



DOLORE



AGGIORNAMENTI CLINICI

Organo ufficiale della Associazione Italiana per lo Studio del Dolore





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In questo numero

Anno Mondiale contro il dolore	4
IASP Statement on U.S. Travel Restrictions	7
New frontiers in cancer pain management a palliative care perspective	8
Paracetamol: Is There Still a Place in Pain Management?	10
Opioid Receptor Agonists and Antagonists	13
NSAIDs for Pain Management: Benefits and Risks	17
Adjuvant Analgesics in Chronic Non Cancer Pain	22
NSAID-Opioid Combinations: Rationale and Clinical Efficacy	25
Interventional Pain Management: Pros & Cons	32
L'analgesia ai tempi dei Faraoni	37
Effetti della statistica nella medicina	38

Associazione Italiana per lo Studio del Dolore AISD

Via Tacito, 7 - 00193 Roma
Tel. 3396195974
info@aisd.it
www.aisd.it

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Anno mondiale contro dolore

L'International Association for the Study of Pain (IASP®) ha dedicato il tema dell'anno mondiale contro il dolore post operatorio

Nel mondo si eseguono ogni anno più di 300 milioni di interventi chirurgici: da interventi minori a operazioni complesse su organi vitali. Il dolore post operatorio viene considerato come inevitabile, da sopportare e in effetti il dolore post operatorio è stato rilevato in circa metà dei pazienti operati in varie indagini. Il dolore che si protrae dopo l'intervento chirurgico è stato focalizzato come argomento di studio sistematico meritevole solo circa 25 anni fa, in parte grazie agli sforzi della IASP®.

Circa 1 paziente su 4 identifica infatti nella chirurgia la causa responsabile dell'insorgenza del dolore cronico di cui soffre. Recenti dati epidemiologici hanno messo in luce come, attualmente, l'incidenza del dolore persistente post-operatorio sia inaccettabilmente alta e possa variare in base alla tipologia di intervento chirurgico. Il dolore cronico si sviluppa approssimativamente nel 50% dei pazienti sottoposti ad amputazioni degli arti inferiori, chirurgia mammaria oncologica e toracotomia.

Sfortunatamente, tale problematica non è limitata solo alla chirurgia maggiore, ma anche procedure chirurgiche considerate



minori, come la riparazione di ernia inguinale, sono caratterizzate da un rischio significativo di sviluppare un dolore cronico post-operatorio (*).

Da un po' di tempo la richiesta dei pazienti per un più efficace trattamento del dolore postoperatorio sostenuto dall'impegno dei medici per tempi di degenza più brevi e liberi dal dolore, ha trasformato l'approccio al controllo del dolore postoperatorio. Inoltre, tecniche chirurgiche minimamente invasive e nuovi metodi per la gestione del dolore post-chirurgico con minori effetti collaterali consentono di effettuare più procedure ambulatoriali o con brevi ricoveri, tuttavia il dolore spesso persiste a lungo dopo l'intervento chirurgico.

Oggi l'approccio al dolore post operatorio dovrebbe essere così concepito:

- occorre presupporre che quasi tutto il dolore dopo intervento chirurgico può e deve essere gestito in modo da ottimizzare la funzionalità fisica ed emotiva;
- valutare l'intensità del dolore a riposo e in azione per personalizzare la terapia del dolore rispetto alle esigenze riabilitative;
- identificare in anticipo quei pazienti che possono richiedere una particolare attenzio-

* Leggi anche: *Dal dolore acuto postoperatorio al dolore persistente postoperatorio: possiamo prevenirlo?* di Paolo Scimia et al *Dol agg clinici* n. 3 2016. Si legga anche nello stesso numero del periodico: *Fattori predittivi del dolore post-operatorio acuto e cronico* di Pasquale Sansone et al.

ne; ad esempio, a causa di problemi comportamentali o terapia con oppioidi precedente l'intervento;

- integrare il controllo del dolore con altri aspetti della preparazione per il recupero post operatorio, come attività o nutrizione e assunzione di liquidi;
- adottare un approccio "multimodale" che combina diversi tipi di farmaci e (quando possibile) l'anestesia locale per ridurre la dipendenza da una sola modalità di trattamento; per esempio, gli oppiacei con i loro numerosi effetti collaterali;
- tener conto delle differenze dei pazienti in termini di esperienza e report del dolore, preferenze tra i possibili trattamenti e risposta alla terapia, con attenzione a fattori

come sesso ed etnia;

- continuare la valutazione del paziente dopo la dimissione per riconoscere e trattare il prima possibile il dolore persistente e altre conseguenze chirurgiche indesiderate;
- prendere atto che la gestione del dolore acuto, post intervento chirurgico, deve diventare una sottospecialità medica, visto il miglioramento di conoscenze e tecniche specializzate, come, per esempio, l'anestesia regionale.

Queste le raccomandazioni per i medici, ma cosa possono fare i pazienti e le loro famiglie per trarre il massimo beneficio da questi recenti progressi?

- Sapere dal chirurgo se la tecnica di interven-



to proposta può generare dolore e, in caso affermativo, farsi indicare la probabile intensità, la durata e come sarà gestito. Alcune operazioni comportano infatti un rischio di dolore postoperatorio persistente più elevato rispetto ad altre.

- Richiamare l'attenzione del chirurgo, o di altri membri del team (anestesista, infermiere, fisioterapista, farmacista), su aspetti rilevanti della propria storia medica o sulla situazione attuale, problemi precedenti di dolore, terapie del dolore in corso e reazioni avverse ai farmaci.
- Chiedere:
 - Chi formulerà il mio "piano di terapia del dolore" (anche se si tratta di un protocollo standard di provata efficacia nei pazienti che già hanno subito la stessa operazione)?
 - Il mio "piano dolore" sarà "multimodale"? Cioè combinerà diversi tipi di farmaci per il trattamento del dolore e/o anestesia locale, per esempio anestesia epidurale o blocco del nervo in modo da ridurre la dipendenza da un singolo farmaco come la morfina?
 - Quali misure saranno adottate nel caso avessi bisogno di un dosaggio di oppioidi superiore al normale per il controllo del mio dolore (per quei pazienti che hanno ricevuto un trattamento con oppioidi prima dell'intervento)?
 - Chi monitorerà il piano di terapia del dolore e lo regolerà o modificherà, se necessario?
 - Quali sono le strategie terapeutiche per il controllo del dolore dopo che sarò dimesso dall'ospedale?
 - Se il dolore persiste dopo dimissione, a chi potrò rivolgermi, giorno e notte, se la terapia non riesce ad assicurarmi riposo e recupero, o se l'antidolorifico mi provoca effetti collaterali inaccettabili, o se il dolore riaffiora o peggiora?



International Association for the Study of Pain

IASP

Working together for pain relief

Raccomandazioni più dettagliate sono tutte disponibili nel sito della IASP: www.iasp-pain.org

- 1 What the Public Should Know About Pain After Surgery
- 2 What Health-Care Professionals Should Know About Pain After Surgery
- 3 Pathophysiology of Acute Postoperative Pain
- 4 Chronic Postsurgical Pain: Definition and Impact
- 5 Management of Postsurgical Pain in Adults: Pharmacotherapy and Regional Anesthesia
- 6 Behavioral Techniques including Hypnosis for Pain After Surgery
- 7 Management of Postsurgical Pain in Children
- 8 Management of Postsurgical Pain in Older Adults
- 9 Management of Postsurgical Pain in Patients Treated Preoperatively with Opioids
- 10 Management of Pain Related to Surgery and Procedures in Patients with Known or Suspected Cancer
- 11 Pain Management in Critical Care
- 12 Acupuncture for Acute Pain and Nausea After Surgery
- 13 Management of Patients First Presenting with Chronic Pain After Surgery
- 14 Using Outcomes to Improve Care: Real-Time, Short-Term, and Long-Term. ◀

IASP Statement on U.S. Travel Restrictions

*Statement of the Executive Committee of the International Association
for the Study of Pain, on behalf of the organization*

Recognizing that scientific progress and medical advances depend on the free exchange of ideas among international networks of diverse health-care professionals and scientists, IASP joins with scientific societies in the United States and worldwide in opposing the recent White House executive order on travel restrictions from certain countries.

For more than 40 years, IASP has convened international meetings of scientists and clinicians who collaborate to advance learning and discover new and better pain treatments. The U.S. travel restrictions place such collaborations at great risk.

Our member scientists and clinicians live on six continents, treating patients suffering in pain throughout the developed and developing world-including those in countries named in the restrictive order. As a direct consequence of the order, IASP members from those countries as well as those who have traveled to them have told us they are unable or reluctant to travel to the United States for fear of harassment or detention at airports. Others have told us they are protesting the travel restrictions by refusing to meet in the United States.

IASP urges a more balanced approach to access to the United States that not only provides for security but also protects important

scientific collaborations. We believe the travel restrictions will have a negative effect on the ability of the United States to attract talented researchers, clinicians, and students whose collaborative work advances science and medical care.

- Judith A. Turner, PhD, President (USA)
- Lars Arendt-Nielsen, Prof., Dr.med., PhD, President-Elect (Denmark)
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- Michael Nicholas, PhD, Secretary (Australia)
- G. Allen Finley, MD, FRCPC, Treasurer (Canada)
- Matthew R. D'Uva, FASAE, CAE, Executive Director (USA)

3 febbraio 2017

More info: www.iasp-pain.org

New frontiers in cancer pain management: a palliative care perspective

July 26, 2017 -Suntec City, Singapore

The 12th edition of the Asia-Pacific Hospices Congress is the perfect occasion to include a workshop on cancer pain and palliative cares. The Fondazione Internazionale Menarini did not lose such appetizing occasion. In fact, with the help of a very well known international Faculty is proposing a WS whose title reminds the potential audience of the border line between Cancer Pain and Palliative Care. This border has changed during the last few years, and the hospice is becoming the place where to care for the suffering people that cannot be cured at home, in his/her terminal part of life. The approach at the moment is quite different than the one perceived in the past, when the Hospice was a place to avoid, not just for the patients but also for the relatives.

This behavioral revolution is the effect of the cultural promotion of the best cares for the cancer pain, and for the patients with cancer, in general. It has been enough to open the discussion on topics that were previously forbidden. Now we are more acquainted with the different aspects and all the necessities of those patients. Hence we are more ready, at international level, to accept the concepts of the terminal care. Part of this cultural revolution has been the consequen-

ce of a better knowledge of the physiopathology of the disease named cancer, and all its consequences, but also of the availability of new drugs. All the topic will be discussed by a team of experts that will start discussing why the patient with cancer has an extremely high prevalence and incidence of pain. Immediately after, many other clinical problems will be presented. Between others, in the last few years one of the aspects that has received the attention of the scientists is the breakthrough cancer pain (BTcP). Part of the WS will be dedicated to this aspect.

Any Oncologist and Pain Doctor, but also the General Practitioners, should know better this difficult part of Pain Medicine. This is the reason why all of us should applaud to the generosity of the Menarini

International Foundation, which has shown great sensibility to accept the proposal to organize a dedicated WS to this important topic. In fact, this is not only important for the better cure of the cancer pain patients, but for their better care in general.



