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FONDAZIONE INTERNAZIONALE MENARINI

WITH THE SCIENTIFIC SUPPORT OF

EuLAP
European League Against Pain

NEW FRONTIERS IN CANCER PAIN MANAGEMENT

A PALLIATIVE CARE PERSPECTIVE

SUNTEC SINGAPORE CONVENTION AND EXHIBITION CENTRE

SUNTEC CITY, SINGAPORE

JULY 26th 2017

Chairman:
Prof. Giustino Varrassi

FINAL PROGRAMME and ABSTRACTS

IN CONJUNCTION WITH

APHC 2017
12TH ASIA PACIFIC HOSPICE CONFERENCE
SINGAPORE

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WELCOME LETTER

The 12th edition of the Asia-Pacific Hospice Congress is the perfect occasion to include a workshop on cancer pain and palliative care. The Fondazione Internazionale Menarini with the help of a renowned International Faculty has proposed a workshop titled to remind the potential audience of the border-line between Cancer Pain and Palliative Care. This border has changed in the last few years, and the Hospice is becoming the place to care for patients in their terminal part of life. The approach at the moment is quite different from the one perceived in the past, when the Hospice was a place to avoid, not just for the patients but also for their relatives.

This behavioral revolution is the result of the cultural promotion of the best care for Cancer Pain, which has opened up the discussion on topics that were previously forbidden. We are now prepared, at the International level, to accept the concepts of the terminal care.

Part of this cultural revolution has been the consequence of a better knowledge of the physiopathology of the disease named Cancer and all its consequences, and also of the availability of new drugs. The topics led to be presented by the International Faculty will begin by discussing why patients with cancer have an extremely high prevalence and incidence of pain. Immediately after, other clinical problems will be presented, with a part of the workshop dedicated to the topic of breakthrough cancer pain (BTcP), an aspect which has received increasing attention in the last few years.

Any Specialist in Oncology, Pain & Palliative Care understands that this is often a difficult part of Pain Medicine. For this reason, we thank the generosity of the Fondazione Internazionale Menarini in dedicating a workshop to this important topic. In fact, this is not only important for the better cure of our Cancer Pain patients, but for their better care in general.

Prof. Giustino Varrassi
Responsible for the Scientific Programme

SCIENTIFIC PROGRAMME

Chairman: *Prof. Giustino Varrassi*

08.00a.m.-08.45a.m. **Registration of the participants**

08.45a.m.-09.05a.m. **Opening of the Workshop**
G. Varrassi, European League Against Pain, World Institute of Pain (Italy)
G. Caracciolo, Fondazione Internazionale Menarini (Italy)

09.05a.m.-12.00p.m. **FROM CANCER PAIN TO PALLIATIVE CARE**
Chairs: *Supranee Niruthisard (Thailand), Alex Yeo (Singapore)*

09.05a.m. // The origins of cancer pain
Sam H. Ahmedzai (UK)

09.35a.m. // Assessment of cancer pain
Richard Chye (Australia)

10.05a.m. // History of palliative care and its impact on cancer pain management
Tony O' Brien (Ireland)

10.35a.m.-11.00a.m. *COFFEE BREAK*

11.00a.m. // Ethical aspects in Palliative Medicine
Michael Lottan (Israel)

11.30a.m. // Care of adults in the last days of life
Sam H. Ahmedzai (UK)

12.00p.m.-01.00p.m. *LUNCH*

01.00p.m.-03.00p.m. THERAPEUTIC ASPECTS AND UNMET NEEDS
Chairs: *Nicholas Chua (Singapore), Giustino Varrassi (Italy)*

01.00p.m // Opioid availability and accessibility
Ghauri Aggarwal (Australia)

01.30p.m // Opioid use in cancer pain
Stephan Schug (Australia)

02.00p.m // Managing opioid side-effects
Eli Alon (Switzerland)

02.30p.m // BTcP
John Zeppetella (UK)

03.00p.m.-03.30p.m. *COFFEE BREAK*

03.30p.m.-05.30p.m. THERAPEUTIC ASPECTS AND UNMET NEEDS
Chairs: *Noreen Chan (Singapore), Jee Youn Moon (South Korea)*

03.30p.m. // NSAIDs and NSAIDs combinations
Stefano Coaccioli (Italy)

04.00p.m. // Co-analgesic use in cancer pain management
Paolo Marchettini (Italy)

04.30p.m. // Interface between palliative care and interventional pain medicine in cancer pain management
Magdi Ramzi Iskander (Egypt)

05.00p.m. // Neurolytic blocks in palliative care patients
José Rodriguez Hernandez (Puerto Rico)

GENERAL INFORMATION

WORKSHOP VENUE
The Workshop will be held in Room 331 – level 3
Suntec Singapore Convention and Exhibition Centre
1 Raffles Boulevard, Suntec City, Singapore 039593

SECRETARIAT DURING THE WORKSHOP
The Secretariat will be open at the following times:
Wednesday, July 26, 2017 from 8.00am to 5.30pm.
The Secretariat desk will be located at the Congress Venue, outside Room 331.

