IN THE NAME OF GOD

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IUMS

OTC THERAPY FOR PAIN

- Pain can be treated with non-prescription oral and topical analgesics.
- Patients with acute low back pain are candidates for self treatment.
- Management of acute back pain includes rest for 1-2 days and nonprescription oral or topical analgesics.

- Chronic low back pain requires medical evaluation before initiating therapy.

- Non-prescription oral analgesics are aspirin, diclofenac, ibuprofen, naproxen and paracetamol.

- Codeine is co-formulated with paracetamol or ibuprofen in some preparations.

- The NSAIDs are used to treat a wide variety of aches and pains, including headache, migraine, toothache, dysmenorrhoea and muscular and rheumatic pain.

- Topical analgesics are applied externally to relieve a variety of painful conditions. A wide range of preparations is available, including:

- NSAIDs (central and peripheral inhibition of cyclooxygenase (COX))

- local anaesthetics as the main constituents.

Treatment with oral analgesics

- **Non-steroidal anti-inflammatory drugs**
- Products formed from arachidonic acid also have a role in platelet aggregation.

- Aspirin interferes with their synthesis, producing a net anticoagulant effect by inhibiting platelet aggregation.

- In large doses, aspirin also competitively inhibits vitamin K in the synthesis of clotting factors.

- Ibuprofen has much less antiplatelet activity.

- Systemic analgesic therapy should be limited to 10 days of self care use

- Chronic use of NSAIDs leads to more severe and prevalent side effects (e.g., nephropathy, gastrointestinal ulcerations and bleeding, and the potential for cardiac events).

- NSAIDs may decrease renal blood flow and glomerular filtration rate as a result of inhibition of renal prostaglandin synthesis.

- Consequently, increased blood urea nitrogen and serum creatinine values can occur, often with concomitant sodium and water retention.

- Advanced age, hypertension, diabetes, atherosclerotic cardiovascular
- disease, and use of diuretics appear to increase the risk of renal toxicity with ibuprofen use.

- The ACR guidelines do express a strong recommendation to consider using topical NSAIDS rather than systemic NSAIDs in patients 75 years of age and older.

NSAIDs

- Bioavailability
- Metabolized by liver
- Excreted by kidney
- Ibuprofen sodium dehydrate is absorbed more rapidly and has a slightly shorter onset of action than that of standard ibuprofen.
- Duration of activity for naproxen sodium is up to 12 hours and 6-8hours for ibuprofen.

Table 26-4 Selected Nonsteroidal Anti-inflammatory Drugs

Salicylates

Acetylated: aspirin
Nonacetylated: trisalicylate, salsalate

Nonsalicylates[a]

Nonselective (traditional) NSAIDs: ibuprofen, naproxen, tolmetin, fenoprofen, sulindac, indomethacin, ketoprofen, ketorolac, flurbiprofen, piroxicam
Partially selective NSAIDs: etodolac, diclofenac, meloxicam, nabumetone
Selective COX-2 inhibitors: celecoxib, rofecoxib[b], valdecoxib[b]

[a] Based on COX-1/COX-2 selectivity ratio *in vitro*.
[b] Withdrawn from U.S. market.
COX-2, cyclo-oxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

Pharmacokinetics

- Exhibit several pharmacokinetic similarities, including high oral availability, high protein binding, and absorption as active drugs (except for sulindac and nabumetone, which require hepatic conversion for activity)

- The most important difference in NSAIDs is a serum half-life ranging from 1 hour for tolmetin to 50 hours for piroxicam, impacting the frequency of dosing and, potentially, compliance with therapy

- NSAIDs penetrate joint fluid, reaching approximately 60% of blood levels

نیمه عمر NSAID

- نیمه عمر این داروها متفاوت اند

اما به طور کل به دو دسته تقسیم بندی می شوند:

- کوتاه اثر (کمتر از 6 ساعت: ایبوپروفن، دیکلوفناک، کتوپروفن و ایندومتاسین)
- طولانی اثر (بیش از 6 ساعت: ناپروکسن، سلکوکسیب، ملوکسیکام، نابومتون و پروکسیکام)

- شروع اثر و طول اثر ضد درد NSAID ها متفاوت است .
- به طوریکه نیمه عمر طولانی تر دارو معادل شروع اثر آهسته تر داروست.
- علاوه بر این با دوزهای بالاتر، شروع اثر سریعتر، پیک و طول اثر بیشتر مشاهده می گردد. بنابراین بهتر است در شروع درمان، از دوزهای بالاتر داروهای با نیمه عمر کوتاه (مانند ایبوپروفن) استفاده شود و بعد از آنکه اثرات ضد دردی ایجاد شد، دوز دارو را کاهش دهیم.
- برای کنترل دردهای مزمن، تجویز NSAID با نیمه عمر طولانی تر (ناپروکسن، مهارکننده های COX-2) مناسبتر است (بعلت تجویز یکبار یا دو بار در روز آنها که موجب همکاری بیشتر بیمار می گردد).

