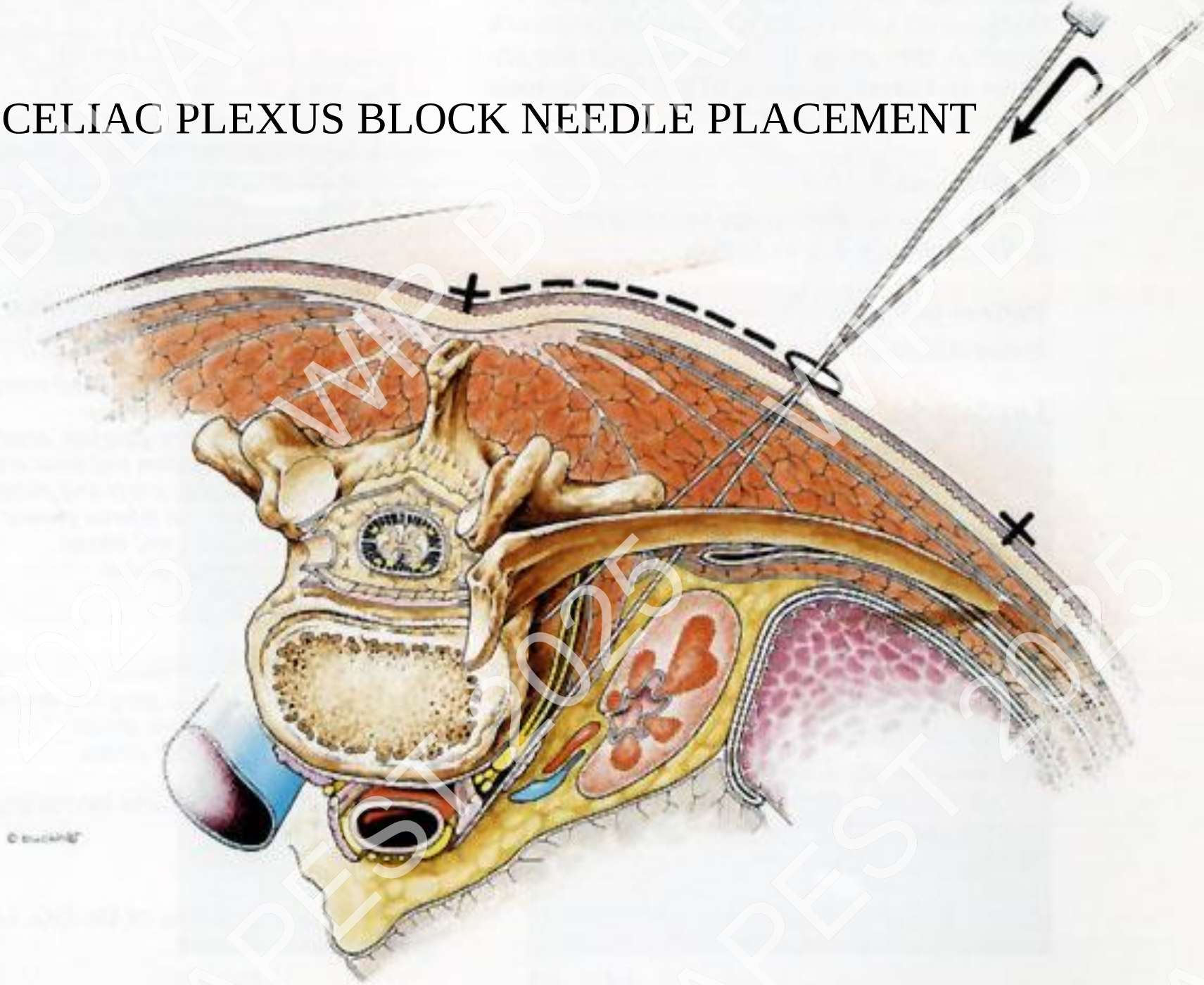
Corresponding Author and Reprints: Peter S. Staats, MD, Division of Pain Medicine, Johns Hopkins University School of Medicine, 550 N Broadway, Suite 301, Baltimore, MD 21205 (e-mail: pstaats@jhmi.edu).