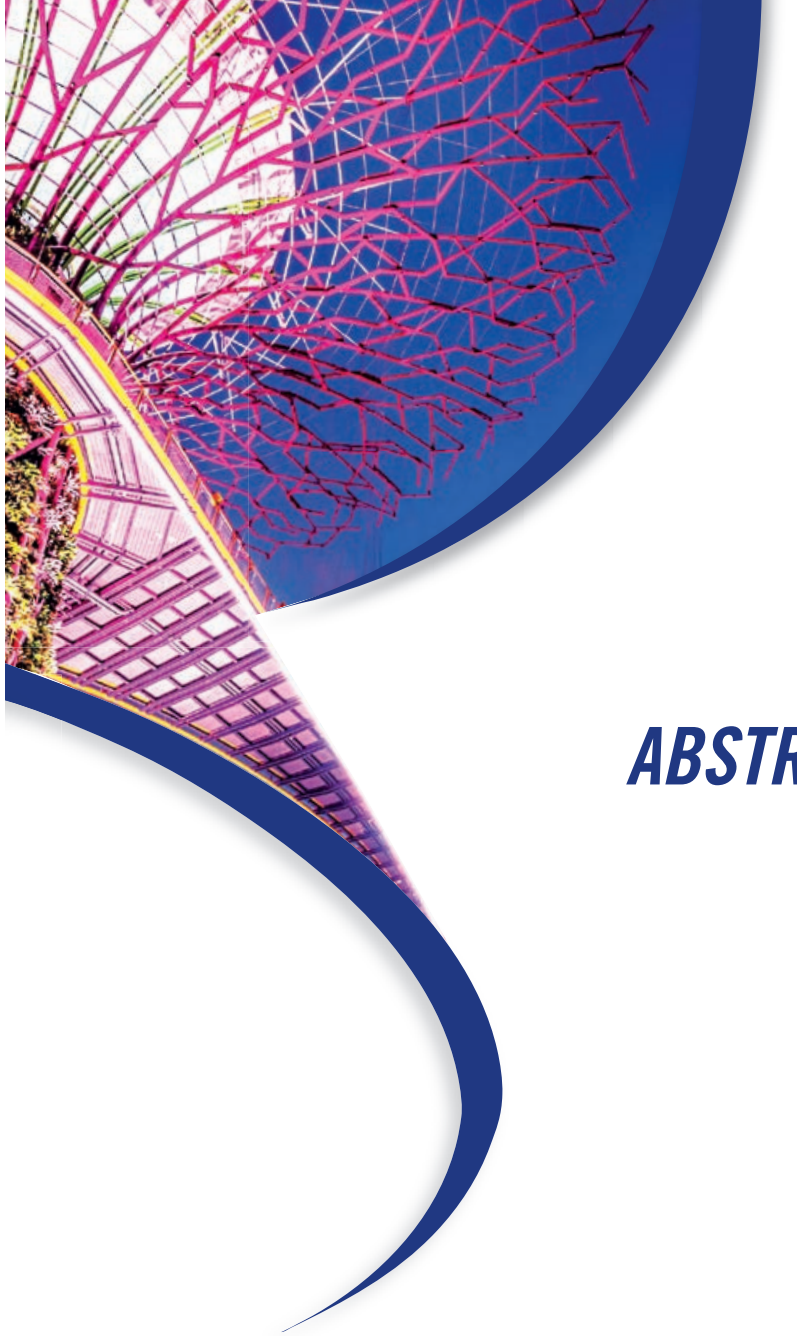
OFFICIAL LANGUAGE
The official language of the Workshop will be English.
Simultaneous translation will not be provided.

REGISTRATION
Registration to the Workshop will be complimentary.
Local attendees could register directly on-site at the Registration Desk.

TECHNICAL FACILITIES
Facilities will be available for computer presentations and overhead projections.
A preview room with PC (Powerpoint for Windows) will be available for check and preview of presentations.
It is essential that speakers take their presentations to the preview room at least one hour before the session starts.

LUNCH AND COFFEE BREAKS
Lunch and coffee break will be served in Room 328-329 for participants regularly registered to the Workshop.

CERTIFICATE OF ATTENDANCE
Participants will receive the certificate of attendance at the Registration Desk.



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ASSESSMENT OF CANCER PAIN

Richard Chye
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Pain is the most feared symptom that a patient with cancer faces. It not only conjures the fear of experiencing uncontrolled pain, but the patient has to also deal with the implications of new cancer pain, as it commonly indicates that cancer is progressing and that treatment is likely not working. Denial or the non-reporting of new cancer pain is common and the assessment and asking the right questions becomes important to ensure good pain control.

Pain management does start with good careful assessment.

1. Believe the patient's complaint of pain
2. Take a careful history of the pain complaint to place it temporally in the patient's cancer history
3. This should include the patient's description of
   a) site of the pain
   b) quality of the pain
   c) exacerbating and relieving factors
   d) its temporal pattern
   e) its exact onset
   f) associated symptoms and signs
   g) interference with activities of daily living
   h) impact on the patient's psychological state
   i) response to previous and current analgesic therapies
4. List and prioritise each pain complaint
5. Evaluate the response to previous and current analgesic therapies
6. Evaluate the psychological state of the patient
7. Ask if the patient has a past history of alcohol or drug dependence.
8. Perform a careful medical and neurological examination
9. Order and personally review the appropriate diagnostic procedure
10. Treat the patient's pain to facilitate the necessary workup
11. Design the diagnostic and therapeutic approach to suit the individual.
12. Provide continuity of care from evaluation to treatment, to ensure the patient compliance and to reduce patient anxiety
13. Reassess the patient's response to pain therapy
14. Discuss advance directives with the patient and the family.

