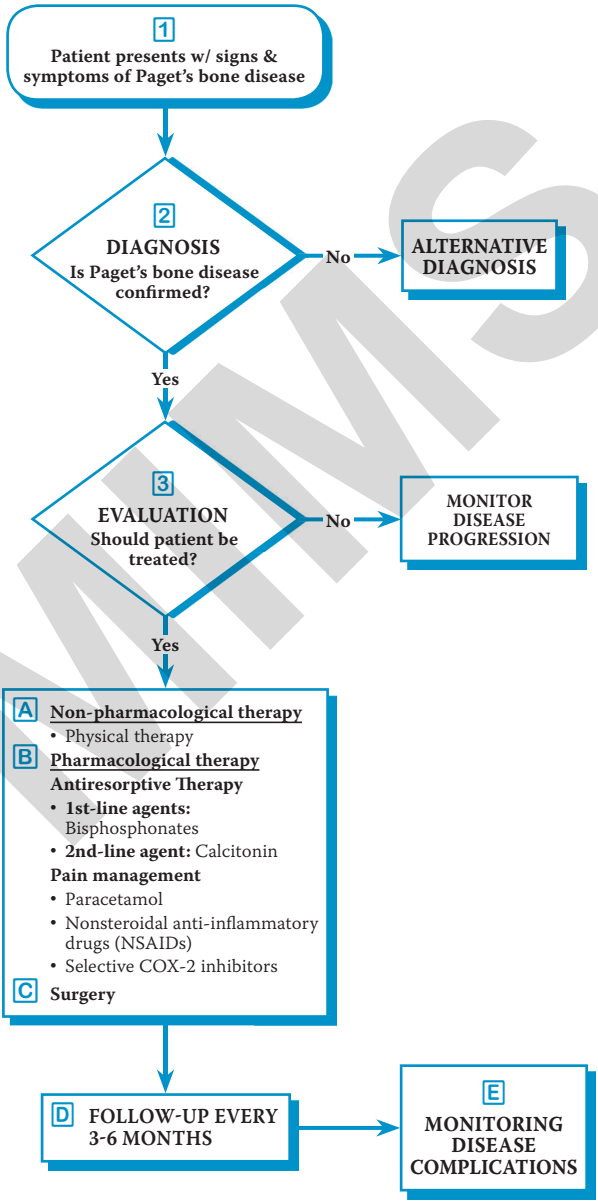
Paget's Bone Disease (1 of 11)



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1 CLINICAL MANIFESTATION

- Paget's bone disease, also known as osteitis deformans, is characterized by a significant increase in bone resorption & turnover in localized parts of the skeleton causing enlargement & thickening of the bone that is disordered & architecturally unstable
  - Prevalence increases w/ age, w/ men more commonly affected than women
  - Genetic factors &/or viral infection may play a role in the etiology
  - May affect one bone (monostotic) or several bones (polyostotic)
  - By decreasing frequency, involved bones may include pelvic bone & sacrum, spine, skull & femur, tibia, humeri & clavicles
  - Complications include fractures &/or fissures due to bone fragility, neurologic symptoms from nerve compression due to bone overgrowth or interference w/ blood supply, heart failure due to increased stress on the heart, & most serious complication is development of bone malignancy
- Pathophysiology:
  - Affected bone specimen (via biopsy) shows an evolution of skeletal lesions that starts as increased bone resorption by enlarged osteoclasts, followed by an increased osteoblastic activity producing a high rate of bone formation which results in deposition of a structurally abnormal bone
  - Late "burn out" phase, is an abnormal bone cell activity, which has markedly reduced & chaotic lamellar bone interspersed w/ woven bone

Signs & Symptoms

- Asymptomatic for a long period of time before signs & symptoms occur
- Bone or joint pain is the most common symptom
- Bone enlargement or bone deformity (eg skull enlargement, bowing of long bones)
  - Pelvis & tibia are one of the most commonly affected bones

2 DIAGNOSIS

Imaging Studies

X-ray

- Confirms the diagnosis of Paget's bone disease
- X-rays of the abdomen, facial bones, skull & both tibias are recommended as an initial diagnostic screening tool in patients suspected w/ Paget's bone disease
  - Detect 93% of bone lesions compared w/ 79% for an abdominal x-ray alone
- Findings include osteoporosis circumscripta in the skull, flame-shaped lesions in long bones, osteolytic lesions near thickened lesions, sclerotic bone, bowed limbs, fractures (ie "banana" or "chalk" transverse fractures)

