



**Guideline for the Management of
Cancer Pain in Adults and Children:
A Review of Key Evidence-based
Practice Recommendations**

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**American Pain Society's Guideline
for the Management of Cancer
Pain in Adults and Children**



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Purpose of Presentation

- Provide an general update on cancer pain management
 - Cancer Pain Guideline from American Pain Society
- Areas addressed in the APS Guideline
 - Epidemiology of cancer pain
 - Methods of guideline development
 - Pain assessment
 - Cancer pain management
 - Management of procedure pain

Prevalence of Cancer Pain

- 50% of patients who are receiving active treatment for their cancer report moderate to severe pain
- 80% to 90% of patients in the terminal phases of their disease report moderate to severe pain
- Percentages have not changed for the past 30 years

Causes of Cancer Pain

- Cancer itself
 - Bone metastasis is the most frequent cause of cancer pain
 - Back pain = spinal cord compression
- Cancer treatment
 - Surgery
 - Chemotherapy
 - Radiation therapy
- Other causes of chronic pain
- Cancer pain can be acute or chronic

Negative Consequences of Unrelieved Cancer Pain



JPSM 10(2):120-128, 1995

- Descriptive study
- Oncology outpatients
- Comparison of patients with and without pain
- ↑ Anxiety
- ↑ Depression
- ↑ Fatigue
- ↓ QOL



Evidenced-Based Guidelines for Cancer Pain Management

- 1994 – Cancer Pain Management Guideline published by the Agency for Health Care Policy and Research
- 2001 – Cancer Pain Guideline published by National Comprehensive Cancer Network
- 2004 – Cancer Pain Guideline published by the American Pain Society




Effective Cancer Pain Management

- Perform pain assessments
 - Universal screening
 - Comprehensive assessment to determine the cause of the pain
 - Ongoing assessments to evaluate the effectiveness of the pain management plan
- Use a multimodal treatment plan
 - Opioid and nonopioid analgesics
 - Coanalgesics
 - Nonpharmacologic strategies
- Provide patient and family caregiver education
- Evaluate the need for a specialist referral




Components of Pain Assessment

- Universal screening
 - Inpatient setting
 - Outpatient setting (90% of cancer care)
- Initial comprehensive pain assessment
- Ongoing pain assessments




Initial Comprehensive Pain Assessment

- Detailed pain history – need to evaluate for:
 - Persistent pain
 - Breakthrough pain
- Psychosocial assessment
- Physical examination
- Diagnostic workup



Persistent versus Breakthrough Pain

- Persistent pain is constant pain that lasts for long periods of time
 - Requires the use of long-acting opioid analgesics
- Breakthrough pain consists of sudden flare-ups of pain that breakthrough the persistent pain
 - Types: spontaneous, incident, end-of-dose failure
 - Requires the use of short-acting opioid analgesics



Detailed Pain History

- Onset and temporal pattern
- Description
- Location
- Intensity/severity
- Aggravating and relieving factors
- Previous and current treatments and effectiveness
 - Pharmacologic
 - Nonpharmacologic
- Effects of pain on function

Psychosocial Assessment

- Effects of the pain problem and/or the chronic illness on the patient and the family caregiver
- Meaning of the pain to the patient and the family caregiver
- Significant past experiences with pain
- Changes in mood
- Typical coping responses to stress or pain
- Expectations regarding pain management
- Concerns about using opioid analgesics
- Economic impact of pain and its treatment
- Evaluation of support systems

Physical Examination and Diagnostic Tests

- Examine the site of the pain and evaluate common referral patterns
- Perform pertinent portions of the neurological examination depending on the pain complaint
- Perform appropriate diagnostic tests to facilitate the diagnosis of the cause of the pain
 - May need to give analgesics to facilitate the diagnostic workup

Ongoing Reassessments

- Use valid and reliable tools
- Perform the reassessments at appropriate intervals
- Document reassessments
- Components of the reassessment
 - Pain intensity
 - Extent to which pain interferes with function
 - Pain relief is a distinct parameter from pain assessment
 - Level of adherence with the pain management plan

