Symposium VI

Total Care in Cancer Pain Management

Advances in cancer pain management

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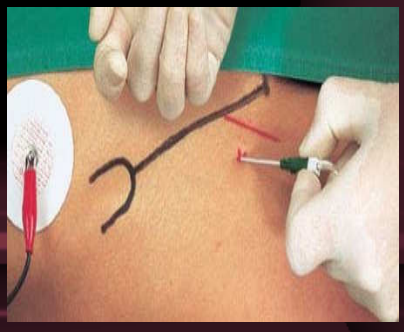
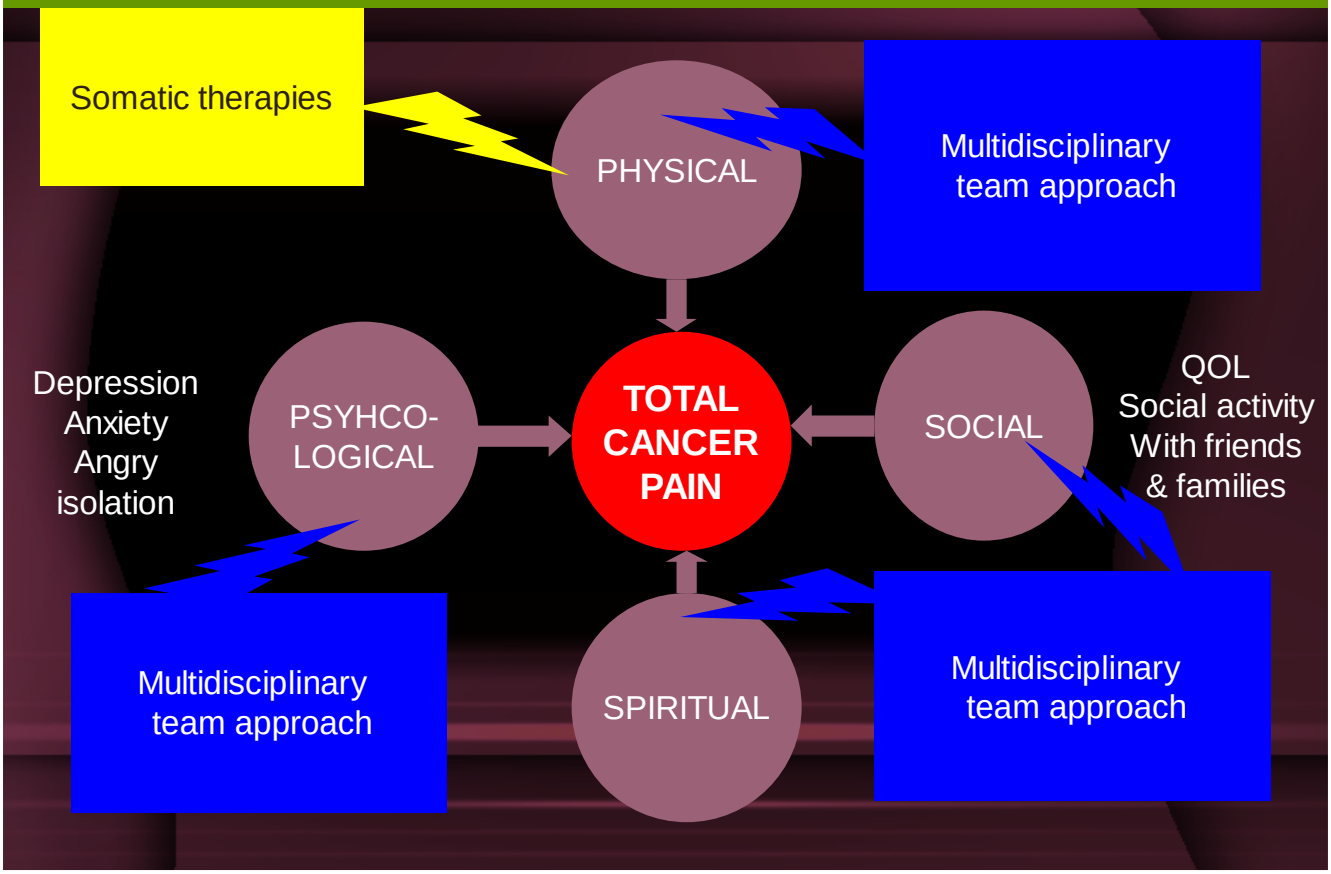
Total Care in Cancer Pain

