

# **PAIN MANAGEMENT THE SCIENCE BEHIND**

**Budapest (Hungary), October 13-15, 2016**  
*Highlights*

## **Introduction**



Prof. Scarpignato and Prof. Varrassi, Chairmen of the Symposium, opened the congress, by highlighting the scientific level of the meeting thanks to the attendance of many top researchers in Pain management. They highlighted also the huge presence of physicians coming from many countries from Europe and other Continents. Also Regional Academic and Health Authorities were involved in this opening ceremony, like the President of the Hungarian Pain Association, the President of the International Association for the

Study of Pain, the President of the European Society of Regional Anesthesia & Pain Therapy (ESRA) and the President of the World Institute of Pain (WIP). All of them presented the main topics and the mission of their Associations and pointed out the very high scientific level of this symposium and its importance in a care global context characterized by the under treatment of Pain of any type and origin.

To follow the presentations of this congress, click on the link below:

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## Ethics and Legal Aspects in Pain Medicine

Pain is unique. It is personal, but public; it is silent but loud; it is material but immaterial; it has sense, but it is nonsense.

### What's New

- New human fiber blast cell culture study shows that Hypertonic saline inhibits fiber blast cell regeneration. Clinical observation of long lasting scar inhibition for 13-20 plus years now has an explanation why.
- Published in 2nd edition Techniques of Neurolysis GB Racz and CE Noe. Publisher: Springer 2016

Prof Racz from Lubbock, TX, (USA), spoke about Pain in Medicine and its care from an ethical and legal point of view, by presenting many data, thanks to his very huge experience in this field. The speaker passed through the explanation of some topics about DRG system, continuing medical education, evidence-based medicine, decision making, surgical procedures for pain management compared to new techniques developed in the field of spinal procedures like hypertonic saline. The speaker went deeper in explaining all of the above topics with a unique background, the humanity needed for taking care of patients affected by pain, essential for endorsing a very close relationship with them who desperately need for.

Pain management is not just science; it is also a human activity where patients put their relationship with doctors only second to their families.

North American Spine Society

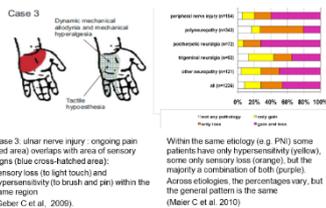
- What is the definition of pain management suggested by the speaker?
- What is the definition of pain from the speaker point of view?
- What are the main complications of the Interventional Management?
- What are the novelties in Pain management highlighted by the speaker?
- What's about the Failed Neck Surgery Syndrome?
- What's about Scarring Triangle?
- What's about bevel and blunt needles?
- What are the main topics about DRG raised by the speaker?
- What are the main issues linked with the Interventional Pain Management?
- What are the main topics of the "Yo Mama Test"?

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# Nerve Dysfunction and Neuropathic Pain.

## Clinical presentation of neuropathic pain



## The future: Mechanism based treatment?



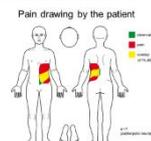
- Concept requires in-depth diagnostics
- Treatment according to symptoms and signs rather than etiologies
- Disease-modifying treatment (neuroprotection)?
- Sodium channel blockade for ectopic activity?
- Calcium channel modulation for central sensitization?
- Noradrenalin reuptake inhibition for deficient endogenous pain control?

Prof. Treede from Mannheim (Germany), spoke about Pain due to nociceptors' activation, the so called nociceptive pain, and that one due to a lesion or a disease of the somatosensory nervous system: the neuropathic pain. In his presentation the speaker went deeper in explaining the main differences between them, their clinical presentations, their etiologies and their pathophysiologic mechanisms of action. Prof. Treede spoke also about the 4 steps of grading and a new revised system. Finally, he presented some topics about the future, highlighting the need for a treatment based on symptoms and sign rather than etiology.



## Grading system with clinical examples

2. Pain with a distinct neuroanatomically plausible distribution. A region corresponding to a peripheral innervation territory or to the topographical representation of a body part in the central nervous system.



RD Treede, TS Jensen, JI Campbell, G Coxon, J Di Stefano, J Griffin, P Hansson, R Hughes, T Kumbako, J Serra (2008) Neurology 72: 1650-1656

- What is the definition of Pain?
- What are the definitions of nociceptive and neuropathic pain?
- What are the differences between the two types of pain?
- What are the mechanisms of neuropathic pain?
- What are the main topics about the revised grading system of neuropathic pain?

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# Pain Experience: Lessons from Placebo and Nocebo Studies.

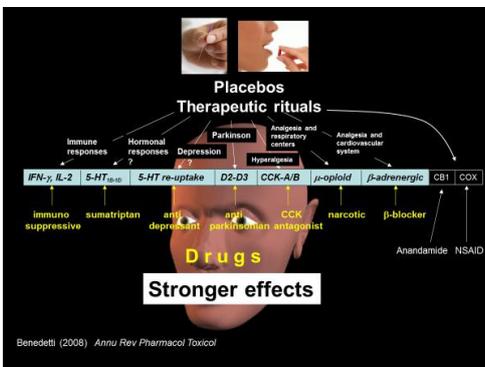


Prof. Benedetti from Turin (Italy) spoke about some mechanisms of placebo responses. Starting from the differences and similarities between drug and placebo, the speaker went deeper in his presentation by highlighting the physiological mechanisms leading to the effects of drugs but also of placebo, related also to the rituals in the

therapeutic act. The speaker pointed out that placebo works thanks to more than one mechanism of action and went deeper in explaining these mechanisms, like opioid and endocannabinoid systems, or the