Pain Management Principles

- Ascertain the cause of the pain
- Prevention of pain is better than treatment
- Manage chronic pain like other chronic medical conditions
- Individualize the dosing regimen
 - Usually with chronic cancer pain use ATC + PRN regimen
- The right dose of medication is the dose that works
- Titrate the dose of an analgesic medication to effect or undesirable side effects
- Anticipate and treat side effects


Cancer Pain Management Algorithms

- Anticipation of the need for pain management
 - Patients should receive a prescription for an analgesic medication, instructed to have the prescription filled, take the medication if pain occurs, and call their HCP
- Initial treatment of cancer pain
- Rapid titration of analgesic medications
- Slow titration of oral opioids
- Ongoing treatment

Pharmacologic Management


- Nonopioid analgesics
 - Acetaminophen
 - NSAIDs
 - COX-2 antagonists
- Opioid analgesics
- Co-analgesics or adjuvant analgesics






Nonopioid Analgesics

- Numerous choices available
- Most prescribed analgesic medications
- Useful for mild to moderate pain (1 to 4 on a 0 to 10 NRS)
- Significant inter-individual variability in response
- Exhibit a ceiling effect
- Narrow therapeutic dosing range
- Very few well-controlled studies in cancer pain management



Side Effects of Nonopioid Analgesics

- Gastrointestinal effects
 - Irritation
 - Bleeding
- Platelet inhibition
- Renal toxicity
- Central nervous system toxicity
- Hepatotoxicity (acetaminophen)



Opioid Analgesics

- Used for moderate to severe cancer pain
- Know the pharmacokinetics of various opioids and opioid preparations
- No ceiling effect to opioid analgesics
- Use equianalgesic doses of opioids
- Recognize and treat side effects
- Monitor patient outcomes and adherence with the analgesic regimen

Use Appropriate Combinations of Opioids and Nonopioids


- Numerous fixed dose combinations are available
 - Vicodin, Tylenol and codeine, Percodan, Percoset
- Analgesic synergy with the combination products
- Limited usefulness for severe cancer pain because of the ceiling doses of the nonopioid analgesic in the combination product
- Evaluate patient's use of OTC analgesics

Pharmacokinetics of Short-Acting Opioids

- Morphine, hydromorphone (Dilaudid)
 - Analgesic effect = 4 hours
 - $\frac{1}{2}$ life = 6 to 8 hours
- Meperidene (Demerol)
 - Analgesic effect = 2 hours
 - $\frac{1}{2}$ life = 4 to 6 hours
 - Normeperidene is a neurotoxic metabolite


Pharmacokinetics of the Relatively Long-Acting Opioids

- Levorphanol (Levodromeran)
 - Analgesic effect = 6 to 8 hours
 - $\frac{1}{2}$ life = 12 to 16 hours
- Methadone
 - Synthetic opioid with two nonopioid receptor activities
 - Serotonin reuptake inhibitor
 - NMDA antagonist
 - Analgesic effect = 6 to 12 hours
 - $\frac{1}{2}$ life = 15 to 60 hours




Use of Methadone for Chronic Pain Management

- Give methadone every 8 hours
- For oral morphine dose of < 90 mg/day give a methadone dose ratio of 1:4 (methadone to morphine)
- 90 to 300 mg of morphine = 1:8 ratio
- > 300 mg of morphine = 1:12 ratio
- Recent reports of patients on high doses of methadone (mean dose = 397 ± 283 mg) were at increased risk for Torsade de Pointes syndrome



Methadone Drug Interactions

<u>Increase methadone concentration</u>	<u>Decrease methadone concentration</u>
■ Ciprofloxacin	■ Phenobarbital
■ Diazepam	■ Phenytoin
■ Ethanol (acute use)	■ Rifampin
■ Fluconazole	■ Carbamazepine
■ Cimetidine	
■ Fluoxetine	



Controlled Release Opioids (morphine, oxycodone, hydromorphone, oxymorphone)

- Mainstay of chronic cancer pain management
- Opioid contained within a matrix
- Determine appropriate dosing using short-acting opioids
- Administer every 8 or 12 hours
- Prescribe a short-acting opioid for BTP – 10% to 15% of the ATC dose q2h

Transdermal Fentanyl


- Dose of drug controlled by a rate release membrane
- Pharmacokinetic considerations
 - 1 hour for onset of action
 - 17 to 40 hours to achieve steady state
- Fever and decreased peripheral circulation will effect absorption

Equianalgesic Dosing

Opioid	Oral	Parenteral
Morphine	30	10
Hydromorphone	7.5	1.5
Oxycodone	20	---
Meperidene	300	75
Fentanyl patch	50 mcg patch	100 mg of oral morphine


Oral Transmucosal Fentanyl Citrate

- OTFC (Actiq) consists of fentanyl incorporated into a sweetened lozenge
- Rapid absorption through the oral mucosa
 - Onset of action in 5 minutes
 - Peak effect = 5 to 10 minutes
- Approved for use in cancer patients with BTP who are tolerant to opioid analgesics (i.e., one week of therapy)
 - ≥ 60 mg/day of oral morphine
 - > 50 mcg/hour of transdermal fentanyl




Side Effects of Opioid Analgesics

- Anticipate the occurrence of the most common side effects
 - Constipation
 - Nausea and vomiting
 - Sedation
- Treat side effects prophylactically and aggressively
- Tolerance develops to all opioid-induced side effects except constipation




Side Effect Management

- Constipation
 - Most troublesome side effect
 - Treatment should be initiated when the opioid is initiated
 - Colace and senna
- Sedation
 - May be beneficial
 - Tolerance develops if dose is not titrated
 - Methylphenidate = 5 to 10 mg/day
 - Caffeine
- Respiratory depression
 - Differential diagnosis
 - Use of naloxone




Neuropathic Pain in Cancer

- Post-surgical pain syndromes
 - Occurs 6-8 weeks after surgery
 - Exact etiology is unknown
- Post-radiation therapy pain syndromes
 - Nerve plexus
- Post-chemotherapy pain syndromes
 - Platinum compounds
 - Taxanes
 - Thalidomide




Pharmacotherapeutic Considerations

- Efficacy (clinical trial data; clinical experience)
- Safety/tolerability
 - Potential drug interactions
- Ease of use (dosing, titration, drug-drug interactions, patient acceptability)
- Co-morbidities that may be relieved by independent effects of the analgesic (sleep disturbance, depression, anxiety)
- Cost
- Potentials risks of medication abuse or intentional or unintentional drug overdose




First-Line Medications for Neuropathic Pain

- Evidence-based treatment recommendations
(Arch Neurol 60:1524-1534, 2003; revision is submitted)
- Positive results from multiple RCTs
 - 35 different medications have been studied in over 100 RCTs --- with contradictory results
 - 30% reduction in pain intensity scores
- Extrapolation of efficacy in one type of neuropathic pain to another type is reasonable and clinically necessary
 - However, some types of neuropathic pain respond differently to treatment




First-Line Medications for Neuropathic Pain

- Four medications or medication classes are recommended for first line treatment
 - Antidepressant medications
 - Calcium channel alpha2-δ ligands
 - Topical lidocaine
 - First line medications under certain circumstances
 - Opioid analgesics
 - Tramadol




Mechanisms of Action

- **Anticonvulsants**
 - sodium-channel blockade; calcium-channel blockade
- **Tricyclic Antidepressants**
 - inhibit reuptake of norepinephrine and serotonin into presynaptic neurons
- **Opioids**
 - block neurotransmitter-release by nociceptive fibers, thus decreasing transmission of pain-producing signals
- **Topicals**
 - sodium-channel blockade; vanilloid receptor (VR1)




Topical Treatments for Neuropathic Pain

- **Aspirin preparations**
 - eg, aspirin in chloroform or ethyl ether
- **Capsaicin**
 - extracted from chili peppers
- **EMLA (eutectic mixture of local anesthetics)**
- **Topical lidocaine patch 5% (Lidoderm)**