Breakthrough cancer pain has to be additionally assessed by asking the following questions based on our better understanding of breakthrough pain.

A. How quickly does the breakthrough pain start?
B. How long does your BTcP last? Is it 30mins? More than 2 Hrs?
C. Does your breakthrough opioid make you sleepy?

This will help us differentiate which of the immediate release opioids or the rapid onset opioids is required.

Ultimately, the above assessments should provide initial clues to the cause of the pain, and allow the initiation of appropriate analgesia. Appropriate investigations may be required especially if neuro-blockade or anticancer treatment such as radiotherapy have a role as an opioid sparer.

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HISTORY OF PALLIATIVE CARE AND ITS IMPACT ON CANCER PAIN MANAGEMENT - DAME CICELY SAUNDERS (1918 – 2005)

Tony O'Brien
Marymount Hospice, Cork, Ireland - Cork University Hospital, Wilton, Cork, Ireland

We are taught about death by the dying themselves, and as they do so, they show us something about the meaning of life
(Saunders 1962)

The history of modern palliative care and the core principles that underpin our approach to cancer pain management may be traced back to the life of one remarkable English woman who was born on June 22nd 1918, some months before the end of the First World War. Cicely Mary Strode Saunders was the eldest child of an affluent family and based on her own account, she did not have a particularly happy childhood and adolescence. She went to boarding school aged 10 years and struggled to fit in with her peers. Perhaps, this unfortunate experience gave her an understanding of the challenges faced by those who feel isolated or marginalised. Although her preference on leaving school was to become a nurse, her father disapproved of this choice and consequently, with respect for his wishes, Cicely studied politics, philosophy and economics at Oxford. With the advent of the Second World War, Cicely reasoned that she would be of greater benefit to her country by acquiring more practical skills, and this enabled her to pursue training in her preferred profession as a nurse. She therefore left Oxford in 1940 to train as a nurse at St Thomas' hospital, London from where she qualified on June 23rd, 1944.

Cicely revelled in her role as a nurse and it was evident that she had found her true vocation. However, her nursing career was cut brutally short by a recurring severe back problem that forced her to leave the profession she loved so dearly. Cicely returned to Oxford where she began training as a medical almoner (social worker) and qualified in 1947. It was during this period of her life that she developed a strong Christian faith that had such a profound impact on her life course thereafter. Working as a medical almoner at Archway Hospital in North London in 1948, Cicely met and befriended a Jewish Refugee from the Warsaw ghetto named David Tasma. David was aged 40 years and had worked as a waiter. He had an inoperable colorectal cancer and his life expectancy was limited. David had no family in London and very few friends. Over the course of a few short weeks, David and Cicely developed

an intensely close and trusting relationship. They explored the many and varied needs of patients approaching end of life. Writing of this relationship, Cicely recorded:

First of all came the moment in 1948 when David Tasma, a Jewish patient, asked me for comfort. So, respecting his Jewish faith, I said the 23rd psalm and one or two others I knew by heart. When I offered to read to him, he said – 'I only want what is in your mind and in your heart'. It seemed to me as I pondered this later over the years, that his request should be seen as a plea for all the science and learning of the mind, coupled with the vulnerability of one person with another. It looked to the bridge between love and science'.

Together, David and Cicely started to imagine how good, holistic care of the terminally ill might be developed. They spoke of developing a dedicated home for the dying. In his will, David left Cicely a gift of £500.00 and the prophecy 'I'll be a window in your home'. Following David's death, which coincided with the death of Cicely's father, she felt inspired to build a home for dying people, where scientific knowledge would be combined with care and love. She sought advice from a surgeon at St Thomas' Hospital, Mr Norman Barrett, who urged her to study medicine – 'If you want to work with the dying, go study medicine; it is the doctors who desert the dying'. Cicely started her medical studies in 1951 aged 33 years, and qualified in 1957. In her early post graduate years, Cicely worked at St Mary's Hospital, Paddington where she studied pain management in the terminally ill. Concurrently, she also worked at St Joseph's Hospice in Hackney, East London. During these formative years, Cicely learned how to listen attentively to her patients. Her primary motivation when entering medical school was 'to do something about pain'. She described observing how ill patients had to 'earn their morphine' by suffering prolonged periods of pain. She noted how frail, cachectic patients were given parenteral morphine rather than oral morphine. She promoted the concept of oral administration where possible and highlighted the fact that analgesia should be administered in advance of the pain. She identified that pain and suffering are inexplicably linked and that attention must be paid to social, emotional and spiritual dimensions of suffering. She also identified that real progress would be made only on the basis of well-structured and ethically based research. Cicely made detailed records of her experiences using opioids in pain management and published her findings demonstrating the safety and efficacy of morphine.