Prof. Giustino Varrassi

Responsible for the Scientific Programme

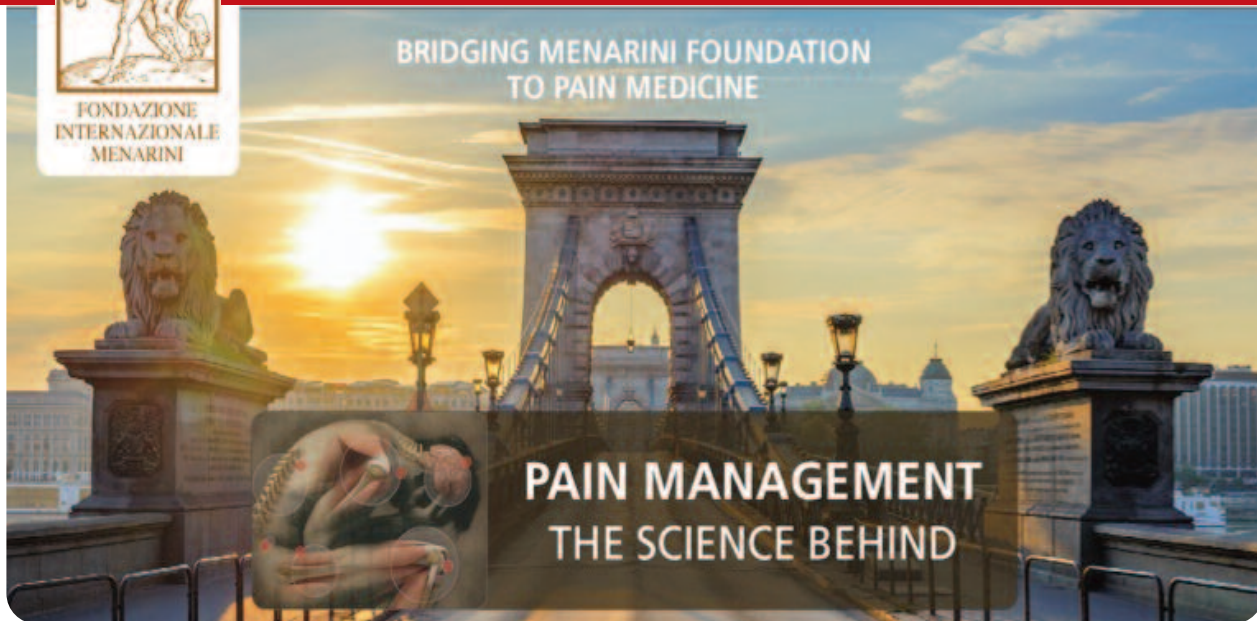
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BUDAPEST, October 13-15, 2016

SYMPOSIUM VENUE: PESTI VIGADÓ



L'ottobre scorso, dal 13 al 15 ottobre, a Budapest, il Simposio Internazionale "Pain Management: the Science Behind" ha riunito esperti internazionali sul dolore, esperti che hanno costituito le colonne portanti della scienza di base, che ha consentito lo sviluppo organico e armonico delle basi neurofisiologiche e terapeutiche indispensabili per capire e curare al meglio il dolore. Presidenti del Comitato Scientifico del Congresso: il prof. Carmelo Scarpignato (Università di Parma) e il prof. Giustino Varrassi (Università Ludes, Malta).

Al Simposio, promosso dalla Fondazione Internazionale Menarini, con la collaborazione scientifica di EuLAP®, European League against Pain, abbiamo già dato ampio spazio nel numero precedente di Dolore aggiornamenti clinici. Ora, sottoponiamo all'attenzione dei nostri lettori la sintesi di alcune delle relazioni presentate.

Ricordiamo che i video di tutti gli interventi sono disponibili online, previa registrazione, nel sito www.fondazione-menarini.it (sezione archivio eventi). Ringraziamo la Fondazione Internazionale Menarini per l'autorizzazione a pubblicare.

Nelle pagine seguenti:

- ***Paracetamol: Is There Still a Place in Pain Management?***, Stephan Reichenbach
- ***Opioid Receptor Agonists and Antagonists***, Stephan A. Schug
- ***NSAIDs for Pain Management: Benefits and Risks***, David J. Hunter
- ***Adjuvant Analgesics in Chronic Non Cancer Pain***, Nadine Attal
- ***NSAID-Opioid Combinations: Rationale and Clinical Efficacy***, Carmelo Scarpignato
- ***Interventional Pain Management: Pros & Cons***, Serdar Erdine



Paracetamol: Is There Still a Place in Pain Management?

Stephan Reichenbach, MD

Associate Professor of Rheumatology,
University Hospital and Head Musculoskeletal Research Group,
Institute of Social and Preventive Medicine,
University of Bern, Switzerland

Introduction

Paracetamol (or acetaminophen, as it is called in the USA), is one of the oldest pain killers. Its names derive from the chemical name, N-acetyl-paraaminophenol.

It was introduced to the market in 1955 as an antipyretic and analgesic drug for children, and 1 year later, as 500 mg tablets, as an over-the-counter drug in Great Britain. Although discovered more than 100 years ago, its mechanism of action has not been completely elucidated. Paracetamol is prescribed for the symptomatic treatment of fever and painful conditions such as postoperative pain, dental pain, dysmenorrhea, headache, and acute and chronic musculoskeletal disease such as osteoarthritis or low back pain.

On the WHO analgesic ladder, which does not differentiate among origins of pain, it is included in all three steps. It can be combined with other analgesics such as non-steroidal anti-inflammatory drugs and either weak or strong opioids.

Effectiveness of Paracetamol in Acute Painful Conditions

For postoperative painful conditions, a single oral dose of 1000 mg paracetamol provides pain relief provides at least 50% pain

relief for 4 hours in about 50% of patients, with a number needed to treat (NNT) of 3.6 [1]. Similar results were obtained for intravenous (i.v.) formulations, where at least 50% pain relief is achieved in 36% of patients, corresponding to a NNT of 5 [2]. For the treatment of episodic tension-type headache in adults, the NNT for a single oral dose of 1000 mg paracetamol was 22 to be pain free at 2 hours, with no significant difference after 1 hour [3]. In patients with migraine, the NNT for paracetamol 1000 mg was 12 for pain-free response at 2 hours [4]. Data derived from randomized controlled trials comparing paracetamol to placebo for other acute painful conditions are scarce.

Effectiveness of Paracetamol in Acute and Chronic Musculoskeletal Diseases

In 2014, a large randomized placebo controlled trial was published in the Lancet, questioning the so far universal endorsement of paracetamol for acute low back pain [5]. A Cochrane review published in 2016 did not find any evidence to support the use of paracetamol at 4 g day up to 12 weeks [6]. The use of paracetamol was also

questioned for osteoarthritis of the knee and hip [7], where only a small effect on short-term follow-up was found. We performed a network meta-analysis where we compared different non-steroidal anti-inflammatory drugs (NSAIDs) against

paracetamol and placebo [8, Figure 1]. We found an effect size of 0.17 for a dosage of 4 g paracetamol a day, corresponding to a 4-mm difference on a 1000 mm visual analogue scale, which we considered to be not clinically meaningful (Figure 2). In addition,

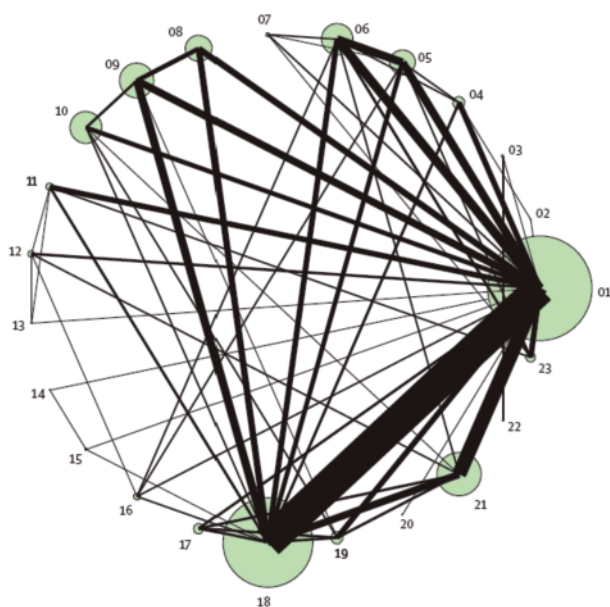


Figure 1: Network of comparisons of different NSAIDs, paracetamol and placebo. The size of each circle is proportional to the number of randomly assigned patients and indicates the sample size. The width of the lines corresponds to the number of trials. 01 = placebo. 02 = paracetamol <2000 mg. 03 = paracetamol 3000 mg. 04 = paracetamol 3900–4000 mg. 05 = rofecoxib 12.5 mg. 06 = rofecoxib 25 mg. 07 = rofecoxib 50 mg. 08 = lumiracoxib 100 mg. 09 = lumiracoxib 200 mg. 10 = lumiracoxib 400 mg. 11 = etoricoxib 30 mg. 12 = etoricoxib 60 mg. 13 = etoricoxib 90 mg. 14 = diclofenac 70 mg. 15 = diclofenac 100 mg. 16 = diclofenac 150 mg. 17 = celecoxib 100 mg. 18 = celecoxib 200 mg. 19 = celecoxib 400 mg. 20 = naproxen 750 mg. 21 = naproxen 1000 mg. 22 = ibuprofen 1200 mg. 23 = ibuprofen 2400 mg [8].

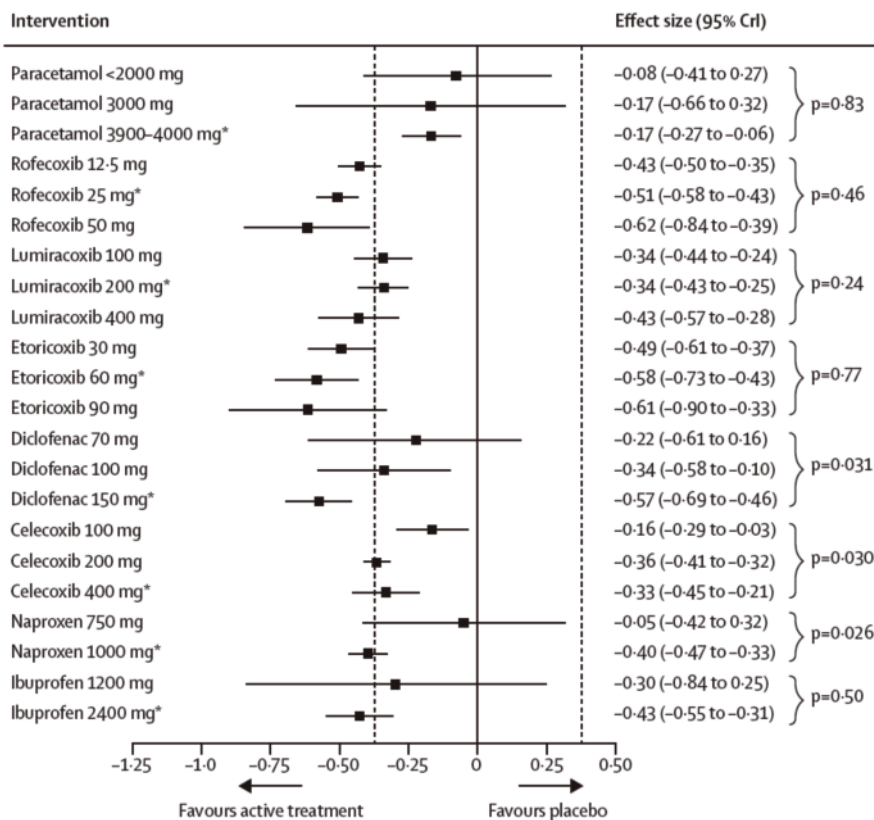


Figure 2: Estimates of the treatment effects on pain for different daily doses of NSAIDs and paracetamol compared with placebo. Analysis considers that data from all timepoints are available. Area between dashed lines shows the treatment effect estimates below the minimum clinically important difference.



tion, we found no evidence that treatment effects varied over time.