Topical Lidocaine Patch 5%

- Lidocaine 5% in pliable patch
- Up to 3 patches applied once daily directly over painful site
 - 12 h on, 12 h off (FDA-approved label)
 - recently published data indicate 4 patches (18–24 h) safe
 - Adequate trial is 3 weeks
- Efficacy demonstrated in 3 randomized controlled trials on postherpetic neuralgia
- Systemic side effects unlikely
 - most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels
- Mechanical barrier decreases allodynia




Calcium Channel $\alpha 2-\delta$ Ligands

- Gabapentin (Neurontin) and pregabalin (Lyrica) both bind to the $\alpha 2-\delta$ subunit of voltage-gated calcium channels
 - Decrease the release of glutamate, NE, and substance P)
- RCTs with gabapentin show decreases in pain in PHN, DPN, phantom limb, diverse NP pain conditions




Gabapentin (Neurontin) in Neuropathic Pain Disorders

- FDA approved for postherpetic neuralgia
- Limited intestinal absorption
- Usually well tolerated; serious adverse effects rare
 - Dizziness, sedation, peripheral edema
- Peak effect: 2 to 3 h; elimination half-life: 5 to 7 h
- No significant drug interactions




Gabapentin for Neuropathic Pain

- Beginning dose = 100 to 300 mg every night or 100 to 300 mg TID
- Titration – increase by 100 to 300 mg three times daily every 1 to 7 days as tolerated
- Maximum dose = 1200 mg TID
- Adequate trial = 3 to 8 weeks for titration plus 2 weeks at the maximum tolerated dose




Pregabalin (Lyrica) for Neuropathic Pain

- Demonstrated efficacy in RCTs of PHN, DPN, and in mixed types of NP
- Onset of pain relief can be more rapid than with gabapentin
- Usually well-tolerated
- Produces dose dependent side effects like gabapentin
- No clinically important drug interactions
 - Dose reduction needed in patients with renal impairment
- Relatively new drug – no long-term safety data are available



Pregabalin (Lyrica) for Neuropathic Pain

- Beginning dose = 50 mg TID or 75 mg BID
- Titration – increase to 300 mg daily after 3-7 days, then by 150mg/d every 3-7 days as tolerated
- Maximum dose = 600 mg daily (200 mg TID or 300 mg BID)
- Adequate trial = 4 weeks



Antidepressants in Neuropathic Pain Disorders

- Classes of antidepressants
 - Tricyclic antidepressants
 - Tertiary amines (amitriptyline (Elavil))
 - Secondary amines (nortriptyline (Pamelor, Aventyl), desipramine (Norpramin))
 - Selective serotonin and NE reuptake inhibitors (SSNRIs)
 - Duloxetine (Cymbalta)
 - Venlafaxine (Effexor)
- Multiple mechanisms of action
- Randomized controlled trials and meta-analyses demonstrate benefit of tricyclic antidepressants (especially amitriptyline, nortriptyline, desipramine) for postherpetic neuralgia and diabetic neuropathy



Antidepressants in Neuropathic Pain Disorders

- Selective serotonin reuptake inhibitors (SSRIs): have demonstrated inconsistent results in diabetic neuropathy
- Duloxetine (Cymbalta) is a dual reuptake inhibitor of both serotonin and NE (SSNRI)
 - Demonstrated significant pain relief compared to placebo in three RCTs of DPN.
- Venlafaxine (Effexor) is a SSNRI that inhibits serotonin reuptake at lower doses and both serotonin and NE reuptake at higher doses
 - Demonstrated efficacy in RCTs of DPN, painful polyneuropathies, and post-mastectomy pain



Tricyclic Antidepressants for Neuropathic Pain Disorders

- Typically inexpensive
- Convenient once a day dosing
- Side effects are common
- Consider the possibility of more serious toxicities with TCAs
 - Sinus tachycardia
 - Increased ventricular ectopy
 - Risk for MI and sudden cardiac death



Tricyclic Antidepressants for Neuropathic Pain Disorders

- Use lowest effective dose of a TCA
- Avoid the use of TCAs in patients with:
 - Ischemic heart disease
 - Increased risk of sudden cardiac death
- Screening ECG is recommended before beginning treatment in patients > 40 years of age
- Use with caution in patients at risk for suicide or accidental death from overdose
- Increased risk for cognitive impairment, gait disturbances and falls in the elderly
- Toxic TCA levels can occur if they are administered together with drugs that inhibit cytochrome P450 2D6, such as SSRIs

Tricyclic Antidepressants: Adverse Effects

■ Commonly reported AEs (generally anticholinergic):

- blurred vision
- cognitive changes
- constipation
- dry mouth
- orthostatic hypotension
- sedation
- sexual dysfunction
- tachycardia
- urinary retention

AEs = adverse effects.