In parallel with her clinical work Cicely set about securing the necessary funding to open her own institution. In 1967, this dream was realised with the opening of St Christopher's Hospice in South London, the first of the modern teaching and research hospices. Within ten years of graduating in medicine, she had not only opened her own institution, but she had established a new medical speciality. From the outset, Cicely insisted on a fully integrated model of clinical excellence, robust research and quality education. She appointed Dr Robert Twycross as a research fellow and together they published essential principles of cancer pain management throughout the 1980s. The principles of cancer pain management as described by Robert Twycross and Cicely Saunders are as follows:

- Pain is not simply a physical sensation – holistic care / whole-person care is required
- There is always more to analgesia than analgesics
- Undertake a detailed assessment of each patient's pain(s)
- Use analgesics prophylactically to prevent pain
- Use breakthrough analgesia as required
- Administer medication orally whenever possible
- Administer analgesics regularly at a frequency consistent with the drug's duration of action
- Titrate the dose of medication for each individual patient against the clinical response
- Use adjuvant measures, both pharmacological and non-pharmacological
- Follow a simple analgesic ladder:
  - Non-narcotic, e.g. Aspirin
  - Weak narcotic. e.g. Codeine
  - Strong narcotic, e.g. Morphine
- Always prescribe a laxative when initiating an opioid – constipation may be more difficult to control than pain

Dr Robert Twycross contributed to the WHO Cancer Pain Relief guideline which was published in 1986. The experience of Dame Cicely Saunders and Dr Twycross at St Christopher's Hospice are clearly evident throughout this publication.

'Life is above all about learning to love and most of us have merely begun when we die'
C. Saunders

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ETHICS, LAW AND PALLIATIVE MEDICINE

Michael Lottan
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Treatment of palliative patients requires not only a multidisciplinary medical approach, but furthermore, a consideration of the aspects respecting among the rest, human and patients' rights and wills, looked at simultaneously through the perspective of ethical and legal values and aspects, since Palliative Care is one of the most challenging tasks where Doctors and medical personnel are expected to consider in the same time, medical aspects, ethical considerations and legal limits.

It is impossible to get to know all the laws of a country and various aspects of Ethics and Medicine; it is normal that Doctors often have difficulty understanding the terms belonging to other professions.
Dealing particularly with palliative patients Doctors should have notions to understand the principles, the differences, the common, and the meaning of the worlds that constitute the Triangle: Ethics, Law and Medicine.

Medicine has undergone changes due to social and economic events, legal impositions, evolution of informatics and social networks, all influencing the Doctor- Patient relation.
Being required to decide upon life discontinuation, the definition of life and its' expectancy, the Doctor sometimes regarded as a "God", is expected to have a broad multi-professional view, to act as a human and sometimes even….as a Prophet.

This overview, should allow the doctors to extend their perspective from merely medical decisions, to a global approach where lawyers and ethics professionals involvement is required.

In every country, Laws are different, Ethics are in the same time, universal and local.
In this presentation I will expose some principles regarding the differences between Ethics and Law and the interaction between Ethic Law and Medicine that need to be adapted, implemented and extrapolated in medicine in general and particularly with Palliative patients.

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OPIOID AVAILABILITY AND ACCESSIBILITY

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Cancer pain management has evolved over the last few decades with more of an emphasis on the biopsychosocial approach to pain management. Many pharmacological and non-pharmacological measures are available to treat cancer pain effectively. Opioids, however, remain the mainstay of cancer pain management. Their availability and accessibility worldwide is hugely variable (83 % of the world's Morphine use for medical purposes is used by 7 countries only. International Narcotics Control Board, Annual Report 2009).

Cancer is an increasing health care problem: It is estimated that by 2020, there will be 20 million new cases of cancer each year around the world. 70 % of those cases will occur in developing countries. Of patients with cancer approximately 70 % will experience pain that is caused by the cancer or its treatment.

As many more preparations, combinations of opioids with adjuvants and improved opioid delivery systems flood the markets, disappointingly the majority of opioids are available only to a small percentage of developed or high-income countries (US, Canada, Australia and Western Europe). Countries with large populations face the challenges of lack of opioids, opioid phobias, intense drug regulations and lack of governance structures to address these issues. Opioid consumption is often seen as a surrogate for palliative care development in the country. Sadly many parts of Asia, Africa and Eastern Europe continue to have minimal opioid availability and poor consumption per capita. The WHO and United Nations health and regulatory agencies have stressed the priority for effective cancer pain management and appealed to professionals and government organisations to address issues around accessibility and to overcome barriers to opioid analgesic availability.

Pain management as a human right has been the point of discussion and advocacy for a number of years and is taken up by many leading bodies. For example The Declaration of Montreal September 2010: Declaration that Access to Pain Management Is a Fundamental Human Right (International pain summit IASP).

The UN Special Rapporteur on the Right to Health and the UN Special Rapporteur on the question of torture and other cruel, inhuman, and degrading treatment stated: "The failure to ensure access to controlled medicines for the relief of pain and suffering threatens fundamental rights to health and to protection against cruel, inhuman and degrading treatment."