■ Safety

Data from randomized controlled trials demonstrated no increased risk for any adverse events or serious adverse events [7]. However, a recently published meta-analysis of cohort studies suggested a potentially increased risk of cardiovascular, gastrointestinal and renal adverse events [9]. The most feared complication, though, is that of paracetamol poisoning, either accidental or intentional, leading to liver failure and approxima-

tely 150 deaths per year in the United Kingdom [10].

■ Conclusions

Evidence from randomized controlled trials does not support the use of paracetamol in acute or chronic musculoskeletal pain such as low back pain or osteoarthritis.

Accordingly, guidelines need to be modified. For the treatment of acute headache and postoperative pain, there seems to be a small, clinically questionable effect. The role of the combination of paracetamol with opioids should be carefully evaluated.

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Opioid Receptor Agonists and Antagonists

Stephan A. Schug, MD(Cgn) FANZCA FFPMANZCA

Professor of Anaesthesiology, Pharmacology and Anaesthesiology Unit, University of Western Australia & Director of Pain Medicine, Royal Perth Hospital Perth, Australia

The extract of the poppy seed, opium, is among the oldest medicines used by human kind. While its pain relieving effects were described as early as 2000 BC, the sedative effects and the abuse potential were also noticed early; Paracelsus described it as “a potent pain killer”, but to “be used sparingly”. A balancing act between the therapeutic use of opioids and the medical needs for their use on the one hand and their misuse and abuse on the other hand continues. In view of the importance of opioids, it is impossible to separate their pharmacology and clinical use from the societal issues of their abuse (1).

The German pharmacist Friedrich Sertürner isolated the alkaloid morphine in 1804, but the unravelling of the basic pharmacology of opioids primarily took place in the last 40 years and continues until today. This understanding started with the finding of endogenous ligands to opioid binding sites in the early seventies. These substances became known as endorphins and enkephalins and permitted understanding the complex interactions between opioids and their receptors.

Opioid receptors are G protein-coupled receptors with seven hydrophobic transmembrane domains). Three major opioid receptor subtypes, the mu-, delta- and kappa-receptors, have been identified. These receptors are highly homologous, in particular with regard to transmembrane domains and intracellular loops. By being coupled to inhibitory proteins, opioids are inhibiting voltage-dependent calcium channels as well as activating

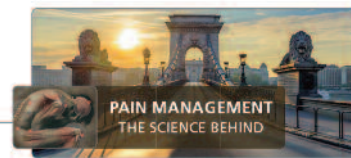
rectifying-potassium channels. Other molecular effects include the inhibition of the cyclic adenosine monophosphate pathway and the activation of phosphorylation cascades. The overall effect is to inhibit neuronal activity.

It is obvious that mu-receptors mediate all morphine activities and it might, therefore, be impossible to separate the beneficial effects of analgesia from the potential adverse effects such as respiratory depression, tolerance and dependence. The discovery of opioid receptors in the superficial dorsal horn (Laminae I and II) permitted the development of the concept of spinal analgesia.

Current understanding of analgesic effect provided by opioids suggests a pre- and post-synaptic effect in the dorsal horn of the spinal cord, as well as supraspinal effects in the rostromedial medulla and the peri-aqueductal grey (2). Here opioids activate so-called OFF-cells and inhibit ON-cells.

Overall the resulting effect is analgesia, however, these beneficial effects are accompanied by adverse effects including the potentially life-threatening respiratory depression [1]. Nausea and vomiting are disturbing patients primarily in the acute setting, while constipation can be a significant problem with long-term use and in cancer patients. Other side effects include urinary retention, sedation and cognitive impairment, hallucinations and delirium, rigidity, myoclonus and seizures as well as pruritus.

Relevant adverse effects of long-term use



include the development of tolerance, although true tolerance is rarely seen with the use of opioids in pain settings. Another pharmacological long-term effect is physical dependence resulting in withdrawal symptoms after abrupt discontinuation or administration of an antagonist. In practical terms, this can be easily overcome by tapering the dose gradually. As outlined before, the issue of addiction or abuse has resulted in most of the societal consequences of opioid use. Such abuse is characterised by a behavioural pattern of compulsive drug use resulting in physical, psychological and social harm (3). Addiction or abuse were regarded as extremely rare in the setting of medical use of opioids. This continues to seem to be true for the management of acute and cancer pain. However, the increasing long term use of opioids, either in patients with increasing survival times after a cancer diagnosis or even more pronounced in the setting of chronic non-malignant pain, has challenged this assumption. In the latter setting aberrant drug-taking behaviour has been reported in 24% and current substance abuse in 43% of patients (4). On the other hand it is also important to recognise the issue of pseudo-addiction (5). This is defined as behaviour that is perceived as addiction, but represents abnormal behaviour developing as a direct consequence of inadequate pain management, usually triggered by insufficient prescription of analgesics in settings of extreme pain.

With regard to use of opioids in specific clinical settings, opioids are an essential component of the management of severe acute pain after trauma and surgery (6). The use of opioids by titration to effect, ideally by means of patient-controlled analgesia (PCA), has proven to be highly effective and satisfying for patients. However, even in this setting, there

is an increasing interest in the use of opioid-sparing techniques; the acute adverse effects of opioids, in particular with regard to gastrointestinal function (nausea, vomiting, constipation), but also sedation and cognitive impairment, are delaying recovery after surgery and trauma. This is leading to increased complications, impaired rehabilitation, delayed discharge and increased hospital costs. The concept of multimodal analgesia, i.e. combining opioids with analgesics with different sites or mechanisms of action, has proven to be a useful concept here; most acute pain services worldwide are now utilising multimodal analgesia to achieve opioid-sparing effects and thereby reduce the reliance on opioids in this setting.

Similarly, in cancer pain, opioids are essential to control severe pain and improve the quality of life of patients (7). The British Hospice movement, and subsequently the World Health Organisation as outlined in a previous presentation at this meeting, have aggressively promoted the use of opioids for the management of cancer pain. Again in this setting, there may be advantages of multimodal analgesia, but it is impossible to treat severe cancer pain appropriately without use of opioid analgesics.

The positive experiences with the use of opioids in the setting of acute and even more so cancer pain by the end of the last century have resulted in the increasing use of opioids in the management of chronic non-cancer pain. There was a dramatic increase in the use of opioids in the highly industrialised countries of the world, in particular Canada, the United States, Australia and the European Union. On the other hand, in about 150 countries of the world, even simple oral morphine for treatment of appropriate indications such as cancer, postoperative and trauma pain is restricted or barely available (8).

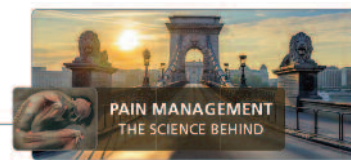


From a historical point of view, the world has swung from the 19th century, when opioids were pretty much unregulated and, for example, freely available in the United States, to strict controls initiated by the Harrison Narcotic Tax Act in 1914 and further spread around the world by the International Opium Convention, which led to the Single Convention on Narcotic Drugs (1). The adherence to this convention is the task of the International Narcotics Control Board (INCB). This approach resulted in a time of significant 'opiophobia', which made it nearly impossible to use opioids even in the setting of cancer pain (9). This was successfully overcome by, initially, the British Hospice movement and then the World Health Organisation with their publication of the first Guidelines on Cancer Pain Relief in 1986. Regrettably, this approach has not been successful in the whole world and, therefore, there are now significant discrepancies in availability of opioids. For example, in 2014 countries like Canada, The United States of America and Australia had an annual per capita consumption of opioids expressed in milligram morphine equivalents in the range of 500-1000 milligrams, while these numbers for countries like India, Zambia and Nicaragua were in the range of 0.5-1.0 milligrams (10).

In retrospect it might have been a mistake to assume that simply transferring the concept of acute and cancer pain management to the treatment of chronic non-cancer pain is a valid approach (11). In the setting of chronic non-cancer pain, opioids might be more useful in well-defined nociceptive conditions such as osteoarthritis or neuropathic pain, where there are good data on efficacy. However, even in these settings there are no good data on long-term efficacy and safety of opioids. This has led to opioids being for example only third-line treatment for neuropathic pain

despite proven efficacy, as concerns about diversion, abuse and long-term safety have to be considered (12). The situation becomes even more complicated in chronic pain states, which are mainly based on central sensitisation and often multifactorial such as fibromyalgia, nonspecific chronic low back pain, chronic visceral pain states and headaches (11). It is obvious that in such conditions, which are not only the result of biological, but also psychological and social issues, opioids cannot overcome suffering, dysfunction, relevant psychosocial factors and are actually increasing the dependence on the health care system and strengthening passive strategies of pain management. Therefore, it is not surprising that outcome data on use of opioids in this setting have only limited evidence of some short-term efficacy; meta-analysis of randomised controlled trials and epidemiological data suggest only weak evidence for clinically significant pain relief and inconclusive and sometimes even negative effects on functional outcomes and quality of life. In addition, long-term opioid use, in particular in higher doses, can result in opioid-induced hyperalgesia and endocrine consequences such as opioid-induced androgen deficiency (OPIAD).

The increasing use of opioids in chronic non-malignant pain had significant consequences not only for patients not receiving optimal pain management, but also for the societies in countries, which adopted this approach. This has been exemplified in a paper in the New England Journal of Medicine in 2010 with the disturbing title "A Flood of Opioids, a Rising Tide of Deaths" (13). There are now frightening statistics suggesting that from 1999 to 2014 more than 165,000 people in the United States died from prescription opioid overdose with an annual rate of currently beyond 14,000 such overdose deaths (14). In



countries such as Canada, the USA, Australia and the European Union, the use of opioids in the last 20 years has increased so dramatically that prescription opioids going on to the black market are now the main source of illegal opioid use in these countries.

We are now in a situation where opiophobia has been overcome in many industrialised countries and has actually led to such relaxed attitudes that opioid use is resulting in increased mortality and significant societal

problems. In those countries, like the United States, regulatory authorities are developing new approaches to the use of opioids such as the FDA a risk evaluation and mitigation strategy (REMS). On the other hand, the World Health Organisation continues to try to convince governments in other countries to make basic opioids available for patients with cancer pain. The search for a useful balance between appropriate use of opioids in pain and prevention of abuse will have to continue. ◀

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NSAIDs for Pain Management: Benefits and Risks

David Hunter, MBBS, MSc, PhD, FRACP

Professor of Medicine and Florence and Cope Chair of Rheumatology,
Chair of the Institute of Bone and Joint Research, University of Sydney, Australia

■ Rationale underlying importance of analgesics

Pain is the dominant symptom in patients with osteoarthritis (OA) and a major driver of clinical decision-making (1). Due to its associated pain, approximately 80% of patients with OA have some degree of movement limitation, 25% are unable to perform major activities of daily living (ADL's) and 11% require help with personal care (2).

Insights into the mechanisms of pain in OA are emerging and have revealed a complex bio-psychosocial process, in which the subchondral bone, inflammatory mediators and sensitization of peripheral and central nociceptive pathways play a role in the initiation and perpetuation of pain (3). In addition to the structural pathology of OA, other factors may also influence the perception of pain such as psychosocial (e.g., social isolation, catastrophizing, coping strategies, mood disturbances) and environmental factors (e.g., culture and lifestyle) (4).