Aspirin and ibuprofen

- **Uses**
- Both aspirin and ibuprofen are licensed for treatment of mild and moderate pain from a wide variety of causes, including:
- dental
- musculoskeletal pain and
- dysmenorrhoea,
- where their anti-inflammatory activity is particularly useful, and as antipyretics.

- Aspirin is no longer licensed for use in children under 16 years of age;
- **Child dosage depends on age. The dosages are 160 mg every 4 hrs for children 2 to 4 years of age**
- and 400 to 480 mg every 4 hrs for children 9 to 12 years of age.
- Salicylates should be given for no longer than 5 days for pain,
- 3 days for fever,
- and 2 days for sore throat without consulting a physician.
- breastfeeding mothers should also avoid aspirin.
- There is no evidence of an association between ibuprofen and Reye's syndrome.

TABLE 5-2 FDA-Approved Dosages for Nonprescription Analgesics in Children Younger than 12 Years[a]

		Ibuprofen (mg) Dose by Body Weight (mg/kg)	*Acetaminophen (mg)*	*Aspirin (mg)*
Age (years)	***Weight (lb)***	***5-10 mg/kg***	***10-15 mg/kg***	***10-15 mg/kg***
<2	<24	Ask a doctor[a]	Ask a doctor[a]	Ask a doctor[a]
2-3	24-35	100	160	160
4-5	36-47	150	240	240
6-8	48-59	200	320	320
9-10	60-71	250	400	400
11	72-95	300	480	480

[a] OTC labeling limits use to children over age 3. For patients seeking dosing advice for younger children, weight-based dosing is recommended.

- The most common side-effects are gastric irritation and bleeding.

- Minor gastric side-effects can be reduced by taking the drugs with or after food.

GI Effects of Nonselective NSAIDs

- In a meta-analysis of controlled trials involving some of the most commonly prescribed NSAIDs :

- The risk of gastrointestinal complications was highest with:

- Indomethacin >Naproxen>Diclofenac >Piroxicam >Tenoxicam >Ibuprofen> Meloxicam

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- Are age 60 or older.
- Have had stomach ulcers or bleeding problems.
- Take a blood thinning (anticoagulant) or steroid drug.
- Take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others).
- Have 3 or more alcoholic drinks every day while using this product.
- Take more or for a longer time than directed.

Ask a doctor before use if the stomach bleeding warning applies to you:

- You have a history of stomach problems, such as heartburn.
- You have high blood pressure, heart disease, liver cirrhosis, or kidney disease.
- You are taking a diuretic.

Stop use and ask a doctor if:

- You experience any of the following signs of stomach bleeding:
    - Feel faint.
    - Vomit blood.
    - Have bloody or black stools.[34]
    - Have stomach pain that does not get better.

NSAIDs are associated with increased risk for myocardial infarction, heart failure, hypertension, and stroke. The mechanism by which the risk is conferred is not clear, but it may be related to increased thromboxane A2 activity and

- Hypersensitivity reactions to aspirin are much more likely to occur in patients with asthma or allergic problems than in the normal population

واکنش های افزایش حساسیت

- واکنش های افزایش حساسیت به آسپرین با علایم بالینی شامل :