Effective strategies must incorporate education on pain management and opioids to all health care professionals and good communication between clinicians and professional organisations involved in cancer care. Clinicians and these organisations must have an understanding of strategies to manage opioid diversion, addiction and misuse. These barriers must not dictate the closure to opioid availability in countries. Proper governmental processes must be in place for the adequate availability of opioids, their regulation within the country and within its healthcare systems. Two aspects for optimum patient care must be addressed, 'opioid availability' and 'opioid accessibility'. Firstly, national stocks of opioid analgesics and availability from entry into the country to the level of institutional access. Secondly, addressing the patient's ability to receive opioid analgesics not only at large cancer hospitals but importantly into the smaller rural hospitals and the community/ home where patients will spend most of their days. This is an important factor in rural areas and developing countries. Therefore good communication between clinicians working in pain management (pain and palliative care) and government regulators must be developed and strengthened for better equitable access to optimum cancer pain management.

I will explore the issues around availability, accessibility and cancer pain management in focussing on the Asian region, exploring the varied challenges mentioned above. I will describe some of the challenges I've faced in working with a number of countries developing and teaching palliative care in this region, where the availability and access to opioids has been a critical aspect to its successful development.

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OPIOID USE IN CANCER PAIN

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Weak opioids

The World Health Organisation separates in its guidelines weak from strong opioids and advises use of 'weak opioids' if pain is not controlled by non-opioids. Practically, this term refers to a small number of less potent opioids (e.g. codeine, dihydrocodeine and dextropropoxyphene) and tramadol. This recommendation is currently debated; there is increasing support for the omission of this step and direct progression to low-dose strong opioids. However, in many countries, weak opioids are an important option to treat cancer pain in view of poor access to strong opioids. In particular tramadol, a centrally acting atypical analgesic, may play a role here; worldwide availability, low abuse potential, reduced opioid-related adverse events (e.g., constipation) and specific activity in neuropathic pain make it possibly the most useful of the weak opioids. Codeine with its issues related to genetic polymorphism of its metabolism, dextropropoxyphene and dihydrocodeine are not very useful in the setting of cancer pain, as long as other opioids are available.

Strong opioids

The most commonly used 'strong opioids' for the treatment of cancer pain include among others morphine, oxycodone, hydromorphone, methadone, fentanyl, buprenorphine and tapentadol.

There are a number of fears associated with strong opioids including concerns about addiction, excessive sedation and respiratory depression – all of which have been shown to be rather unfounded. Strong opioids can be initiated at any time during the patient' s cancer journey, continued safely, escalated effectively if required and reduced or discontinued if the pain is ameliorated by other means. There is no evidence that the use of strong opioids negatively impacts on survival in cancer patients.

Morphine has been the gold standard for moderate-to-severe cancer pain. However, in recent years, it has become more accepted that the 'right' opioid is the one that works best for an individual patient, is affordable and is well understood by the prescriber. There are few data showing important differences between morphine, oxycodone and hydromorphone, when given by the oral route, and therefore any of these three drugs could be used as the first-choice strong opioid. However, morphine has active metabolites, which are retained in renal failure and can cause toxicity.

Methadone can be another option for cancer pain as it is also a weak N-methyl d-aspartate (NMDA) receptor antagonist and can be considered by experienced practitioners.

Transdermal fentanyl is an effective alternative to oral slow-release opioids; however, systemic drug concentrations may be lower in patients with significant cachexia, reducing its efficacy, and it is not recommended unless opioid requirements are relatively stable. It is preferred by many patients and may result in less constipation. Buprenorphine is a mixed opioid agonist–antagonist, also available in transdermal preparations. It appears to be safer than other opioids in terms of respiratory depression and immune suppression, causes less constipation and does not accumulate in renal failure. Tapentadol is a centrally acting novel analgesic developed for the management of mild-to-moderate pain, successfully used in cancer pain. The reduced μ-receptor affinity confers less opioid-related side effects, mainly of GI origin (nausea, vomiting and constipation) than equianalgesic doses of conventional opioids, while the monaminergic effects enhance efficacy in neuropathic pain.

Starting opioids in cancer pain patients

There is ongoing debate on the method to initiate opioids in cancer pain management, but only limited evidence to support one single approach. Titration of the starting dose is required for patients who are new to strong opioids. The simplest method is to give an oral dose of immediate-release opioid (e.g., morphine 5 mg/oxycodone 5 mg/ hydromorphone 1 mg) every 4 h, with the same dose for breakthrough pain. Once the 24-h requirement seems stable, the patient can be converted to a slow-release oral formulation (given every 12 or 24 h depending on the formulation) or the equivalent strength of a transdermal preparation. Alternatively, opioid titration using sustained-release and immediate-release preparations has been supported. Subsequent to the titration phase, dosage is adjusted according to patient's response. Conventionally, the dose increment is calculated 33 - 50% of average total daily dosage during the preceding few days.

Management of breakthrough pain

Once patients are stabilized on a slow-release preparation, they will continue to require access to an immediate-release, short-acting opioid to manage breakthrough pain. Breakthrough pain is defined as episodic bursts of pain of short duration on the background of stable pain controlled by opioids. Guidelines recommend comprehensive assessment followed by an individualized plan. Commonly the same drug as in the slow-release preparation is given as an immediate-release preparation in a dose of around one-sixth of the daily dose. Transmucosal and intranasal fentanyl preparations are another option for treatment here, as they show rapid onset and short duration of effect; they have been shown to be more efficacious than oral morphine in this setting.

