Guideline Summary NGC-7978

Guideline Title

Cancer pain management (general). In: Guidelines on pain management.

Bibliographic Source(s)

Cancer pain management (general). In: Bader P, Echtle D, Fonteyne V, Livadas K, De Meerleer G, Paez Borda A, Papaioannou EG, Vranken JH. Guidelines on pain management. Arnhem, The Netherlands: European Association of Urology (EAU); 2010 Apr. p. 13-42. [204 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cancer pain management (general). In: Bader P, Echtle D, Fonteyne V, De Meerleer G, Papaioannou EG, Vranken JH. Guidelines on pain management. Arnhem, The Netherlands: European Association of Urology (EAU); 2009 Mar. p. 13-44. [204 references]

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

Drug Withdrawal

- November 19, 2010 – Propoxyphene (Darvon, Darvocet) [x]: The U.S. Food and Drug Administration notified healthcare professionals that Xanodyne Pharmaceuticals has agreed to withdraw propoxyphene, an opioid pain reliever used to treat mild to moderate pain, from the U.S. market at the request of the FDA, due to new data showing that the drug can cause serious toxicity to the heart, even when used at therapeutic doses.

Additional Notices

- January 10, 2011 – Acetaminophen-containing Prescription Products [x]: The U.S. Food and Drug Administration (FDA) notified healthcare professionals that it has asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients. A Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) will be added to the label of all prescription drug products that contain acetaminophen.

Scope

Disease/Condition(s)

Cancer pain

Guideline Category

Evaluation

Management

Prevention

Treatment

Clinical Specialty

Anesthesiology

Neurology

Oncology

Radiation Oncology

Surgery

Urology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assist medical professionals in appraising the evidence-based management of pain in urological practice

Target Population

Patients with urological cancer requiring pain management

Interventions and Practices Considered

Treatment/Management

1. Imaging to detect bone metastases
2. Non-pharmacological therapies
   - Surgery
   - Radionuclides (strontium-89 chloride, samarium-153 lexidronam, renium-186 etidronate)
   - Radiotherapy for metastatic bone pain
   - Radiotherapy scheme
   - Physical/psychological therapy
3. Pharmacotherapy
   - Antibiotics
   - Chemotherapy
   - Bisphosphonates
   - Non-opioid analgesics
   - Opioid analgesics
   - Noninvasive routes of opioid administration
   - Invasive routes of opioid administration
   - Dosing
   - Management of opioid adverse effects
4. Treatment of neuropathic pain
   - Antidepressants
   - Anticonvulsant medication
   - Topical analgesics
   - N-methyl-D-aspartate (NMDA) receptor antagonists
   - Other drug treatments
5. Invasive analgesic techniques
   - Peripheral nerve catheterisation
   - Neurolytic blocks to control visceral pain
   - Epidural and intrathecal opioid application
   - Chemical rhizotomy
   - Cordotomy

Major Outcomes Considered
- Pain relief
- Pain intensity score
- Function
- Quality of Life
- Adverse effects of therapy

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The recommendations provided in the current guidelines are based on a systemic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence
Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

1a Evidence obtained from meta-analysis of randomized trials

1b Evidence obtained from at least one randomized trial

2a Evidence obtained from one well-designed controlled study without randomization

2b Evidence obtained from at least one other type of well-designed quasi-experimental study

3 Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports

4 Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Methods Used to Analyze the Evidence
Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations
Expert Consensus

Description of Methods Used to Formulate the Recommendations

- The first step in the European Association of Urology (EAU) guidelines procedure is to define the main topic.

- The second step is to establish a working group. The working groups comprise about 4-8 members, from several countries. Most of the working group members are academic urologists with a special interest in the topic. Specialists from other medical fields (radiotherapy, oncology, gynaecology, anaesthesiology, etc.) are included as full members of the working groups as needed. In general, general practitioners or patient representatives are not part of the working groups. Each member is appointed for a four-year period, renewable once. A chairman leads each group.

- The third step is to collect and evaluate the underlying evidence from the published literature.

- The fourth step is to structure and present the information. All main recommendations are summarized in boxes and the strength of the recommendation is clearly marked in three grades (A-C), depending on the evidence source upon which the recommendation is based. Every possible effort is made to make the linkage between the level of evidence and grade of recommendation as transparent as possible.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation

A. Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial

B. Based on well-conducted clinical studies, but without randomized clinical trials

C. Made despite the absence of directly applicable clinical studies of good quality

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation
Internal Peer Review

Description of Method of Guideline Validation

There is no formal external review prior to publication.

The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used to analyse and assess a range of specific attributes contributing to the validity of a specific clinical guideline.

The AGREE instrument, to be used by two to four appraisers, was developed by the AGREE collaboration

(www.agreecollaboration.org) using referenced sources for the evaluation of specific guidelines.

Recommendations

Major Recommendations

Levels of evidence (**1a-4**) and grades of recommendation (**A-C**) are defined at the end of the "Major Recommendations" field.

General Principles of Cancer Pain Management

The therapeutic strategy depends on the four goals of care:

1. Prolonging survival
2. Optimising comfort
3. Optimising function
4. Relieving pain (see Figure 3 in the original guideline document)

The hierarchy of general treatment principles in the table below is intended to offer guidance through the decision-making process.

Table: Hierarchy of General Treatment Principles

1. Individualised treatment for each patient
2. Causal therapy to be preferred over symptomatic therapy
3. Local therapy to be preferred over systemic therapy
4. Systemic therapy with increasing invasiveness (World Health Organization [WHO] ladder)
5. Conformance with palliative guidelines
6. Both psychological counseling and physical therapy from the very beginning

The guiding principle of care is the individualisation of therapy. Through a process of repeated evaluations, the selection and administration of therapy is individualised so that a favorable balance between pain relief and adverse effects is achieved and maintained.