Significant progress has been made in the last few years to uncover the pathogenesis of the disease and enable the development of more effective drugs to alleviate symptoms and minimize structural damage of the joint. However, no cure for established disease or efficacious drugs for disease modification have been approved or are likely to appear in the immediate future (5). On

the other hand, non-pharmacological measures have been associated with positive outcomes targeting the main goals of the treatment of OA: pain relief and improvement in joint function. Weight loss and low impact exercises can reach improvements in pain up to 50% (6) and, perhaps more importantly, are able to prevent a large number of new cases of knee OA, even when focused on people aged 50 years and over. Despite this favorable evidence, the rate of implementation of these non-pharmacological strategies is low and the current care for patients with knee OA is typically inappropriate (7). Care is largely focused on the management of established disease, as opposed to prevention, and predominantly directed to surgical replacement of the knee and palliative therapies with little or no impact on the protection of joint structures (8). Adequate intervention in a timely fashion is critical to minimize the consequences of knee OA such as functional decline and slow further deterioration of the joint (Table 1).

In the context of changing evidence, polypharmacy in the elderly and a plethora of available options, drug selection for pain relief in OA has been and will remain a challenge. Every therapeutic decision involves consideration of risks versus benefits and finding a balance between efficacy and tolerability.



■ What should the first-line analgesic be for OA pain?

NSAIDs are often considered to be the preferred first-line drug treatment for osteoarthritis. They have shown efficacy similar or superior to paracetamol (9, 10). Systematic reviews have found NSAIDs are superior for rest pain and overall pain (11). The current OA Research Society International (OARSI) guidelines suggest topical or oral NSAIDs, depending on the clinical context, as well as consideration of comorbidities and potential for harm (12).

Oral NSAIDs have larger effects on pain compared to paracetamol, albeit a higher risk of renal, gastrointestinal (GI) and cardiovascular (CV) complications frequently limits their use (13).

Gastrointestinal toxicity causes over 16.500 deaths and hospital admissions per year in the USA (14). Associated cardiovascular and renal risks are also a concern. These risks pertain to both non-selective and COX-2-selective NSAIDs, even though COX-2 inhibitors have a better safety profile. A meta-analysis of 26 studies comparing the two found that COX-2 inhibitors reduced the relative risk of dyspepsia by 12% and the absolute risk by 3.7% (15). Other systematic reviews and meta-analysis also confirm similar findings (16).

GI toxicity related to NSAIDs have been reported by several studies and includes severe complications such as clinically significant ulcers, bleeding and perforation (17). Advanced age is recognized as a major risk factor for adverse events related to NSAIDs. For this reason, prescription of gastroprotective drugs such as proton-pump inhibitors (PPIs) is recommended for

this demographic group as well as for patients with co-morbidities (18). Combining an NSAID with a proton pump inhibitor reduced the relative risk of dyspepsia by 66% and the absolute risk by 9% compared to an NSAID alone (15).

There is no superiority of any particular NSAID over the others but safety profiles differ between COX-2 selective and non-selective drugs and should be considered in the decision of the best NSAIDs type for each individual patient. COX-2 selective drugs have a safer GI profile with lower risk of ulcer complications at short-term but less clear evidence for long-term safety (16). On the other hand, risk of CV harm is lower with naproxen than with any other non-selective or COX-2 selective NSAIDs (16).

NSAIDs should be avoided when risks outweigh benefits such as in patients with multiple comorbidities or with little response to this type of medication. Particularly in older patients, serum creatinine can underestimate the degree of renal failure and is an unreliable indicator of glomerular filtration rate. Alternative methods such as the Modification of Diet in Renal Disease (MDRD) formula should be used for this purpose in this population (19). The treatment strategy should be based on the minimum dose and duration necessary to control symptoms and according to prescribing limits.

The optimum duration of NSAID therapy is unclear. A meta-analysis of randomized trials (16) found no clear association between the duration of therapy with selective or non-selective NSAIDs and the risk of cardiovascular events. One small trial found continuous celecoxib use to be slightly more effective than intermittent use on pain and function, with similar rates of withdrawals due to adverse events (20). No trials have been designed to assess serious gastrointe-



stinal or cardiovascular harms associated with intermittent dosing strategies. OA pain is characterized by marked fluctuations or flares. NSAIDs are effective analgesic agents, but they do not modify the underlying disease. In light of their well-publicized toxicity profiles (especially adverse gastrointestinal and cardiovascular effects), their prescription on a long-term daily basis is counterintuitive and rather they should be given on an 'as-needed basis' at the lowest therapeutic dose.

Topical NSAIDs are a good alternative to alleviate joint pain, with similar efficacy to oral NSAIDs (especially with topical diclofenac solution) but no higher systemic side effects than placebo, due to the reduced systemic absorption of topical formulations (5-17 fold lower systemic absorption of topical diclofenac compared to its oral preparation) (21, 22).

■ Context within the management of osteoarthritis

The management of OA is frequently inappropriate, and there are marked deficits in the uptake of non-pharmacological treatments, particularly weight loss and exercise (23) (Figure 1). One thing is certain, when looking at options for managing patients with OA, we need to look no further than the areas we are currently underperforming in. Exercise and weight loss prescription should form the core of our management, and we can all do better in reinforcing this message to our patients and providing them the tools to implement these behavioral changes. There are many therapeutic options available for patients with OA, and the decision about how to manage disease

should consider the risks and benefits of a treatment, tailored advice to the individual to maximize functional gain as well as patient comorbidities. Treatment in OA should be tailored to the individual and target modifiable risk factors that lead to progression of disease. Pain is an unmet need as far as research priorities are concerned, and further work is required to develop more effective and safer means of delivering better outcomes to our patients.

General recommendations

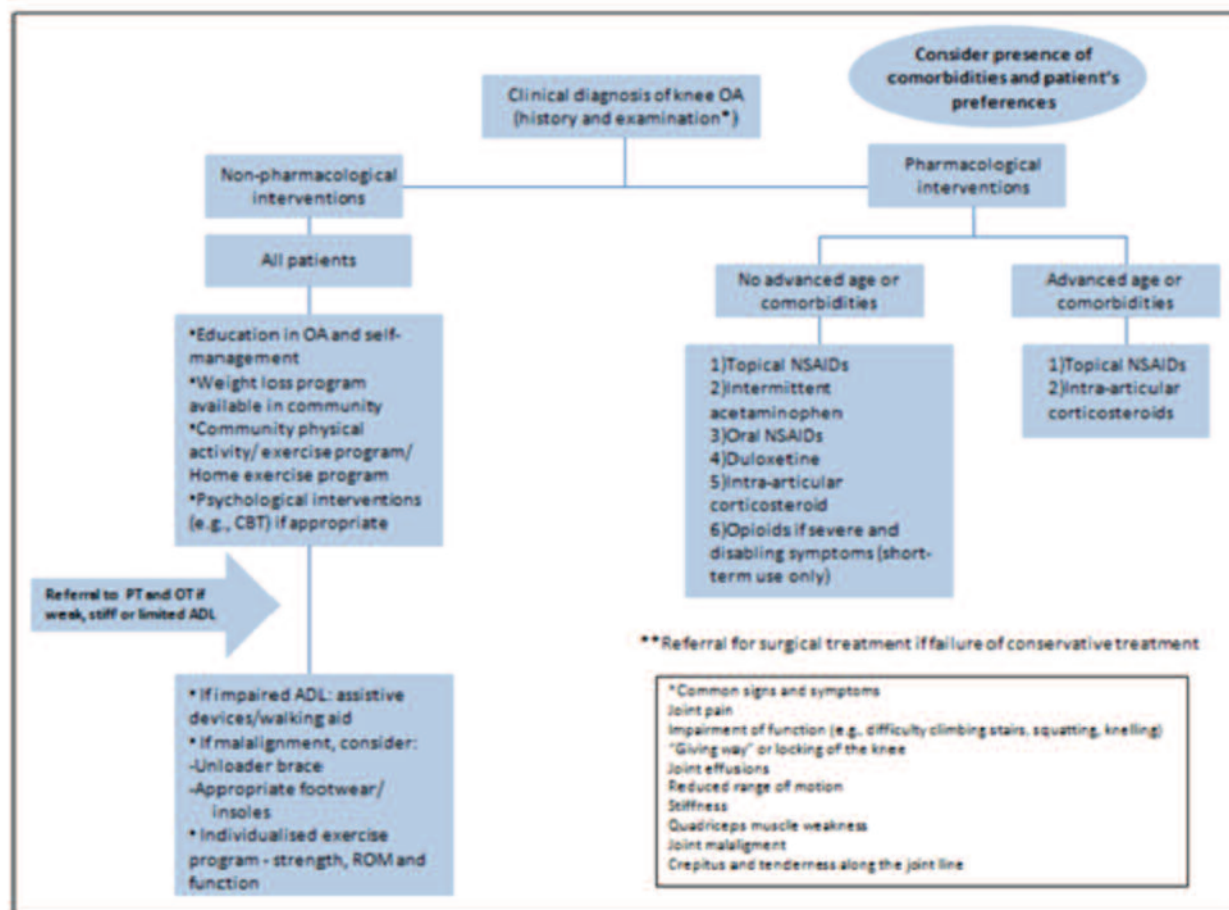
- Comprehensive evaluation of the patient with OA is essential for improving patient-centered outcomes
- Common misconceptions about OA (e.g., "inevitable consequence of aging") may hamper adherence if not identified and countered properly
- Establish short- and long-term goals and assess them periodically
- Fully inform and direct the focus of treatment to the patient, encouraging engagement and self-management

Treatment recommendations

- A multidisciplinary approach is advisable for optimal delivery of interventions
- Exercises and weight management should be indicated to all patients
- Paracetamol has little benefit for pain and increases GI, renal, and CV risk
- Conservative use of NSAIDs is recommended. Individual risks and benefits should be considered
- Glucosamine, chondroitin, and IA HA has little, if any, effect on symptoms
- Refer to surgery when there is persistent moderate to severe symptoms after appropriate conservative management.
- Arthroscopy is not appropriate for treating pain

Legend: CV cardiovascular, GI gastrointestinal, HA hyaluronic acid, IA intra-articular, NSAIDs non-steroidal anti-inflammatory drugs, OA osteoarthritis

Figure 2: Key messages for clinicians for the optimal management of osteoarthritis. Excerpt from (24)



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Adjuvant analgesics in chronic non cancer pain

Nadine Attal, MD

INSERM U-987, Centre d'Evaluation et de Traitement de la Douleur
CHU Ambroise Paré, Boulogne-Billancourt, and Université Versailles Saint-Quentin, Versailles, France

Adjuvant analgesics generally refer to medications that are not primarily designed to control pain, but can be used for this purpose. Some adjuvant analgesics are useful in several painful conditions (antidepressants, antiepileptics), while others are more specific for neuropathic pain (local anesthetics, N-methyl-D-aspartate receptor antagonists). Here, we will briefly review the evidence supporting the use of major adjuvant analgesics (Table 1) administered at repeated dosages or as topical/local agents (antidepressants, antiepileptics, local anesthetics, capsaicin, botulinum toxin A) for the treatment of chronic non cancer pain with particular emphasis on two largely studied conditions: neuropathic pain and fibromyalgia (1-4).