Pain Assessment

Pain Management



Total Pain Concept



Advances in cancer pain management

Advances in cancer pain

Opioid switching

Breakthrough pain

Neuropathic pain

Use of bisphosphonates in cancer related bone Pain

Role of Cannabinoids in cancer pain

Morphine and alternative opioids in cancer pain: the EAPC recommendations

Expert Working Group of the Research Network of the European Association for Palliative Care

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Summary An expert working group of the European Association for Palliative Care has revised and updated its guidelines on the use of morphine in the management of cancer pain. The revised recommendations presented here give guidance on the use of morphine and the alternative strong opioid analgesics which have been introduced in many parts of the world in recent years. Practical strategies for dealing with difficult situations are described presenting a consensus view where supporting evidence is lacking. The strength of the evidence on which each recommendation is based is indicated. http://www.bjcancer.com

Keywords: morphine; alternative opioids; European guidelines

EAPC Guidelines: Summary Points

1. Morphine is the first choice of strong opioid for moderate to severe pain

   Evidence Grade C

2. Methadone is an effective alternative but it have pronounced inter-individual differences in its plasma half life (17-100hrs), relative analgesic potency and duration of action

   Evidence Grade C

3. Transdermal fentanyl is an effective alternative but is best reserved for patients whose opioid requirement are stable

   Evidence Grade B

A substantial minority of patients treated with morphine (10-30%) do not have successful outcome because of:

1. Intolerable adverse effect – CNS, GI
2. Inadequate analgesic even rapid increase the dose of opioids
3. Combination of both

Opioid Switching

become one of the common practice in Palliative Care

What is Opioid Switching ?

Is defined as the practice of converting a patient from one opioid to another,

aimed at finding the most favorable balance between analgesic and side effects

Cochrane review on opioid switching to improve pain relief and drug tolerability

Quigley C. Cochrane Review 2009

- 52 reports identified, comprising 23 case reports, 15 retrospective studies, 14 prospective uncontrolled studies.
- Majority use morphine as first line opioid and most frequently used second-line opioid was methadone
- All reports apart from one, concluded that opioid switching is a useful clinical manoeuvr for improving pain control and reduce opioid-related side effects

Conclusion:

- For patients with inadequate pain relief and intolerable opioid-related toxicity, a switch to an alternative opioid may be the only option for symptomatic relief
- However evidence to support the practice of opioid switching is largely anecdotal or based on observational and uncontrolled studies
- Randomised trial including studies where a patient acts as their own control are needed to
  1. Establish the true effectiveness of this practice
  2. To determine which opioid should be used as first line or second line
  3. To standardise conversion ratio

Morphine-Methadone Opioid Rotation in Cancer Patients: Analysis of Dose Ratio Predicting factor

MA Benitez-Rosario, et al

J Pain Symptom Management, 2009;37(6), 1061-1068

Evaluate potential predictive factors of Morphine-Methadone dose ratio (MMEDR) in a cohort of cancer patients who underwent opioid switching because of uncontrolled pain and/or morphine side effects

MMEDR predicted from Multivariate Linear Regression Analysis

Reason for rotation	Previous oral morphine dosage	MMEDR
Side effects of Morphine	>300mg/day	9.1:1
Pain	> 300mg/day	4.9:1
Side effects of Morphine	<300mg/day	5.6:1
Pain	<300mg/day	3:1

Postulated mechanism

- Incomplete cross tolerance with previous opioids, which make methadone more potent than anticipated
- Hyperalgesic state induced by previous chronic opioid (morphine) used
- NMDA antagonist characteristics of methadone make methadone more potent when doing switching

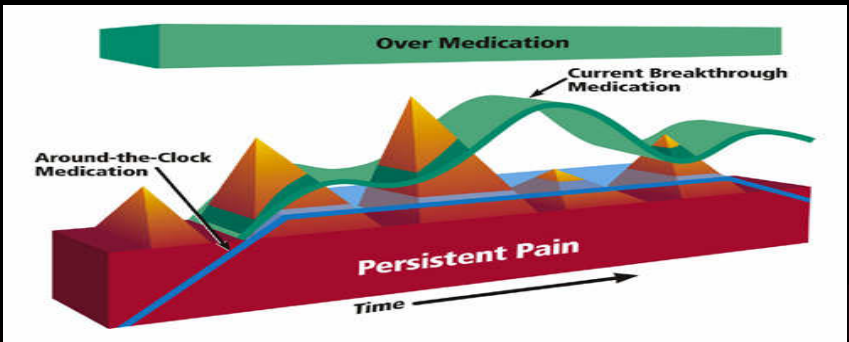
Challenges in Cancer Pain Management

Breakthrough Pain

Neuropathic Pain

Breakthrough pain

- Abrupt, short lived and intense pain that “breaks through” the around the clock analgesia that control persistent pain