OVERVIEW
Definition of drug and definition of placebo
Similarities between drugs and placebos
- The opioid system
- The endocannabinoids
- The cyclooxygenase pathway
- The dopamine receptors
The nocebo response
The emerging model: clinical implications

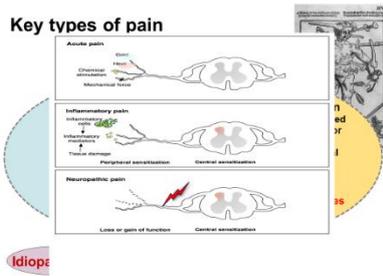
cyclooxygenase pathway and the dopamine receptors pathway. In the last part of his presentation, the speaker talked about the nocebo response, that is the effect related to negative verbal suggestions driven by the doctor to patients in pain condition after placebo intake. Finally, Prof. Benedetti spoke about the emerging model of drug administration, where the psychological effect driven by the patients involved in the ritual of the therapeutic act, plays a key role in drug activity.



- What is a drug from the speaker point of view?
- What's about placebo and ritual in therapeutic acts?
- What are the main placebo mechanisms of actions?
- What are the mechanisms leading to the nocebo effect?
- What is the emerging model of drug administration and its clinical implications?

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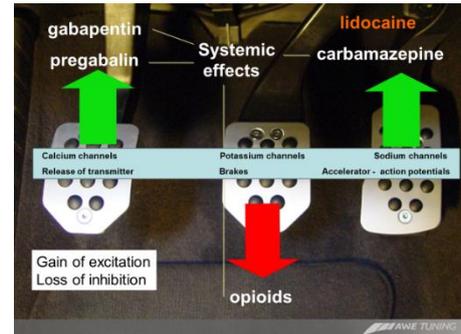
# Receptors and Channels in Pain.



Prof. Dickenson from London (UK), spoke about Pain, its receptors and channels for understanding its mechanisms. Starting from a description of the key types of pain the speaker went deeper in explaining the physio pathological and molecular mechanisms leading to pain's symptomatology. More

in particular the speaker talked about Inflammation, grown factors and neuropathic components as the main actors for the raising of

pain. Starting from these mechanisms of action, the speaker pointed to the pharmacological classes able to act for any presented mechanism and to the pharmacology of descending controls, highlighting the major role played by the Limbic System. In the last part of his presentation, Prof. Dickenson spoke about the Noxious Inhibitory Control and its inhibition due to some pathologies like fibromyalgia, osteoarthritis, peripheral neuropathy and opioid



- Reduced CPM in many pain conditions**
- Peripheral neuropathy
  - Fibromyalgia, Irritable Bowel Syndrome,
  - Migraine, Tension-type headache, Temporomandibular joint (TMJ) disorders,
  - Osteoarthritis and muscle pain,
  - Interstitial cystitis,
  - Patients at risk of developing chronic post-surgical pain
  - Cancer pain patients with greater opioid-induced hyperalgesia.

Yamshly D, Curr Opin Anaesth. 2010; 23:411-415

hyperalgesia.

- What is the role played by the neurofactors?
- What are the main pharmacological classes active in pain reduction from the pathophysiological point of view?
- What's about central Sensitisation and the related pathologies?
- What is the pharmacology of descending controls?
- What are the main brain functions changed by pain?
- What is the role played by Noradrenaline and 5-HT in pain transmission?

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# Is the WHO Analgesic Ladder Still Valid?

Prof Varrassi from L'Aquila (Italy) talked about WHO analgesic ladder and the new potential approach to chronic pain management. Starting from the historical and cultural background of the WHO analgesic ladder, the speaker went deeper in analysing the criticisms raised by its clinical use and the scientific background related with. Prof.

Table 3 - A basic drug list

- Non-opioids: aspirin or paracetamol
- Weak opioids: Codeine or dextropropoxyphene
- Strong opioids: Morphine or methadone, pethidine, buprenorphine, standardized opium, hydromorphone, levorphanol
- Adjuvants: carbamazepine or phenytoin, prochlorperazine, haloperidol or chlorpromazine, diazepam, hydroxyzine, amitriptyline, prednisolone, dexamethasone



Varrassi highlighted that WHO analgesic ladder was conceived 30 years ago and also its revision, performed in 1996, failed to consider the new pathophysiological information and the new pharmacological data on novel

available drugs for pain

treatment in cancer patients. Two of the main concerns about the WHO ladder raised by the speaker, was about the misuses of Opioids in cancer pain treatment and the misuse of the invasive procedures very useful and effective in cancer patients. Prof. Varrassi concluded his presentation by highlighting the need for taking care of chronic pain patients in a different way, in order to reduce their sufferance and the burden exerted on health care systems and on society.

## Criticisms

- Eisenberg E, Marinangeli F, Birkhahn J, Paladini A, Varrassi G. Time to modify the WHO Analgesic Ladder? Pain Clinical Updates 13 (5); December 2005

### Conclusions

Proposal of a new algorithm for pharmacological cancer pain treatment.