- آبریزش بینی، خس خس سینه خفیف تا شدید، تنگی نفس و برونکواسپاسم مشخص می گردد.
- معمولا علایم آسم ناشی از داروها (شایعترین داروهای القا کننده آسم بتابلاکرها و NSAID هستند) خفیف است اما آسم کشنده نیز با بعضی داروها ایجاد شده است.
- زمانی که این واکنش رخ داد، عموما برای یک دوره 2 تا 5 روزه علایم پایدار است.
- در صورتی که بیمار دچار آسم به آسپرین حساس باشد، احتمال واکنش با مابقی NSAID نیز وجود دارد. این واکنش ها ناشی از مهار سیکلواکسیژناز و فعالیت بیشتر لیپواکسیژناز و افزایش تولید لکوترین ها می باشد.
- بنابراین مهارکننده های ضعیف سنتز پروستاگلاندین ها (مثل کولین سالیسیلات) می توانند جایگزین مناسبی در بیماران دچار عدم تحمل آسپرین باشد
- . به همین ترتیب، مهارکننده های انتخابی COX2 در بیماران آسمی حساس به آسپرین، ایمن هستند زیرا این داروها COX1 و تولید پروستاگلاندین E2 که نقش مهمی در کاهش سنتز لکوترین ها را دارند مهار نمی کنند.

- مصرف NSAID می تواند منجر به واکنشهای آلرژیک و سودوآلرژیک شود
- واکنشهای سودوآلرژیک با مهار COX1 مرتبط است و با آسپرین و هر NSAID که واکنش متقاطع با آسپرین دارد ایجاد می گردد.
- برای درمان دردهای خفیف در بیمارانی که واکنش سودوآلرژیک به NSAID نشان می دهند می توان استامینوفن تا دوز 650 میلی گرم در هر دوز تجویز کرد .
- برای درمان دردهای شدید می توان از نارکوتیک ها بهره جست.
- علاوه بر استامینوفن می توان از مهارکننده های ضعیف COX1 در دوزهای پایین استفاده کرد که شامل سالیسیلاتهای غیر استیله (سالسالات یا کولین منیزیم تری سالسیلات تا 2000 میلی گرم روزانه، دیفلونیزال تا 1000 میلی گرم روزانه) است.

جدول ۱-٤ واکنشهای متقاطع میان آسپرین و سایر NSAIDs

NSAIDs که بطور ارجح COX 1 مهار میکنند و واکنش متقطع با آسپرین دارند پیروکسیکام سولینداک ایندومتاسین کتورولاک اتودولاک نابومتون ناپروکسن ایبوپروفن تولمتین مفنامیک اسید دیکلوفناک فنوپروفن
NSAIDs که مهار کننده ضعیف COX 1 هستند و با دوزهای بالاتر واکنش متقاطع با آسپرین دارند استامینوفن سالسلات
NSAIDs که ترجیحا مهار کننده COX 2 هستند اما در دوزهای بالاتر مهار کننده COX 1 هستند و با دوزهای بالاتر واکنش متقاطع با آسپرین دارند ملوکسیکام
مهار کننده های انتخابی COX 2 ; واکنش متقاطع با آسپرین ندارند سلکوکسیب رفوکوکسیب والدکوکسیب

- بیماران با واکنشهای آلرژیک به یک NSAID، حداقل یک تماس قبلی با این دارو داشته اند که در تماس بعدی به علت حساس شدن ماست سل ها منجر به ظاهر شدن علایم می گردد.
- این بیماران از مصرف آن NSAID خاص باید اجتناب کنند و می توانند NSAID دیگر با ساختار شیمیایی متفاوت استفاده کنند.
- با این وجود تشخیص و تمایز واکنشها آلرژیک و سودوآلرژیک در اکثر موارد سخت می باشد و تجویز NSAID با ساختار شیمیایی متفاوت باید با احتیاط صورت گیرد.

- دسته های دارویی با ساختارهای شیمیایی متفاوت NSAID شامل:
- سالیسیلات ها:
- Aspirin, salsalate, diflunisal , magnesium choline, salicylate
- مشتقات اسید پروپیونیک:
- Fenoprofen, flurbiprofen , ibuprofen, ketoprofen, naproxen, oxaproxin
- مشتقات اسید استیک:
- Diclofenac, etodolac , indomethacin, ketorolac, nabumetone , sulindac, tolmetin
- اسیدهای آنترانیلیک:
- Meclofenamate sodium, mefnamic acid
-
- مشتقات اکسیکام:
- Piroxicam , meloxicam
- مهارکننده های انتخابی COX-2:
- Celecoxib

- Aspirin and ibuprofen should not be recommended to patients with
- renal
- cardiac or
- hepatic disease, as, like all NSAIDs, these drugs may impair both liver and kidney function.

- the cardiovascular risk of nonselective NSAIDs appears to depend on dose and duration.

- Ibuprofen has been associated with a significant increase in cardiovascular risk, whereas naproxen has not;

- thus, naproxen is considered the preferred, safer option.