IDEAL MEDICATIONS:
Rapid onset, short acting, easy administered

Breakthrough Pain – Recent Review

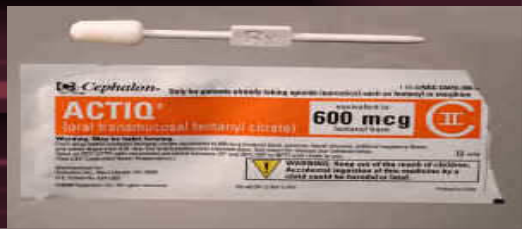
A review on use of opioids for management of breakthrough pain in cancer patient included:

- 4 randomised control studies with 393 participants,
- all studied the efficacy of transmucosal fentanyl citrate (OTFC) compared to placebo and morphine

Cochrane database of systemic review, 2005

Oral Transmucosal Fentanyl Citrate (OTFC)

- OTFC consists of a fentanyl impregnated sweetened and hardened lozenge on a plastic handle and designed for breakthrough pain
- Rapid onset 5-15 min, short duration of action of around 2 hrs
- 6 doses available 200, 400, 600, 800, 1200 and 1600mcg available



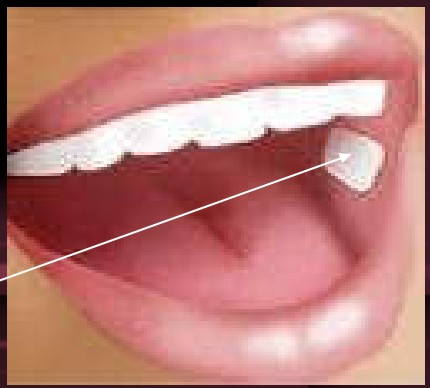
Results

- OTFC was superior to (1) placebo, (2) normal release morphine, (3) previous rescue medication in providing breakthrough pain relief at 15min and 30min.
- Successful dose of OTFC is determined by titration
- Mean dosage of successful OTFC varies from 587mcg to 811mcg (+/- 335 to 468mcg)
- No relationship between the successful dose of OTFC and the total daily around the clock opioid

Cochrane database of systemic review, 2005

New preparation – Fentanyl Buccal Soluble Film (FBSF)

- Fentanyl Buccal Soluble Film (Onsolis)
- FDA approved product for breakthrough cancer pain in 2009
- 5 doses strength available - 200mcg, 400mcg, 600mcg, 800mcg and 1200mcg
- Place the FBSF inside the cheek, it will dissolves 15-30min
- Rapid onset – within 3min
- Duration of action – 2 hr