Opioid rotation

Opioid rotation or opioid switching describes the process of substituting a strong opioid

with another strong opioid. The indications are inadequate pain relief and/or unacceptable toxicity despite appropriate titration and attention to the control of expected side effects. The differences in effect between opioids may be due to the phenomenon of incomplete cross-tolerance, active metabolites, the presence of variable responses at multiple μ-receptor subtypes, variations in the pharmacokinetics and effects on non-opioid receptors. The reported success rates of rotation vary from 40% to 80%. For dose calculation of equivalency, conversion tables are being used. Such tables need to be used with caution due to the interindividual variability of response to opioids; to minimize the risk of overdose, dose reduction and clinical judgment is important.

Subcutaneous opioids

If patients require parenteral opioids, the preferred route is by continuous subcutaneous infusion using portable, battery-operated syringe drivers.

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MANAGING OPIOID SIDE-EFFECTS

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Opioid medications are considered key therapeutic interventions in the management of both acute pain and cancer-related pain among patients of all ages; however, their role in treating patients with chronic noncancer pain remains controversial [(1)]. While the debate about the appropriate role of opioids in the treatment of chronic pain continues, the fact remains that many clinicians prescribe opioids to patients in the outpatient setting or treat patients already taking an opioid. These patients include those with acute pain, those receiving palliative care (eg. patients with advanced heart or renal disease), as well as those with persistent noncancer pain disorders, such as postherpetic neuralgia, spinal stenosis, and osteoarthritis. While many factors must be considered when treating the primary care patient receiving an opioid in accordance with clinical practice guidelines [(1,2)], clinical decision-making must take into account the unique considerations for treating older adults, including age-related physiologic changes, multimorbidity, frailty, sensory and/or cognitive impairment, and polypharmacy—all of which can increase the risk for adverse treatment outcomes [(3)].

This review describes four approaches to managing opioid-induced side effects that can be implemented both before and during opioid treatment: dose reduction, opioid rotation, altering the route of opioid administration, and symptomatic management of adverse effects. More than a decade ago, these four approaches were formulated and published by the Expert Working Group of the European Association of Palliative Care (EAPC) with specific attention paid to managing adverse effects of oral morphine; however, this set of guidelines continues to be a timely and valuable resource that can be used to manage the side effects of any opioid analgesic [(4)]. Successful implementation of these approaches can lead to improvements in medication adherence, opioid tolerability, and analgesic effect. A summary of the evidence-based rationales for each approach and our recommendations for how to implement these strategies in the clinical care of geriatric patients are provided.

With the population of older adults in the United States projected to more than double by 2050, the combined impact of acute pain, cancer-related pain, and chronic non-cancer pain can be expected to rise significantly. Opioid medications can provide essential pain relief for many older adults, but the development of bothersome side effects, such as constipation, nausea, sedation, and

pruritus, can significantly impact quality of life and result in patients abandoning treatment altogether. Awareness of common opioid-related side effects and expertise in managing them constitute key components of effective pain care for all patients irrespective of age. These skills are particularly critical when managing pain in the older patient given the established association between advancing age and increased occurrence of treatment-related side effects and older adults' fears regarding the side effects related to opioid use.

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BREAKTHROUGH CANCER PAIN

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Pain management is a central part of the overall care of patients with cancer. However, even when background cancer-related pain is controlled with analgesia scheduled regularly around the clock, some patients will experience transient episodes of pain exacerbation, known as breakthrough pain. Although such episodes are short-lived and self-limiting, the pain is often severe, and can be associated with functional impairment and psychological distress [Zeppetella 2009].

The management of breakthrough pain is aimed at reducing the severity and intensity of episodes, and thus limiting the effect it has on the patient and their quality of life [Zeppetella 2009]. There is currently no universally agreed definition of breakthrough pain. The Science Committee of the Association for Palliative Medicine of Great Britain and Ireland proposed that, "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain" [Davies 2009].

The reported prevalence of breakthrough pain in cancer patients varies from 24 to 95% and there are two main subtypes:

- Spontaneous (idiopathic): the pain occurs without a specific trigger, and can be random and unpredictable.
- Incident: the pain is precipitated by factors that may be volitional (such as movement), non-volitional (such as coughing). [Davies 2009; Zeppetella 2009].

Like other types of pain, breakthrough pain may be nociceptive, neuropathic or mixed. It is estimated that breakthrough pain is somatic in 33–46% of patients, visceral in 20–30%, neuropathic in 10–27% and mixed in 16–20% [Portenoy 1990; Zeppetella 2000]. Breakthrough pain appears to relate to the tumour itself in 70–80% of cases, and to be the result of cancer therapy in 10–20% of patients [Portenoy 1990]. It is often associated with metastases, and in particular bone lesions.

Breakthrough pain can cause patients considerable distress, and can have a negative effect on their quality of life and ability to function. It can cause insomnia, limit the patient's mobility, be associated with psychological problems, and lead to social isolation and difficulty at work [Davies 2009

Breakthrough pain is also associated with increased levels of anxiety and depression [Portenoy 1999].