Radionuclide Bone Scan

- Most sensitive test in identifying pagetic bone lesions
- Determines extent of bone involvement
- May also identify possible asymptomatic bones
- Areas of increased uptake of technetium-99m
- "Mouse face, clover or heart sign" pattern on scan of affected vertebra

CT Scan & MRI

- Enlarged bones w/ trabecular coarsening & increased cortical thickness may be seen in cross-sectional CT or MRI
- Anatomy is well demonstrated in complex structures (eg spine)
- Recommended for assessment of Paget's disease complications (eg basilar invagination, osteosarcoma, spinal stenosis)
  - Not routinely used as initial diagnostic tool

Lab Tests

- Serum total alkaline phosphatase (ALP) is recommended as the 1st-line biochemical screening test for patients suspected w/ Paget's bone disease

Measure biochemical markers to monitor the degree of bone formation & resorption

- Bone turnover: Measure serum alkaline phosphatase or bone specific alkaline phosphatase if the previous is normal
  - Serum alkaline phosphatase rises further if patient develops osteosarcoma
- Bone resorption: Measure type I collagen breakdown markers (eg serum C-telopeptide or urinary N-telopeptide)
- Serum calcium may be elevated in extensive Paget's disease that causes immobilization
- Urinary excretion of calcium & phosphorus may be normal or increased

3 EVALUATION

- Patient should be treated depending on the following:
  - Signs & symptoms of active Paget's bone disease (eg pain at pagetic site & bone deformity)
  - Asymptomatic but w/ biochemically active Paget's bone disease likely to cause complications in the future (eg skull base involvement that may lead to deafness)
  - Sites of pagetic lesions
  - Metabolic activity as determined by bone scan or bone turnover markers
  - Heart disease & extensive Paget's bone disease
- Patient w/ hypercalcemia resulting from immobilization should receive pharmacotherapy

PRINCIPLES OF THERAPY

- Goals of treatment are to ease pagetic pain, reduce activity of the disease, obtain full remission & prevent complications
- Important to note the location of the pagetic bone lesion & presence of comorbidities in treating asymptomatic patients
  - May initiate treatment if the serum ALP level is >2-4x the upper limit of normal (ULN) value
- Patients should receive adequate doses of Ca (1500 mg/day) & Vit D (800 units/day) to avoid hypocalcemia
- Patient should receive pharmacotherapy prior to elective surgery on pagetic site
- Response to therapy is guided by the following factors:
  - Pain reduction
  - Decrease in serum ALP level & normalization of other bone turnover markers
  - Abnormal bone replacement w/ normal lamellar bone
  - Radiographic healing
  - Improvement in patient's quality of life

A NON-PHARMACOLOGICAL THERAPY

Physical Therapy

- Improves muscle strength to help control certain types of pain
- Helps to maintain flexibility & joint range of motion, increase endurance & avoid deconditioning

B PHARMACOLOGICAL THERAPY

Antiresorptive Therapy

Bisphosphonates

- Eg Alendronic acid, Etidronic acid, Pamidronic acid, Risedronic acid, Tiludronate, Zoledronic acid
- Inhibit osteoclast activity & decrease bone resorption
- Decrease bone pain, improve neurological complications, stabilize hearing loss, heal bone lesions
  - Biochemical effects: Decrease by 50% of serum ALP concentrations & urinary excretion of hydroxyproline, pyridinoline & collagen-derived N-telopeptides
  - Prolonged effectiveness; effects remain after years of withdrawal
  - Relatively safe w/ variable side effect profiles among different bisphosphonates
- Recommended for active Paget's bone disease patients at risk of future complications & prior to surgery of pagetic bone
- Bisphosphonates may be used in patients presenting w/ fracture secondary to pagetic bone lesion
  - May be administered once the patient is stable
- Zoledronic acid is the most potent bisphosphonate approved in the United States for Paget's bone disease
  - Biochemical remissions are sustained & can last up to 1-2 years in most patients
  - Preferred drug because of its efficacy especially in patients w/ more extensive disease & those who are already on several drug treatment for other conditions

B PHARMACOLOGICAL THERAPY (CONT'D)

Bisphosphonates (Cont'd)