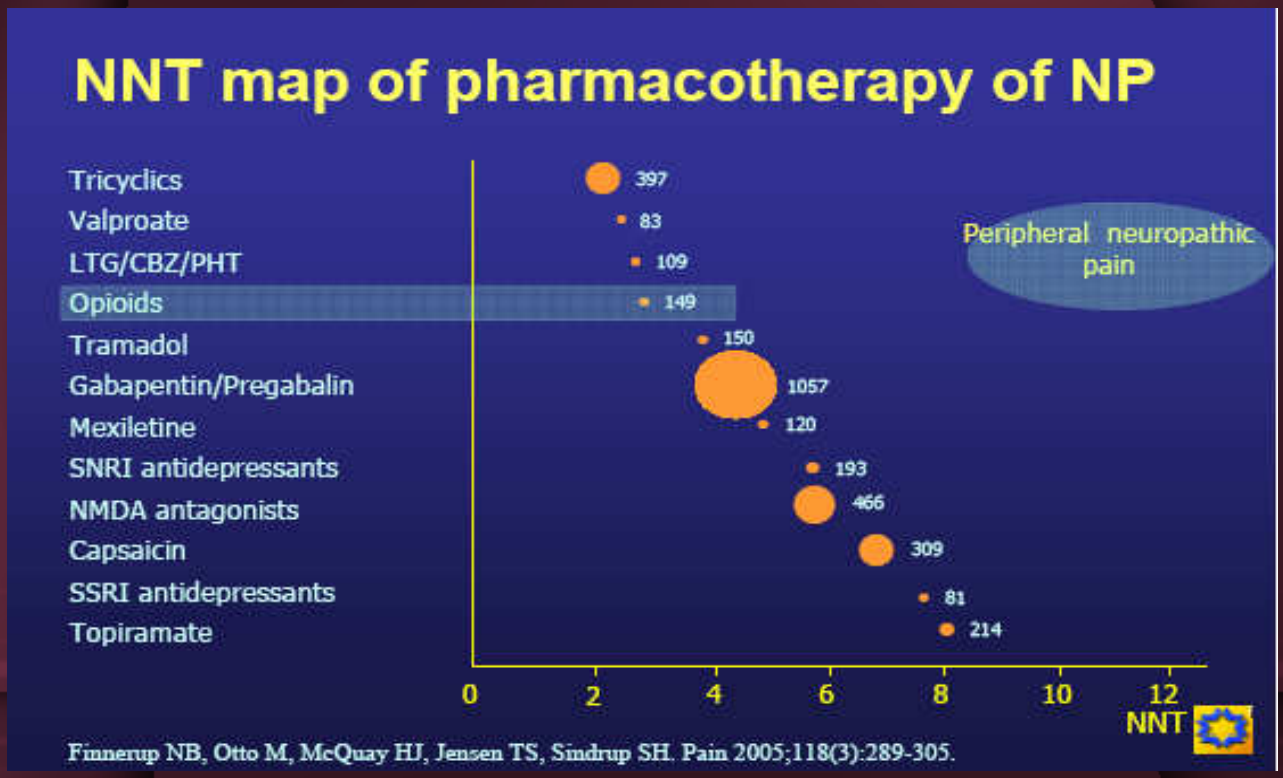
Neuropathic pain in cancer patient

Systemic review on pharmacological treatment on neuropathic pain

Search for studies on neuropathic pain related to cancer

Drug		Proposed machanism of action
Anti-depressant	TCA SNRI	Inhibition of serotinin & norepinephrine reuptake
Opioid	Opioid	Modulates the perception of pain via opioid receptor
	Tramadol	Acts through both u opioid receptor & inhibit uptake of norepinephrine
Anti-convulsant	Carbamazepine	Modulation of high voltage activated Ca channels
	Valproate, lamotrigine, carbamaepine	Blockade of voltage-gated sodium channels
	Gabapentin, pregabalin	Modulates voltage-gated Ca channels via binding to $\alpha_2\delta$ subunit of presynaptic neurons
NMDA antagonist	Ketamine, dextromethorphan, memantine, and amantadine	NMDA antagonist Modulate u opioid receptors, inhibits serotonin & nor epinephrine uptake
Topical anesthetic	Lidocaine patch	Acts by blocking sodium channels thereby reducing ectopic nerve impulses

Pharmacotherapy of Neuropathic pain



Antidepressant – Cancer Pain

Only few clinical trials have specifically evaluated the use of antidepressant and anticonvulsant for cancer pain, results are controversial.

Kalso E, et al. Pain, 1996
Mercadante S, et al. Tumori 2002
Tasmuth T, et al, Pain 2002
Reuben SS et al. Journal of Pain and Symptom management 2004
Cochrane Database of systematic Reviews, 2005

Neuropathic Pain:

Is Methadone superior to Morphine ?

- Methadone also has NMDA receptor activity as an antagonist
- No trial evidence to support the postulation that methadone has a particular role in neuropathic pain of malignant origin

Cochrane Database of systematic Reviews, 2008

Ketamine – Cancer Pain

- Only limited studies on use of ketamine in subanesthetic dose for neuropathic pain in cancer patients, most of studies were case reports
- Latest Cochrane Review 2009 identified only 4 RCTs. Only two were included (Yang 1996, Mercadante 2000)

Original Article

Analgesic Effect of Intravenous Ketamine in Cancer Patients on Morphine Therapy: A Randomized, Controlled, Double-Blind, Crossover, Double-Dose Study

Sebastiano Mercadante, MD, Edoardo Arcuri, MD, Walter Tirelli, MD, and Alessandra Casuccio, BS