1. Mild pain: non-opioids, with the supplement of low dose strong opioids, if not reduced
2. Moderate pain: low doses of strong opioids, with or without non-opioids
3. Severe pain: titration to high doses of strong opioids, with or without non-opioids, and invasive procedures, when indicated

*The use of "...weak opioids should be limited to the countries where strong opioids are not readily available or physicians are not well trained in using them."*

## Criticisms: Invasive procedures



Vargan-Schaffer G. Is the WHO analgesic ladder still valid? Can Pain Physician 2002;5(4):5-17

- What is the basic drug list stated by WHO analgesic ladder in the 1986?
- What are the main route of administrations of these drugs stated by the WHO analgesic ladder in 1986?
- What are the main criticisms of the WHO analgesic ladder, raised by the speaker?
- What's about the misuse of Opioids in cancer patients' treatment?
- What's about the rapidity of pain relief?
- What are the main criticisms about the origin of Pain?
- What are the new perspectives for chronic cancer pain treatment?

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# Visceral versus Somatic Pain: Similarities and Differences.

*"Pain is subjective, invisible and variable"*

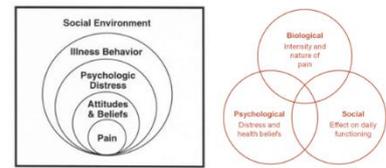


McGill PAIN

books, for the pain is subjective, invisible and variable. Prof. Cervero went deeper in describing the Bio-Psycho-Social approach to pain, starting from the sensory characteristics of

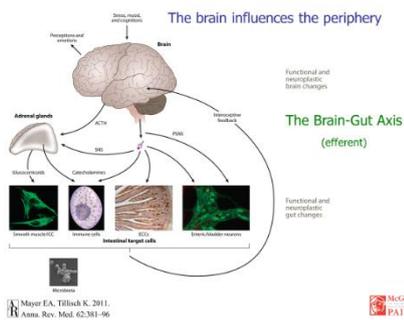
Prof. Cervero from Montréal, QC (Canada) talked about visceral pain versus somatic pain, their similarities and differences. Starting from the history of the pain pathway from the 1664 till now, the speaker highlighted that the real pain is quite different from the pain pathway description present in the main human physiology

Bio-Psycho-Social approach to Pain



McGill PAIN

visceral pain and their related mechanisms. The second part of the talk was spent by the speaker in presenting the main mechanisms of action of central sensitisation secondary to peripheral stimulations. In conclusion Prof. Cervero highlighted that somatic and peripheral pain show fundamental mechanistic differences and many functional pain states can be maintained by hormonal imbalance acting in the CNS or generated primarily in the CNS.



Mayer EA, Tillack K. 2011. Annu Rev Med. 62:381-96

- What are the milestones of the Bio-Psycho-Social approach to pain?
- What are the main mechanistic features of visceral pain?
- What's about CB1 and TRPV1 receptors?
- What are the main viscera-somatic convergences in the CNS?
- What are the main Brain mechanisms for influencing the periphery?
- What are the main causes of Neuropathic visceral pain starting from the CNS?

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# Paracetamol: Is There Still a Place in Pain Management?

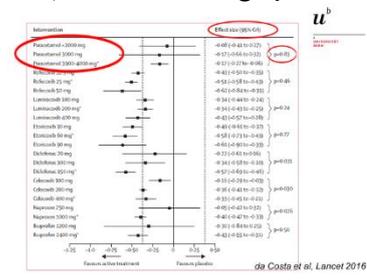
**Indication**

**Mild to moderately painful conditions**

- Postoperative pain
- Dental pain
- Dysmenorrhea
- Headache
- Osteoarthritis
- Low back pain

Prof. Reichenbach from Berne (Switzerland) spoke about paracetamol and its role in pain management. Starting from the consideration that paracetamol is characterized by a very huge use in a lot of pathologies with pain as a major symptom, the speaker analysed the effects of paracetamol thanks to data taken by some clinical trials and meta-analyses involving patients treated with this drug. The speaker highlighted that the first results

were total negative, no difference between paracetamol and placebo in reducing the low-back pain in the randomized patients. Prof. Reichenbach presented also data taken from other studies with the same result: no effect of paracetamol in patients affected by low-back pain and osteoarthritis. In the last part of his presentation Prof. Reichenbach spoke about the safety of paracetamol thanks to many data taken by two meta-analysis published in 2010 and in 2015. In conclusion the speaker highlighted that the use of paracetamol in acute back pain, osteoarthritis and tension head ache is not supported by evidence from RCTs.