- Pamidronic acid is an alternative intravenous agent but is less potent & takes longer to infuse compared w/ Zoledronic acid & some patients may develop drug resistance
- Risedronic acid is more effective than Etidronic acid
  - Preferred in younger patients w/ limited disease
- Alendronic acid is more effective than Pamidronic acid in patients previously treated w/ other bisphosphonates
  - Alendronic acid is also more effective than Etidronic acid
  - Also preferred in younger patients w/ limited disease
- Neridronate is a nitrogen-containing bisphosphonate w/ comparable efficacy to Zoledronic acid as shown in a randomized trial & can be given intravenously or intramuscularly but is available only in some countries
- Associated w/ possible risk of atypical subtrochanteric & diaphyseal femur fractures

Calcitonin

- 32 amino acid hormone secreted by C cells of the thyroid gland
- Inhibit osteoclast activity & decrease bone resorption
- Alternative for patients who cannot tolerate bisphosphonates or when bisphophonates are contraindicated
- Decrease bone pain, improves neurological complications, stabilizes hearing loss, heals bone lesions
  - Biochemical effect: Up to 30-50% decrease in serum ALP & urinary hydroxyproline within 3-6 months & remain at these levels as long as treatment continues
  - Short-lived effectiveness; recurrences occur rapidly after withdrawal; high incidence of adverse effects (nausea, flushing)

Pain Management

- Resorptive therapy generally relieves pagetic pain
- Manage pain due to bone deformity, arthritis or neurological complications
- Relieve pagetic pain in addition to resorptive therapy

Paracetamol (Acetaminophen)

- Analgesic w/ antipyretic properties

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Act as non-selective inhibition of cyclooxygenase (COX)-1 & COX-2 pathway
- Have analgesic, anti-inflammatory & antipyretic properties

COX-2 Inhibitors

- Selective inhibition of COX-2 pathway without inhibiting COX-1 pathway
- Have analgesic, anti-inflammatory & antipyretic properties w/ reported improved gastrointestinal (GI) tolerance

C SURGERY

- Eg joint replacement, osteotomy, fracture repair
- Surgical patients should be pretreated w/ bisphosphonates to prevent serious bleeding during surgery due to hypervascularity, a symptom of active Paget's bone disease
  - No clinical trials yet on the recommended timing of such treatment
- Recommended for:
  - Pagetic fracture repair
  - Knee realignment to decrease mechanical pain, especially in cases where pharmacotherapy is ineffective
  - Hip/knee replacement especially in cases where antiresorptive therapy or osteoarthritis (OA) treatment is ineffective
  - Relief of compression due to pagetic vertebrae on the spinal cord or nerve roots

D FOLLOW-UP & MONITORING

Frequency & extent of follow-up will depend upon severity of disease

- Monitor serum ALP every 3-6 months to determine the biochemical response to bisphosphonate therapy
  - Once the value of serum ALP plateaus after 3-6 months of assessment, it can be measured 1-2x/year as a marker of bone activity
- A more specific bone formation/resorption marker other than ALP (ie amino-terminal propeptide of type 1 collagen [P1NP], β C-terminal propeptide of type-1 collagen [βCTx], N-terminal propeptide of type 1 collagen [NTx] assay) may be measured for patients w/ untreated monostotic Paget's disease
- Serial imaging tests (eg bone scan) are not generally useful in routine monitoring of treatment response
  - Bone scan may be helpful in monitoring treatment response after 6-12 months of treatment in patients w/ monostotic disease
- If treatment failure is apparent consider re-treatment 6 months after the initial therapy for the following:
  - Symptom relapse or persistence
  - >25% above nadir of serum ALP in asymptomatic patient
- Long-term evolution increases the risk for osteosarcoma on pagetic bone

E MONITORING DISEASE COMPLICATIONS

Complications & Management of Paget's Disease of the Bone

Hearing loss

- A potential complication of Paget's disease when the temporal bone is involved
- It is suggested to use a potent bisphosphonate to prevent worsening of hearing deficit

Osteoarthritis

- A relatively common complication, particularly in weightbearing joints such as the hip or knee
- The use of analgesics is suggested as an adjunctive therapy for mild-to-moderate joint pain caused by joint cartilage deterioration
- In patients w/ severe osteoarthritis, bisphosphonate therapy is recommended before undergoing elective total joint replacement