Anesthesia and Intensive Care Unit, Pain Relief and Palliative Care Unit (S.M.), La Maddalena Clinic for Cancer, and Pain Relief and Palliative Care Program (S.M.), SAMOT, Palermo; Department of Pain Therapy and Intensive Care (E.A., W.T.), National Cancer Institute Regina Elena, Rome; and Department of Hygiene and Microbiology (A.C.), University of Palermo, Palermo, Italy

Journal of Pain and Symptom Management 2000;20:246

- 10 Patients with KPS 50 or above
- Pain not controlled by morphine. No adjuvant drugs.
- In slow iv bolus over 30 min: Ketamine **0.25mg/kg** or **0.5mg/kg** or **saline**
  - Each subject will receive all the three treatments in randomized order
  - Given on 3 separate days, at least 2 days apart
- Evaluated at T0, T30, T60, T120, T180 for pain and side effects

Results: Pain intensity significantly decrease since T30 till T 180
More effective at higher dose, but more drowsiness in higher dose

"Burst" Ketamine for Refractory Cancer Pain : An Open-Label Audit of 39 Patients

Jackson K. et al. *Journal of Pain and Symptom Management* 2001:22(4):834

- Prospective, multicenter, unblinded
- Pain not controlled by opioid with adjuvants
- Pain score >3 on a 0-10 VRS
- Burst ketamine infusion for 3 to 5 days in doses of 100mg to 500mg

Results:

67% had 50% decrease in pain intensity or reduction in opioid dose
After cessation of ketamine 70% maintain good control up to 8 weeks
12 reported psychomimetic S/E like hallucinations, drowsiness and dizziness

Ketamine – Cancer Pain

Current evidence is insufficient to assess the benefits and harms of ketamine in neuropathic pain management due to limited randomized control trials

Cochrane Database of systematic Reviews, 2009

Use of bisphosphonates in cancer related bone pain

Generation of bisphosphonates

1. Clodronate – oral (limited by GI side effect), iv
2. Pamidronate – iv doses range from 60-90mg over 2hrs every 3-4 weeks
3. Zoledronic acid – iv doses 4-8mg over 15 min every 3-4 weeks
4. Ibandronate (New generation) – oral 50mg daily, iv 6mg over 1hr every 3-4 weeks

Focus on:

- Evidence of use of zoledronic acid and Ibandronate on prevention of skeletal-related events and bone pain

Efficacy of zoledronic acid in patients with various tumor types

Jean-Jacques Body, Support Care Cancer, 2006

Endpoint	Breast cancer and multiple myeloma (25 months)		Hormonal-refractory prostate cancer (24months)		Lung and other solid tumors (9 months)	
	Zoledronic acid, 4mg (n=561)	Palmidronate, 90mg (n=555)	Zoledronic acid, 4mg (n=214)	Placebo (n=208)	Zoledronic acid, 4mg (n=257)	Placebo (n=250)
Primary Patients with >/=1 SRE (%)	47	51	38	49 p=0.028	38	44 P=0.127
Secondary Time to first SRE (days)	376	356 P=0.151	488	321 P=0.009	230	163 P=0.023
Skeletal morbidity rate (SMR)	1.04	1.39 P=0.084	0.80	1.49 P=0.006	2.24	2.73 P=0.017

SRE : Pathological fracture, spinal cord compression, RT to bone and surgery to bone
SMR: Mean annual incidence of skeletal related events

Zoledronic acid: Prevention of SRE

- Zoledronic acid 4mg iv shown evidence of effectiveness of SRE reductions in breast cancer, multiple myeloma, prostate cancer, lung and other solid tumor.
- Whereas previous generation of bisphosphonate (clodronate and palmidronate) only shown efficacy in breast cancer and multiple myeloma

Jean-Jacques Body, Support Care Cancer, 2006

Zoledronic acid: Effect on bone pain

- In patient with breast cancer and bone metastasis, significant difference in pain score treated with zoledronic acid Vs placebo (p=0.0004)
- In patient with bone pain due to other primary, zoledronic acid had NO significant effect

Jean-Jacques Body, Support Care Cancer, 2006

Ibandronate: Prevention of SRE

- Iv Ibandronate (6mg over 1-2 hr) and oral ibandronate (50mg qd), significantly↓skeletal morbidity period (p=0.004) and risk of SRE (40% and 38%, p = 0.003 and p< 0.001 respectively) in patients with breast cancer and bone metastasis