The next steps in the hierarchy, especially points 2 to 4, necessitate a continuing risk-to-benefit assessment between therapeutic outcome versus tolerability and willingness to accept adverse effects.

The more invasive the therapy, the more difficult the decisions become. This is particularly true of palliative medicine, since here there are limited prospects of healing and there is also the problem of working against time.

If local therapy is not feasible or cannot be well tolerated, then symptomatic measures are appropriate, although local therapy is to be given preference over systemic treatment. In simple cases, measures such as drainage and stenting can make analgesic medication redundant. Examples include inserting a gastric probe, a ureteral stent, a percutaneous nephrostomy, or a bladder catheter. To cite another example, patients who receive an artificial anus due to recurrent subileus caused by peritoneal carcinomatosis are relieved of their pain immediately.

The indication stands in direct relation to the severity of the disease and the operation, especially if there are no prospects of healing. Cases such as these, however, are sometimes in particular need of the invasive measures described above. This is not only to relieve pain for the rest of the patient's days, but also to improve the general quality of life, even though invasive operations may also have a negative impact on the patient's well-being. Examples can include evisceration to prevent cloaca in cervical carcinoma, or implanting a prosthetic hip due to a pathological fracture originating in metastasised bladder or kidney cancer.

A gradual strategy (**Level of evidence: 4**) can be considered when dose escalation of a systemically administered opioid fails to yield a satisfactory result. The steps to follow are as follows.

- Switch to another opioid
- Intervene with an appropriate primary therapy or other non-invasive analgesic approach
- Pursue psychological, rehabilitative and neurostimulatory techniques (e.g., transcutaneous electrical nerve stimulation)
- Use invasive analgesic techniques. This approach should be based on a careful evaluation of the likelihood and duration of the analgesic benefit, the immediate risks, and the morbidity of the procedure (epidural infusion)
- Use neurodestructive procedures (chemical or surgical neurolysis, coeliac plexus blockade)
- Finally, some patients with advanced cancer who have comfort as the overriding goal of care can elect to be deeply sedated.

Non-pharmacological Therapies

Surgery

Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures and compression of neural tissues or draining of symptomatic ascites. The potential benefits must be weighed against the risks of surgery, the anticipated length of hospitalization and convalescence, and the predicted duration of benefit. Radical surgery to excise locally advanced disease in patients with no evidence of metastatic spread may be palliative, and potentially increase the survival of some patients (**Level of evidence: 2b**).

Radionuclides

In single lesions, bone stability and pain reduction can be achieved by external beam radiotherapy (**Level of evidence: 1b**; **Grade of recommendation: A**).

Indications and Contraindications

Strontium-89 chloride (^{89}Sr) and Samarium-153 lexidronam (^{153}Sm) are indicated for the treatment of bone pain resulting from skeletal metastases involving more than one site and associated with an osteoblastic response on bone scan but without spinal cord compression (**Level of evidence: 2, Grade of recommendation: B**).

^{89}Sr and ^{153}Sm lexidronam have no place in the management of acute or chronic spinal cord compression or in treating pathological fracture (**Level of evidence: 2, Grade of recommendation: B**).

Of patients presenting with osteoblastic metastases, 60-80% benefit from ^{89}Sr and/or ^{153}Sm lexidronam (**Level of evidence: 2**). The choice between the two radiopharmaceuticals depends solely on practical considerations. ^{89}Sr and/or ^{153}Sm lexidronam should be administered by a slow (^{89}Sr) or bolus (^{153}Sm lexidronam) injection using an intravenous catheter. The recommended doses to be administered are 148 MBq (^{89}Sr) and 37 MBq/kg (^{153}Sm) (**Level of evidence: 2**).

There is a risk of temporary increase in bone pain (pain flare) in about 10% of the patients. This "flare phenomenon" generally occurs 2-4 days after ^{153}Sm lexidronam and 1-2 weeks after ^{89}Sr (acute side-effect) and is associated with good clinical response (**Level of evidence: 2**). A transient increase in analgesia is sometimes necessary. Pain reduction is unlikely to occur within the first week, and can occur as late as one month after injection. Analgesics should therefore continue to be prescribed to patients until bone pain improves (**Grade of recommendation: B**).

Late side-effects include temporary myelosuppression (platelets, white blood cells). Recovery occurs 4-6 weeks later depending on bone marrow reserve. In general, there is no significant effect on haemoglobin.

Radiation exposure to family members and the public can be present for 2-4 days after ^{153}Sm lexidronam, and 7-10 days after ^{89}Sr (**Level of evidence: 2**). Information concerning radioprotection should be provided (**Grade of recommendation: B**).

If the pain responds to the initial treatment, administration of ^{153}Sm lexidronam can be repeated at intervals of 8-12 weeks in the presence of recurrent pain (**Level of evidence: 2, Grade of recommendation: B**). The response rate for second and subsequent treatments may be lower than on the first occasion (**Level of evidence: 2**).

Contraindications

<u>Absolute Contraindications</u>

- During or shortly after (less than 4 weeks) myelotoxic chemotherapy (all compounds except cisplatin) or hemibody external radiation therapy (less than 12 weeks). The delay between the end of these treatments and the start of metabolic radiotherapy is necessary in order to avoid severe haematopoietic toxicity. However, treatment can be safely combined with limited local field external beam radiotherapy (**Level of evidence: 3, Grade of recommendation: C**).

- Known hypersensitivity to ethylene diamine tetramethylene phosphonate (EDTMP) or similar phosphonate compounds for ^{153}Sm lexidronam

- Glomerular filtration rate (GFR) <30 mL/min

- Pregnancy; continued breastfeeding

<u>Relative Contraindications</u>

- Radiopharmaceuticals are not recommended for women of child-bearing age (negative pregnancy test and contraception absolutely required).

- Acute or chronic severe renal failure (GFR of 30-60 mL/min): the dose administered should be adapted (if the GFR is >60 mL/min, reduce the normal dosage by 25%; if the GFR is between 30 mL/min and 60 mL/min, reduce the normal dosage by 50%) (**Expert opinion: Level 4**). Measurement of GFR is performed in the presence of elevated creatinine >20 mg/L.

- Solitary painful lesion: external limited field radiotherapy should be performed (**Level of evidence: 1b**).

<u>Caution</u>

Caution must be used in the following circumstances:

- Risk of fracture

- Nervous or spinal cord compression that requires other treatments in an emergency: external radiotherapy or surgery, or a combination of the two

- Urinary incontinence: special recommendations including catheterization before administration of the radionuclide. The catheter should remain in place for 4 days (^{89}Sr), 3 days (^{186}Re) and 24 hours (^{153}Sm) respectively (**Grade of recommendation: A**)

- Compromised bone marrow reserve

- White blood cell count of <2500/µL (**Expert opinion, Level 4**) (preferably >3500/µL according to European Association of Nuclear Medicine guidelines)

- Platelets <80,000/µL (**Expert opinion, Level 4**) (preferably > 100,000/µL according to European Association of Nuclear Medicine guidelines)

- Haemoglobin <90 g/l

Radiotherapy for Metastatic Bone Pain

Clinical Background

The role of radiotherapy in the palliation of symptomatic bone metastases is well established. Radiation therapy alleviates metastatic bone pain efficiently in the majority of patients and is particularly useful in treating metastatic bone pain (**Level of evidence: 1a**). According to controlled studies, complete pain relief is obtained in 20-50% of patients, with partial relief in 50-80% (**Level of evidence: 1a**). The onset of pain relief varies from a few days to 4 weeks. Re-irradiation should therefore not be considered sooner than 4-6 weeks after the first radiotherapy (**Level of evidence: 2b**). Pain relief can be obtained for 3-6 months (**Level of evidence: 1a**).

Mechanism of Pain Relief by Radiotherapy

The main mechanisms by which pain relief is obtained after radiotherapy are tumour shrinkage (**Level of evidence: 3**) and inhibition of the release of chemical pain mediators (**Level of evidence: 3**). However, tumor shrinkage is unlikely to account for the early period of pain relief. One hypothesis is that early reacting and very sensitive cells, plus the molecules they produce, are involved in the rapid onset of pain relief. Obvious candidate cells are the inflammatory cells that are largely present in the bone metastasis microenvironment. Reduction by ionizing radiation of the inflammatory cells inhibits the release of chemical pain mediators and is probably responsible for the rapid reaction seen in some patients (**Level of evidence: 3**).

Imaging

The detection of bone metastases is usually based on technetium-99m bone scintigraphy, which lacks diagnostic specificity (**Level of evidence: 3**). The addition of single photon emission computed tomography (SPECT) to planar acquisition has been reported to improve the diagnostic accuracy of bone scintigraphy (**Level of evidence: 2b**). Regions of increased uptake must be further investigated. Plain films have a false-negative rate of 10-17% (**Level of evidence: 3**). At least 50% erosion must be present for a change to be seen on plain films (**Level of evidence: 3**). The combination of bone scintigraphy and plain films results in specificity of 64% and sensitivity of 63% (**Level of evidence: 3**).

Because of the complex anatomy of the vertebrae, computed tomography (CT) is more useful than conventional radiography for evaluating the location of lesions and analysing bone destruction and condensation. When combined with myelography, excellent information about the bony anatomy and an accurate view of the compressed neural elements is provided (**Level of evidence: 3**). However, CT myelography is invasive and time-intensive, and so, particularly when spinal cord compression is suspected, MRI is currently the gold standard for detection and therapeutic management (**Level of evidence: 2B**), with sensitivity of 93% (**Level of evidence: 3**) and specificity of 96% (**Level of evidence: 3**).

Radiotherapy Scheme

Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (**Level of evidence: 1a**). However, the rates of retreatment and pathological fractures are higher after single fraction radiotherapy (**Level of evidence: 1a**).

A single fraction is the treatment of choice for alleviating bone pain because of its greater convenience for the patient (**Level of evidence: 1a**), as well as its faster patient turn-over for the radiotherapy unit and lower cost (**Level of evidence: 3**). The recommended dose is 8 Gy (**Level of evidence: 1a**). With lower doses, pain relief can be achieved in a significant number of patients (**Level of evidence: 1b**). However, studies have indicated that 4 Gy is less effective than 8 Gy (**Level of evidence: 1b**). A dose of 6 Gy gives similar results to those obtained with 8 Gy, but has been insufficiently studied (**Level of evidence: 1b**). These lower doses should be borne in mind in case there is a need for a third retreatment, or if there is concern about radiation tolerance (**Level of evidence: 2b**).

In cases of oligometastases (≤5 metastases), a case can be made for aggressive therapy, such as radiosurgery or high-dose radiotherapy, in order to improve survival (**Level of evidence: 3**).

Spinal Cord Compression

Corticosteroids reduce oedema and might have an oncolytic effect on certain tumours (e.g., lymphoma, breast cancer, leukaemia). However, both the extent of the benefit obtained from corticosteroids, and what the optimal dosage is, are unclear. High dose corticosteroids carry a significant risk of adverse effects. One randomised controlled trial of patients with carcinomatous metastatic spinal cord compression compared radiotherapy with or without dexamethasone, and showed significantly better functional outcome when dexamethasone was added (**Level of evidence: 1b**).

Radiotherapy is recommended as the primary treatment for patients who do not fulfill the recommendations for surgery listed below. For patients whose chances of survival are estimated to be poor, a short course of radiotherapy is advised (e.g., 1 x 8 Gy or 2 x 8 Gy) (**Level of evidence: 3**).

There have not been any trials comparing radiotherapy doses in patients with a good prognosis, so no conclusions can be drawn about the optimal dose of radiotherapy for those patients. However, in general, a multifraction regimen (10 x 3 Gy) is preferable in these patients as it allows for a higher dose and thus greater reduction in tumour size (**Level of evidence: 2a**).