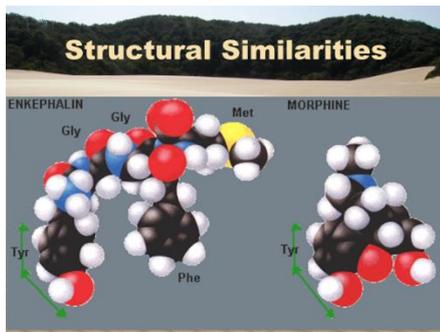
**Results network meta-analysis**

Intervention	Relative Risk (95% CI)	Number of Events	Number of Patients
Paracetamol 1000mg	1.00 (0.95; 1.05)	15	15
Paracetamol 500mg	1.00 (0.95; 1.05)	15	15
Paracetamol 325mg	1.00 (0.95; 1.05)	15	15
Paracetamol 200mg	1.00 (0.95; 1.05)	15	15
Placebo	1.00 (0.95; 1.05)	15	15
Etanercept 50mg	0.95 (0.90; 1.00)	15	15
Etanercept 25mg	0.95 (0.90; 1.00)	15	15
Lidocaine 200mg	0.95 (0.90; 1.00)	15	15
Lidocaine 100mg	0.95 (0.90; 1.00)	15	15
Etanercept 50mg	0.95 (0.90; 1.00)	15	15
Etanercept 25mg	0.95 (0.90; 1.00)	15	15
Diclofenac 50mg	0.95 (0.90; 1.00)	15	15
Diclofenac 75mg	0.95 (0.90; 1.00)	15	15
Celecoxib 200mg	0.95 (0.90; 1.00)	15	15
Celecoxib 100mg	0.95 (0.90; 1.00)	15	15
Naproxen 250mg	0.95 (0.90; 1.00)	15	15
Naproxen 125mg	0.95 (0.90; 1.00)	15	15
Rapaprodol 1200mg	0.95 (0.90; 1.00)	15	15
Rapaprodol 600mg	0.95 (0.90; 1.00)	15	15

- What are the main indication for the use of paracetamol?
- What's about the safety of paracetamol from the speaker point of view?
- What are the other treatment's options other than paracetamol?
- What is the mortality rate in patients treated with paracetamol?
- What's about the problem raised by self-poisoning from a safety point of view?

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# Opioid Receptors Agonists & Antagonists.



Prof. Schug from Perth, WA, (Australia), spoke about opioids stating from their ancient history from 2100 BC till our time. The speaker presented data on opioid receptors, their effects on cells, their types and localisations in Brain, Spinal cord and Periphery. Prof. Schung spoke also about the opioids' adverse effects resulting in the onset of

the Opiophobia phenomenon. The main part of his talk was spent by presenting data about the opioid effect on acute pain and patients affected by cancer. One of the main problem linked with opioids is the risk of addiction



and the speaker

highlighted that in patients affected by debilitating chronic pain but who do not have a fatal illness, non-pharmacologic therapy is better than opioid therapy. The speaker concluded his talk by highlighting the need for more data in order to better define when opioid should be prescribed, taking in mind that patients use opioids for relieving pain and maintaining a normal relationship with the real world, than addicts take opioids for escaping from reality.

## CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

United States, 2016

Prepared by

Dorothy Dowell, MD

Tamara M. Hargraves, PhD

Roger Chou, MD

<sup>1</sup>Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC, Atlanta, Georgia

1. **Nonpharmacologic therapy** and nonopioid pharmacologic therapy are preferred for **chronic pain**.
2. If opioids are used, they should be **combined with nonpharmacologic therapy and nonopioid pharmacologic therapy**, as appropriate.
3. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including **realistic goals for pain and function**, and should consider how **therapy will be discontinued if benefits do not outweigh risks**.

- What are the main Opioid Receptor Effects?
- Where are the opioids receptors localized in the human body?
- What is the effect of opioids in acute pain relief?
- What is the role of opioids in Cancer pain treatment?
- Why is it time to flip the Pain Curriculum?

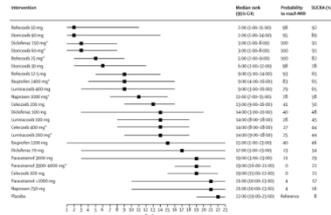
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# NSAIDs for Pain Management: Benefits and Risks.



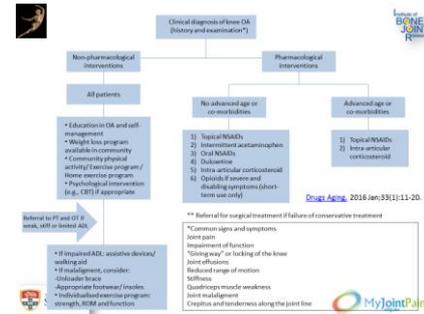
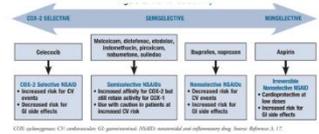
NSAIDs ranking



Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis  
Lancet, Volume 387, Issue 10033, 2016, 2060-2100

Prof. Hunter from Sydney, NSW, (Australia), spoke about NSAIDs for pain management. More in particular the speaker presented data on NSAIDs benefits, risks and their application within the disease context. From an efficacy point of view not all NSAIDs are equal according to the data presented by the speaker. Prof. Hunter presented also data comparing CX-1 vs COX-2, their efficacy and safety and the main adverse events linked to NSAIDs administration. In conclusion the speaker highlighted that NSAIDs have an important role in pain treatment, but doctors have to remain wary about their toxicity.

COX selectivity- benefits and risks



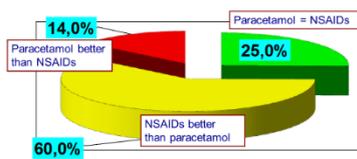
- What are the more effective NSAIDs from the speaker point of view?
- What are the benefits and risks related to the COX-selectivity?
- What are the most COX-selective NSAIDs presented by the speaker?
- What is the main NSAIDs risk presented by the speaker?
- What are the mechanisms of pain in osteoarthritis?
- What are the rank benefit-risk score in patients affected by multi-joint Osteoarthritis?

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# NSAID-Opioid Combinations: Rationale and Clinical Efficacy.