Paralysis

- Paraplegia occurs when there is a Paget's disease of the spine
  - Immediate treatment w/ a potent IV bisphosphonate is suggested along w/ neurosurgical consultation
- Due to correction of ischemia, most patients w/ paralysis recover well after medical therapy
- But in cases of severe structural damage, surgery may be required although the outcome may not be always optimal

Bowing of lower extremity

- Associated w/ impaired ambulation &/or severe joint pain
- A potent bisphosphonate prior to elective surgery is suggested on patients requiring an osteotomy to correct severe bowing of the lower extremity

Neoplasms

- A rare complication that arise from pagetic bone due to osteoblast proliferation
- Osteosarcoma or a giant cell tumor patients should be evaluated by an orthopedic surgeon
- For planned surgery, pretreatment w/ a potent bisphosphonate is suggested to reduce bleeding from adjacent pagetic bone

Congestive heart failure

- High output cardiac failure may occur, but is not common
- Both high cardiac output & low peripheral vascular resistance are present for patients suffering from extensive skeletal involvement
- An effective treatment improves the symptoms
- Bisphosphonate treatment in patients w/ Paget's disease w/ congestive heart failure is recommended

Dosage Guidelines

ANALGESICS (NON-OPIOIDS)		
Drug	**Dosage**	**Remarks**
Anilide		
Paracetamol (Acetaminophen)	500-1000 mg PO 4-6 hrly **Max dose:** 4 g/day	**Adverse Reactions** • Dermatologic effect (rash); Metabolic effects (may increase uric acid, glucose); Hematologic effects (anemia, neutropenia); Hepatic effects (increase bilirubin, alkaline phosphatase); Other effects (nephropathy, hypersensitivity reactions) **Special Instructions** • Avoid use in patients w/ severe hepatic or active liver disease • Used w/ caution in patients w/ chronic malnutrition, alcoholic liver disease, G6PD deficiency, severe renal impairment
Salicylic Acid & Derivatives		
Aspirin (Acetylsalicylic acid)	**Initial dose:** 2.4-3.6 g/day PO in divided doses **Maintenance dose:** 3.6-5.4 g/day PO in divided doses	**Adverse Reactions** • GI effects (N/V, dyspepsia, ulceration, hematemesis); Hematologic effect (iron deficiency anemia after long-term use, hypoprothrombinemia); Dermatologic effects (urticaria, angioedema); Hypersensitivity reactions (bronchospasm, dyspnea); Other effect (hepatotoxicity) • Salicylism (dizziness, tinnitus, deafness, sweating, N/V, headache, confusion) may occur after repeated use of large doses **Special Instructions** • May be given w/ food to decrease GI effects • Avoid use in patients w/ hemophilia or other hemorrhagic disorders, history of allergy to other NSAIDs, severe renal or hepatic impairment, pregnancy (especially 3rd trimester) • Used w/ caution in patients prone to dyspepsia, w/ gastric ulcer, asthma or allergic disorders, renal or hepatic impairment, dehydration, uncontrolled hypertension, G6PD deficiency, DM • Aspirin should be stopped several days prior to scheduled surgery

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Dosage Guidelines

ANALGESIC (OPIOID)

Drug	Dosage	Remarks
Dihydrocodeine	30 mg PO 4-6 hrly May increase up to 240 mg/day for severe pain **Max dose:** 60 mg/dose	**Adverse Reactions** • GI effects (N/V, constipation); CNS effects (drowsiness, confusion, raised intracranial pressure); Other effects (sweating, hypothermia, restlessness, decreased libido, miosis, muscle rigidity, pulmonary edema which may be potentially fatal) • High doses may lead to resp depression & hypotension w/ circulatory failure & deepening coma **Special Instructions** • Contraindicated in patients w/ resp depression, obstructive airways disease, acute alcoholism, convulsive disorders, head injuries & raised intracranial pressure • Use w/ caution in patients w/ hypothyroidism, adrenocortical insufficiency, asthma, impaired renal or hepatic function, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, myasthenia gravis • Oxycodone: Contraindicated for use in patients <18 yr
Oxycodone	*Individualize dose* **Opioid-naive patients:** **Initial dose:** 5-10 mg PO 12 hrly ***or*** 7.5 mg SC 24 hrly **Max dose:** 160 mg/day **Patients on chronic opioid therapy:** 5 mg PO 4-6 hrly ***or*** 1-10 mg IV bolus over 1-2 min 4 hrly ***or*** 2 mg/hr IV infusion starting dose, increased as necessary ***or*** 5 mg SC 4 hrly **Max dose:** 400 mg/day	