Until the mid-1980s, posterior **decompressive laminectomy** was viewed as the only surgical option for patients with spinal cord compression. However, several studies have shown that decompressive laminectomy offers no additional benefit over conventional radiotherapy in terms of maintaining and recovering neurological function and pain control (**Level of evidence: 2b**). In addition, laminectomies are associated with important complications, most significantly wound infections, and new or worsened pre-existing spinal instability (**Level of evidence: 2b**).

Several uncontrolled surgical trials and one meta-analysis have since indicated that **direct decompressive surgery** is superior to radiotherapy alone with regard to regaining ambulatory function, pain relief and recovering sphincter function (**Level of evidence: 1a**). However, the decision to pursue surgery must be tempered by awareness of the significant morbidity and mortality risks that accompany it. Careful patient selection is of utmost importance. The criteria for the selection of candidates for primary therapy for spinal cord compression are shown in the table below (**Level of evidence: 3**).

Criteria for Selecting Patients for Primary Therapy for Spinal Cord Compression

Absolute Criteria	Surgery	Radiotherapy
Operability	Medically operable	Medically inoperable
Duration of paraplegia	<48 h	≥48 h
Life expectancy	≥3 months	<3 months
Radiosensitivity		Highly sensitive
Relative Criteria		
Diagnosis of primary tumour	Unknown	Known
Bone fragments with compression	Present	Absent

Number of foci of compression	1 focus	>1 foci

A randomised, prospective trial has demonstrated that patients treated with a combination of **surgery** followed by **radiotherapy** can remain ambulatory longer, and those who are not ambulatory at presentation have a better chance of regaining ambulatory function, than those treated with radiotherapy alone (**Level of evidence: 1b**).

Pathological Fractures

In patients with impending pathological fracture, a prophylactic orthopaedic procedure should be considered. Several publications advise post-operative radiotherapy after (prophylactic) orthopaedic procedures for bone metastases (**Level of evidence: 3**). Some authors argue that if bone cement is used for fixation, postoperative radiotherapy is not needed (**Level of evidence: 3**).

Side-effects

Side-effects are related to the total dose, fractionation size and the localisation of the metastases (**Level of evidence: 3**) and include:

- Pain flare-up (within 24 hours and due to oedema)
- Symptoms depend on the treatment field and location and can include:
  - Nausea (especially with larger fields)
  - Diarrhea
  - Irritation of the throat and oesophagus

These side-effects are mostly transient within a few days.

Physical/Psychological Therapies

Physical Therapies

Physical techniques can be used to optimize function in patients with chronic cancer pain or enhance analgesia through the application of modalities such as electrical stimulation, heat or cryotherapy. The treatment of lymphoedema with wraps, pressure stockings or pneumatic pump devices can both improve function and relieve pain and a feeling of heaviness. The use of orthotic devices can immobilise and support painful or weakened structures, and assistive devices can be of great value to patients with pain precipitated by weight-bearing or ambulation (**Level of evidence: 4**).

Psychological Therapies

Psychological approaches are an integral part of the care of cancer patients with pain. All patients can benefit from psychological assessment and support. Therapies include the following.

- Cognitive-behavioural interventions can help some patients decrease the perception of distress engendered by the pain through the development of new coping skills, and the modification of thoughts, feeling and behaviours.
- Relaxation methods may be able to reduce muscular tension and emotional arousal, or enhance pain tolerance.
- Other approaches reduce anticipatory anxiety, which can lead to avoidant behaviours, or lessen the distress associated with the pain.

Pharmacotherapy

Antibiotics

Antibiotics may be analgesic when the source of the pain involves infection (e.g., pyonephrosis, abscess, osteitis pubis). In some cases, infection may be occult and confirmed only by the symptomatic relief provided by empirical treatment with these drugs (**Level of evidence: 2b**).

Chemotherapy

The likelihood of a successful effect on pain is generally related to the likelihood of tumour response. There is a strong clinical impression that tumour shrinkage is generally associated with relief of pain, although there are some reports of analgesic value even in the absence of significant tumour shrinkage (**Level of evidence: 1a**).

Bisphosphonates

Effects and Side Effects

The main effects are:

- Decrease of the risk of skeleton-related events (for example hormone refractory prostate cancer with bone metastasis (**Level of evidence: 1b**) (**Grade of recommendation: A**).
- Pain response in 60-85% of the patients (**Level of evidence: 1b**) (**Grade of recommendation: A**).

Points for Attention

The main points to note are (**all grade B recommendations**):

- Recognise and treat dehydration before administration of bisphosphonates
- A reduction in the dose is necessary in the event of impaired renal function while using zoledronate (**Level of evidence: 2**).
- Avoid simultaneous administration of aminoglycosides
- Perform clinical examination of the patient's mouth and jaws; avoid oral/dental surgery during administration of IV bisphosphonates (**Level of evidence: 2**).

Systemic Analgesic Pharmacotherapy — the 'Analgesic Ladder'

An expert committee convened by the Cancer Unit of the WHO has proposed a useful approach to drug selection for cancer pain, which has become known as the 'analgesic ladder'. When combined with appropriate dosing guidelines, this approach is capable of providing adequate relief to 70-90% of patients. Emphasizing that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps (**Level of evidence: 1a**).

Step 1

Patients with mild to moderate cancer-related pain should be treated with a non-opioid analgesic, which should be combined with an adjuvant analgesic if a specific indication for one exists.

Step 2

Patients who present with moderate to severe pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesic, should be treated with a weak opioid. This treatment is typically accomplished using a combination product containing a non-opioid (e.g., aspirin or paracetamol) and an opioid (such as codeine, oxygenate or propoxyphene*). This drug can also be co-administered with an adjuvant analgesic.

*Note from the National Guideline Clearinghouse (NGC): On November 19, 2010, the U.S. Food and Drug Administration (FDA) notified healthcare professionals that Xanodyne Pharmaceuticals has agreed to withdraw propoxyphene, an opioid pain reliever used to treat mild to moderate pain, from the U.S. market at the request of the FDA, due to new data showing that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. See the FDA Web site for more information.

Step 3

Patients who present with severe pain, or who fail to achieve adequate relief following appropriate administration of drugs on the second rung of the 'analgesic ladder', should receive a strong opioid, such as morphine or hydromorphone. This drug may also be combined with a nonopioid analgesic or an adjuvant drug.

Opioid Analgesics

Opioid Administration

Non-invasive Routes

Oral routes are the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia, and those who are unable to utilise or tolerate the oral route.

Rectal suppositories containing oxycodone, hydromorphone, oxycodone and morphine in combination have been formulated, and controlled-release morphine tablets can also be administered per rectum. The potency of opioids administered rectally is believed to approximate to oral dosing.

Transdermal routes: fentanyl and buprenorphine are the opioids for transdermal administration. The system has been demonstrated to be effective in post-operative pain and cancer pain. In addition, the fentanyl transdermal therapeutic system dosing interval is usually 72 hours, but some patients require a 48-hour schedule. There is some interindividual variability in fentanyl bioavailability by this route, and this phenomenon, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases. The efficacy of fentanyl administered transdermally is equal to morphine. The incidence of side-effects such as sedation and constipation are lower compared with morphine (**Level of evidence: 1b**).

Sublingual absorption of any opioid could potentially yield clinical benefits, but bioavailability is very poor with drugs that are not highly lipophilic and the likelihood of an adequate response is consequently low. Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief of mild to moderate cancer pain. Overall, however, the sublingual route has limited value due to the lack of formulations, poor absorption of most drugs, and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl, which incorporates the drug into a sugar base, is useful for providing rapid relief of breakthrough pain. Additionally, this opioid delivery system using fentanyl is more effective in terms of pain relief than oral morphine (**Level of evidence: 2**).

Recommendation

Oral transmucosal administration of fentanyl should be used to provide rapid pain relief of breakthrough pain. The starting dose is 400 micrograms; or 200 micrograms in the elderly, those with a history of opioid sensitivity or underlying pulmonary disease (**Grade of recommendation: B**).

Invasive Routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is not available. Repeated parenteral bolus injections, which can be administered by intravenously (IV), intramuscularly (IM) or subcutaneously (SC), may be useful in some patients, but are often compromised by the occurrence of prominent 'bolus' effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repetitive IM injections are a common practice, but they are painful and offer no pharmacokinetic advantage; their use is not recommended.

Changing Routes of Administration

The switch between oral and parenteral routes should be guided by a knowledge of relative potency to avoid subsequent overdosing or under dosing. In calculating the equianalgesic dose, the potencies of the IV, SC and IM routes are considered equivalent. Perform changes in steps slowly (e.g., gradually reducing the parenteral dose and increasing the oral dose over a 2-3 day period) (**Level of evidence: 3**).

Adverse Effects and their Management

Addiction and Dependence

Confusion about physical dependence and addiction augment the fear of opioid drugs and contribute substantially to the under treatment of pain. Patients with chronic cancer pain have a 'therapeutic dependence' on their analgesic

pharmacotherapy. This relationship may or may not be associated with the development of physical dependence, but is virtually never associated with addiction. The medical use of opioids is very rarely associated with the development of addiction. Although there are no prospective studies in patients with chronic cancer pain, there is extensive clinical experience that affirms the extremely low risk of addiction in this population (**Level of evidence: 3**). Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is extremely small.

<u>Adjuvant Analgesics</u>

An 'adjuvant analgesic' is defined as a drug that has a primary indication other than pain but is analgesic in some conditions. These drugs may be combined with primary analgesics in any of the three steps of the 'analgesic ladder' to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side-effects. In the management of cancer pain, adjuvant analgesics can be broadly classified on the basis of conventional use. The following three groups are distinguished.

- **Corticosteroids**: These are among the most widely used adjuvant analgesics. They have been demonstrated to have analgesic effects, to improve quality of life significantly, and to have beneficial effects on appetite, nausea, mood and malaise in the cancer population. The mechanism of analgesia produced by these drugs may involve anti-oedemic effects, anti-inflammatory effects, and a direct influence on the electrical activity in damaged nerves. Patients with advanced cancer who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroids (e.g., dexamethasone 1-2 mg twice daily) (**Level of evidence: 2a**).

- **Neuroleptics**: The role of neuroleptic drugs in the management of cancer pain is limited. Methotrimeprazine is a proven analgesic that has been very useful in bedridden patients with advanced cancer who experience pain associated with anxiety, restlessness or nausea. In this setting, the sedative, anxiolytic and antiemetic effects of this drug can be highly favorable, and side-effects, such as orthostatic hypotension, are less of an issue. A prudent dosing schedule begins with 5-10 mg every 6 hours, which is gradually increased as needed (**Level of evidence: 1a**).

- **Benzodiazepines**: Benzodiazepines have an analgesic effect, but this must be balanced by the potential for side-effects, including sedation and confusion. These drugs are generally used only if another indication exists, such as anxiety or insomnia (**Level of evidence: 2b**).

Treatment of Neuropathic Pain

<u>Antidepressants</u>

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain. The primary mode of action is an interaction with pathways running through the spinal cord from serotoninergic and noradrenergic structures in the brain stem and mid-brain. Tricyclic antidepressants (TCA) including amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine), are often the first drugs selected to alleviate neuropathic pain (**Level of evidence: 1a**).

Duloxetine enhances both serotonin and norepinephrine function in descending modulatory pathways. It has weak affinity for the dopamine transporter and insignificant affinity at several neurotransmitters, including muscarinic, histamine, glutamate, and gamma-aminobutyric acid (GABA) receptors. Duloxetine has demonstrated a significant pain-relieving effect with a generally favourable side-effect profile in painful diabetic neuropathy (**Level of evidence: 1b**).