OA Patients Do Prefer NSAIDs to Paracetamol



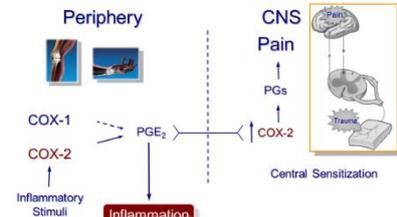
[Wolfe et al., Arthritis Rheum 2001; 44: 2451-2455]

Prof. Scarpignato from Parma, (Italy) spoke about NSAIDs Opioid combinations, by presenting interesting data on the need for drug combinations in pain management, which drugs should be combined, their pharmacology and safety and the currently available combinations. More in particular Prof.

Scarpignato started his lecture by presenting data on paracetamol and its combinations, than spoke about two fixed combinations like Ibuprofen-hydrocodone and dexketoprofen-



Peripheral and Central Involvement of COX-2 in Pain

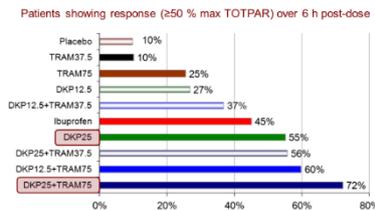


[Smith et al., PNAS 1998; 95: 13313-3318]

tramadol. In the second part of his presentation the speaker talked about the NSAIDs side effects on GI tract, Kidney, Hemostasis, CV system, Liver and Skin. Finally, Prof. Scarpignato spoke about opioids, their main side effects and their combinations with non-opioid analgesics, more in particular with paracetamol and dexketoprofen.



Efficacy of Different Fixed Combinations on Moderate-to-Severe Pain after Dental Surgery\*



\* Impacted third mandibular molar extraction

[Moore et al., J Headache Pain 2015; 16: 541]

- What's about paracetamol and its combination with codeine?
- What's about the peripheral and central effects of COX-2 NSAIDs?
- What are the main reasons at the basis of the development of the dexketoprofen-tramadol fixed combination?
- What are the most common opioid-induced adverse events?
- What are the common adverse events of the weak opioid combination with paracetamol?

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# Topical Analgesics: Which Role in Pain Management?

## PAINFUL DIABETIC NEUROPATHY



<https://www.youtube.com/watch?v=ka5VtZeYRkE>

In conclusion, here a list of **potentially effective** topicals used as **single agents or in combination** for neuropathic / inflammatory pain and itch:

- 1) Lidocaine and other Local Anesthetics
- 2) Diclofenac +/- Lidocaine
- 3) Aspirin +/- Diclofenac
- 4) Botulinum Toxin Type A (intradermal)
- 5) Capsaicin (HC)
- 6) Clonidine
- 7) Loperamide and other Opioids
- 8) Amitriptyline, Doxepin +/- Ketamine
- 9) Baclofen, Clonazepam
- 10) DMSO
- 11) Natural S-EH inhibitors +/- diclofenac
- 12) Phytocannabinoids, PEA
- 13) Strontium Chloride and Nitrate

Prof. Pappagallo from New York, NY, (USA) spoke about topical analgesics, pointing to the pathologic pain conditions amenable to their use and the main pharmacological classes eligible for topical use. In the main part of his talk, the speaker went deeper in presenting some data on Capsaicin, Clonidine, Botulinum, Ketamine, Cyclooxygenase

## POST-SURGICAL NEUROPATHIC PAIN



Inhibitors and K+ Channel Openers, topical opioids, GABA agonists, S-EH Inhibitors, Endocannabinoids and Phytocannabinoids, Anti-oxidants – Dimethylsulfoxide and Strontium. This was a very complete and comprehensive lecture on topical analgesics and their role in pain management, characterised by some indications on their use

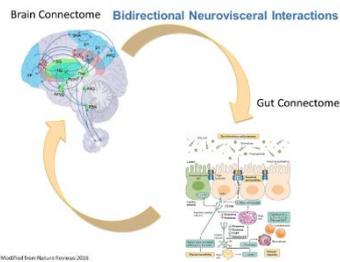
as single agents or in combination for the treatment of neuropathic / inflammatory pain and itch.

- What are the four therapeutic advantages of topical therapies?
- What are the main pain states amenable to topical medications?
- What are the main emerging topical therapies available for neuropathic pain and pathologic itch?
- What are the main mechanisms of action of topical analgesics?
- What are the Local Anaesthetics for Topical Use presented by the speaker?

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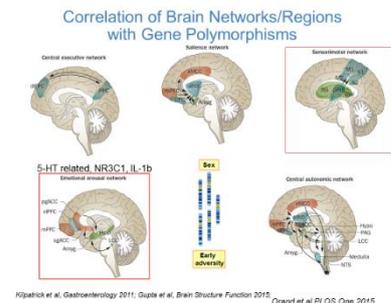
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# Clinical Science of Visceral Pain.

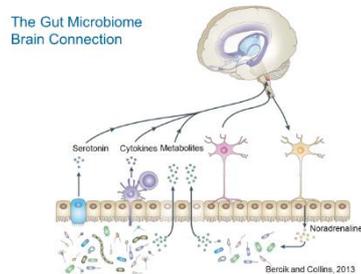


Prof. Mayer from Los Angeles, CA, (USA) spoke about chronic visceral pain disorders starting from the main clinical considerations. The speaker went deeper in explaining the linkage between visceral pain and Brain signalling as a major topic in chronic visceral hyperalgesia. Prof. Mayer highlighted the deep connections between Brain and Gut, addressing to their bidirectional neurovisceral

interactions as an example of the Brain involvement in the chronic abdominal/pelvic pain. In the main part of his talk the speaker went deeper in explaining the functional neuroanatomy of the chronic visceral pain pointing to the sensorimotor regions for their increased GM volume in Interstitial Cystitis patients compared to healthy controls and presented data about the brain networks involved. More in particular Prof. Mayer spoke



about the so called Salience assessment and its related consequences. In the last part of his presentation the speaker addressed to the main mechanisms involved in the interactions between Brain and viscera able to produce changes in Brain, Periphery and symptoms. In conclusion Prof. Mayer highlighted that chronic pain is a brain disorders and pointed to the brain imaging approach as a method useful for the clinical care of chronic viscera pain patients.