■ Antidepressants

The analgesic efficacy of antidepressants is independent of their antidepressant effect. It is probably largely mediated by their action on descending modulatory inhibitory controls, but other mechanisms such as a blockade of sodium channels and glutamate receptors, and effect on beta2 adrenergic receptors have been proposed. Two antidepressant classes have been found beneficial in neuropathic pain or fibromyalgia: tricyclic antidepressants (TCAs) particularly amitriptyline in neuropathic pain and serotonin–norepinephrine reuptake

inhibitors (SNRIs) duloxetine, venlafaxine and milnacipran (the latter has only been studied in fibromyalgia). Somnolence and constipation are the most common side effects of antidepressants, while dry mouth is more common with TCA and nausea is more common with duloxetine. Tertiary amine TCAs (imipramine, amitriptyline, and clomipramine) have a poorer side effect profile with major anticholinergic effects including postural hypotension and cardiac conduction slowing, sedative side effects and consequently risk of falls.

■ Antiepileptics

Pregabalin and gabapentin

In preclinical studies, the analgesic effects of pregabalin and gabapentin are mainly related to a decrease in central sensitization and nociceptive transmission through action on the alpha-2-delta subunit of calcium channels. Their efficacy is established in peripheral or central NP and to a lesser extent in fibromyalgia. Extended-release formulations of gabapentin (gabapentin extended release or enacarbil) have similar efficacy and safety in clinical trials in NP and can be used BID. Similar efficacy as compared to antidepressants has been reported and their efficacy is probably higher when combined to antidepressants. Most common side effects include somnolence, dizziness and weight gain. These agents have a generally good safety profile with no drug drug



interaction.

Other antiepileptics

Antiepileptics other than pregabalin and gabapentin (e.g. topiramate, oxcarbazepine, carbamazepine, valproate, zonisamide, lacosamide) have mainly been tested in NP and have weak or inconsistent results, with the notable exception of carbamazepine in trigeminal neuralgia. All the studies of levetiracetam are negative in neuropathic pain.

■ Local anesthetics

Lidocaine may reduce ectopic discharges through its sodium channel-blocking properties. The efficacy of lidocaine 5 % patches has been assessed mainly in post-herpetic neuralgia in small duration trials (less than 3 weeks). The therapeutic gain is modest as compared with placebo and one large-scale trial using an enriched enrollment design failed to show a difference between lidocaine patches and placebo on the primary outcome measure. However given the excellent safety profile of this treatment, particularly in the lack of alternative safe and well tolerated medications, it is still recommended in peripheral NP especially in the elderly.

■ Capsaicin cream and high concentration patches

Capsaicin activates TRPV1 ligand-gated channels on nociceptive fibers. This causes depolarization, the initiation of an action potential, and the transmission of pain signals to the spinal cord. After several days of application, TRPV1-containing sensory axons are desensitized, a process also referred to as “defunctionalization”. Standard capsaicin-containing creams (0.075%) have been found to be moderately effective in post-herpetic neuralgia, but they require many applications per day and cause a

burning sensation for many days before the analgesic effect starts. The efficacy of a single application of high-concentration capsaicin patch (8%) for up to 3 months compared to a low concentration patch (0.04%) has been demonstrated in PHN and HIV neuropathy, more recently in diabetic painful neuropathies. Better results were noted for the 60-min application in post-herpetic neuralgia and 30-min application in HIV-related painful polyneuropathy. Common adverse effects include local pain and erythema, but there is a potential risk of blood pressure elevation due to the immediate pain caused by the application. The long-term safety of repeated applications in patients has not been clearly established particularly with respect to degeneration of epidermal nerve fibers, which may be a concern in progressive neuropathy.

■ Botulinum toxin type A

Botulinum toxin type A (BTX-A), a potent neurotoxin commonly used for the treatment of focal muscle hyperactivity, may have analgesic effects independent of its action on muscle tone. Several single center randomized controlled trials have reported the long-term efficacy of BTX-A (one single set of subcutaneous injections into the painful area) in peripheral neuropathic pain, but one unpublished study (sponsored by Allergan) was negative (3). We have recently reported long term efficacy of two repeated administrations of BTX-A in peripheral neuropathic pain, with enhanced efficacy of the second injection (5). In published studies, the onset of efficacy (about 1 week) and duration of effects (3 months) is remarkably similar.

■ Emerging drug treatments

A few drugs targeting novel mechanisms of action are under clinical development particu-



larly for the treatment of neuropathic pain. These include for example subtype selective sodium blocking agents particularly Nav1.7 antagonists and novel angiotensin type II antagonists.

Conclusion

Adjuvant analgesics are increasingly used for

chronic non cancer pain, particularly fibromyalgia and neuropathic pain. Recommendations have recently been proposed concerning their use in these chronic pain conditions (1-4). New drug treatments are also being developed and should contribute to reduce the therapeutic failures which are still a major concern in chronic non cancer pain.

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NSAID-Opioid Combinations: Rationale and Clinical Efficacy

**Carmelo Scarpignato, MD, DSc, PharmD (h.c.),
MPH, FRCP (Hon), FACP, FCP, FACP, AGAF**

Professor of Clinical Pharmacology, University of Parma, Italy
Associate Professor of Gastroenterology, University of Nantes, France
General Secretary, World Organization for Esophageal
Diseases (OESO), Paris, France
Governor for Italy, American College of Gastroenterology (ACG)

with the cooperation of Anna Bertelé, MD
Consultant Physician & Gastroenterologist

Pain is the most common symptom reported in both the general population and the general medical setting [1-3] and pain medications are the second most prescribed class of drugs (after cardiac-renal drugs), accounting for 12% of all medications prescribed during ambulatory office visits in the United States [4].

Although pain treatment remains suboptimal, pain medicine research has led to significant pharmacologic, behavioral, and rehabilitation advances, including the development of neurobiologic therapies targeted at specific neural networks and systems. Major progress in the understanding of opioid pharmacology has offered to clinicians a wider range of indications for these drugs, alone or in combination with other agents, especially in non-cancer pain [5].

It is difficult to achieve effective pain control using a single treatment, for several reasons. Most analgesics cannot be prescribed at unlimited doses due to the ceiling of efficacy and/or safety and tolerability concerns, such as liver damage (this is the case of paracetamol, for instance), gastrointestinal (GI) and cardiovascular (CV) risks [for both non-selective and cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs)], or sedation, constipation and other effects of

opioid agonists [6]. Combining drugs from different classes offers effective analgesia at reduced doses of individual agents, which may reduce the severity of dose-related adverse events [7]. Another limitation of single-agent analgesia is that many patients experience pain due to multiple causes. It is very unlikely that any single therapy will be able to target every pain mechanism for these patients, so it is logical to combine drugs with different mechanisms of action. This approach offers increased efficacy due to additive or synergistic effects without increasing the dose. The ideal combination regimen would both enhance analgesic efficacy and reduce side effects compared with either treatment alone.

Currently Available Analgesic Drug Combinations

A number of analgesic drug combinations have been tested for the management of post-operative pain, including paracetamol with weak, (e.g. tramadol or codeine) or strong, (e.g. morphine or oxycodone) opioids. Besides being less effective than NSAIDs [8, 9], paracetamol may not be as safe as originally believed,



both from a GI and CV perspective, not to mention the well-known hepatotoxicity (especially at doses higher than 3 g daily) [10, 11]. Despite adding codeine to paracetamol produces worthwhile additional pain relief [12], none of the available studies found this combination to be superior to NSAIDs in controlling postoperative pain [13]. Combining an effective NSAID with weak opioids could represent therefore a better alternative.

■ NSAIDs: Pharmacology and Clinical Use of Selected Compounds

NSAIDs are very effective drugs [14-15], but their use is associated with a broad spectrum of adverse reactions involving the liver, kidney, CV system, skin and gut [16]. GI side effects are the most common and cover a wide clinical spectrum ranging from dyspepsia, heartburn and abdominal discomfort to more serious events, such as peptic ulcer with life-threatening complications of bleeding and perforation [17,18]. Different attempts have been made to reduce NSAID-induced gastro-duodenal damage [18]. These include enteric-coated preparations or soluble formulations of NSAIDs to reduce the gastric residence time and thus contact with gastric mucosa, buffered preparations, non-acidic pro-drugs and the development of enantiomers. The chiral switch of NSAIDs proved to be a rational approach to improve both efficacy [19] and safety [20] of this class of drugs.

Ibuprofen is one of the most popular NSAIDs, introduced in the United Kingdom in the 60's and in the United States in 70's. Ibuprofen is a racemate. The R(-) isomer is converted in the

body to the more active S(+) isomer after absorption in the GI tract. Ex vivo inhibition of both COX-1 and COX-2 isoenzymes at the plasma concentrations, achieved following ingestion of 400 mg ibuprofen in dental and other inflammatory pain models, provides evidence of its main mechanism of action. R(-)-ibuprofen inhibits leucocyte activation, neural activity and spinal transmission, thus contributing to the effects of racemic ibuprofen in inflammatory pain [21]. Recent evidence from large-scale clinical trials with the newer **COX-2 selective inhibitors**, where this NSAID was as a comparator, has confirmed earlier studies, showing that ibuprofen has comparable therapeutic benefits with COX-2 selective and non-selective NSAIDs. Both clinical trials and epidemiological studies have shown that ibuprofen has relatively low risks for GI and hepato-renal adverse effects, compared to other NSAIDs. A higher risk of CV events has been reported in some studies, but the risks are in general lower than observed with some COX-2 inhibitors (like rofecoxib or etoricoxib) and diclofenac. The possibility that ibuprofen may interfere with the anti-platelet effects of aspirin has given rise to caution on its use in patients that are at CV risk, who take aspirin for primary or secondary prevention [22]. While inhibition of prostanoid synthesis remains an important analgesic mode of action for NSAIDs both in the periphery and the central nervous system (CNS), other mechanisms should be considered [23]. Some NSAIDs, in addition to their effects on prostanoid synthesis, also affect the synthesis and activity of other neuroactive substances, believed to have key roles in processing nociceptive input within the dorsal horn. It has been argued that these other actions, in conjunction with COX inhibition, may synergistically augment the effects of NSAIDs on spinal nociceptive processing. When the clinical efficacy of



NSAIDs in dental pain is plotted against the ratio between anti-inflammatory and analgesic activities in experimental models, ketoprofen appears to be the most effective analgesic amongst the different NSAIDs [23]. Along the same lines, a recent meta-analysis of 13 randomized controlled trials (RCTs) involving 898 patients [24] found that the efficacy of oral ketoprofen in relieving moderate to severe pain was significantly better than that achieved with ibuprofen and/or diclofenac.

Dexketoprofen trometamol is a water-soluble salt of the active stereoisomer of ketoprofen, one of the most potent COX inhibitors in vitro. The analgesic efficacy of oral dex-ketoprofen trometamol (10 to 20 mg) is superior to that of placebo and similar to that of ibuprofen 400 mg in patients with moderate to severe dental pain. The time to onset of pain relief appears to be shorter in patients treated with dex-ketoprofen trometamol than in those treated with ibuprofen. This NSAID is well tolerated, with a reported incidence of adverse events similar to that of placebo [25]. A systematic review of the available studies concluded that dex-ketoprofen is at least as effective as other NSAIDs or paracetamol/opioid combinations [26].

■ Opioids: Pharmacology and Clinical Use of Selected Compounds

Opioid therapy continues to be an important “mainstream” option for the relief of pain, despite continued debate over the efficacy and safety of utilizing opioids with chronic non-cancer populations. The recognition that opioid therapy can relieve pain and improve mood and functioning in many patients with chronic pain has led experts on pain to recommend

that such patients not be denied opioids [5]. Opioids represent indeed the most effective pain relieving medications. This has led guidelines to recommend their use in patients with persistent moderate-to-severe pain [27-31]. Despite these recommendations, many clinicians without specialist knowledge of pain management remain reluctant to prescribe opioids for chronic pain of non-malignant origin.