Recommendation

- Amitriptyline and nortriptyline are the first line treatment for neuropathic pain; nortriptyline has fewer side-effects (**Grade of recommendation: A**).

- TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention

- Duloxetine is the first-line treatment for neuropathic pain due to diabetic polyneuropathy (**Grade of recommendation: A**).

- Duloxetine may be tried as an analgesic in other neuropathic pain syndromes (**Grade of recommendation: Good Clinical Practice**).

<u>Anticonvulsant Medication</u>

The rationale for the use of antiepileptic drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain. Different anticonvulsants have demonstrated pain relief by a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca2+ or Na+), effects on neurotransmitters (enhancement of gamma-aminobutyric acid [GABA], inhibition of glutamate release), and/or neuromodulation systems (blocking the N-methyl-D-aspartate [NMDA] receptor). Initially, carbamazepine and phenytoin were used for the treatment of trigeminus neuralgia. Although both drugs reduce neuropathic pain, their attendant side-effects and complicated pharmacokinetic profile limit their use in treating neuropathic pain. Despite the introduction of these newer anticonvulsants with a more favourable side-effect profile, carbamazepine remains the drug of choice in treatment of trigeminus neuralgia (**Level of evidence: 1a**). However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with similar mechanism of action to that of carbamazepine but with a better side-effect profile, may replace carbamazepine for treating trigeminus neuralgia.

Gabapentin and pregabalin (**Level of evidence: 1a**) are emerging as first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy.

Recommendation

Gabapentin and pregabalin are first line treatments for neuropathic pain, especially if TCAs are contraindicated (**Grade of recommendation: A**).

<u>Topical Analgesics</u>

Topical treatments for neuropathic pain include the 5% lidocaine patch, and capsaicin. The 5% lidocaine patch, a targeted peripheral analgesic, is effective in the treatment of post-herpetic neuralgia and a variety of other focal peripheral neuropathies (first-line pharmacological treatment; **Level of evidence: 1b**). The 5% lidocaine patch (up to three patches, once daily for 12 hours) is applied to the painful skin, covering as much of the affected area as possible.

Capsaicin causes pain due to a release of substance P (initiating nociceptive firing) from the nociceptive terminals. Subsequently, an analgesic response follows because prolonged exposure to capsaicin desensitises the nociceptive terminals and elevates the pain threshold. Capsaicin (third-line pharmacological treatment) reduces pain in a variety of neuropathic pain conditions (including post-herpetic neuralgia, diabetic neuropathy and painful polyneuropathy), and it is applied in a 0.075% concentration (**Level of evidence: 3**).

> **Recommendation**
>
> - Lidocaine 5% should be used as an adjuvant in patients suffering from postherpetic neuralgia (**Grade of recommendation: A**).
> - Capsaicin may be used as an adjuvant in patients with neuropathic pain (**Grade of recommendation: C**).

N-methyl-D-aspartate (NMDA) Receptor Antagonists

Subanaesthetic doses of ketamine, and its active enantiomer S (+)-ketamine, given parenterally, neuraxially, nasally, transdermally or orally, alleviate pain post-operatively and in a variety of neuropathic pain syndromes, including central pain (**Level of evidence: 2b**).

> **Recommendation**
>
> Ketamine is effective as an analgesic in neuropathic pain. However, it may be responsible for severe life-threatening side-effects and should be reserved for specialized pain clinics as a last resort (third-line treatment) (**Grade of recommendation: B**).

Other Drug Treatments

Baclofen, a muscle relaxant, exerts its analgesic effect via an agonistic effect on the inhibitory GABAB-receptors. Baclofen has demonstrated efficacy in patients with trigeminal neuralgia, but not in patients with other neuropathic pain conditions. However, this analgesic also has antispasticity properties and may induce analgesia by relieving muscle spasms, a frequent accompaniment of acute neuropathic pain. Baclofen can be considered a second-line agent for trigeminus neuralgia, or a third-line agent in neuropathic pain syndromes (**Level of evidence: 3**).

Clonidine, an alpha 2-adrenoreceptor agonist, is available as a patch for transdermal administration and has been used in neuropathic pain states. When used topically, it seems to enhance the release of endogenous encephalin-like substances. Its use in neuropathic pain treatment, however, is focused on intrathecal or epidural administration, in combination with an opioid and/or local anaesthetics. Clonidine has been shown to improve pain control in combination with intrathecal opioids and/or local anaesthetics because of a possible supra-additive effect during neuropathic pain treatment (**Level of evidence: 2b**).

See Figure 5 in the original guideline document for a summary of the treatment of neuropathic pain.

Invasive Analgesic Techniques

Peripheral Nerve Catheterization in the Management of Cancer Pain

Tumour infiltration or compression of a peripheral nerve or plexus can result in severe neuropathic pain resistant to pharmacological treatment. In these patients the following is recommended.

> **Recommendation**
>
> Reversible regional anaesthetic techniques must be considered for the management of neuropathic pain (**Grade of recommendation: Good Clinical Practice**).

Neurolytic Blocks to Control Visceral Cancer Pain

A coeliac plexus block is indicated to treat pain secondary to malignancies of the retroperitoneum or upper abdomen (distal part of the stomach, pancreas, liver, gall bladder) (**Level of evidence: 1b**). A superior hypogastric plexus block has proven utility for pelvic pain (rectum, vaginal fundus, bladder, prostate, testes, seminal vesicles, uterus and ovaries) due to a neoplasm that is refractory to more conservative (i.e., pharmacological) treatment (**Level of evidence: 3**).

Epidural and Intrathecal Opioid Application

The delivery of low opioid doses near the sites of action in the spinal cord may decrease supraspinally-mediated adverse effects. Compared with neuroablative therapies, spinal opioids have the advantage of preserving sensation, strength and sympathetic function. Contraindications include bleeding diathesis, profound leucopenia and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter. In some patients, the addition of a low concentration of a local anaesthetic, such as 0.125-0.25% bupivacaine, to an epidural/intrathecal opioid has been demonstrated to increase analgesic effect without increasing toxicity. The potential morbidity for these procedures indicates the need for a well-trained clinician and long-term monitoring (**Level of evidence: 2**).

> **Recommendation**
>
> Continuous intrathecal or epidural administration of morphine may be considered in patients with inadequate pain relief despite escalating doses with sequential strong opioids, or the development of side-effects (nausea, vomiting, constipation, drowsiness, sedation) limiting further dose increase (**Grade of recommendation: B**).

Chemical Rhizotomy

Because of the significant risk of increased disability through weakness, sphincter incompetence and loss of positional sense, chemical rhizotomy of lumbosacral nerve roots is best reserved for patients with limited function and pre-existent urinary diversion. Adverse effects can be related to the injection technique (spinal headache, mechanical neural damage, infection and arachnoiditis) or to the destruction of non-nociceptive nerve fibres (**Level of evidence:**

4).

> **Recommendation**
>
> Lower end block may be considered in patients with intractable perineal pain (bladder, rectum) that has insufficient responded to more conservative therapy. This technique may only be performed in patients with loss of sphincter function (rectum and/or bladder) (**Grade of recommendation: C**).

Cordotomy

During cordotomy, the anterolateral spinothalamic tract is sectioned to produce contralateral loss of pain and temperature sensibility. The patient with severe unilateral pain arising in the torso or lower extremity is most likely to benefit from this procedure. The percutaneous technique is generally preferred. Significant pain relief is achieved in more than 90% of patients during the period immediately following cordotomy. Of surviving patients, 50% have recurrent pain after 1 year. Repeat cordotomy can sometimes be effective. The neurological complications of cordotomy include paresis, ataxia and bladder dysfunction (**Level of evidence: 3**).

Definitions:

Level of Evidence

1a Evidence obtained from meta-analysis of randomized trials

1b Evidence obtained from at least one randomized trial

2a Evidence obtained from at least one well-designed controlled study without randomization

2b Evidence obtained from at least one other type of well-designed quasi-experimental study

3 Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports

4 Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Grade of Recommendation

A. Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial

B. Based on well-conducted clinical studies, but without randomized clinical studies

C. Made despite the absence of directly applicable clinical studies of good quality

Clinical Algorithm(s)

None provided

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for some of the recommendations (see "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate pain management for patients that includes:

- Prolonged survival
- Optimal comfort
- Optimal function
- Relief of pain

Potential Harms

Surgery

Risks of surgery

Radionuclides

There is a risk of temporary increase in bone pain (pain flare) in about 10% of patients. Late side effects include temporary myelosuppression (platelets, white blood cells). Radiation exposure to family members and the public can be present for 2-4 days after samarium 153 (^{153}Sm) lexidronam, and 7-10 days after strontium 89 (^{89}Sr).

Radiotherapy

Side-effects are related to the total dose, fractionation size, and the localization of the metastases and include:

- Pain flare-up (within 24 hours and due to edema)

- Symptoms depend on the treatment field and location and can include:
  - Nausea (especially with larger fields)
  - Diarrhea
  - Irritation of the throat and esophagus

Non-opioid Analgesics

Potential adverse effects: bleeding diathesis due to inhibition of platelet aggregation gastroduodenopathy (including peptic ulcer disease) and renal impairment are the most common; less common adverse effects include confusion, precipitation of cardiac failure and exacerbation of hypertension; particular caution must be used in elderly patients and those with blood-clotting disorders, predisposition to peptic ulceration, impaired renal function and concurrent corticosteroid therapy.

Opioid Analgesics

Tolerance

Patients vary greatly in the opioid dose required to manage pain (400-2000 mg of intramuscular [im] morphine per 24 hours). The induction of true analgesic tolerance that could compromise the utility of treatment can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g., progressive disease) that would be capable of explaining the increase in pain.

Adverse Drug Interactions

The potential for additive side-effects and serious toxicity from drug combinations must be recognised. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs, such as anxiolytics, neuroleptics, and antidepressants. Likewise, constipation produced by opioids is probably worsened by anticholinergic drugs.

Respiratory Depression

Respiratory depression is potentially the most serious adverse effect of opioid therapy. All phases of respiratory activity (rate, minute volume and tidal exchange) may be impaired by these drugs. Clinically significant respiratory depression is always accompanied by other signs of central nervous system depression, including sedation, and mental clouding.

Sedation

Sedation usually persists until tolerance to this effect develops, usually within a period of days to weeks. It is useful to forewarn patients of this potential, and thereby reduce anxiety and encourage avoidance of activities such as driving that may be dangerous if sedation occurs. Some patients have a persistent problem with sedation, particularly in combination with other sedating drugs or co-existent diseases such as dementia, metabolic encephalopathy, or brain metastases.

Confusion and Delirium

Confusion is a greatly feared effect of opioid drugs, and mild cognitive impairment is common. However, similar to sedation, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to 1-2 weeks. Although persistent confusion attributable to opioids alone does occur, the aetiology of persistent delirium is usually related to the combined effect of the opioid and other contributing factors, including electrolyte disorders, neoplastic involvement of the central nervous system, sepsis, vital organ failure, and hypoxaemia.

Constipation

Constipation is the most common adverse effect of chronic opioid therapy.

Nausea and Vomiting

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility and delayed gastric emptying). In ambulatory patients, the incidence of nausea and vomiting has been estimated to be 10% to 40% and 15% to 40%, respectively. The likelihood of these effects is greatest at the start of opioid therapy.