Body JJ, et al. Ann Oncol, 2003
Body JJ, et al. Br J Cancer, 2004

Ibandronate: Prevention of SRE

- A trial included 73 patients with colorectal cancer metastasis to bone:
  - treated with iv ibandronate 6mg
  - significant lower proportion of patient with SRE
  - (39 Vs 78% for placebo, p =0.019)

Heres P et al. EUR J Cancer Care, 2007

Ibandronate: Effect on bone pain

- Both iv and oral ibandronate shown significant reduction in bone pain score compared with placebo ($p < 0.001$) in breast cancer with bone metastasis

Diel IJ, et al. Eur J Cancer, 2004
Body JJ, et al. Pain, 2004

High dose Ibandronate: Effect on bone pain

- Open labelled trial of 18 patients with opioid - resistant bone pain due to various primary tumor:
  - 4mg iv ibandronate x 4 consecutive days,
  - leading to significant reduction in bone pain scores within 7 days ($p< 0.001$)
  - Pain reduction effect sustained for 6 weeks

Mancini I, et al. J Clin Oncol, 2004

Can bisphosphonate recommended as first line therapy for bone pain ?

A review included 30 randomised controlled studies of 3682 patients with bone metastasis from different primary tumors:

- evidence to support effectiveness of bisphosphonate in providing some pain relief for bone metastasis but insufficient evidence for immediate effect or as first line therapy
- It should only be considered when other analgesic and RT are inadequate for pain control

Cochrane Database of systematic Reviews, 2008

What are cannabinoids and how do they function ?

- Cannabis contains 60 or more cannabinoids (CBs)
- Two active components shown evidence in relieving cancer related pain
  - Delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
- Act through specific CB receptors:
  - CB1 : distributed in CNS
  - CB2 : associated with cells and tissues related to immune system

Pharmacological effects of THC and CBD

Pharmacological effect of THC
Analgesia
Muscle relaxation
Antiemesis
Appetite stimulant
Psychoactivity

Pharmacological effects of CBD
Analgesia ? through anti-inflammatory and immunomodulatory effect
Muscle relaxation
Neuroprotective effects
Anticonvulsant
Anxiolytic effects
Reduce psychoactive effects of THC

Original Article

Journal of pain and Symptom Management, 2010

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

- Multicenter, double-blind, randomized, placebo controlled trial
- Total 177 patients with cancer pain,
- who experienced inadequate analgesia (NRS >4)
- despite chronic opioid dosing,
- random assigned to 3 groups (THC: CBD, THC extract, placebo)
- self titrate to optimal dose dose during 1st week

	THC:CBD extract (Sativex) N= 60	THC extract N= 58	Placebo (N=59)
Change from baseline mean pain NRS	-1.37 P=0.014	-1.01 P=0.245	-0.69
% of patients had > 30% pain reduction in intensity	43% P=0.006	23% P=0.28	21%
Median dose of background opioid medications	79% no change	77% no change	80% no change
Change from baseline the number of breakthrough opioid	56% no change	56% no change	63% no change
Adverse effect	Mild to moderate somnolence , dizziness and confusion, similar in all 3 groups		

Conclusion

- This study concluded the THC: CBD extract is a useful adjunctive treatment for relief cancer pain
- However the role of CBD in cannabis preparation is still unclear
- Further studies are warranted

What is Sativex (THC:CBD)