BISPHOSPHONATES

Drug	Dosage	Remarks
Alendronic acid (Alendronate)	40 mg PO 24 hrly x 6 mth	**Adverse Reactions** • Upper GI effects (GI discomfort, esophagitis, esophageal ulcers); Rashes (occasionally w/ photosensitivity) **Special Instructions** • Contraindicated in patients w/ severe renal impairment (Cr_{Cl} <35 mL/min), pregnancy, lactation • Administer w/ plain water 30 min before 1st food, beverage or medication of the day to enhance absorption - In an upright position, swallow the tablet, do not chew or suck - Do not lie down or ingest any food, liquid or drugs for 30 min following administration to facilitate drug delivery to stomach & to avoid esophageal irritation - Do not administer at bedtime or before arising for the day • Monitor serum ALP to assess effectiveness of treatment • Re-treatment may be considered for patients w/ evidence of relapse after 6 mth post-treatment evaluation period • Ca & Vit D supplementation is recommended if inadequate dietary intake

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Dosage Guidelines

BISPHOSPHONATES (CONT'D)		
Drug	**Dosage**	**Remarks**
Etidronic acid (Etidronate)	**Initial dose:** 5 mg/kg/day PO x <6 mth Doses >10 mg/kg/day should be reserved for severe cases & should not be given for >3 mth at a time **Max dose:** 20 mg/kg/day	**Adverse Reactions** • GI effects (abdominal cramps, diarrhea); Metabolic effects (mild hyperphosphatemia, hypocalcemia); CNS effects (depression, headache); Other effects (increased bone pain from mineralization defect, rarely rashes) **Special Instructions** • Should be taken on an empty stomach w/ no food, vitamins, minerals or antacids 2 hr before or after administration • Monitor serum ALP to assess effectiveness of treatment • Ca & Vit D supplementation recommended if inadequate dietary intake - Separate administration w/ Etidronic acid by 2 hr • Re-treatment (w/ initial or increased dosage) may be considered for patients w/ evidence of relapse after 3 mth post-treatment evaluation period
Pamidronic acid (Pamidronate)	30 mg slow IV once wkly up to total dose of 180 mg ***or*** 30 mg slow IV initially, then 60 mg slow IV once every other week up to total dose of 210 mg (60 mg: infusion rate of ≤15-30 mg/2 hr) **Max dose:** 90 mg/L May repeat dose after 6 mth until remission of disease or relapse occurs	**Adverse Reactions** • CNS effects (transient fever, fatigue, headache, insomnia); Metabolic effects (hypophosphatemia, hypokalemia); GI effects (N/V, anorexia, abdominal pain); Hematologic effects (anemia, granulocytopenia); Renal effect (increase in serum creatinine); Other effect (GU infection) **Special Instructions** • Use w/ caution in patients w/ renal impairment, severe hepatic impairment, cardiac disease - Each dose should not be >90 mg due to risk of renal toxicity • Do not give as bolus inj or w/ other bisphosphonates or Ca-containing IV infusions • Patients w/ pre-existing anemia, leukopenia or thrombocytopenia should be closely monitored during the 1st 2 wk of treatment • Monitor renal function, creatinine, serum electrolytes, Ca & phosphate before each dose • Monitor serum ALP to assess effectiveness of treatment • Ca & Vit D supplementation is recommended to help prevent hypocalcemia
Risedronic acid (Risedronate)	30 mg PO 24 hrly x 2 mth	**Adverse Reactions** • GI effects (abdominal discomfort, esophagitis, esophageal ulcers, glossitis, diarrhea, N/V); CNS effects (headache, dizziness, depression); CV effects (hypertension, peripheral edema); Other effects (musculoskeletal pain, cataract, tinnitus, infection, rarely osteonecrosis of the jaw) **Special Instructions** • Contraindicated in patients w/ abnormalities of the esophagus (eg stricture, achalasia), severe renal impairment • Administer same as Alendronate • Monitor serum ALP to assess effectiveness of treatment • Re-treatment w/ the same dosage may be considered for patients w/ evidence of relapse 2 mth after post-treatment evaluation period • Ca & Vit D supplementation is recommended if inadequate dietary intake, but to be taken a few hr apart from Risedronic acid