Bisphosphonates

The main side-effects are:

- Flu-like symptoms (20% to 40%), bone pain, fever, fatigue, arthralgia and myalgia (all <10%)
- Hypocalcaemia (caution: rapid infusion – older patients with vitamin D deficiency)
- Acute renal failure (rapid infusion); always check renal function (glomerular filtration rate)
- Osteonecrosis of the jaw bones (only after intravenous [IV] therapy)
- Gastrointestinal symptoms can occur after oral administration (2% to 10%)

Chemical Rhizotomy

Because of the significant risk of increased disability through weakness, sphincter incompetence and loss of positional sense, chemical rhizotomy of lumbosacral nerve roots is best reserved for patients with limited function and pre-existent urinary diversion. Adverse effects can be related to the injection technique (spinal headache, mechanical neural damage, infection and arachnoiditis) or to the destruction of non-nociceptive nerve fibres.

Ketamine

Ketamine may result in unwanted changes in mood, conscious perception, and intellectual performance. Additionally, psychomimetic side-effects (including visual and auditory hallucinations, dissociation, and nightmares) are prominent with ketamine, limiting its usefulness and widespread use in treating neuropathic pain.

Cordotomy

The neurological complications of cordotomy include paresis, ataxia, and bladder dysfunction.

Contraindications

Contraindications

Radionuclides

Absolute Contraindications

- During or shortly after (less than 4 weeks) myelotoxic chemotherapy (all compounds except cisplatin) or hemibody external radiation therapy (less than 12 weeks). The delay between the end of these treatments and the start of metabolic radiotherapy is necessary in order to avoid severe haematopoietic toxicity. However, treatment can be safely combined with limited local field external beam radiotherapy.
- Known hypersensitivity to ethylene diamine tetramethylene phosphonate (EDTMP) or similar phosphonate compounds for samarium-153 lexidronam (^{153}Sm)
- Glomerular filtration rate (GFR) <30 mL/min
- Pregnancy; continued breastfeeding

Relative Contraindications

- Radiopharmaceuticals are not recommended for women of child-bearing age (negative pregnancy test and contraception absolutely required).
- Acute or chronic severe renal failure (GFR of 30-60 mL/min): the dose administered should be adapted (if the GFR is >60 mL/min, reduce the normal dosage by 25%; if the GFR is between 30 mL/min and 60 mL/min, reduce the normal dosage by 50%). Measurement of GFR is performed in the presence of elevated creatinine >20 mg/L.
- Solitary painful lesion: external limited field radiotherapy should be performed.

Epidural and Intrathecal Opioid Application

Contraindications include bleeding diathesis, profound leucopenia, and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter. In some patients, the addition of a low concentration of a local anaesthetic, such as 0.125% to 0.25% bupivacaine, to an epidural/intrathecal opioid has been demonstrated to increase analgesic effect without increasing toxicity. The potential morbidity for these procedures indicates the need for a well-trained clinician and long-term monitoring.

Qualifying Statements

Qualifying Statements

- These guidelines include general advice on pain assessment, with a focus on treatment strategies relating to common medical conditions and painful procedures. No attempts have been made to exhaustingly cover the topic of pain.
- It has to be emphasized that the current guidelines contain information for the treatment of an individual patient according to a standardized general approach.

Implementation of the Guideline

Description of Implementation Strategy

The European Association of Urology (EAU) Guidelines long version (containing all 19 guidelines) is reprinted annually in one book. Each text is dated. This means that if the latest edition of the book is read, one will know that this is the most updated version available. The same text is also made available on a CD (with hyperlinks to PubMed for most references) and posted on the EAU Uroweb website (http://www.uroweb.org/guidelines/online-guidelines).

Condensed pocket versions, containing mainly flow-charts and summaries, are also printed annually. All these publications are distributed free of charge to all (more than 10,000) members of the Association. Abridged versions of the guidelines are published in European Urology as original papers. Furthermore, many important websites list links to the relevant EAU guidelines sections on the association websites and all, or individual, guidelines have been translated to some 15 languages.

Implementation Tools

Foreign Language Translations

Personal Digital Assistant (PDA) Downloads

Pocket Guide/Reference Cards

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need
End of Life Care

Getting Better

Living with Illness

Staying Healthy

IOM Domain
Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Cancer pain management (general). In: Bader P, Echtle D, Fonteyne V, Livadas K, De Meerleer G, Paez Borda A, Papaioannou EG, Vranken JH. Guidelines on pain management. Arnhem, The Netherlands: European Association of Urology (EAU); 2010 Apr. p. 13-42. [204 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

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The European Association of Urology (EAU) Guidelines Group for Pain Management

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Financial Disclosures/Conflicts of Interest

All members of the General Pain Management Guidelines Writing Panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is kept on file in the European Association of Urology (EAU) Central Office database. This guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organization and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cancer pain management (general). In: Bader P, Echtle D, Fonteyne V, De Meerleer G, Papaioannou EG, Vranken JH. Guidelines on pain management. Arnhem, The Netherlands: European Association of Urology (EAU); 2009 Mar. p. 13-44. [204 references]

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Association of Urology Web site .

Print copies: Available from the European Association of Urology, PO Box 30016, NL-6803, AA ARNHEM, The Netherlands.

Availability of Companion Documents

The following is available:

- Guidelines on pain management in urology. Pocket guideline. Arnhem, The Netherlands: European Association of Urology (EAU); 2010 Apr. 13 p. Electronic copies: Available in English, Russian, Portuguese, and Spanish from the EAU Web site . The English version is also available as a handheld resource from the EAU Web site .

Print copies: Available from the European Association of Urology, PO Box 30016, NL-6803, AA ARNHEM, The Netherlands.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on June 25, 2010. This NGC summary was updated by ECRI Institute on Sept 23, 2010. The updated information was verified by the guideline developer on October 20, 2010. This summary was updated by ECRI Institute on March 16, 2011 following the U.S. Food and Drug Administration advisory on acetaminophen-containing prescription products.

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