A systematic review of 34 trials including 4212 patients provided information on adverse events related to opioid use in treating non-cancer pain [32]. Only three side effects occurred significantly more frequently with opioids: nausea, constipation and somnolence, with excess rates over placebo of 14%, 9% and 6%, respectively. A substantial proportion of patients on opioids (22%) withdrew because of adverse events. Because most trials were short (<4 weeks) and did not titrate the dose, the implications for long-term use in clinical practice are less certain. Eisenberg et al. [33] also reported on adverse events in their systematic review of opioids for neuropathic pain. Opioid therapy compared to placebo resulted in higher reporting of nausea (33% versus 9%), constipation (33% versus 10%), drowsiness (29% versus 12%), dizziness (21% versus 6%) and vomiting (15% versus 3%). Where reported, more patients on opioids withdrew because of adverse effects (11% versus 4%).

Oxycodone is a semisynthetic opioid analgesic that acts as an agonist at μ - and κ -opioid receptors in the CNS and has additional effects on smooth muscle. It is available as immediate release and controlled release formulations. Oxycodone has good oral bioavailability and produces more predictable plasma concentrations than morphine, which has a poor and more variable bioavailability. Oxycodone has



clinically significant drug interactions with drugs affecting cytochrome P450 3A enzymes. The efficacy of oxycodone in managing neuropathic and somatic pain, both of malignant and non-malignant origin, has been established in a wide range of settings [34]. Side effects are those common to opioids: mainly nausea, constipation and drowsiness. Vomiting, pruritus and dizziness are less common. The intensity of these side effects tends to decrease over time. Oxycodone causes somewhat less nausea, hallucinations and pruritus than morphine [35].

Tramadol is an analgesic with dual mechanisms of action: opioid receptor activation and enhancement of serotonin and norepinephrine transmission [36]. Although the relative degree of contribution of each mechanism toward pain control is not fully understood, the drug proved to be beneficial in the treatment of a wide range of acute and chronic pain syndromes, including neuropathic pain. Its analgesic efficacy can further be improved by combination with a non-opioid analgesic [37]. Most importantly, tramadol does not induce significant respiratory depression or constipation and proved to be an effective and well-tolerated analgesic agent in the perioperative setting [38].

■ NSAID-opioid Fixed-dose Combinations

Oxycodone-ibuprofen (5 mg/400 mg) is an oral fixed-dose combination tablet. It is approved in the US for the short-term (up to 7 days) management of acute, moderate-to-severe pain and was the first fixed-dose combination (FDC), containing an NSAID and an opioid. A single tablet provided better analgesia than low-dose oxycodone or ibuprofen, administered alone, in most trials and appeared to be more effective than a single dose of some other fixed-dose combination analgesics.

While co-administration of ibuprofen and oxycodone in experimental models produces synergistic analgesia, clinical trials showed only an additive effect [39].

Onset of pain relief was experienced by 90% of oxycodone/ibuprofen recipients compared with 36% of placebo recipients over the 6-hour post-administration period. The oxycodone/ibuprofen combination was generally well tolerated in patients with acute, moderate-to-severe postoperative pain. Nausea, dizziness and somnolence were the treatment-related adverse events that occurred most frequently after a single dose or multiple doses. Most (52%) adverse events that occurred with multiple doses of oxycodone/ibuprofen were of mild severity.

Oxycodone/ibuprofen FDC is therefore an effective, convenient treatment option for the short-term management of acute, moderate-to-severe pain [39]. Animal studies have shown that the combination of dex-ketoprofen with tramadol is synergistic for the inhibition of nociception in different models of inflammatory pain [40]. Along the same lines, the intra-articular administration of both drugs produced synergistic antinociceptive effects in the model of monosodium iodoacetate-induced osteoarthritis in rats [41]. **A dexketoprofen-tramadol** FDC was recently evaluated for its analgesic activity in acute dental pain. Four different fixed combinations and as single components in comparison to placebo, on moderate to severe acute pain following impacted third mandibular molar tooth extraction. This phase II study was performed in more than 600 patients in 16 clinical sites located in 6 European countries. Dexketoprofen trometamol 25 mg combined with tramadol hydrochloride 75 mg provided the best analgesia with rapid onset and long (median: 8.1 h) duration (Figure 1). The combination proved to be cost-effective, with a number needed to treat (NNT) of 1.2 (Figure 2). Adverse events were unre-

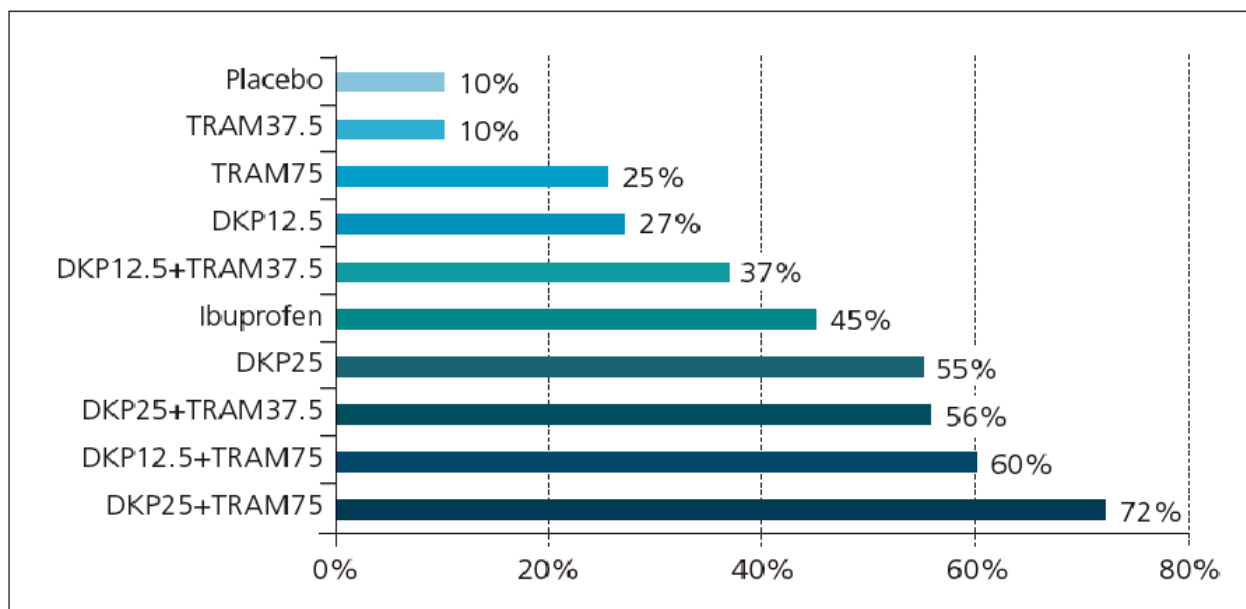


Figure 1: Percentage of patients showing response (> 50% max TOTPAR) over 6 h post-dose (Primary Endpoint). Maximum TOTPAR corresponds to the theoretical maximum possible time-weighted sum of the PAR scores, measured on a 5-point VRS (0='none' to 4='complete') (from Moore et al. [42]).

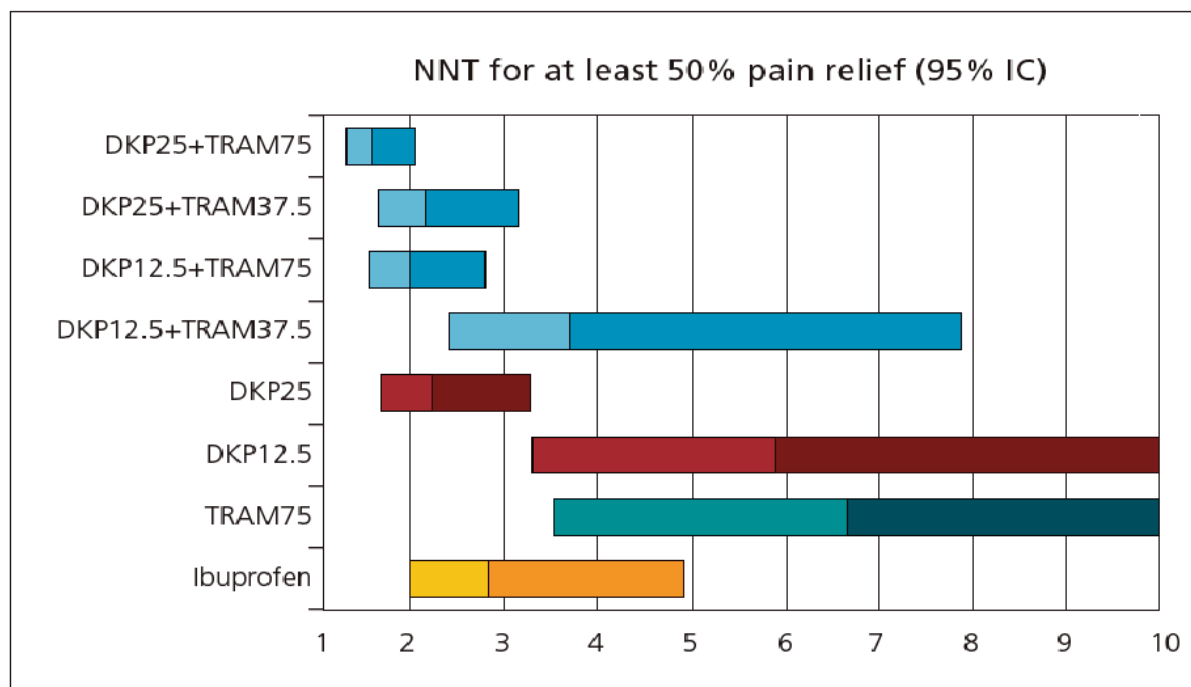


Figure 2: NNT for > 50% max TOTPAR compared with placebo over six hours post-dose. Maximum TOTPAR corresponds to the theoretical maximum possible time-weighted sum of the PAR scores, measured on a 5-point VRS (0='none' to 4='complete'). Bars show 95% confidence interval of NNT, with colour change as point estimate (Note that TRAM37.5 was not significantly better than placebo) (from Moore et al. [42]).



markable [42]. Two phase III clinical trials [43, 44] in post-surgical moderate to severe acute pain, have been completed and included some 1200 patients in about 80 clinical centers located in 14 European and Asian countries. The studies confirmed that the dexketoprofen trometamol 25 mg + tramadol hydrochloride 75 mg FDC was able to provide a level of analgesia above the one achievable by each component alone and presented a safety profile consistent with what

was previously reported for dexketoprofen trometamol and tramadol hydrochloride when used as single agents [43, 44].

In conclusion the US approved ibuprofen-oxycodone combination and the recently EMA approved dexketoprofen-tramadol combination are effective analgesic medications and represent useful addition to our therapeutic armamentarium to fight pain.

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Interventional Pain Management: Pros & Cons

Serdar Erdine, PhD, FIPP

Chair, Istanbul Pain Institute, Turkey

Interventional pain management techniques are minimally invasive procedures, including percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves and some surgical techniques, such as laser or endoscopic discectomy, intrathecal infusion pumps and spinal cord stimulators, for the diagnosis and management of chronic, persistent or intractable pain. The interventional pain procedures are indicated when pain cannot be relieved by conservative management or there are unacceptable side effects for other treatments of chronic pain. In the last three decades there is a visible increase in the number of interventional pain procedures (1).

The classification of interventional pain procedures are presented in Table 1 (2).