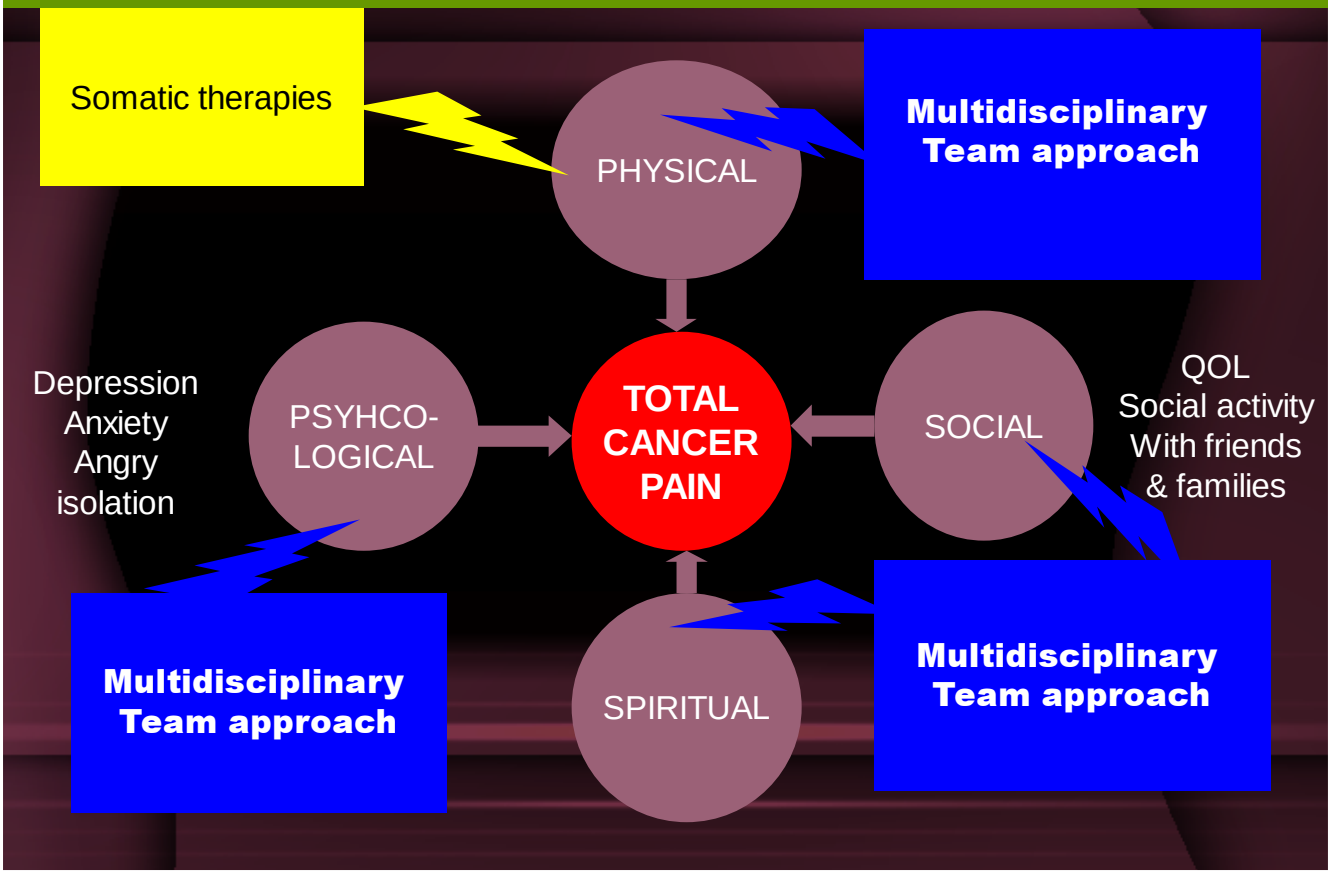
- Sativex is an oromucosal spray
- 1 spray contain 2.7mg THC and 2.5mg CBD
- Approved in Canada for adjunctive analgesic treatment in patient with advanced cancer pain despite highest tolerated strong opioid in 2007
- Not approved by FDA

No matter how advance in pharmacology

The key for good cancer pain control, should include detail Pain Assessment

&

Total Pain Concept



Methadone Versus Morphine As a First-Line Strong Opioid for Cancer Pain: A Randomized, Double-Blind Study

Eduardo Bruera, J. Lynn Palmer, Snezana Bosnjak, Maria Antonieta Rico, Jairo Moyano, Catherine Sweeney, Florian Strasser, Jie Willey, Mariela Bertolino, Clarissa Matthias, Odette Spruyt, and Michael J. Fisch

A B S T R A C T

Purpose
To compare the effectiveness and side effects of methadone and morphine as first-line treatments with opioids for cancer pain.

Patients and Methods
Patients in international palliative care clinics with pain requiring initiation of strong opioids were randomly assigned to receive methadone (7.5 mg orally every 12 hours and 5 mg every 4 hours as needed) or morphine (15 mg sustained release every 12 hours and 5 mg every 4 hours as needed). The study duration was 4 weeks.

Results
A total of 103 patients were randomly assigned to treatment (49 in the methadone group and 54 in the morphine group). The groups had similar baseline scores for pain, sedation, nausea, confusion, and constipation. Patients receiving methadone had more opioid-related drop-outs (11 of 49; 22%) than those receiving morphine (three of 54; 6%; $P = .0159$). The opioid escalation index at days 14 and 28 was similar between the two groups. More than three fourths of patients in each group reported a 20% or more reduction in pain intensity by day 8. The proportion of patients with a 20% or more improvement in pain at 4 weeks in the methadone group was 0.49 (95% CI, 0.34 to 0.64) and was similar in the morphine group (0.60, 95% CI, 0.47 to 0.73). The rates of patient-reported global benefit were nearly identical to the pain response rates and did not differ between the treatment groups.

Conclusion
Methadone did not produce superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first-line strong opioid for the treatment of cancer pain.

J Clin Oncol 22:105-102. © 2004 by American Society of Clinical Oncology

Methadone Vs Morphine as a first line strong opioid for cancer pain: A randomized, double-blind Study

Bruera E, et al. Journal of Clinical Oncology, 2004

A total of 103 cancer patients were randomly assigned to methadone group and morphine group

Methadone group	Morphine group
49 patients	54 patients
Methadone 7.5mg bd orally	SR morphine 15mg bd orally
Methadone 5mg q4h prn	Immediate release morphine 5mg q4h prn
70% reported more than 20% improvement in pain at 4 weeks	70% reported more than 20% improvement in pain at 4 weeks
22% opioid-related drop outs	6% opioid-related drop outs (p=0.019)

Methadone Vs Morphine as a first line strong opioid for cancer pain: A randomized, double-blind Study

Bruera E, et al. Journal of Clinical Oncology, 2004

Conclusion of the study:

Methadone did not produce superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first line strong opioid for cancer pain

Conversion ratio morphine → Methadone

- A dose ratio when switching from morphine to methadone varies widely in different studies from 16:1 to 2.5:1

Pereira J, et al. J Pain Symptom Manage, 2001

- Conversion regime:
  - Fixed dose ratio
  - Ad Libitum

Total daily oral dose of morphine (EDDM) before conversion	Morphine: Methadone ratio
30 - 90mg	4:1
90 - 300mg	8:1
> 300mg	12:1

Mercadante S, et al. J Clini Oncol 2001: 19 (11): 2898-2904

Ad Libitum

D Tse, et al. Pall Med, 2003; 17: 206-211

- A fixed dose of methadone, 1/12 of total daily oral dose of morphine (EDDM), up to 30mg per dose of methadone was given to patient Q3h PRN when patient rated pain as moderate or above in severity
- Ad libitum prescription continues until the demand for methadone reduce or stabilise
- Calculate total daily dose of methadone and then divided to be given bd or tds
- If pain not controlled after 1 week on regular bd/ tds dose of methadone, methadone increased by 50% according to the same time schedule

Rationale: high variable pharmacokinetics, difficult to have fixed ratio

Gabapentin – Cancer Pain

- Gabapentin also demonstrated to have beneficial analgesic effect in neuropathic pain specifically related to cancer
- A multicentre, randomized, double-blind, placebo controlled trial included 121 patients with neuropathic pain due to cancer found significant difference of pain intensity between gabapentin (600-1800mg/d) and placebo group, p = 0.025.

Caraceni A, et al. Journal of Clinical Oncology, 2004

Zoledronic acid: Effect on Renal function

- Adverse Event Reporting System of US FDA:
  72 cases of renal dysfunction associated with zoledronic acid were identified from Aug 01 to March 03
- Of 72 patients, 27 required dialysis and 18 died

JT Cheng, et al .N Eng J Med, 2003

Warning of nephrotoxicity
and restrictions for patient with
varying degrees of renal impairment
was updated in product label

Ibandronate: Effect on renal function

- Results from clinical studies demonstrated that ibandronate has a renal safety profile comparable with placebo
- No dosage adjustment is required in mild to moderate renal impairment
- Renal function monitoring is not mandatory at physician's direction

Summary

- Strong evidence suggested the use of bisphosphonate on prevention of skeletal complication in multiple myeloma and breast cancer with bone metastasis
- No consensus on its use in other tumor
- Bisphosphonate can be used for pain relief in bone metastasis but it should be considered as adjunct to other analgesic or RT

Summary

- Zoledronic acid is the first bisphosphonate demonstrated to have beneficial effect in reduction of SRE in patient with bone metastasis from lung and other solid tumor other than breast cancer and multiple myeloma
- Ibandronate is available in both iv and oral form which shown beneficial effect in reduction of SRE and pain score in breast cancer with bone secondary.
- Use of intense and high dose of ibandronate in severe and refractory bone pain need further investigation