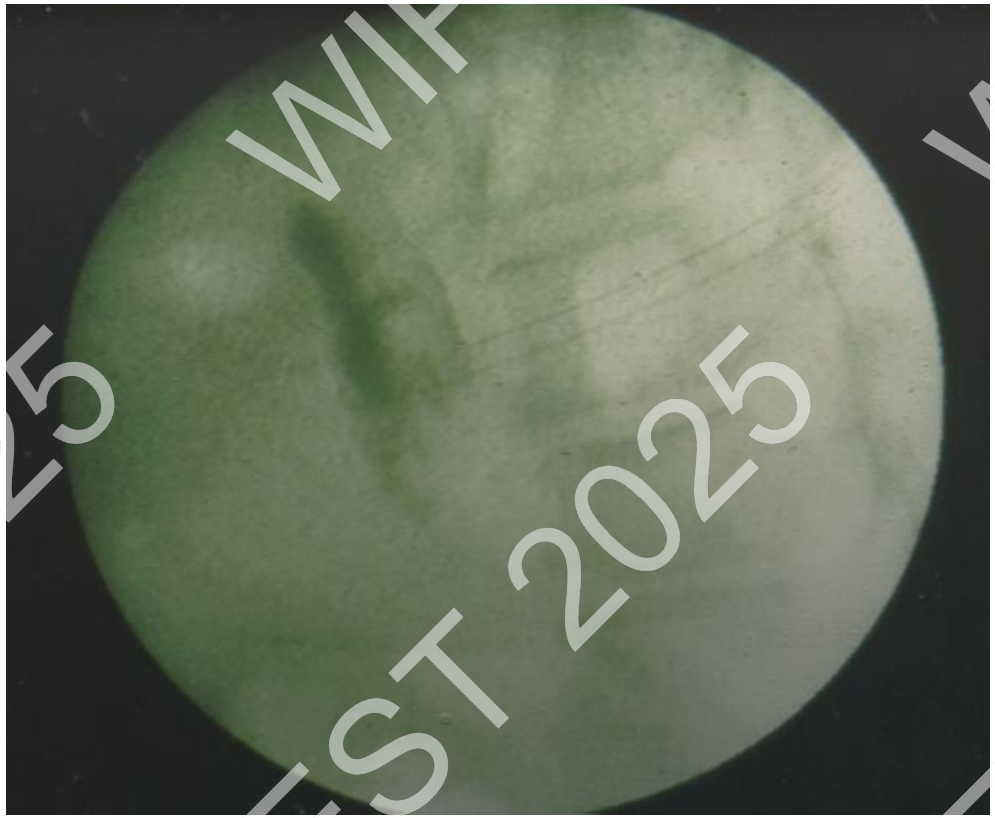
CELIAC PLEXUS BLOCK NEEDLE PLACEMENT



Chemical Splanchnicetomy

Methods:

- Feb ‘87 - Dec ‘91 informed consent 371 patients explored for pancreatic cancer
- Standardized questionnaire preoperatively
- 50% alcohol or normal saline injected
- Questionnaire every 2 months until death



Chemical Splanchnicectomy

- Preoperative Assessment
- Resected/Excluded
- Randomized
- Unable to perform splanchnicectomy

- 371 patients
- 232 patients
- **139 patients**
- 2 patients

Chemical Splanchnicectomy

	Alcohol No Pain (N=45)	Saline No Pain (N=55)	P
Pain Free	7.2 mo	3.0 mo	<0.01
Narcotics req	46%	68%	<0.05
Pain a death	44%	68%	<0.05

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JOURNAL ARTICLE

The Effects of Alcohol Celiac Plexus Block, Pain, and Mood on Longevity in Patients With Unresectable Pancreatic Cancer: A Double-blind, Randomized, Placebo-controlled Study

Get access >

Peter S. Staats, MD ✉ , Hamid Hekmat, PhD , Patricia Sauter, RN , Keith Lillemoe, MD

Pain Medicine, Volume 2, Issue 1, March 2001, Pages 28–34,
https://doi.org/10.1046/j.1526-4637.2001.002001028.x
Published: 21 December 2001

Conclusion. In these subjects, the neurolytic block, as compared with medical management alone, improved pain, elevated mood, reduced pain interference with activity, and was associated with an increase in life expectancy.

PAIN MEDICINE

ANESTHESIOLOGY

Neurolytic Splanchnic Nerve Block and Pain Relief, Survival, and Quality of Life in Unresectable Pancreatic Cancer: A Randomized Controlled Trial

Daosong Dong, M.D., Mingfang Zhao, M.D., Jingmei Zhang, M.D., Ming Huang, M.D., Yanwei Wang, M.D., Liang Qi, M.D., Cheng-fu Wan, M.D., Xue Yu, M.D., Tao Song, M.D.

ANESTHESIOLOGY 2021; 135:686–98

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What This Article Tells Us That Is New

- A multicenter study was designed in which patients with unresectable pancreatic cancer and moderate to severe pain were randomized to lytic splanchnic nerve block or block using saline. All patients received opioids according to a set protocol.
- Pain relief was superior for those receiving lytic blocks for 3 months, and opioid use was lower for 5 months. Quality of life was not affected, however.

Conclusions: Neurolytic splanchnic nerve block appears to be an effective option for controlling pain and reducing opioid requirements in patients with unresectable pancreatic cancer.

EDITORIAL

Reassessing the Role for Sympathetic Neurolysis in Patients with Pancreatic Cancer

James P. Rathmell, M.D., Elizabeth M. Rickerson, M.D., James A. Tulsky, M.D., Keith D. Lillemoe, M.D.

Conclusions

- While opioids remain a tool in the toolbox, there are other strategies
- By using interventional strategies we can improve pain control, side effects, QOL, and possibly survival