- Patients taking aspirin for cardiovascular prophylaxis should take it at least 1 hour before or 8 hours after ibuprofen to avoid a pharmacodynamic interaction that inhibits the antiplatelet effect of aspirin.

- In doses of 1200-2400 mg/day, ibuprofen does not appear to affect the INR in patients taking warfarin.

- However, ibuprofen should not be recommended for self treatment in patients:

- who are concurrently taking anticoagulants because its antiplatelet activity could increase GI bleeding.

Diclofenac

- is licensed for short-term relief of
- headache,
- dental pain,
- period pain,
- rheumatic pain,
- muscular pain,
- backache and the symptoms of colds and flu, including fever, in adults and children aged 14 years and over.

- **Naproxen**
- **Paracetamol**
- When given by suppository, rectal bioavailability of acetaminophen is approximately 50%-60% of that achieved with oral administration.

- Onset of analgesic activity of acetaminophen is about 30 minutes after oral administration. Duration of activity is about 4 hours and is increased to 6-8 hours with an extended release formulation.

- Hepatotoxicity from acetaminophen is probably dose related and is uncommon at recommended doses.

- The review also stated that paracetamol is well tolerated and effective in treating mild to moderate pain.
- A review stated that low-dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with OTC medications and

- is associated with the lowest risk of gastrointestinal toxicity of any NSAIDs.

- Early symptoms of acetaminophen intoxication can include nausea, vomiting, drowsiness, confusion, and abdominal pain, but these symptoms may be absent, belying the potential severity of the exposure.

- Serious clinical manifestations of hepatotoxicity begin 2-4 days after acute ingestion of acetaminophen and include:

- increased plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT); increased plasma bilirubin with jaundice; prolonged prothrombin time.

Interactions

- Aspirin potentiates the anticoagulant effect of warfarin because of
- its inhibitory effect on platelet aggregation and inhibition of vitamin K synthesis.
- A daily dose of only 600 mg can significantly increase blood clotting time,
- so patients on anticoagulant therapy must avoid over-the-counter (OTC) aspirin products.

- Aspirin also reduces excretion of methotrexate and can cause life-threatening rises in serum levels of the drug.

- concurrent administration of ibuprofen should therefore be avoided.

- Ibuprofen reduces the excretion of lithium and can raise plasma concentrations to toxic levels.

- The drug may also antagonize the diuretic and antihypertensive effects of diuretics and should not be recommended to patients taking these drugs.

TABLE 5-5 Clinically Important Drug-Drug Interactions with Nonprescription Analgesic Agents

Analgesic/Antipyretic	*Drug*	*Potential Interaction*	*Management/Preventive Measures*
Acetaminophen	Alcohol	Increased risk of hepatotoxicity	Avoid concurrent use if possible; minimize alcohol intake when using acetaminophen.
Acetaminophen	Warfarin	Increased risk of bleeding (elevations in INR)	Limit acetaminophen to occasional use; monitor INR for several weeks when acetaminophen 2-4 grams daily is added or discontinued in patients on warfarin.
Aspirin	Valproic acid	Displacement from protein-binding sites and inhibition of valproic acid metabolism	Avoid concurrent use; use naproxen instead of aspirin (no interaction).
Aspirin	NSAIDs, including COX-2 inhibitors	Increased risk of gastroduodenal ulcers and bleeding	Avoid concurrent use if possible; consider use of gastroprotective agents (e.g., PPIs).
Ibuprofen	Aspirin	Decreased antiplatelet effect of aspirin	Aspirin should be taken at least 30 minutes before or 8 hours after ibuprofen. Use acetaminophen (or other analgesic) instead of ibuprofen.
Ibuprofen	Phenytoin	Displacement from	Monitor free phenytoin levels; adjust