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BISPHOSPHONATES (CONT'D)		
Drug	**Dosage**	**Remarks**
Tiludronic acid (Tiludronate)	400 mg PO 24 hrly x 3 mth	**Adverse Reactions** • CV effects (flushing, peripheral edema, hypertension); CNS effects (fatigue, insomnia, headache, dizziness); GI effects (dysphagia, N/V); Metabolic effects (hypocalcemia, hypophosphatemia); Other effects (musculoskeletal pain, rashes, asthenia, ocular disturbances, rarely osteonecrosis of the jaw) **Special Instructions** • Contraindicated in patients w/ severe renal impairment, pregnancy • Use w/ caution in patients w/ mild to moderate renal impairment • Administer 2 hr apart from food, beverage & medication at any other time of the day or 30 min before bedtime - In an upright position, swallow the tablet w/ plenty of plain water (200 mL), do not chew or suck • Monitor serum ALP to assess effectiveness of treatment • Ensure Ca & Vit D supplementation to be taken 2 hr apart from Tiludronic acid
Zoledronic acid	5 mg IV infusion as single dose yearly	**Adverse Reactions** • Acute reaction may occur within the 1st 3 days following infusion • Metabolic effects (dehydration, hypocalcemia, hypophosphatemia); GI effects (N/V, constipation, anorexia, abdominal pain); Musculoskeletal effects (increased bone pain from mineralization defect, back pain); Renal effect (renal deterioration); CNS effects (fatigue, fever, headache, dizziness, insomnia); Other effects (rigors, anemia, neutropenia, dyspnea) **Special Instructions** • Contraindicated in patients w/ severe renal impairment • Use w/ caution in patients w/ mild to moderate renal impairment • Infuse over 15 min in a line separate from other medications - Ensure adequate hydration throughout therapy & maintain urinary output of 2 L/day • Monitor serum ALP to assess effectiveness of treatment • Monitor serum electrolytes, Ca, phosphate & Mg - Assess renal function before each dose • Consider dental exam w/ appropriate corrective action before initiating treatment in patients at risk of osteomyelitis & osteonecrosis of the jaws - Avoid invasive dental procedures while on treatment - Assess hard & soft tissues of oral cavity every 3-4 mth • Supplement w/ Calcium 1500 mg/day & Vit D 800 units/day 14 days after administration

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Dosage Guidelines

CALCITONIN

Drug	Dosage	Remarks
Calcitonin (Calcitonin salmon, Salcatonin)	50-100 IU IM/SC 24 hrly or every other day **Nasal spray:** 200-400 IU/day intranasal or in divided doses Duration: 3-18 mth	**Adverse Reactions** • Resp effects (rhinitis, nasal ulceration) CV effects (flushing, angina, hypertension); CNS effects (fatigue, depression, dizziness); GI effects after inj (N/V, diarrhea, abdominal pain); Other effects (musculoskeletal pain, flu-like symptoms, abnormal vision, inj site reaction, rashes) **Special Instructions** • Monitor serum alkaline phosphatase & urinary hydroxyproline concentration to assess effectiveness of treatment • Skin test should be administered before initiating therapy if parenteral soln will be used • Monitor for nasal irritation for use of nasal spray • Avoid ethanol which can increase risk of osteoporosis

