PHARMACEUTICAL PRODUCTS

Therapeutic categories such as vitamins, laxatives, analgesics, non-steroidal contraceptives, Antibiotics, biological, hormones examples with respect to system.

Therapeutic vitamins towards human system

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol

Food sources of vitamin D include:

- Cod liver oil
- Salmon (sockeye)
- Mackerel
- Tuna fish canned in water
- Milk, non-fat, reduced-fat, and whole, vitamin D-fortified
- Orange juice fortified with vitamin D
- Yogurt fortified with 20 percent of the daily value of vitamin D
- