Guide to Pain Management

NATIONAL CANCER INSTITUTE

MIDDLE EAST CANCER CONSORTIUM
MECC

Shaare Zedek Medical Center

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Treatment of Cancer Pain

This Guide is intended to help medical staff to provide effective treatment by setting out basic rules for diagnosis together with quick and succinct information about medication suitable for treating chronic pain in general, and cancer pain in particular.

Pain is one of the most common symptoms among cancer patients. Research shows that pain appears in 30% of patients in the active stage of treatment, and in two thirds of patients in advanced stages of the disease[1-6].

Exacerbation of pain severely impairs the quality of life and physical and mental functioning of the patients, as well as their relationships with family and friends. Good control of cancer pain by medication therapy can be achieved in 90% of patients . Only a minority of patients will need treatment by sophisticated invasive methods. Effective pain management is based on basic knowledge of the pathophysiology of pain, the ability to diagnose the pain syndrome, familiarity with existing therapeutic methods, and communication with the patient and his family. All this knowledge is essential for selecting the correct treatment choice. The primary rule in medication therapy for pain management is that the medicine must be adjusted to pain severity according to the analgesic scale developed by the World Health Organization (Diagram 2). At the end of this Guide is a list of recommended sources for reading on the subject.

The recommended therapeutic approach:

* Ask about pain routinely and assess pain systematically.
* Believe that the patient and his family are giving a reliable report of the pain and the degree of relief.
* Choose the treatment option that is most suitable for the patient, his family and the framework in which he lives.
* Treatment must be timely, logical and coordinated.
* Allow the patient and his family to be partners during the course of the treatment.

Barriers to the treatment of pain originating in cancer:

I. Problems associated with the attending staff:

* Lack of knowledge in the field of pain management
* Inadequate pain assessment
* Reservations related to legal restrictions
* Fear of addiction
* Fear of side effects
* Fear of developing tolerance and loss of efficacy

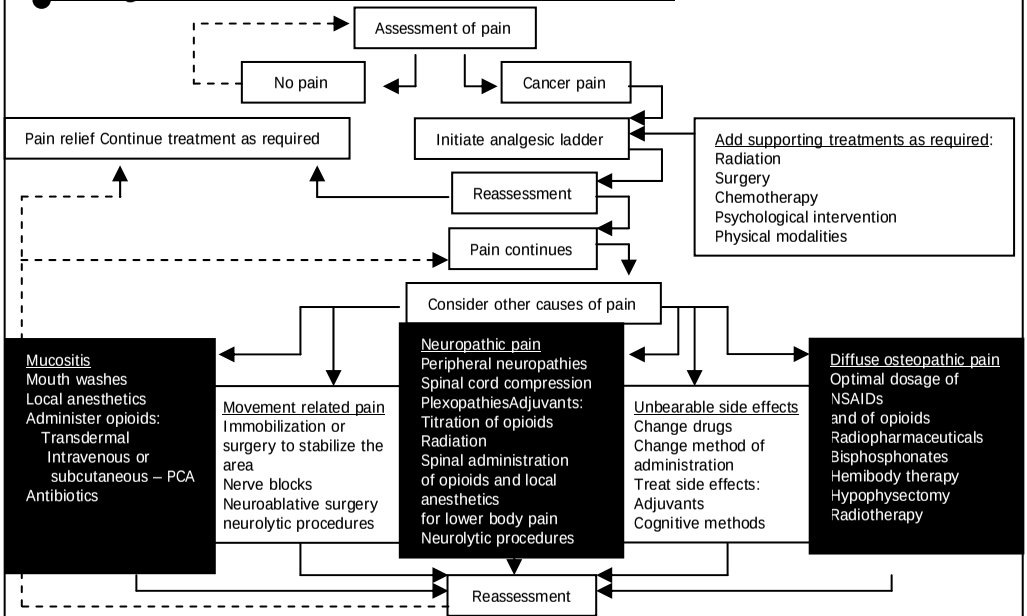
II. Problems associated with the patient:

* Reservations about reporting pain
* Fear that the pain indicates disease progression and worsening
* Fear of being a “bad patient”
* Reservations about taking medications and the accompanying status
* Fear of addiction
* Fear of untreatable side effects
* Fear of developing tolerance to the medicine

III. Problems associated with the health system:

* Low priority for treatment of cancer pain
* Lack of suitable remuneration
* Legal restrictions on controlled medications
* Availability of medications and treatments

Diagram 1: Flow Chart for Treatment of Pain



Pain assessment:

Inadequate assessment of pain may lead to sub-optimal treatment. Assessment of pain involves the doctor, the nurse and the patient, and it must take place:

* At fixed intervals upon treatment initiation;
* Whenever the patient reports pain;
* At suitable intervals after pharmacological or other intervention, for example 15-30 minutes after parenteral administration of medication or an hour after oral administration of medication.

Assessing the cause or the reason for pain is essential for providing treatment. Doctors treating cancer pain should recognize the most common symptoms of pain due to peripheral neuropathic pain. Early diagnosis and treatment of these symptoms can reduce the morbidity associated with unrelieved pain.

Preliminary assessment:

The purpose of the preliminary assessment is to characterize the pain by its location, intensity and cause/ source.

The elements of the preliminary assessment:

* Detailed medical history
* Physical examination
* Psychosocial evaluation
* Diagnostic evaluation: the stage of the disease and the aims of treatment

Self report of the patient:

Self report of the patient is the central component of pain assessment. In order to improve the quality of pain treatment in all frameworks, therapists must teach the patients' families to use pain assessment tools at home, and assist patients in describing their pain.

Pain: listen to the patient's description of the type of pain (burning, stabbing, stinging, etc.) and its causes. Examples of descriptive and numerical scales for self reporting on the intensity of pain are given on page 10 of this guide.
Location: with the patient's help, find the exact location of the pain. A diagram of a body, like the one on page 10, can be used for assistance.
Intensity and frequency: encourage the patient to keep a pain journal, in which he documents the intensity of pain in the intervals between visits (particularly in the case of ambulatory patients).
Factors that alleviate or intensify the pain: document the response to treatment in the medical file.
Cognitive response to pain: note behaviors that indicate pain in a patient who has cognitive impairment or communication difficulties related to problems of education, language, ethnic background or cultural background. Use simple evaluation tools.

Follow-up assessment:
Ongoing assessment of pain is essential. Changes in features and course of the pain require reevaluation and change of the treatment plan. Persistent pain indicates the need to consider possible additional factors associated with disease progression, as well as alternative treatment options.

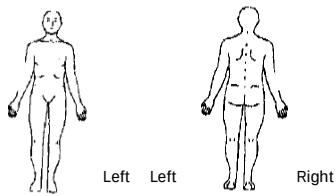
Brief Pain Inventory (short form)

Date: _____ Time: _____

Given name: _____Family name: _____ID:_____

1. During our lives, most of us occasionally suffer pain (such as mild headaches, sprains and toothache). Today did you feel pain that was different from common pains?
Yes__ No__

2. On the diagram mark the areas of your body where you feel pain.
Put an X on the area that is the most painful.



3. Grade the **strongest** pain you felt during the last 24 hours. Circle the number that best represents the intensity of this pain.

0 1 2 3 4 5 6 7 8 9 10

No pain at all Unbearable pain

4. Grade the **weakest** pain you felt during the last 24 hours Circle the number that best represents the intensity of this pain.

0 1 2 3 4 5 6 7 8 9 10

No pain at all Unbearable pain

5. Grade the **average** pain you felt during the last 24 hours Circle the number that best represents the intensity of this pain.

0 1 2 3 4 5 6 7 8 9 10

No pain at all Unbearable pain

6. Grade the pain you are feeling **now**.
Circle the number that best represents the intensity of this pain.

0 1 2 3 4 5 6 7 8 9 10

No pain at all Unbearable pain

7. What treatment or medication are you receiving for your pain?

_____

8. Mark the percentage that best reflects the degree of pain relief in the last 24 hours following the last treatment:

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

No relief Complete relief

9. To what extent did the pain interfere with your activities during the last 24 hours?. Circle the number that most accurately describes the degree of interference:

a. General activity

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

b. Mood

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

c. Walking

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

d. Routine work (including work outside / inside the home)

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

e. Communication with other people

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

f. Sleeping

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

g. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Did not interfere at all Interfere a great deal

Appendix 1: Scales for assessing pain intensity

1. Simple scale for verbal description

Unbearable Pain	Very Severe pain	Severe Pain	Moderate Pain	Slight Pain	No Pain
5	4	3	2	1	0

2. Numerical scale to describe pain intensity

1	2	3	4	5	6	7	8	9	10

No pain Unbearable pain

3. Visual Analogue Scale (VAS)

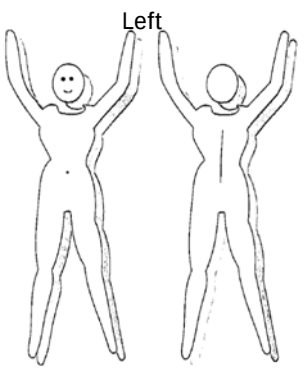
I I

No pain Unbearable pain

Using this method, the patient indicates the intensity of the pain that he feels and the therapist measures the length of the line with a ruler to obtain a number representing the pain intensity.

Source: Dr. Charles Cleeland, Anderson Cancer Center, Pain Research Group, Houston, Texas

Appendix 2: Body diagram to mark the pain location



Pharmacological Therapy

Pharmacological therapy is the cornerstone of treating cancer pain. It is effective, safe, usually acts quickly, and is relatively inexpensive.

The main principle when using drugs to treat cancer pain is to adjust the treatment plan specifically for the individual patient.

Even drugs from the same pharmacological group may act differently and produce different side effects for different people. The recommended pharmacological treatment is based on the 3-step analgesic ladder of the WHO (Diagram 2). According to the three-step ladder, the analgesic should be appropriate for pain severity.

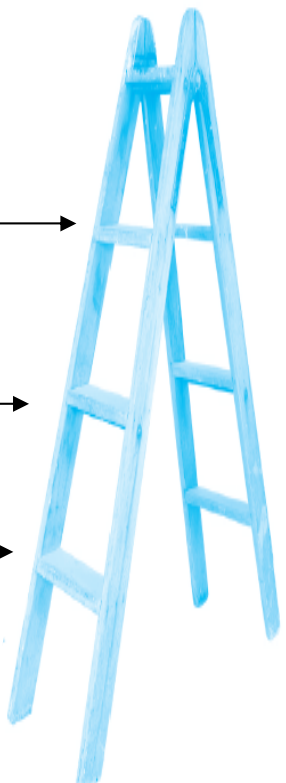
* The medication should be administered by the least invasive method using the most convenient dosing schedule.
* For mild to moderate pain, the use of non-opioid (first step) analgesics is recommended, such as Aspirin, Paracetamol, Non-steroidal anti-inflammatory drugs (NSAIDs), Dipyrone.
* If the pain persists or becomes stronger, a change to an opioid from the second step is recommended.
* If the pain persists or becomes stronger, a change to an opioid from the third step is recommended.
* At each step, it is possible to add adjuvant analgesics, such as steroids, anti-depressants, bisphosphonates – see details below.
* Medications should be administered on a regular basis – taking drugs on the principle of “round the clock” medication, with the option to take “rescue doses” as necessary for sudden outbreaks of pain.
* The patient and his family should be involved in preparing the treatment plan.

Diagram 2: The Analgesic Ladder of the World Health Organization (WHO)

3) Opioids for
severe pain
+/- adjuvant drugs
Severe pain

2) Opioids for
moderate to severe pain
+/- adjuvant drugs
Moderate pain

1) Non-opioid analgesics
+/- adjuvant drugs.
Slight pain



Non-Opioid Analgesics

Drugs of this group are suitable for treating mild pain when administered as monotherapy. These drugs may be combined with opioids from the second and third steps to treat moderate or severe pain. Drugs belonging to this group are heterogeneous in terms of chemical structure, but share certain pharmacological features.
Unlike opioids, drugs in this group have a "ceiling effect" ; they do not induce tolerance or physical dependence.
Their pharmacological action is predominantly peripheral.
Safe use of these drugs requires knowledge of their possible side effects and the methods of treating them.

* Dosage: the patient's analgesic response is the best indicator of the effective dose. If no pain control is achieved with the maximal dose of one of these drugs, one should generally consider switching to the next step analgesic.
* Method of administration: generally, oral drugs are preferable (tablets, capsules, suspensions/syrups). If the patient is not able to swallow, suffers from nausea and vomiting or mucositis, rectal administration can be employed.
* Contraindications: NSAIDs must not be used in patients with thrombocytopenia, impaired platelet function or coagulopathy.
* Other side effects: epigtastric discomfort, renal failure, impaired liver function, bleeding, peptic ulcer. It is possible to protect against GI damage by adding Famotidine (H2 blocker) or Misoprostol (Prostaglandin E1), or a proton pump blocking agent.

Since NSAIDs have a high protein binding capacity , there is a risk of change in the activity and/or toxicity of other drugs being administered concurrently.

* The renal and cardiovascular effects of NSAIDs are generally dose dependent. These effects may contribute to a long term risk of developing cardiovascular disorders. Currently available evidence does not indicate that selective blocking of COX II plays, by itself, a significant role in risk determination.
* There is an exaggerated concern regarding the development of agranulocytosis when using Dipyrone. This is a rare phenomenon that is not dose dependent and does not justify avoiding the use of an effective, available and relatively inexpensive drug.
* For patients who need treatment with Dipyrone for more than a week, the recommendation is to perform a blood count to exclude neutropenia. In the rare event of neutropenia, treatment should be stopped immediately and a hematologist should be consulted. Neutropenia can be treated by G-CSF administration.

Opioid Analgesics

Opioids are the main group of drugs for the treatment of moderate and severe pain. With extended use of opioids, one can expect the development of physical dependency, which is often confused with psychological dependency or addiction, which is observed in cases of abuse of these drugs. This confusion between the two phenomena may result in inadequate prescription, use and supply of opioid analgesics. This often leads to under treatment of pain. Physicians frequently have reservations about prescribing high doses of opioids for patients with advanced disease due to concerns of side effects. In most cases, the physician's fear of shortening the patient's life by increasing opioid dosages is unjustified. The doctor is responsible for improving the patient's condition by prescribing opioid dosages capable of relieving his pain, with minimal adverse events.

Opioids: in terms of their pharmacological action and the receptors to which they bind, opioids are generally divided into three groups:

Pure morphine-like agonists: this group includes: Codeine, Oxycodone, Methadone, Fentanyl, Morphine, Hydromorphone.

These substances are called pure agonists because their activity increases with increasing dose, with no ceiling effect, and is not inhibited by another agonist administered simultaneously.

Partial agonists: this group includes drugs such as Buprenorphine (Butrans) which have a ceiling effect.

Mixed agonists-antagonists: drugs of this group are inactive when bound to one receptor and active when bound to another receptor.

They must not be used in patients already treated with an agonist due to the risk of causing withdrawal symptoms and pain. This group includes Pentazocine and Nalbuphine. Their action is limited by a dose-dependent ceiling effect.

Titration:

In order to obtain a significant change in response, the next dose should be increased or reduced by at least 25-50% of the current dose.

Switching mode of administration:

When switching from oral to rectal administration, start with the same dose, then increase it frequently and carefully. When switching from oral to parenteral or subcutaneous administration, the dose must be decreased by an appropriate ratio and vice versa.

Dose scheduling:

Prevent recurrence of the pain by administering drugs continuously – around the clock – taking into account the estimated duration of the drug's action.

Definitions related to the use of opioids for pain management[16]:

Stopping treatment with opioids:

When the patient has stopped feeling pain, due to the success of the treatment or due to a response to palliative care such as destruction/blockage of a nerve, the dose should be gradually reduced by 25% daily to avoid withdrawal symptoms.

Treatment with opioids for special populations:

Attention should be paid to special instructions for elderly patients, children, patients with physical or cognitive disabilities, and patients with addictive tendencies. It should be noted that the risk of developing addiction during use to treat chronic pain is extremely low (<1:1000)[7].

Tolerance:
Tolerance is a situation in which a previously effective dose is no longer sufficient for pain relief, and dose increase is required. Tolerance is not equivalent to addiction.
Previous use of opioids including Methadone must be taken into account when calculating the suitable dosage. A patient who has already been treated with opioids may need a larger initial dose than a patient who is opioid-naive.

Addiction:
Addiction is a chronic neurobiological primary illness, which is affected by genetic, psychosocial and environmental factors, and is characterized by one or more of the following phenomena: obsessive use of the drug (in spite of the damage it causes to the user and/or his surroundings), inability to control use of the drug, and urge for the drug not for the purpose of pain relief.
The rate of addiction to opioids among patients receiving transient or chronic treatment is very low:
* Out of 11,882 hospital patients who took Morphine at least once, only four (0.03%) developed an addiction[17].
* Out of 10,000 patients who received opioids to alleviate pain due to burns, no case of addiction was observed[18].

Physical dependence:
A situation in which the patient develops a physiological adaptation to drugs from certain groups, including opioids, beta blockers and steroids.
* Physical dependence is characterized by the appearance of withdrawal symptoms upon sudden discontinuation of the drug treatment, rapid dose reduction, and/or in response to taking an antagonist drug.
* Opioid withdrawal symptoms include: sweating, dilated pupils, diarrhea, anxiety, and more.
* Physical dependence rarely occurs in a clinical setting if the discontinuation of opioids, whether used for severe pain

or cancer pain, is performed according to the guidelines in a gradual manner, which prevents withdrawal symptoms.

Opioids for moderate pain:

According to the original WHO recommendation, patients with moderate pain should be treated with preparations containing a combination of a non-opioid drug such as paracetamol or aspirin with an opioid – codeine (CodAcamol), oxycodone (Percocet) or propoxyphene (Algolysin Forte).

The maximal daily doses of these preparations are restricted by the maximal daily dose of the non-opioid component (for example, 4000 mg of paracetamol per day).

In the recent years, new formulations of controlled- release opioids have been introduced, which make it easier to take opioid drugs such as preparations of morphine, oxycodone and tramadol.

These preparations are available in dosages enabling their use for moderate pain relief. The advantage of these preparations is lack of maximal daily dose restriction, and the possibility of dose adjustment in cases of pain exacerbation, without the need to switch to another medication.

Tramadol exerts its central analgesic action via two mechanisms of action:

1. Binding to opioid receptors.
2. Inhibiting the uptake of noradrenaline and serotonin.

This drug has an antinociceptive action mediated by both the opioid and the non-opioid mechanisms.

The affinity of tramadol to mu- type opioid receptors is much lower than that of morphine. Although it binds to opioid receptors, the respiratory and cardiovascular adverse events are not significant in most patients.

Tramadol is suitable for treating moderate pain.

The maximum daily dose is 400mg.

Side Effects Caused by Opioids

Medical staff monitoring patients undergoing extended treatment with opioids should be aware of the possible side effects of this treatment, and be knowledgeable about the proper use of medications required to treat these effects.

Constipation and OIBD (Opioid Induced Bowel Dysfunction)

When opioids bind to peripheral receptors of the GI tract, they interfere with the ability of the intestinal muscles to contract, which affects intestinal motility, secretion, absorption of fluids, and blood flow, and ultimately interferes with passage through the intestines, thus blocking the expulsion of feces. The variety of GI disorders induced by opioid treatment is called OIBD (opioid induced bowel dysfunction). It is characterized by hard, dry feces, effort in bowel movement, incomplete emptying, vomiting, swelling of the abdomen and gastroesophageal reflux.

Constipation is the most common and troublesome symptom that may affect up to 90% of patients treated with opioids.

Since this side effect is almost certain to occur, preventive treatment for constipation should be started simultaneously with opioid treatment initiation.

Until recently, regular use of mild laxatives such as Docusoft (docusate sodium) or Peglax (polyethylene glycol) was recommended. In the case of severe constipation, stimulant / cathartic preparations were added such as: bisacodyl, and senna preparations or hyperosmotic agents such as lactulose, glycerine.

Today, there is an innovative approach to selective and local inhibition of the GI effects of opioids. The innovation is based on administering a combination of an opioid agonist (Oxycodone) with an opioid antagonist of negligible

bioavailability (such as oral Naloxone).
Targin is a new drug combining an opioid agonist effective in relieving moderate and severe pain (Oxycodone) with a local antagonist of opioid receptors (Naloxone delivered orally), which acts locally in the intestines and blocks the GI opioid receptors. This action preserves proper GI functioning and prevents constipation caused by opioids.

Nausea and vomiting:

In most cases, these symptoms resolve within 10-14 days following treatment initiation. It is recommended to use anti-nausea preparations such as phenothiazines or metoclopramide and to monitor the development of excessive drowsiness.

Drowsiness and confusion:

In most cases these symptoms resolve within two or three days following treatment initiation.
In cases of persistent effects, confusion can be treated by reducing the dose while increasing the frequency of opioid administration; alternatively, addition of haloperidol can be considered.
Excessive drowsiness can be treated with stimulants such as methyphenidate or pemoline (see page 40).

Subacute overdose:

A phenomenon much more common than acute overdose, which is manifested by a gradual increase in drowsiness and respiratory depression.
In such a case one or two doses of the drug should be skipped, until the symptoms disappear, and subsequent doses should be reduced by a quarter (25%).

Respiratory depression – rare with oral use:

With extended use of opioids, tolerance to respiratory depression caused by the drug usually develops.
In the case of respiratory depression, the antagonist Naloxone should be used. Gradual titration is carried out

with small increases in dosage to bring about an improvement in respiratory status.
The patient must be continuously monitored after the incident.

Other side effects – rare:

Dry mouth, urinary retention, changes in cognitive function, dysphoria, sleep disturbances, sexual dysfunction, and abnormal secretion of antidiuretic hormone. Myoclonus can be treated by adding Clonazepam (0.5 mg x 2).

Modes of Administration

Oral administration is the preferred method. When oral administration is not possible, the alternative administration mode chosen should be as non-invasive as possible. Parenteral mode of administration should be kept only for cases where there is no alternative.

It is recommended to try different opioid preparations before changing the mode of administration and switching to sedation, neurosurgery or other invasive methods.

Rectal administration:

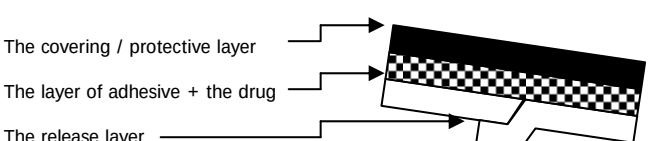
This is a safe, inexpensive and effective way of administering opioids and non-opioid drugs to patients suffering from nausea and vomiting. This method is not suitable for patients suffering from diarrhea, or patients with anal or rectal lesions. This method is also not suitable for patients with thrombocytopenia or neutropenia. It is not advisable to choose this method for patients who are unable or unwilling to insert the suppositories themselves.

Transdermal administration (patches):

This method is suitable for treating stable pain when there is no requirement or expectation of rapid changes in the level of anesthesia. This is not a suitable method for cases where rapid titration is required.

Preparations available for transdermal administration are Durogesic, Fenta (Fentanyl TTS), Butrans.

In Buprenorphine and Fentanyl TTS patches active substance release is based on a different technology, called Transdermal Matrix System.



In the new patch, the active substance is completely dissolved in the semi-solid formulation of the material forming the adhesive layer.
In terms of tolerance, pharmacokinetic parameters and efficacy, the two systems have been found to be equally effective.
Advantages of the matrix type patches: the patch is smaller and causes less irritation to the skin at the site of adhesion. Since it contains no free substance, there is less risk of illegal use of the traces when therapeutic use is complete.

Injection or drip:

Intravenous or subcutaneous administration is an effective way of administering opioids and other drugs.
Intra-muscular (IM) injection should be avoided, as it causes the patient additional pain and is not reliable in terms of absorption.
With intravenous injection, the effects begin to be felt quickly, but the duration of the active stage is relatively short.
When the patient uses an infusion for medication delivery or other treatments, this route can be used for continuous infusion of opioids.

Subcutaneous administration:

Studies have shown that subcutaneous morphine infusion is as effective as intravenous morphine infusion for chronic pain treatment. Subcutaneous infusion can be given by a nurse without the need for a physician or a nurse with special permission to insert an IV line.
In terms of side effects, the only difference between the two modes of administration is that subcutaneous infusion is associated with a higher risk of local irritation, requiring infusion site change.

Use of subcutaneous administration for bolus doses: Even in cases where immediate injection of a morphine dose is required, it is possible to use subcutaneous injection through a butterfly. This option was also examined for elderly patients after surgery and found to be effective[20].

If there is no available IV line, it is possible to use subcutaneous infusion. This is a practical way of administering opioids to hospitalized as well as ambulatory patients.

Oral transmucosal administration:

This method of administration is suitable only for lypophilic drugs. Among the opioids in use, Methadone and Fentanyl are lypophilic substances well absorbed through the mucosa. (Methadone syrup can be administered sublingually.)

The only commercial preparation available for this type of administration is ACTIQ – a Fentanyl "lollipop".

Use of patient-controlled analgesia (PCA):

Use of PCA enables the patient to be a partner in his pain management. Using a PCA pump, the patient can control his pain independently by adding medication doses as required. The PCA pump is relatively light and small and allows the patient to be mobile. The pump can be connected to a transfusion set for parenteral or subcutaneous administration.

Intraspinal administration:

This invasive mode of administration should only be considered for patients whose pain cannot be controlled in other ways or in the case of failure to overcome side

effects. Use of this method requires a specialist's expertise and special conditions in the system. The main indication for intraspinal administration is unbearable and uncontrollable pain in the lower body. Full pain relief can be achieved without affecting the patient's mobility and sensation, and without sympathetic blockade.

Table 1: Modes of Administration or Drugs NOT Recommended for Use in the Treatment of Cancer Pain

Method / Drug		Reason
Intramuscular administration (IM)		Painful, unpredictable/unreliable absorption, not for use on children, patients with a tendency to develop dependent edema, patients with thrombocytopenia.
Group	**Drug**	
Opioids	Pethidine	Short active time: 2-3 hours, repeated and extended use could cause toxicity of the central nervous system (trembling, confusion, convulsions).
Opioid-Agonist Antagonist	Pentazocine Nalbuphine	Risk of inducing withdrawal systems in patients being treated with opioids, ceiling effect, risk of causing unpleasant psychomimetic phenomena such as dysphoria, hallucinations.
Antagonist	Naloxone	Induces withdrawal symptoms, use should be restricted to cases of life threatening respiratory depression.
Combinations	Pethidine + Promethazine	Low level of efficacy as compared to the risk of causing side effects.
Sedative / Hypnotic separately	Barbiturates Benzodiazepines	Analgesic effect not proven. Excessive drowsiness that limits the dose of opioids.
Anxiolytics separately	Benzodiazepines such as Alprazolam	Analgesic effect not proven, except for a few cases of neuropathic pain. Excessive drowsiness that limits the dose of opioids.

Table 2: Non-Opioid Analgesics

Generic name	Preparations	Starting dose in mg	Max. daily dose in mg	Notes
PARACETAMOL	ABROL, ACAMOL, ALDOLOR, DEXAMOL, Tab. 500mg / Sup. 500mg	500 every 4 hours	6000	Caution required for patients with hepatic insufficiency
ETORICOXIB	ARCOXIA, Tab. 60mg, 90mg, 120mg		120	
ASPIRIN	ACETOSAL, ASPIRIN, Tab. 500mg	500 every 4 hours	6000	
DIFLUNISAL	DOLOBID Tab. 500mg	500 every 12 hours	1500	Less toxic for the GI tract than aspirin
DIPYRONE	OPTALGIN, NOVALGIN, Tab. 500mg NOVALGIN, Sup. 300mg OPTALGIN Drops, 500 mg/ml	500 every 4-8 hours	8000	A blood count is recommended
ETODOLAC	ETODOLAC, Tab. 400mg ETOPAN, Tab. 400mg, Cap. 200mg, 300mg ETOPAN XL Tab. 400mg, 600mg		1000	

Table 2: Non-Opioid Analgesics - Con.

Generic name	Preparations	Starting dose in mg	Max. daily dose in mg	Notes
IBUPROFEN	ADEX 200, ARTOFEN, BRUFEN, Tab. 200mg ARTOFEN, BRUFEN, IBUFEN, Tab. 400mg ARTOFEN, IBUFEN, Tab. 600mg.	400 every 6 hours	4200	Tablets of 200 mg can be purchased without a doctor's prescription
KETOPROFEN	KETONAL, Cap. 50mg ORUVAIL, Cap. 200mg	50 every 8 hours	200	
NAPROXEN	NAXYN, NAPROXI, Tab. 250mg, 500mg NAXYN, Sup. 500mg	250 every 12 hours	1000	
INDOMETHACIN	INDOMED, INDOVIS, Cap. 25mg INDOTARD, INDOMED SR, Cap. 75mg INDOMED Sup. 100mg7	25 every 8-12 hours 75 every 12-24 hours 100 once a day	200	

Table 2: Non-Opioid Analgesics - Con.

Generic name	Preparations	Starting dose in mg	Max. daily dose in mg	Notes
DICLOFENAC	BETAREN, ABITREN, VOLTAREN, Tab. 25mg, 100mg; Sup. 50mg; Inj. 75mg	25 every 8 hours 100 once a day	200	
NABUMETON	RELIFEX, Tab. 500mg NABUCO, Tab. 500mg	500 every 12 hours	2000	For patients with a history of peptic ulcer.
NIMESULIDE	MESULID, Caplet 100mg	100 every 12 hours	400	Permitted for asthmatic patients who do not tolerate NSAIDs
CELECOBIX	CELEBRA / CELCOX, Caps. 100mg/200mg	100-200, 1-2 times a day	400	Not recommended in cases of active ischemic heart disease
LORNOXICAM	XEFO, Tab. 4mg, 8mg		12	

Table 3a: Dose Equivalents for Opioid Analgesics for Adults

Opioids for treatment of moderate pain		Dose relative to IV Morphine 10mg – approx. equianalgesic dose				
Generic name / preparation name	**Dose**	**Parenteral**	**Oral**	**Duration of action in hours**	**Initial dose**	**Notes**
OXYCODONE			**20mg**			
OXYCONTIN	Controlled release Tab. 5mg, 10mg, 20mg			12	10mg-20mg	With patients in poor condition start with a dose of 5 mg.
OXYCOD	Immediate release syrup 2mg/ml			3-4	10mg-20mg	For titration and treatment of breakthrough pain.
TARGIN Oxycodone/ Naloxone	Prolonged release Tab. 10/5 mg, 20/10 mg			12	10/5 mg	Relieves pain while maintaining proper intestinal function and preventing constipation.

Table 3a: Dose Equivalents for Opioid Analgesics for Adults- Con

Opioids for treatment of moderate pain		**Dose relative to IV Morphine 10mg – approx. equianalgesic dose**				
Generic name / preparation name	**Dose**	**Parenteral**	**Oral**	**Duration of action in hours**	**Initial dose**	**Notes**
PERCOCET, PERCODAN	Tab. 5mg with paracetamol / aspirin			3-4	½-1 tablet	For titration and treatment of outbursts of pain.
CODEINE			**200mg**			
COD-ACAMOL CODABROL	Tab. 20mg Tab. 15mg			3-4	Tablet	Codeine in combination with Paracetamol
PROPOXYPHENE			**130mg**			
ALGOLYSIN FORTE, PROXOL-FORTE	Tab. 40mg Tab. 50mg			3-4	Tablet	In combination with Paracetamol

Table 3a: Dose Equivalents for Opioid Analgesics for Adults- Con

Opioids for treatment of moderate pain		Dose relative to IV Morphine 10mg – approx. equianalgesic dose				
Generic name / preparation name	**Dose**	**Parenteral**	**Oral**	**Duration of action in hours**	**Initial dose**	**Notes**
TRAMADOL			**120mg**			
TRAMADEX TRAMAL TRABAR	Tab. 50mg, 100mg Drops 100 mg/ml Caplets 50mg			6-8	50mg	Patients with poor renal function (creatinin clearance <30 ml/min), daily dosage **up to** 200 mg. Patients with poor hepatic function – recommended to administer a dose every 12 hours.
BUPRENORPHINE			**20ug**			
BUTRANS TRANSDERMAL MATRIX PATCH	5 μg/h 10 μg/h 20 μg/h			7 days	5 μg	Recommended to begin with low dose of 5μg/h, & increase as necessary

Table 3b: Dose Equivalents for Opioid Analgesics for Adults

Opioids for treatment of severe pain		**Dose relative to IV Morphine 10mg – approx. equianalgesic dose**			
Generic name / preparation name	**Dose**	**Parenteral**	**Oral**	**Duration of action in hours**	**Initial dose**
MORPHINE		**10mg**	**30mg**		
MCR UNO	CR Caps, 120, 200mg			24	
MCR	CR Tab. 10mg, 30mg, 100mg			8-12	See explanation (page 39)
MIR	IR Tab. 15mg, 30mg			3-4	
MSP	Supp. 5mg, 20mg			3-4	
INJ. MORPHINE Preservative free	Inj. 10mg/ml – 1ml 200mg/ml – 5ml 100mg/5ml, 5mg/5ml, 1mg/2ml			3-4	

Table 3b: Dose Equivalents for Opioid Analgesics for Adults- Con.

Opioids for treatment of severe pain		**Dose relative to IV Morphine 10mg – approx. equianalgesic dose**			
Generic name / preparation name	**Dose**	**Parenteral**	**Oral**	**Duration of action in hours**	**Initial dose**
OXYCODONE			**20mg**		
OXYCONTIN	Controlled release Tab. 10mg, 20mg, 40mg, 80mg			8-12	10mg-20mg
OXYCOD	Immediate release syrup 2mg/ml			3-4	10mg-20mg
TARGIN Oxycodone/ Naloxone	Prolonged release Tab. 10/5 mg, 20/10 mg			12	10/5 mg
PERCOCET, PERCODAN	Tab. 5mg with paracetamol / aspirin			3-4	½ -1 tablet
FENTANYL		**0.1mg**			

IR = Immediate Release **CR** = Controlled Release

Table 3b: Dose Equivalents for Opioid Analgesics for Adults- Con.

Opioids for treatment of severe pain		**Dose relative to IV Morphine 10mg – approx. equianalgesic dose**			
Generic name / preparation name	**Dose**	**Parenteral**	**Oral**	**Duration of action in hours**	**Initial dose**
BEATRYL	Inj. 50μg/ml – 2ml, 50μg/ml – 10ml		0.3mg		
DUROGESIC / FENTA Transdermal patches	12μg/hr, 25μg/hr, 50μg/hr, 75μg/hr, 100μg/hr			48-72	See explanation (page 39)
ACTIQ Transmucosal	200μg, 400μg, 800μg, 1200μg, 1600μg				
HYDROMORPHONE		**1.5-2.0mg**			
PALLADONE INJ. Preservative free	Inj. 10mg/ml – 2ml			3-4	1-2mg
METHADONE			**5mg**		
SYR. METHADONE	Syr. 5mg/ml (0.5%) Syr. 50mg/ml (5%)				See explanation (page 40)

Morphine:
Treatment with morphine begins with titration with an immediate release preparation. The treatment starts with ½ to 1 tablet (7.5 mg-15 mg) of MIR every 4 hours, with a recommendation to take additional doses ("rescue doses") of ½ to 1 tablet (7.5 mg-15 mg) as needed (up to a maximum of every hour) if there is pain. Once the pain is stabilized, the total daily dosage required by the patient is added up and divided by 2, giving the appropriate dosage of a controlled release preparation (MCR), which the patient will receive twice a day. The patient should be permitted to take "rescue doses" as needed in addition to the fixed MCR doses during sudden pain exacerbations.
For example: a patient who took a tablet of MIR (15 mg) every 4 hours and also needed 2 rescue doses to alleviate his pain, consumed a total of 120 mg of morphine. When switching to treatment with MCR, we will prescribe the patient 60 mg of MCR every 12 hours and add a rescue dose of MIR (15 mg) as needed.
If the daily dose is not sufficient to achieve good pain control , it should be increased by 30-50% to obtain a significantly improved response.

Oxycodone:
For patients who have never been treated with opioids, we recommend initial treatment with 10 mg of OxyContin every 12 hours. If there are bursts of pain, a "rescue dose" should be given – immediate release Oxycodone at 25-50% of the previous dose of Targin/OxyContin.
If more than two rescue doses are needed during a 24 hour period, the daily dose of OxyContin should be increased accordingly.
For patients receiving opioids, the daily dose of the current opioid taken by the patient , as well as the appropriate dose of Targin/OxyContin, should be calculated based on

the ratio of potency between the two drugs, and divided into two doses plus rescue doses of immediate release OxyContin.

For example: a patient treated with a daily dose of 60 mg of morphine P.O.: we start treatment with 2 x 20 mg of OxyContin tablets plus rescue doses of 5 mg immediate release Oxycodone.

Fentanyl:

When determining the initial dose, we recommend distinguishing between the situations of achieving and not achieving good pain control .

For a patient who achieved good pain control, the initial dose should be 50-75% of the relative dose calculated according to the potency relative to morphine (equianalgesic dose) – see Table 3b.

For a patient who has not achieved good pain control , the dose can be 75-100% of the relative dose calculated according to the potency relative to morphine (equianalgesic dose).

A simple way of calculating the initial dose of Fentanyl administered transdermally is to take the total daily dosage of morphine and divide it by 3. We recommend choosing a patch in which the hourly dose is the closest to the number obtained.

For example: if the patient has received a total dose of 120 mg MCR, we start treatment with a patch with a strength of 50 mcg/hr.

Methadone:

Methadone is a pure opioid agonist and is a therapeutic alternative for patients with difficulties swallowing tablets or low tolerance for other opioids. In view of the long half life of Methadone, the recommended method of treatment initiation is the loading method.

Using this method, the patient receives doses as required (up to one dose of Methadone per hour) under supervision,

until pain relief is achieved or side effects appear.
The dose of the drug is determined according to the dose of opioid received by the patient that is equivalent to a dose of Morphine administered orally:

* A patient who received a dose equivalent to <300 mg of Morphine will start with a dose of 5 mg Methadone.
* A patient who received a dose equivalent to 300-1000mg of Morphine will start with a dose of 10 mg Methadone.
* A patient who received a dose equivalent to >1000 mg of Morphine will start with a dose equivalent to 5% of the opioid dose.
* When pain relief is achieved, the patient will continue to receive a dose equivalent to 50% of the loaded dose.

The initial doses will be given upon pain recurrence until the duration of the drug's action for the individual patient is clarified

For example: if the loaded dose was 15 mg, the dose of 7.5 mg is to be initially given upon pain recurrence.
For most patients it will be necessary to give the drug 2-3 times a day.

Table 4: Examples of Morphine Dosage Titration Plans for the Common Modes of Administration[3]

Oral administration of immediate release Morphine preparations (MIR)

Stage*	Dose in mg. Administration every 4 hours around the clock	Rescue dose
1	15	7.5 as needed up to every hour
2	30	15 as needed up to every hour
3	45	22.5 as needed up to every hour
4	60	30 as needed up to every hour
5	90	45 as needed up to every hour

Oral administration of controlled release Morphine (MCR)

Stage*	Dose in mg. around the clock	Rescue dose in mg. of immediate release Morphine (MIR)
1	30 every 12 hours	7.5 as needed up to every hour
2	30 every 8 hours	15 as needed up to every hour
3	60 every 12 hours	15 as needed up to every hour
4	100 every 12 hours	30 as needed up to every hour
5	100 every 8 hours	45 as needed up to every hour

Extended transfusion of Morphine

Stage*	Dose in mg/hr	Rescue dose in mg.
1	3	2 up to every 30 min.
2	5	2.5 up to every 30 min.
3	7	3.5 up to every 30 min.
4	10	4 up to every 30 min.
5	15	5 up to every 30 min.

*** The indications for dose increase to the next stage are:**
1. The need for more than 2 rescue doses in intervals of 4 hours between 2 fixed doses.
2. The need for more than 6 rescue doses in a day (24 hours).

Table 5: Adjuvant Analgesics

Adjuvant drugs have no analgesic action in the pharmacological sense, but contribute to pain management and symptom relief by enhancing the analgesic effect. These drugs can play a role in the treatment of various types of pain, at each stage of pain management. These drugs are particularly important in the treatment of pain not responding sufficiently to maximum doses of morphine, including neuropathic pain and pain due to increased intracranial pressure.

The drug	Method	Estimated initial dose in mg	Indications for administration
ANTICONVULSANTS CARBAMAZEPINE	PO	100-200 mg twice a day. Later increase the dose according to blood levels	Neuropathic pain
GABAPENTIN		100-300 mg before sleep. Later titration up to a maximum dose of 3200 mg.	
PREGABALIN (LYRICA)	PO	150-600 mg	Neuropathic pain-official indication for the drug
ANTIDEPRESSANTS AMITRIPTYLINE IMIPRAMINE PAROXETINE	 PO PO PO	 25 25 20	Neuropathic pain

Table 5: Adjuvant Analgesics- Con.

The drug	Method	Estimated initial dose in mg	Indications for administration7
DULOXETINE (CYMBALTA)	PO	60 mg	Neuropathic pain
BACLOFEN	PO	5 mg 2-3 times a day	Neuropathic pain
BISPHOSPHONATE CLODRONATE CLODRONATE PAMIDRONATE ZOLEDRONATE	 PO IV IV IV	 800 mg x 2/day 1500 mg q 21 day 90 mg q 28 day 4 mg q 28 day	For treatment of malignant hypercalcemia; to prevent pathological fractures; to treat bone pain
CALCITONIN	SC intranasal	100U 200U	Bone pain, neuropathic pain
CORTICOSTEROIDS METHYLPREDNISOLONE PREDNISONE DEXAMETHASONE	 IV PO PO/IV	 125 5-15 4-16	Perineural edema, lack of appetite, pressure on nerves, increase in intracranial pressure, pressure on spinal cord. In case of pressure on spinal cord – 100 mg as initial dose and continue treatment with 24 mg x 4/d until initiation of radiation. When beginning radiation, reduce the dose gradually.

Table 5: Adjuvant Analgesics- Con.

The drug	Method	Estimated initial dose in mg	Indications for administration
LOCAL ANESTHETICS / ANTIARRYTHMICS MEXILETINE	PO	 300 1000 maximum dose	Neuropathic pain
PSYCHOSTIMULANTS METHYLPHENIDATE (RITALIN) PEMOLINE (NITAN)	PO PO	5 x 2 18.5 x 2	For treatment of drowsiness caused by administration of opioids
TOPICAL ANALGESICS LIGNOCAINE	TOPICAL	Lignocaine Viscous 2% Lignocaine Gel 2% Lignocaine 2% 20 ml in 400 ml suspension MAALOX MAGEL	Mucositis

Palliative Radiation Therapy

One of the most effective methods of treating cancer pain is radiation therapy. For patients with bone metastases, radiation therapy relieves pain in over 80% of cases, with pain disappearance in about half of the cases. Particularly important is awareness of the fact that back pain may be the first sign of spinal metastasis , leading to pressure on the spinal cord, limb weakness and even paralysis. Early radiation treatment in these cases can prevent such paralysis.

Radiation therapy is effective in treating pain due metastases in the bones and other parts of the body, inducing pain or function impairment due to local pressure on an organ, such as the brain.

Bone metastases are very common in advanced stages of the disease, such as among women with breast cancer and men with prostate cancer at advanced stages. The main purpose of radiation treatment is to reduce and eliminate pain. Another purpose is to ensure continued organ function, particularly in cases of limb and spine metastases. Radiation treatment usually focuses on the area of the painful bone metastasis. For patients suffering from pain in a number of areas due to painful bone metastases, it is possible to give focused treatment to each pain area or to apply radiation to a wide area of the body that includes most of the painful areas.

Radiation treatment is sometimes given as one dose, and sometimes as a series of 5-10 daily treatments for a period of one or two weeks, depending on the location of the disease and the patient's general condition. Side effects of radiation include weakness and fatigue that usually resolve at the end of the treatment. Sometimes the pain becomes worse on the first day of radiation

treatment, prior to pain relief occurring on subsequent days. When there is a bone fracture, the physician will recommend rest for a number of weeks after the radiation therapy, until the pain subsides or disappears.

Invasive Methods of Pain Management

Studies have demonstrated that it is possible to successfully treat 70-90% of patients suffering from pain with the aid of medication therapy. Failure of such treatment is usually due to the inability of finding the appropriate balance between the analgesic effects and the side effects of the drugs.
For 10-30% of people suffering from cancer pain, it will be necessary to use invasive methods of treatment in order to achieve good pain control[8-13]. There is a deficit in literature reports on these methods (precise information about the process of choosing the patients, the treatment methods used before transition to the invasive method), as well as in long term follow up reports on the outcomes. Invasive treatment should only be used when all non-invasive treatment methods have been exhausted, and be given by appropriately qualified and experienced specialists.
When indicated, the selection of one of the invasive treatment methods must be based on the following rules:
1. Start with the least invasive treatment method .
2. Choose a treatment known to be the most effective. If there is a choice between a number of options, choose the option with the least likelihood of causing serious side effects.
3. For a patient at an advanced stage of disease, it is highly likely that the pain will have multiple foci. Even if treatment brings local relief in one area, the patient will continue to suffer pain in other areas.
4. When possible, neurolysis should be performed only after ensuring the success of local anesthesia of the nerve by a single application of a local anesthetic.
5. Since there is a learning curve for successful performance of invasive treatment methods, patients should be referred to an experienced specialist.

As a rule, local analgesia methods such as intraspinal administration of opioids and intrapleural/interpleural administration of local anesthetics are the first line of treatment, since they do not involve neurological damage. Nerve destruction is a treatment method required in only a very limited sub-group of patients.