Today's medicine is increasingly based on the biomedical system. Biomedicine is a failed promise of the late Industrial Age. It does not work well for most chronic diseases, especially pain. The schism between those providers who function with a biomedical model and those who utilize a biopsychosocial model has impaired the development of pain management. The biomedical system uses the interventional pain procedures in its own way harming the patient (3).

On the other hand the biopsychosocial system accepts the patient as a human being, as a chronic pain patient having a chronic pain disease in its own right.

Over the past several decades, some of the changes have been positive, whereas others have been deleterious. An interventionalist perceives a multidisciplinary or comprehensive pro-

gram as one with interventional techniques as the primary modality and physical and psychological applications as secondary components.

In contrast, a psychiatrist, rehabilitation specialist, or surgeon practicing interventional pain management may put emphasis on psychology/psychiatry, physical therapy/functional rehabilitation or surgical techniques, with multidisciplinary management provided by secondary application of other modalities, such as interventional techniques in this case.

There are large gaps and controversies in the literature describing the interventional procedures for pain management. The literature is limited. There is lack of double-blind studies, and there are problems with randomization. The diagnosis are not homogeneous. There are difficulties in arranging the appropriate comparison groups. There are problems with standardized assessment of treatment outcomes, and agreement on the definition of a successful treatment response. The variability in assessed outcomes, particularly how and when pain intensity or disability is measured, is especially problematic since it precludes combining data across studies with different methods in a meaningful way.

Clinical trials are challenging. Recruiting well-defined patient samples appropriate for and willing to undergo investigation of an interventional pain procedure is especially difficult. The placebo response, which is substantial in pain trials in general, may be even larger in response to sham surgery and sham interventions (4).

To test and validate a single intervention requires



Interventional Pain Procedures

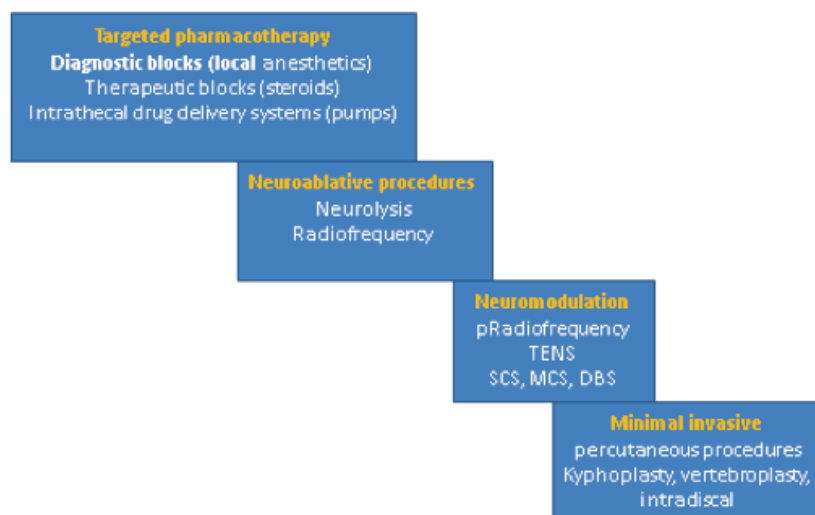


Table 1: Interventional pain procedures.

enormous funding. For example, a double-blind, placebo-controlled trial of radiofrequency neurotomy for neck pain cost some \$500,000. The costs of a placebo-controlled trial of intradiscal electrothermal therapy were estimated at over \$1,000,000. Producing a single study of each would result in an estimated conservative cost of \$19.5 million. Reproducing these studies could result in a potential total cost of \$58.5 million (5).

Meanwhile, in an effort to reign in increasing costs, third-party payers are implementing “evidence based medicine” (EBM) standards. Conversely, when randomized controlled trials are lacking, their absence is becoming accepted as proof of ineffectiveness of a procedure, and reimbursement is being denied. As a result, a conflict has developed. Practitioners unfortunately are faced with patients today whose treatment cannot be ignored while waiting for someone to generate the evidence (5).

Conducting well designed observational studies may help to proceed with these interventions as they provide prima facie evidence of efficacy.

The other side of the coin is that Invasive proce-

dures are nearly completely rejected by some authorities like NICE (National Institute for Health and Clinical Excellence) in UK. It was mentioned in the report published in 2009 in section related with invasive procedures;

“1.6.1 Consider offering a course of acupuncture needling comprising up to a maximum of 10 sessions over a period of up to 12 weeks.

1.6.2 Do not offer injections of therapeutic substances into the back for non-specific low back pain.” (6).

If such academic nihilism continues, soon there will be not even one single interventional procedure left for the treatment of chronic pain.

Industry relationships with physicians, insurers, and lawmakers have affected pain management profoundly, influencing policy and insurance coverage, and increasing the use of medical devices and instrumentation. Advertising pain treatments has changed the expectations of patients and decreased emphasis on the patient role in pain management. Insurance reimbursement patterns have decreased the availability of multidisciplinary pain treatment and increased the economic attractiveness of invasive proce-

dures. Competition among pain medicine practitioners has often resulted in a stress on new technologies and high-paying procedures, with a reduction in less profitable treatment options (7).

Conflicts of interest can create self-serving biases that are unconscious and unintentional, and that do influence patient care. The growing demand for therapeutic and diagnostic injections has generated the "injectionists" (8).

Another important issue is the misuse and abuse of interventional pain management. Interventional techniques increased significantly in Medicare beneficiaries from 1997 to 2006: 197% increase in IPM service. Exponential increase in facet joint and sacroiliac joint injections." (9) (Figure 1).

Lumbosacral injections increased dramatically in Medicare population from 1994-2001. Less than 1/2 performed for sciatica or radiculopathy. Professional fees increased from \$24 million to \$175 million. Costs per injection doubled from \$115 to \$227. Non-anesthesiologists (especially radiologists) increased their percentage of procedures (2).

Widespread use of inadequately tested or unne-

cessary pain management diagnostic and treatment techniques, decreased use of some treatments with well documented effectiveness, and lack of adequate pain education are major concerns. The future of interventional pain management depends on proper understanding of the practice of interventional pain management, the appropriate use of interventional techniques, the research aimed at elucidating the pathophysiologic basis of pain, the studies validating evidence-based approaches for interventional pain management, and the good faith effort to eliminate fraud and abuse with contained and appropriate utilization.

Clinicians may often be applying an acute care model to a chronic condition. There are no "magic bullets" for chronic back pain, and expecting a cure from a drug, injection, or operation is generally wishful thinking. Instead of measuring only technical success (solid bony fusion or properly placed injection), research should clarify a treatment's safety and its effects on pain, function, and return to work.

The practice of pain medicine, involving those with chronic pain of cancer and non-cancer origin, more closely resembles that of our surgical colleagues. The practice resembles surgical-based practices because it is based on office evaluation and procedure-based treatment. It is a new discipline, a subspecialty and even specialty in the future which required a through training (10). Pain management is an art. It is a science and it is a business. The business of pain management influences patients' attitudes toward pain, their expectation for pain relief and cure, and their choices of

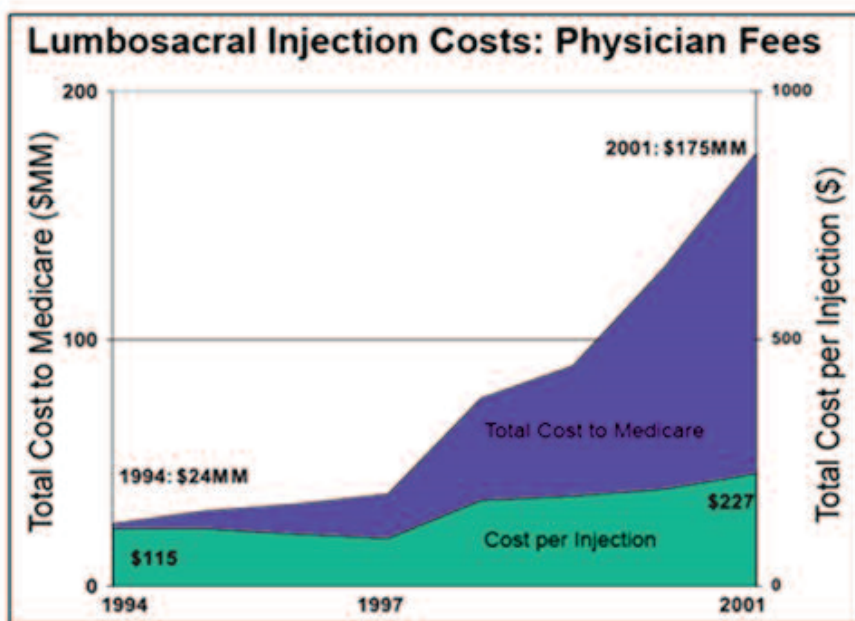


Figure 1: Increase in physician fees.

Friedly et al. 2007

treatments. The place of the interventional pain medicine in an optimistic way is, to be a part of a multimodal approach. It can palliate natural course of disease, can facilitate rehabilitation for chronic pain and sustain a better balance between benefit and risks especially in comparison with surgical techniques. Interventional pain management should adopt a biopsychosocial perspecti-

ve on pain and operate within a framework of multidisciplinary pain rehabilitation to improve its effectiveness. Interventional pain management is progressing despite diversity. Interventional pain management must provide a leading role in the human society, which is afflicted by chronic persistent pain.

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- To improve the treatment, prevention and rehabilitation of pain patients
- To promote research in the field of pain
- To foster and improve excellence in education of health professionals, with traditional and online educational courses and workshops, giving the participants the opportunity to meet and exchange experiences and ideas
- To foster the publication of updated guidelines, best practices, books and journals

FACULTY

- Eli Alon, Zürich (*Anesthesiology*)
- Mirjam Baechler, Luzern (*Chiropractic*)
- Daniel Bärlocher, Zürich (*Psychology*)
- Florian Brunner, Zürich (*Physical Medicine*)
- Stefano Coaccioli, Terni-Perugia (*Rheumatology*)
- Wolfgang Dumat, Nottwil (*Psychology*)
- Dominik Ettl, Zürich (*Dentistry*)
- Karin Fattinger, Schaffhausen (*Internal Medicine*)
- Andreas Gantenbein, Zürich (*Neurology*)
- Michael Hartmann, Zürich (*Anesthesiology*)
- Antje Heck, Aarau (*Cl. Pharmacology*)
- Monika Jaquenod, Zürich (*Anesthesiology*)
- Michael Lottan Tel Aviv (*Anesthesiology, Lawyer*)
- Thomas Maier, St. Gallen (*Psychiatry*)
- Chantal Manz, Basel (*Pharmacy*)
- Antonella Palla, Zürich (*Neurology*)
- Sandro Palla, Zürich (*Dentistry*)
- Daniel Richter, Zürich (*Lawyer*)
- Angie Röder, Winterthur (*Physiotherapy*)
- Wilhelm Ruppen, Basel (*Anesthesiology*)
- Peter Sandor, Zürich (*Neurology*)
- David Scheiner, Zürich (*Gynecology*)
- Dagmar Schmid, Basel (*Psychiatry*)
- Kyrrill Schwegler, Basel (*Psychiatry*)
- Andreas Siegenthaler, Bern (*Anesthesiology*)
- Giustino Varrassi, L'Aquila, Malta (*Anesthesiology*)

To register and for information:

e-mail: paincourse@eulap.org

Number of participants is limited.

Venue: **Hotel Zürichberg**, Orellistrasse, 21

Close ranks against pain!