The effective management of breakthrough cancer pain can confer important benefits to the patient in terms of improvement in quality of life and total pain control. The Science Committee of the Association of Palliative Medicine of Great Britain and Ireland (APM) has made a series of recommendations for the generic management of cancer-related breakthrough pain [Davies et al. 2009]. Although the guidelines are based on limited evidence (i.e. cases series and expert opinion), they provide practical advice on the management of cancer-related breakthrough pain and emphasise the importance of individualised patient management. In addition, the guidelines highlight the role of primary therapies in treating the underlying cause of pain and the importance of symptomatic management, incorporating optimisation of the background (around-the-clock) analgesic regimen, provision of specific 'rescue' analgesia for breakthrough pain and the use of interventional techniques and non-pharmacological methods.

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NSAIDS AND NSAIDS COMBINATIONS

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Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs that provide analgesic, anti-inflammatory, and antipyretic effects [(1)]. The term non-steroidal distinguishes these drugs from steroids, which, among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. Most NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and thereby the synthesis of prostaglandins and thromboxanes [(1)]. It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1 may cause gastrointestinal bleeding and ulcers. NSAIDs are useful in the management of post-operative dental pain following invasive dental procedures such as dental extraction [(2)]. Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the COX-1 and COX-2 [(3)]. Many aspects of the mechanism of action of NSAIDs remain unexplained, and for this reason, further COX pathways are hypothesized. The COX-3 pathway was believed to fill some of this gap but recent findings make it appear unlikely that it plays any significant role in humans and alternative explanation models are proposed. NSAIDs interact with the endocannabinoid system and its endocannabinoids, as COX2 have been shown to utilize endocannabinoids as substrates, and may have a key role in both the therapeutic and adverse effects of NSAIDs, as well as in NSAIDs-induced placebo responses [(4)].

Chirality. Most NSAIDs are chiral molecules (diclofenac is an exception). However, the majority are prepared in a racemic mixture. Typically, only a single enantiomer is pharmacologically active. For some drugs (typically profens), an isomerase enzyme in vivo converts the inactive enantiomer into the active form, although its activity varies widely in individuals. Ibuprofen and ketoprofen are now available in single, active enantiomer preparations (dexibuprofen and dexketoprofen), which offer quicker onset and an improved side-effect profile [(5)]. Dexketoprofen (DKP) is available in a pharmaceutical combination with salt of trometamol that enhances the absorption as well as the speed of action of the entire molecule [(6)].

Fixed Drug Combinations (FDCs). FDCs represents a choice in clinical therapeutic approach where two or more substances are within a single pharmaceutical form [(7)]. FDCs have been increasingly used due to the benefit of the combined effects of active substances

given together. Moreover, the combination of two different molecules provides potential advantages in the field of Multimodal Therapy (MT). MT represents a new way in therapy because it is possible to take advantage by the levels of action of the different molecules. In other words, in pain therapy it is possible to demonstrate such action both at peripheral as well as at central level in order to realize a multilevel approach. An example of FDCs in pain therapy is represented by DKP plus Tramadol in a FDC, where DKP acts at peripheral and central level and Tramadol acts a t central level, so that a MT and a multilevel therapy may be realized [8].

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CO-ANALGESIC USE IN CANCER PAIN MANAGEMENT

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The term “adjuvant analgesic” encompasses drugs originally marketed for indications other than pain and serendipitously found to be useful as analgesics in patients receiving opioid therapy. Over the past three decades, the number, diversity and uses of these drugs have exponentially increased, and nowadays several belong to the first-line therapy for specific types of pain. Consequently, the definition “adjuvant analgesic” has become somewhat of a misnomer, although still commonly applied in the context of cancer pain. Adjuvant is used interchangeably with the term “co-analgesic.”

Opioid therapy remains the paramount resource for treating moderate or severe pain in populations affected by cancer related pain. The multifaceted aspects of cancer pain impose however a more comprehensive management of pain in patients with cancer. The often-overlooked presence of active inflammation requires expertise in the use of the non-opioid analgesics, such as steroids, non-steroidal anti-inflammatory agents (NSAIDs), and acetaminophen (paracetamol).

Glucocorticoids alleviate inflammatory and edematous pain, nausea, fatigue, anorexia, and malaise, and improve overall quality of life. Prescription of glucocorticoids figures in a variety of pains: neuropathic and bone pain, pain associated with capsular expansion, duct obstruction, bowel obstruction, lymphedema, and headache due to increased intracranial pressure. NSAIDs and paracetamol remain the first HMO treatment ladder and they are the mainstay for treating inflammatory pain. Their potentiating effect on the analgesic action of opioids allows opioid sparing and minimization of opioid side effects.