Ibuprofen	Phenytoin	Displacement from protein-binding sites	Monitor free phenytoin levels; adjust dose as indicated.
NSAIDs (several)	Bisphosphonates	Increased risk of GI or esophageal ulceration	Use caution with concomitant use.
NSAIDs (several)	Digoxin	Renal clearance of digoxin inhibited	Monitor digoxin levels; adjust dose as indicated.
Salicylates and NSAIDs (several)	Antihypertensive agents, beta-blockers, ACE inhibitors, vasodilators, diuretics	Antihypertensive effect inhibited; possible hyperkalemia with potassium-sparing diuretics and ACE inhibitors	Monitor blood pressure, cardiac function, and potassium levels.
Salicylates and NSAIDs	Anticoagulants	Increased risk of bleeding, especially GI	Avoid concurrent use, if possible; risk is lowest with salsalate and choline magnesium trisalicylate.
Salicylates and NSAIDs	Alcohol	Increased risk of GI bleeding	Avoid concurrent use, if possible; minimize alcohol intake when using salicylates and NSAIDs.
Salicylates and NSAIDs (several)	Methotrexate	Decreased methotrexate clearance	Avoid salicylates and NSAIDs with high-dose methotrexate therapy; monitor levels with concurrent treatment.

- **Headache**
- A comparative trial of ibuprofen 400 mg against paracetamol 1000 mg concluded that:
- both are efficacious analgesic agents for muscle-contraction headache, and
- that ibuprofen is significantly more effective than paracetamol at these doses.

- **Dental pain**
- Ibuprofen at a dose of 400 mg has been found to be more effective for dental pain than equivalent doses of aspirin or paracetamol.

- **Dysmenorrhoea**

  Naproxen
- **Back pain and muscular pain**
- NSAIDs are effective for short-term symptomatic relief in patients with acute low back pain,
- less effective or ineffective in patients with low back pain with sciatica and in patients with sciatica with nerve root

- **Pain and fever in children**
- Ibuprofen appears to have a longer duration of action and is more effective than paracetamol 4–6 hours after administration, which may make it preferable in some circumstances.

- Ibuprofen reduces fever more effectively than paracetamol.

TABLE 5-2 FDA-Approved Dosages for Nonprescription Analgesics in Children Younger than 12 Years[a]

		Ibuprofen (mg) Dose by Body Weight (mg/kg)	*Acetaminophen (mg)*	*Aspirin (mg)*
Age (years)	***Weight (lb)***	***5-10 mg/kg***	***10-15 mg/kg***	***10-15 mg/kg***
<2	<24	Ask a doctor[a]	Ask a doctor[a]	Ask a doctor[a]
2-3	24-35	100	160	160
4-5	36-47	150	240	240
6-8	48-59	200	320	320
9-10	60-71	250	400	400
11	72-95	300	480	480

[a] OTC labeling limits use to children over age 3. For patients seeking dosing advice for younger children, weight-based dosing is recommended.

- **Treatment with combination products**
- Codeine as additional ingredient
- Systematic reviews and meta-analyses have concluded that codeine in combination products adds little or nothing to analgesic efficacy.
- dysmenorrhoea and dental and rheumatic pain, are not opioid-sensitive.

- **Caffeine as additional ingredient**
- The value of caffeine in OTC compound analgesic products is disputed.
- Some trials have shown proprietary products to be more effective than single analgesics,
- while some systematic reviews and meta-analyses have concluded that they caffeine adds little or nothing to efficacy.

Treatment with topical analgesics

- avoiding the systemic adverse effects and
- side-effects that can result from oral administration.
- Systematic reviews have found topical NSAIDs to be effective over short periods (up to 2 weeks) for chronic muscular conditions and osteoarthritis.
- Topical NSAIDs are licensed for the treatment of backache, rheumatic and muscular pain, and sprains and strains, including sports injuries, and for pain relief in non-serious arthritic conditions.

- Topical NSAIDs should not be used with occlusive dressings.

- The systemic side-effects associated with oral NSAIDs can occur with topical agents;

- the risk is increased with application of large amounts of drug.

- They are not recommended for use by pregnant or breastfeeding women, or for children under 14 years of age.

- Serum levels of NSAIDs after topical administration are low,

- and clinically significant drug interactions are unlikely.

- **Capsicum**
- produce a burning sensation on the skin that is not accompanied by vasodilatation.
- **methyl salicylate**
- causes vasodilation
- topically applied methyl salicylate products inhibit both central
- and peripheral prostaglandin synthesis.
- Concomitant use of salicylate containing topical analgesics and maintenance warfarin therapy has been implicated in prolonging prothrombin time.

Local anaesthetics

Freeze sprays

- Freeze sprays contain pressurized liquids that evaporate at low temperature
- when sprayed on to the skin, producing a loss of sensation until
- the nerve endings warm up again
- They are most useful for treating the sharp but short-lived pain caused by minor knocks and sports injuries.


Thank you
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