Monday 11 ●●

10.00-10.15
Opening
E. Alon, G. Varrassi

10.15-10.45
Societal aspects of pain
E. Alon

10.45-11.30
Economical aspects of chronic pain
C. Manz

11.30-12.15
Anatomical and physiological considerations about pain
D. Ettl

•Lunch

13.30-14.15
Opioid treatment of chronic pain patients
M. Jaquenod

14.15-15.00
WHO ladder for chronic pain - still valid?
G. Varrassi

15.00-15.45
Opioid Analgesic dependence
G. Varrassi

•Break

16.15-17.00
Neuropathic pain
A. Gantenbein

17.00-17.45
Chronic pain and psychiatric diseases
K. Schwegler

Tuesday 12 ●●

08.00-08.45
Nociceptive pain
TBA

08.45-09.30
TBA

09.30-10.15
Trust between patient and physician
K. Schwegler

•Break

10.45-11.30
Chronic facial pain
S. Palla

11.30-12.15
Pain anamnesis
S. Coaccioli

•Lunch

13.30-14.15
Pain and emotion
K. Schwegler

14.15-15.00
Multimodal pain treatment
W. Dumat

15.00-15.45
Transcultural aspects of pain
T. Maier

•Break

16.15-17.00
Sleep disorders and chronic pain
D. Schmid

17.00-17.45
Legal aspects of chronic pain
D. Richter

Wednesday 13 ●●●

08.00-08.45
Pharmacokinetics and -dynamics of pain killers
K. Fattinger

08.45-09.30
Paracetamol, NSAIDs and Opioids
K. Fattinger

09.30-10.15
Pathophysiology of headache
P. Sandor

•Break

10.45-11.30
Antidepressants, benzodiazepines, NMDA antagonist
A. Heck

11.30-12.15
Neuroleptics, antiepileptics, steroids
A. Heck

•Lunch

13.30-14.15
Low back pain
S. Coaccioli

14.15-15.00
Fibromyalgia
S. Coaccioli

15.00-15.45
Arthrose of peripheral joints
S. Coaccioli

•Break

16.15-17.00
Physiotherapy
A. Röder
17.00-17.45
Chiropractic
M. Baechler

Thursday 14 ●●●

08.00-08.45
CRPS
F. Brunner

08.45-09.30
CRPS Therapy
W. Ruppen

09.30-10.15
Cancer pain
W. Ruppen

•Break

10.45-11.30
Primary headache
A. Palla

11.30-12.15
Ethics Law und Medicine
M. Lottan

•Lunch

13.30-14.15
Interventional management in cervical and lumbar region
A. Siegenthaler

14.15-15.00
Interventional management in cervical and lumbar region
A. Siegenthaler

15.00-15.45
Neuromodulation and algorithm for interventional therapy
M. Hartmann

•Break

16.15-17.00
Psychological aspects of chronic pain treatment
D. Bärlocher

17.00-17.45
Closing remarks
E. Alon

Educational Grant Supporters





L'analgesia ai tempi dei Faraoni

Chantal Milani ¹, **S. Malagora** ², **Dorotea Paradiso** ³, **Ilenia Ricchitelli** ³,
Francesco Barbangelo ⁴, **Fabrizio La Mura** ⁴

¹ DMD, MS, Antropologo ed Odontologo Forense – Reparto Investigazioni Scientifiche (R.I.S.) di Roma, Arma dei Carabinieri, Italia

² PhD – Direttore Mummy Project, curatore sezione egizia Castello Buonconsiglio

³ Infermiere, Centro di Cure Palliative – Hospice Don Uva – Casa della Divina Provvidenza, Bisceglie

⁴ Servizio di Anestesia, Rianimazione, Terapia del Dolore, Day Surgery – Presidio Ospedaliero di Bisceglie – Trani, ASL BAT

La pratica della medicina trova in Egitto le più antiche attestazioni, oltre a fonti storiche greche e latine. Fin dal 2650 a.C., la figura del medico, sia nell'accezione moderna, sia con connotazioni religiose è documentata con specializzazioni e gerarchizzazioni. Diversi sono i papiri che documentano pratiche mediche di tipo chirurgico (papiro Smith, papiro Hearst, ecc.) o ricette mediche con fini terapeutici di vario genere (p. es., papiro di Londra, Ebers, Chester Beatty, ecc). In essi è attestato l'uso di medicinali di origine vegetale o minerale utili a fini analgesici, sedativi o ipnoinducenti. Allo stesso modo pitture murarie e oggetti rinvenuti in corredi funerari raffigurano piante dalle note proprietà psicotrope.

Molte sono le fonti risalenti all'Egitto antico che fanno riferimento a sostanze dalla funzione sedativa o narcotica: il lattice proveniente da alcune lattughe, il loto, la mandragora e, probabilmente, anche l'uso di componenti del papavero. Il lattucato estratto dai fusti fiorieri della *Lactuca Serriola*, della *L. Sativa*, e della *L. Virosa*, lasciato asciugare, produce una sostanza resinosa dalle proprietà sedative, ipnoinducenti e anafrodisiache, riconosciute anche dalla farmacopea moderna.

La *Mandragora officinarum* la cui radice, contenente iosciamina, atropina e scopolamina, trovava invece impiego come anestetico e sedativo. È raffigurata in pitture murali di varie tombe tebane della XVIII dinastia e le sue bacche sono presenti in cesti rinvenuti nella tomba di

Tutankhamon. La ritroviamo nel papiro di Leida (I-383) dove, miscelata al vino, viene prescritta come ipnoinducente.

La conoscenza del papavero da oppio (*shepen*) pare essere documentato, invece, da rappresentazioni di capsule in monili: un paio di orecchini in oro recanti il cartiglio di Seti II (XIX dinastia, Museo del Cairo), rappresentano la capsula del papavero con la tipica striatura longitudinale; la stessa si trova in una collana di perline di corallina (XVIII dinastia, British Museum). Tali riscontri non sono, tuttavia, di univoca interpretazione e sono oggetto di discussione, a causa della somiglianza della capsula del papavero con i frutti di alcune specie di ninfea o fiordaliso. Un'anforetta appartenente al corredo funerario dell'architetto Kha (Museo Egizio di Torino) è stata più volte oggetto di indagini: nel 1925 il suo contenuto fu sottoposto ad analisi chimiche che individuarono residui di morfina. Tale riscontro non fu confermato da analisi successive, e non venne rilevata la presenza né degli alcaloidi dell'oppio, né degli alcaloidi tropanici (p. es., mandragora, solanacee, ecc.). Il papiro Smith, forse il più antico trattato di traumatologia risalente al 1500 a.C. circa, copia di un documento antecedente, raccomanda l'uso di fiori di papavero rosso per lenire ascessi e piaghe infette. Il papiro Ebers (1550 a.C., lung. 20 m. circa) che raccoglie circa 700 ricette mediche e formule rituali di vario genere, prescrive la capsula di papavero per le eruzioni del cuoio capelluto o per calmare le grida del bambino.

■ ■ Effetti della statistica nella medicina

Il 24 dicembre u.s. veniva pubblicato un articolo inerente al rapporto fra l'arresto di circolo e l'uso di antinfiammatori non steroidei, FANS (1).

Leggiamo una sintesi di questo articolo pubblicata online (2). Incuriositi dai toni allarmistici del comunicato, rispetto ai pericoli da consumo di FANS senza prescrizione medica, siamo risaliti alla fonte, per leggere l'articolo originale.

L'articolo originale, metodologicamente ben fatto, ammette alla fine di avere alcuni bias, per i quali propone anche dei potenziali fattori mitigativi. Ad esempio, evidenza che nel fare lo studio non si disponeva dei dati di consumo dei farmaci OTC. Chiarisce, però, che in Danimarca esiste solo un FANS OTC. Dallo studio in generale emergerebbe una associazione significativa fra uso di FANS (soprattutto alcuni) e arresto cardiaco. Di fatto, dice lo studio, ben l'11% dei pazienti in cui si è verificato un arresto cardiaco extra-ospedaliero, nell'arco dei 10 anni studiati, usava FANS. Peccato che lo stesso studio non ci dica in che percentuale della popolazione totale danese ci sia stata la stessa modalità di utilizzazione di FANS. Infatti, se questa fosse non significativamente diversa dall'11% renderebbe vano l'intero costrutto scientifico su cui la relazione fra uso di FANS e Arresto Cardiaco Extra-ospedaliero viene sostenuto. Infatti, se l'uso di FANS, con le stesse modalità, nella popolazione generale fosse pari a quello della popolazione studiata si potrebbe evincere che l'uso di FANS non è un fattore influente nella insorgenza di arresto cardio-circolatorio extra ospedaliero.

Ancor più pesanti sono le conseguenze di quanto riferito da DottNet. Dalla lettura di quel report, infatti, sembra emergere che, stando ai dati provenienti dalla Danimarca, la vendita di FANS OTC è potenzialmente pericolosissima (peccato che

in quel lavoro non vengono studiati), in quanto associata con arresto cardiocircolatorio extra-ospedaliero in un numero significativo di casi.

In sintesi, sembrerebbe che la lettura più attenta e critica di alcuni lavori scientifici sia sempre consigliabile.

Questo e solo questo ci consente di non diffondere allarmismi o falsi miti, e di fare un lavoro decisamente più utile per il benessere dei malati, specialmente di quelli con dolore. (G.V.)

1) <https://academic.oup.com/ehjcvp/article/3/2/100/2739709/Non-steroidal-anti-inflammatory-drug-use-is?searchresult=1>.

2) <https://www.dottnet.it/articolo/20390/studio-con-gli-antidolorifici-aumenta-il-rischio-di-arresto-cardiaco/?tag=10318078541&tkg=1&cnt=1>

Corso di formazione ECM

DOLORE E LESIONI CRONICHE



FONDAZIONE
Paolo Procacci

TERNI 13 MAGGIO 2017

AULA "CAMILLO VALORI" POLO DIDATTICO UNIVERSITARIO DI TERNI
VIA C. MAZZIERI, 3 - 05100 TERNI

PROGRAMMA

Ore 8.30 Apertura della segreteria ed accreditamento dei partecipanti

Ore 9.00 Saluto delle Autorità

I SESSIONE Moderatore: Stefano Coaccioli

Ore 9.20 Le ferite croniche: onerosa realtà
Fabrizia Toscanella

Ore 9.40 Eziologia delle lesioni croniche
Fabrizia Toscanella

Ore 10.00 Le ferite degli anziani: skin tears e lesioni da decubito
Angela Peghetti

Ore 10.20 Lesioni cutanee e delle mucose
correlate ai trattamenti radio e chemioterapici
Fabio Trippa

Ore 10.40 Discussione

Ore 11.00 Coffee Break

II SESSIONE Moderatori: Giustino Varrassi, Maurizio Evangelista

Ore 11.20 Dolore acuto: fisiopatologia e trattamento
Stefano Coaccioli

Ore 11.40 Dolore procedurale:
prevenzione e trattamento del dolore attraverso la medicazione
Angela Peghetti

Ore 12.00 Ruolo della nutrizione:
sostegno nutrizionale e malnutrizionale dell'anziano
Giuseppe Fatati

Ore 12.20 Discussione interattiva con televoter

Ore 13.15 Compilazione Questionario ECM

Ore 13.30 Fine Lavori

EDUCAZIONE CONTINUA IN MEDICINA

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L'evento ECM n. 3599-189576 è stato accreditato per n. 50 partecipanti presso la Commissione Nazionale per la Formazione Continua per le seguenti figure professionali:

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RESPONSABILE SCIENTIFICO

Prof. Stefano Coaccioli
Professore Associato
in Medicina Interna,
Università degli Studi di Perugia

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