Local analgesia:

The advantage of local treatment compared to nerve destruction is the possibility of preserving sensation and sympathetic activity while preventing supraspinal side effects. Contra-indications for the use of this method are: bleeding tendency, reduced white blood cell count and sepsis.

* Intrathecal administration of a low dose of opioids, close to the area of activity in the spinal cord. It is important to use this method for a trial period before deciding on the insertion of a fixed catheter. The selection of the appropriate opioid for administration by this mode depends on its solubility and half life.
* Intraventricular administration of opioids by means of an Ommaya catheter or an implanted pump. For patients with pain in the upper part of the body or head pain.
* Local administration of local anesthetics intraspinally or intrapleurally/interpleurally. A single dose can bring relief for a fairly long period but extended administration is recommended for patients with chronic cancer pain.

Sympathetic blockade:

Blockade of the neural conduction of a primary conduction nerve or a ganglion, which is achieved by nerve destruction using chemical substances.

Blockade of the celiac plexus, for treatment of a tumor penetrating abdominal organs such as the pancreas, the retroperitoneum, the gallbladder, the small intestine. The efficacy of this treatment method has been proven in two

controlled studies. Some experts recommend carrying out this action at an early stage, while others recommend celiac plexus blockade only for patients for whom no proper balance has been achieved between pain control and adverse events caused by systemic administration of opioids. The transient side effects of this action are postural hypotension and diarrhea. Remote diffusion of the injected agent may occur, causing involvement of the lower back region and thus neuropathic pain.
Other sympathetic blockades: ganglion impar, superior hypogastric.

Neural destruction to treat somatic or neuropathic pain:

Rhizotomy: destruction of the dorsal root through surgical or chemical intervention or radiation. This method is suitable for treatment of focused pain that is resistant to other treatment. Although the neurological deficit expected from this procedure is in most cases transient, some recommend restricting the use of this method to patients who have already lost control of their excretory functions.

Cordotomy: blockage of the spinothalamic pathway to achieve pain relief and sensitivity to temperature changes on the side opposite to the side where the procedure is performed. There are reports of significant immediate pain relief for 90% of the patients undergoing cordotomy, and 50% of cancer survivors experiencing pain relief for about a year. A repeated procedure can be effective. The most common neurological complications include weakness of the treatment area, ataxia, pain in the bladder and “mirror image” pain, that is, pain on the side where the cordotomy was performed, which is opposite to the side where the original pain was located. In most cases, these effects are transient, with functional impairment in only about 5% of the patients.

Table 6: Selection of the Appropriate Treatment Method According to the Site of the Pain[14]

Location	Treatment method
Gasserian gangliolysis Trigeminal neurolysis Intraventricular opioid	Face-Unilateral
Glossopharyngeal neurolysis Intraventricular opioid	Pharyngeal
Spinal opioid +/- bupivacaine Chemical rhizotomy Surgical rhizotomy	Arm/Brachial Plexus
Spinal opioid +/- bupivacaine Intercostal neurolysis Paravertebral neurolysis Chemical rhizotomy Surgical rhizotomy	Chest Wall
Spinal opioid +/- bupivacaine Chemical rhizotomy Surgical rhizotomy Cordotomy (unilateral pain)	Abdominal Somatic
Celiac plexus neurolysis	Upper Abdomen: Visceral
Hypogastric neurolysis	Low Abdomen: Visceral
Spinal opioid +/- bupivacaine Chemical rhizotomy Surgical rhizotomy Transacral S4 neurolysis	Perineum

Table 6: Selection of the Appropriate Treatment Method According to the Site of the Pain[14]- Con.

Location	Treatment method
Spinal opioid +/- bupivacaine Chemical rhizotomy Surgical rhizotomy	Pelvis + lower limb
Cordotomy	Unilateral Lower Quadrant
Pituitary ablation Cingulotomy	Multifocal or generalized pain

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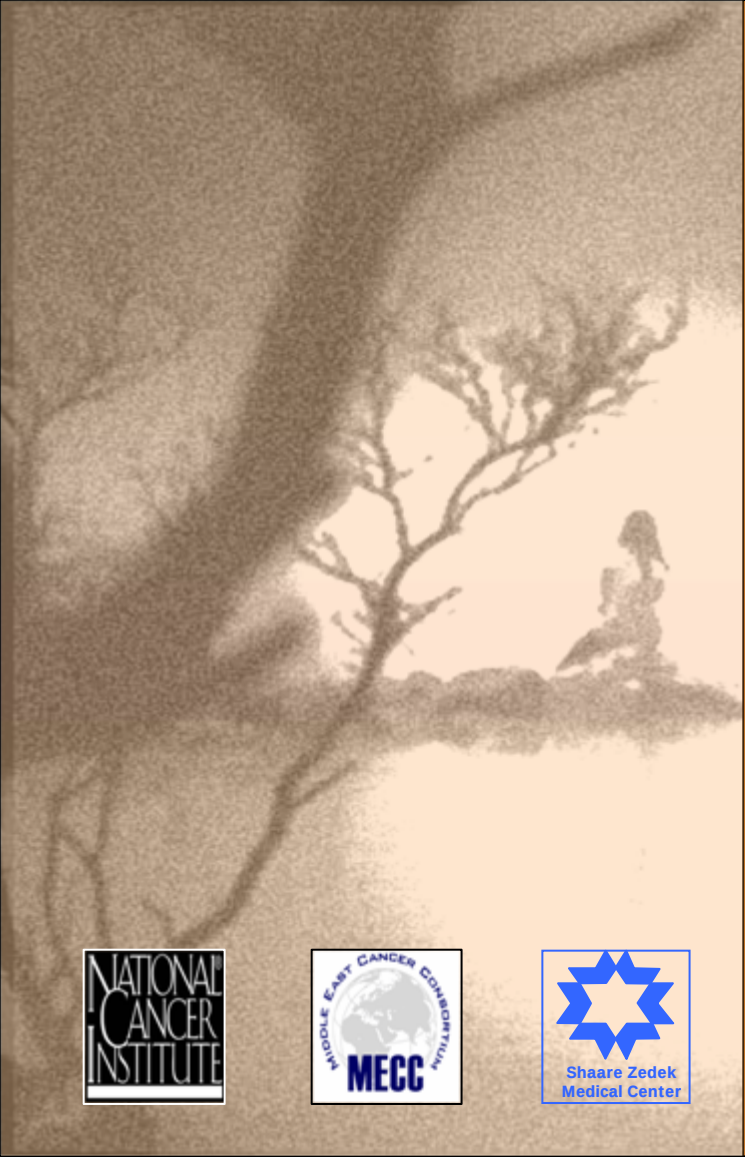

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