Fewest
AEs

Most
AEs


- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

Nortriptyline and Desipramine

- Beginning dose = 25 mg at bedtime
- Titration – increase dose by 25 mg/day, every 3 to 7 days as tolerated
- Maximum dose = 150 mg/day; if blood level of active drug and its metabolite is <100 ng/ml, continue titration with caution
- Adequate trial = 6 to 8 weeks with at least 2 weeks at maximum tolerated dose
- Use tertiary amine TCA only if secondary amine is not available


Duloxetine (Cymbalta)

- Beginning dose = 30 mg once a day
- Titration – increase dose to 60 mg once a day after one week
- Maximum dose = 60 mg twice a day
- Adequate trial = 4 weeks
- Side effects – nausea
- Precautions – hepatic dysfunction, renal insufficiency, alcohol abuse




Venlafaxine (Effexor)

- Beginning dose = 37.5 mg once or twice a day
- Titration – increase dose by 75 mg each week
- Maximum dose = 225 mg/day
- Adequate trial = 4 to 6 weeks
- Major side effects – nausea
- Precautions – concomitant use with tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation




Opioid Analgesics

- Oral opioids have demonstrated efficacy in RCTs with DPN, PHN, and phantom limb
- Opioids studied – oxycodone, morphine, methadone, levorphanol
- Treatment duration has not exceeded two months
- Long-term use of opioids requires additional research (neuroendocrine and immunologic effects)
- Risk of addiction/diversion
- Long-term therapy with opioids for NP is recommended only after trials of other first-line medications have proven ineffective




Opioid Analgesics

- Long-term therapy with opioids for NP is recommended only after trials of other first-line medications have proven ineffective
- Opioid analgesics provide prompt pain relief
- May need to consider the prescription of a short-acting opioid to address episodes of severe pain while another medication is being titrated to effectiveness




Opioid Analgesics

- Morphine, oxycodone
- Beginning dose = 10-15 mg every 4 hours as needed
- Titration = after 1-2 weeks, convert total daily dose to long-acting opioid and continue short-acting opioid PRN
- Maximum dose = non; consider referral to a pain specialist at doses above 120 to 180 mg per day)
- Adequate trial = 4 weeks




Tramadol Hydrochloride (Ultram)

- Mechanism of action
 - Norepinephrine and serotonin reuptake inhibitor
 - Relatively weak μ -opioid agonist
- Several published trials of efficacy
- Most common side effects – somnolence, constipation, dizziness, nausea, orthostatic hypotension
- Can cause or exacerbate cognitive impairment or gait disturbance in the elderly
- Can precipitate seizures in patients with a history of seizures




Tramadol Hydrochloride (Ultram)

- Concurrent use of SSRIs and SSNRIs may increase the risk of serotonin syndrome
- Beginning dose = 50 mg 1x or 2x/day
- Titration = increase by 50 to 100 mg/day in divided doses every 3 to 7 days as tolerated
- Maximum dose = 400 mg/day; in patients over 75 give 300 mg/day in divided doses
- Adequate trial = 4 weeks




Second-line Anticonvulsants

- Carbamazepine (Tegretol)
 - Efficacy in trigeminal neuralgia
 - Inconsistent results with other type of NP
- Lamotrigine (Lamictal)
 - Mixed results in terms of efficacy
 - Serious cutaneous hypersensitivity reactions
- Oxcarbazepine
 - No longer being developed as a treatment for NP