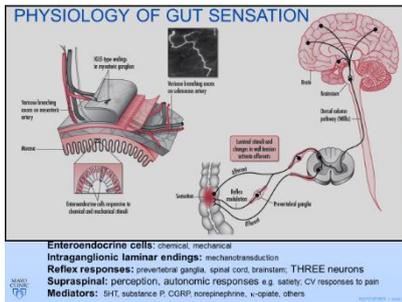


- What are the main Chronic overlapping pain conditions from the speaker point of view?
- What are the two most common chronic visceral pain conditions presented by the speaker?
- What does Brain salience network mean?
- What are the Brain networks involved in Chronic Abdominal/Visceral Pain?
- What are the main Emotional arousal circuits?
- What are the interactions of Sensorimotor with Salience Network in Urologic Chronic Pelvic Pain Syndrome patients?
- How do Brain and Viscera Interact to Produce Changes in Brain, Periphery and in Symptoms?
- What's about microbiota and brain connections?

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# Visceral Analgesics for GI Disorders: How Much Are They Clinically Effective?

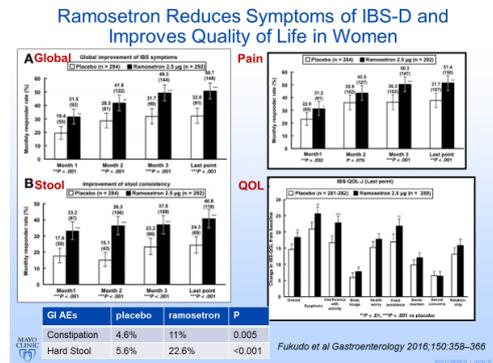


Prof Camilleri from Rochester, MN, (USA) spoke about the drugs used in patients affected by visceral pain for GI disorders and their efficacy from a clinical point of view. Starting from the physiology and anatomy of gut sensation the speaker talked about FODMAPs, Peppermint

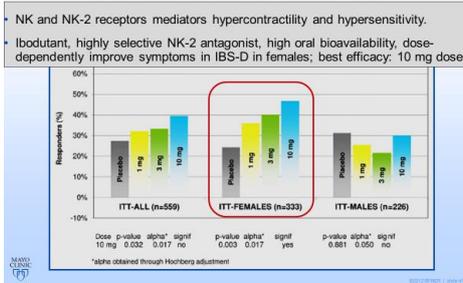
oil, Antidepressants, 5-HT<sub>3</sub> receptors agonists, non-absorbed antibiotic, secretagogues, new opioid receptors agonist and eluxadoline an delta-OR antagonist, the histamine H1 receptors antagonist

ebastine, the Neurokinin -2 receptor antagonist ibodutant and the GABA-ergic agonist

pregabalin. The speaker presented very interesting and updated data on all these topics and highlighted the role of 5-HT<sub>3</sub> receptors agonists as one of the most effective current therapies for the bowel dysfunction and pointed to the histamine and neurokinin antagonists as promising drugs in IBS patients treatment. In conclusion Prof. Camilleri highlighted the need for applying basic neurobiology and pharmacology in the development of new peripheral visceral analgesics free from central AEs .



Neurokinin(NK)-2 receptor antagonist ibodutant improves overall symptoms, abdo. pain and stool pattern in females with IBS-D: Phase 2 RCT

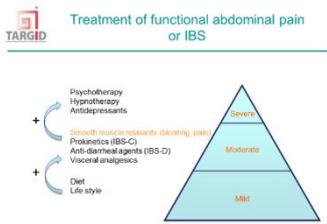


- What is the effect of low FODMAPs diet in IBS patients?
- What's about fiber and IBS pain?
- What's about reifaximin in the treatment of IBS patients?
- What's about the efficacy of antidepressants in IBS patients?
- What's about ebastine and ibodutant in the treatment of visceral pain?
- What is the effect of Pregabalin on visceral pain in IBS patients?

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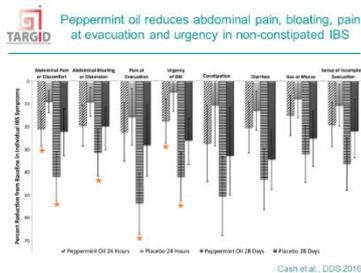
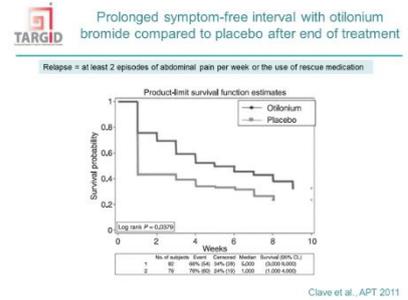
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# Antispasmodics for Management of Chronic Abdominal Pain: Are They All the Same?



these drugs were characterized by very low quality and low number of enrolled patients. Prof. Boeckxstaens spoke about

the effects of pinaverium, otilonium bromide and otilonium peppermint oil on patients affected by IBS, by presenting the results of the main randomized clinical trials on the efficacy and safety of these three drugs compared to placebo in the treatment of patients affected by IBS. The speaker concluded his talk highlighting that not all the antispasmodics are the same.



- What is the reason for the introduction of the antispasmodic drugs for the treatment of IBS patients?
- Are all the antispasmodics the same?
- What are the main changes in diabetes-related complications in the US from 1990 to 2010?
- What's about otilonium bromide for the treatment of IBS patients according to the OBIS study?
- What is the effect of otilonium bromide on abdominal pain in patients affected by IBS?
- What are the results of the meta-analysis of the studies evaluating peppermint oil as a treatment of IBS patients?
- What's about the effect of peppermint oil on abdominal pain in patients with IBS?

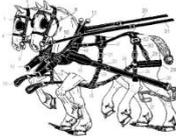
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# Cannabis-based Medicines: from Herbal Medicine to Receptor Therapy.

## Defining the cannabinoid system

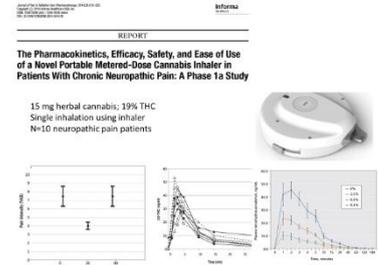
- Exogenous compounds
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Nabilone, dronabinol
    - K2, "Spice"
- Endogenous cannabinoids
  - Anandamide
  - 2-arachidonyl glycerol
- Receptor targets
  - CB1, CB2, TRPV1, PPAR, 5-HT, other...



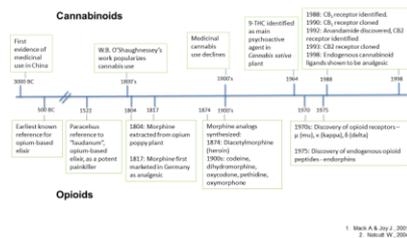
Prof Ware from Montréal, QC, (Canada) spoke about cannabinoids and their therapeutic applications in patients affected by visceral and other types of pain. Starting from the definition of the cannabinoid system and the receptor targets, the speaker presented data on the compounds studied in RCTs for the treatment of chronic non-cancer pain. The data from the literature are consistent in defining the correct use of these

drugs for the treatment of pain syndromes, the speaker pointed out. Prof. Ware spoke also about the synergism between cannabinoids and opioids, very useful in the association therapy protocols. More in particular the speaker presented data on the reduction of the prescriptions of opioid analgesic and other drugs thanks to the so called

“Medical Marijuana Laws”. In the last part of his presentation the speaker talked about the Quebec cannabis registry, by presenting data on diagnosis, concomitant medications, mode of administration and daily cannabis and opioid dose taken by patients affected by chronic pain. In conclusion Prof. Ware highlighted that legislation of cannabis allows for more open and thorough evaluation of the potential for cannabinoids in pain management.



## Cannabinoids and Opioids: A Historical Perspective

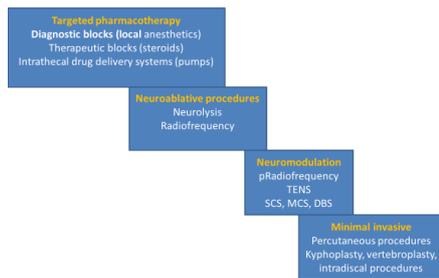


- What are the neuropathic pain models used for testing cannabinoids effectiveness?
- What's about the prescription of cannabinoids?
- What are the main cannabinoids studied in RCTs?
- What are the main effects of the association between cannabinoids and opioids in analgesic treatments?
- What's about cannabinoids as “synaptic circuit-breakers”?
- What are the interactions between cannabinoids and opioids at the receptor levels?

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# Interventional Pain Management: Pros & Cons

## Interventional Pain Procedures



affected by pain for any cause, instead of the so called biomedical approach. More in particular the speaker highlighted that chronic pain is a biopsychosocial phenomenon and has to be treated from a psychological, behavioural, functional and also interventional point of

## Chronic Pain

- “Biopsychosocial Phenomenon”
- Pain Disease or Organic Disease
  - Psychological,
  - Behavioral,
  - Functional,
  - Interventional

Prof Erdine from Istanbul, (Turkey) spoke about interventional pain management, the available techniques and indications. In the first part of his presentation the speaker talked about the interventional pain procedures, by presenting data on Neural blockade from the diagnostic, prognostic and therapeutic point of view. Prof. Erdine pointed out the importance of a biopsychosocial

approach of patients

view. In the main part of his presentation the speaker presented data on the relationship between interventional pain management and literature, clinical trials and industry. Prof. Erdine spoke also about the misuse and abuse of IPM, highlighting the widespread use of inadequately tested or unnecessary pain management diagnostic and treatment techniques as major concerns. Finally, the speaker talked also about the future of IPM by highlighting its role in facilitating rehabilitation for chronic pain.

## Biomedical Approach

- **Objectification**
  - Objective *the* body
  - Subjective/minds and emotions
- **Quantification**
  - turns the patient's bodily signs and symptoms into a set of numbers
- **Pathologization**
  - object of attention and affixes a set of disease
- **Amelioration**
  - Downstage the issue of cause, focusing instead on the urgency of treating the disease
- **Scientism**: Everything that is said and done is rational, objective, logical—in a word, scientific.
- **Reification**: Things that may seem uncertain or unknowable are real, knowable, and known.
- The next two devices stress the truth value of the story and the efficacy and infallibility of the medical project. They divert attention away from the possibility that the disease might be unconquerable or that the doctor might make a mistake:
- **Domination**: Medicine gains mastery over nature by discovering its secrets, determining its limitations, and intervening to fix them.

- What are the main interventional pain procedures?
- What are the indication for interventional pain procedures?
- What are the main procedures available for spinal pain treatment?
- What's about biomedical approach?
- What are the major topics of the Biopsychosocial system approach?
- What is the future of IMP from the speaker point of view?

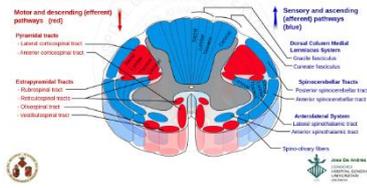
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# Neurostimulation. Indications and Selection of Parameters for a Better Pain Relief

## Dominants Mechanisms

I: antidromic activation of segmental inhibitors circuits  
 II: orthodromic activation of circuits in the brain stem resulting in "descending inhibition"



Prof De-Andrés from Valencia, (Spain) spoke about spinal cord stimulation for a better pain relief. The speaker started his presentation by highlighting the main mechanisms of action of the Neurostimulation. In the main part of his talk Prof. De-Andrés spoke about the anatomical levels of the neuromodulation, its indications, the selection

criteria for the neuroimplants, the fundamental principles about spinal cord stimulation, the computer models to be chosen and the other major technical topics linked to SCS.

## Fundamental Principles of SCS

- Stimulation paresthesias must cover the painful area and be maintained consistently
- The electrical field near the cathode should be focused on the corresponding part of the DCs
- In case of bilateral pain the electrode must be
- In unilateral and segmental pain the electrode may be placed more laterally stimulating primarily the Dorsal Roots (DR)

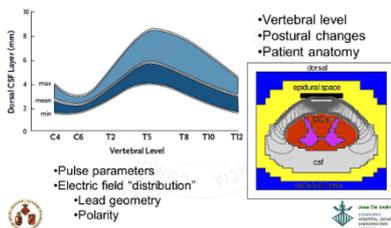


Finally, the speaker highlighted that

Neurostimulation provides a treatment option that is less invasive than surgery, reversible, customizable and cost-effective and may have significant advantages in providing long-term pain relief. In conclusion Prof. De-Andrés pointed out that the presence of complex pain patterns, requires a high degree of flexibility in programming the SCS implanted system.

## Parameters of the electric field

•Distance between the fiber and the cathode (-)



- What are the main dominants mechanisms of the Neurostimulation?
- What are the main indications for practising the neurostimulation?
- What are the criteria for implants?
- What are the main factors associated with success?
- What are the main SCS programming parameters?
- What are the fundamental principles of SCS?

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# Closing Lecture: Neuroimaging of Pain

## Brain plasticity linked to treatment outcomes

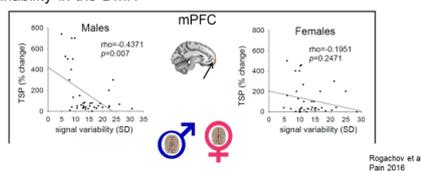


Prof Davis from Toronto, ON, (Canada) spoke about neuroimaging and its applications in pain diagnosis. The speaker started her talk by highlighting that patients affected by chronic pain present some abnormalities at the level of the gray matter. She presented also data on white matter and trigeminal nerve abnormalities related to pain severity and duration and the impact

on CNS they have. In the second part of her presentation the speaker talked about treatments and outcomes. One of the major topics the speaker talked about was about plasticity, that refers to brain and nerves, closely linked to treatments and outcomes. Finally, the speaker talked

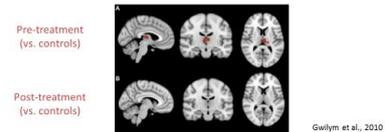
## Sex differences

- no sex differences
  - in TSP
  - in correlation between TSP and BOLD signal variability in the ascending nociceptive pathway or salience network
- Males (not females): TSP correlated with BOLD signal variability in the DMN



## Imaging brain plasticity after Tx

- partial reversal of gray matter abnormalities following effective treatment
  - Rodriguez-Raecke et al., 2009 & 2013; Obermann et al., 2009; Gwilym et al., 2010; Seminowicz et al., 2011



about how to predict the treatment success and the future directions for finding baseline conditions that can predict the effect of the treatment, taking in account the intersubject variability of the brain networks and also the differences between males and females in the adaptation to pain stimulations. More in particular the speaker presented data on two brain connectivity profiles, the so called pro-nociceptive and anti-nociceptive profiles. The speaker concluded her speech by highlighting the importance for a personalized pain management in the view of a medicine based on the need of any single patient.

- What is the white matter implicated in pain?
- What are the trigeminal and brain structural abnormalities related to pain severity and duration?
- What are the trigeminal neuralgia treatments presented by the speaker?
- What's about the differences in sgACC functional connectivity between males and females?
- What's about pain and attention interactions?
- What are the main differences about the two type of connectivities: A type vs P type?
- What are the main topics of the personalized pain management presented by the speaker?
- What does Ouch mean?

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