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Drug	Dosage	Remarks
Acetic Acid Derivatives		**Adverse Reactions** • GI effects (nausea, GI discomfort, diarrhea, peptic ulceration, GI bleeding); CNS effects (headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, insomnia); Hypersensitivity reactions (angioedema, bronchospasm, rashes, Stevens-Johnson syndrome occur rarely); Hematologic effects (anemia, thrombocytopenia, neutropenia); Other effects (hepatotoxicity, nephrotoxicity, hematuria, fluid retention, photosensitivity, pancreatitis) • Coxibs has lesser GI effects **Special Instructions** • May be given w/ food to decrease GI effects • Avoid use in patients w/ active peptic ulceration, severe heart failure, history of allergy to Aspirin or other NSAIDs - Coxibs should not be used in patients w/ moderate heart failure, ischemic heart disease, peripheral arterial disease, cerebrovascular disease • Use w/ caution in patients w/ hypertension, infections, asthma or allergic disorders, hemorrhagic disorders, hepatic or renal impairment - Coxibs should be used w/ caution in patients w/ left ventricular failure, edema, history of cardiac failure, w/ risk factors for developing heart disease
Diclofenac (Diclofenac potassium, Diclofenac sodium)	75-150 mg/day PO in divided doses ***or*** 75-150 mg/day supp administered rectally ***or*** 75 mg IM 12-24 hrly	
Etodolac	200-400 mg PO 6-8 hrly **Max dose:** 1g/day	
Indometacin (Indomethacin)	**Initial dose:** 25-50 mg PO 8-12 hrly May increase dose by 25-50 mg/day at wkly intervals **Max dose:** 150-200 mg/day **For relief of morning stiffness & night pain:** 100 mg PO or supp rectally at bedtime **Max dose:** 200 mg/day (combined oral & rectal doses)	
Sulindac	100-200 mg PO 12 hrly May lower dose based on response **Max dose:** 400 mg/day	
Tolmetin	**Initial dose:** 400 mg PO 8 hrly **Maintenance dose:** 600-1800 mg/day PO in divided doses **Max dose:** 1800 mg/day	
COX-2 Selective Inhibitor		
Celecoxib	**Initial dose:** 400 mg PO once followed by 200 mg if necessary on 1st day **Maintenance dose:** 200 mg PO 12 hrly	
Etoricoxib	120 mg PO 24 hrly **Max dose:** 120 mg PO 24 hrly for 8 days	

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Dosage Guidelines

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) (CONT'D)		
Drug	**Dosage**	**Remarks**
Fenamic Acid Derivatives		**Adverse Reactions** • GI effects (nausea, GI discomfort, diarrhea, peptic ulceration, GI bleeding); CNS effects (headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, insomnia); Hypersensitivity reactions (angioedema, bronchospasm, rashes, Stevens-Johnson syndrome occur rarely); Hematologic effects (anemia, thrombocytopenia, neutropenia); Other effects (hepatotoxicity, nephrotoxicity, hematuria, fluid retention, photosensitivity, pancreatitis) • Coxibs has lesser GI effects **Special Instructions** • May be given w/ food to decrease GI effects • Avoid use in patients w/ active peptic ulceration, severe heart failure, history of allergy to Aspirin or other NSAIDs - Coxibs should not be used in patients w/ moderate heart failure, ischemic heart disease, peripheral arterial disease, cerebrovascular disease • Use w/ caution in patients w/ hypertension, infections, asthma or allergic disorders, hemorrhagic disorders, hepatic or renal impairment - Coxibs should be used w/ caution in patients w/ left ventricular failure, edema, history of cardiac failure, w/ risk factors for developing heart disease
Mefenamic	250-500 mg PO 8 hrly	
Oxicam Derivatives		
Lornoxicam	8-16 mg/day PO divided 8-12 hrly	
Meloxicam	7.5-15 mg/day PO as single dose **Max dose:** 15 mg/day	
Piroxicam	**Initial dose:** 40 mg PO 24 hrly *or* in divided doses x 2 days **Maintenance dose:** 20 mg PO 24 hrly x 1-2 wk	
Tenoxicam	20 mg PO 24 hrly **Maintenance dose:** 10 mg/day	
Propionic Acid Derivatives		
Fenbufen	900 mg/day PO in divided doses *or* 450 mg PO in the morning & 450 mg PO in the evening *or* 300 mg PO in the morning & 600 mg PO in the evening	
Ibuprofen[1]	600-1800 mg/day PO in divided doses May increase dose as required **Max dose:** 2.4 g/day	
Ketoprofen	25-50 mg PO 6-8 hrly **Max dose:** 300 mg/day ***or*** 100 mg to be administered rectally as supp 12-24 hrly	
Naproxen	**Initial dose:** 500 mg PO once **Maintenance dose:** 250 mg PO 6-8 hrly **Max dose:** 1275 mg/day on the 1st day, then 1000 mg/day thereafter	
Salicylic Acid & Derivative		
Diflunisal	500-1000 mg PO initially, then 250-500 mg PO 8-12 hrly **Max dose:** 1500 mg/day	
Other Agents		
Loxoprofen	60 mg PO 8 hrly *or* 60-120 mg PO 24 hrly	
Nabumetone	1000 mg PO as a single dose at bedtime Additional 500-1000 mg may be added as a morning dose in severe cases	
Nimesulide	100-200 mg PO 12 hrly	

[1]Preparations containing Ibuprofen & Paracetamol are available. Please see the latest MIMS for prescribing information.

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