Second-line Antidepressants

- SSRIs - citalopram (Celexa) and paroxetine (Paxil) showed limited efficacy in RCTs of DPN
 - Fluoxetine (Prozac) did not demonstrate efficacy
- Bupropion (Wellbutrine)
 - Inhibits the reuptake of NE and dopamine
 - Effective in the treatment of NP



Step-wise Management of NP

- Step 1
 - Assess pain and establish NP diagnosis
 - Treat the underlying condition
 - Identify relevant co-morbidities
 - Provide patient education
 - Need for titration
 - Need for several analgesic trials
 - Not immediate pain relief

Step-wise Management of NP


- Step 2
 - Initiate therapy for the disease that is causing NP
 - Initiate pain management with one or more first line medications
 - Evaluate the patient for non pharmacologic interventions

Step-wise Management of NP

- Step 3
 - Reassess pain and QOL
 - If substantial pain relief (average pain $\leq 3/10$) and tolerable side effects, continue treatment
 - If partial pain relief (average pain $\geq 4/10$) add one of the other four first line medications
 - If no or inadequate pain relief ($< 30\%$ reduction) at target dose with an adequate trial – switch to an alternative medication


Step-wise Management of NP

- Step 4
 - If trials of first line medications alone and in combination fail, consider second line medications or referral to a pain specialist.




Issues with Cancer Pain Management

- Concerns about pain management and the use of opioids
 - Tolerance
 - Physical dependence
 - Psychological addiction
- Adherence with the analgesic regimen



Major Assumption Regarding Adherence

If a patient receives a prescription for a medication, s/he fills that prescription and takes the medication exactly as prescribed.

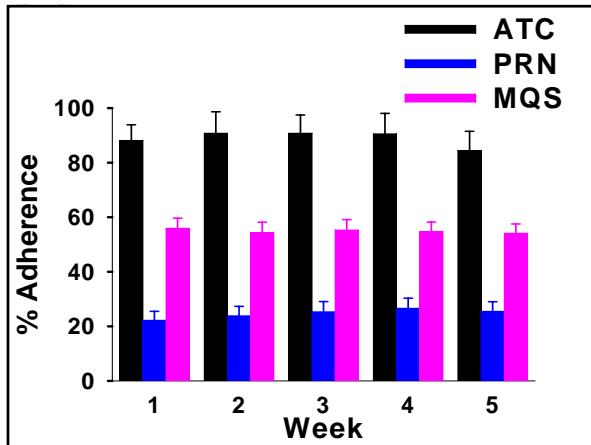


Impact of Non-adherence

- Estimates of non-adherence range from 15% to 93% (Kaplan & Simone, 1990)
- Average rate of non-adherence is 33%
- Cost of non-adherence with 10 medications estimated at \$396-\$792 million

Adherence with Cancer Pain Management

- Not been investigated in detail
- Two cross-sectional studies
 - DuPen & colleagues reported adherence rates for opioids between 62% and 72%
 - Ferrell & colleagues reported adherence rates that ranged from 0 to 270%



7 Difficulties Patients Described in Putting a Pain Management Regimen into Practice in the Home

1. Obtaining the prescribed medications
2. Accessing information
3. Tailoring the prescribed regimen to meet individual needs
4. Managing side effects
5. Cognitively processing and remembering complex information
6. Managing new or unusual pain
7. Managing multiple symptoms simultaneously



Patient Education in Cancer Pain Management

- Cornerstone of effective cancer pain management
- Education should involve the patient and their family caregiver
- Patient education should:
 - Clarify myths and misconceptions
 - Reassure patients and family caregivers that cancer pain can be effectively relieved
 - Reassure patients and family caregivers that addiction and tolerance are not problems associated with effective cancer pain management



Content of Written Pain Management Plan for Patients with Cancer

- The causes of cancer pain
- The types and rationale for analgesic medications
- Instructions for getting the analgesic prescriptions filled
- Specific instructions on how to dose and titrate their analgesic medications



Content of Written Pain Management Plan for Patients with Cancer

- Instructions on how to manage analgesic side effects
- Instructions on the storage and safe keeping of medications
- Who to call if pain is not relieved or increases in intensity or if side effects occur
- When and how to use nonpharmacologic approaches for pain management