Neuropathic pain benefits more from selected antiepileptic and antidepressant drugs formerly referred to as “adjuvant” analgesics or co-analgesics and nowadays openly recognized as first line treatment for pain caused by injury or disease of the nervous system. The first line analgesic antiepleptics are gabapentin and pregabalin both acting by binding to the alpha-2 delta protein modulator of the N-type, voltage-gated calcium channel. Binding to this protein reduces calcium influx into the neuron, and lessens the likelihood of depolarization. Unlike all other anticonvulsants, gabapentin and pregabalin do not have hepatic metabolism and they have no known drug-drug interactions. The kidneys excrete both drugs, which necessitates dose reduction in the setting of renal impairment. Their main side effects are mental clouding, dizziness, and somnolence; edema and weight gain are less common. The main difference between gabapentin and pregabalin is pharmacokinetic. Gabapentin has saturable transporter in the small bowel and central nervous system and consequently a pharmacokinetic “ceiling”. In contrast,

absorption of pregabalin is not dependent on a saturable transport mechanism; the linear pharmacokinetic profile simplifies dosing of pregabalin compared to gabapentin. Dual acting (serotoninergic and adrenergic) antidepressant are the antidepressants of choice for treating neuropathic pain. Venlafaxine and duloxetine are the most studied dual antidepressants for pain in diabetic neuropathy. In the past, a widely prescribed antidepressant in cancer pain was amitriptyline that allows clinically known opioid sparing. The concomitant presence of anxiety and overt mood depression often requires treatment with generic antidepressant and pure serotoninergic agents have a role in the overall management of cancer pain.

Cancer patients frequently suffer from localized neuropathic pain. The most widely used topical therapies for pain contain local anesthetics: lidocaine 5 percent transdermal patches are widely used for the treatment of focal and/or regional pain of all types. Few short-term, open-label nonrandomized studies conducted in patients with postherpetic neuralgia, and other non-cancer disorders causing chronic pain promote their efficacy. Herpetic and postherpetic neuralgia has higher incidence in cancer patients than in the general population and may improve with topical treatment that spare the systemic side effects of the co-administered drugs. Additionally cancer patients often suffer from localized neuropathic pain due to surgery of radiotherapy and might benefit from the “off label” use of topical lidocaine.

When radiation is not applicable, or for making more bearable the first stages of radiation therapy, bone pain is best treated with a combination of NSAIDs or steroids and bisphosphonates, calcitonin, and bone-seeking radionuclides. Osteoclast inhibitors such as bisphosphonates prevent skeletal fracture, and they may improve pain and quality of life for patients with metastatic bone disease. Bisphosphonates act by directly inhibiting osteoclast activity, stimulating osteoblasts to produce osteoclast-inhibiting factor, and causing osteoclast apoptosis.

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INTERFACE BETWEEN PALLIATIVE CARE AND INTERVENTIONAL PAIN MEDICINE IN CANCER PAIN MANAGEMENT

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Interventional therapy for cancer is effective in severe pain resistant to medical treatment. The edge of the pain is controlled by the proper rational anatomical root/ ganglion block. Pharmacotherapy is maintained and slowly modified after reporting pain relief. Pain assessment is important prior and after any procedure using mainly verbal rating scale/ numerical rating scale.

Sympathetic blocks in early complaint are associated with long duration of pain relief. Local anaesthetic (stellate), neurolytic (coeliac, T2/T3, splanchnic, superior hypogastric, ganglion impar), radiofrequency (sphenopalatine) are all acceptable. Phenol 6-10% is the solution used for neurolytic and no more alcohol - particularly in coeliac - being blamed for paraplegia caused by spinal arteries spasm.

Dorsal root ganglion RF in thoracic region is highly effective and associated with long duration of pain relief in primary lung tumors, mesothelioma, resistant post herpetic neuralgia, and thoracotomy pain.

Somatic blocks (interscalene, suprascapular, …) with low fixed volume pump under observation are practical. Neurolytic subarachnoid phenol injection with a functional tilting table is a simple effective intervention in particular extensive thoracic and pelvic buttock pains specifically in uncontrolled sphincters.

Vertebroplasty and cementing in trained hands for metastatic bony pains are worth mentioning . Combination of blocks (e.g. coeliac and splanchnic) are associated with better prolonged pain relief. Percutaneous cordotomy for one sided extensive visceral/ bony severe pain is resorted to in terminal cases but requires interventional theater (CT & C arm).

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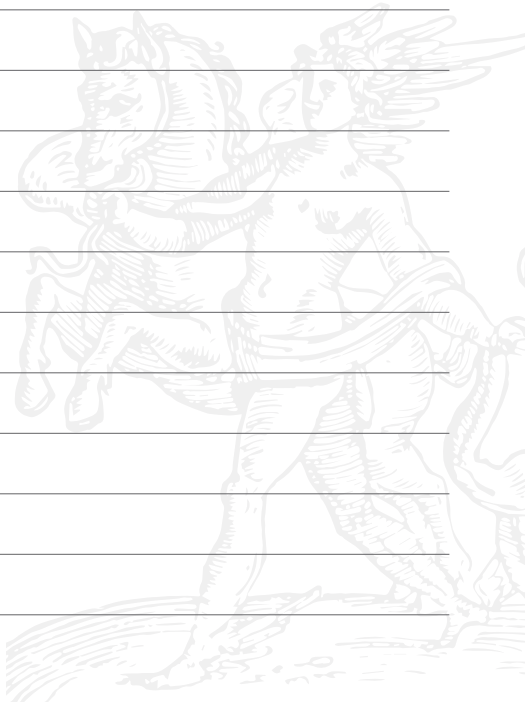
NOTES



DATE AND WORKSHOP VENUE

Wednesday, July 26th 2017
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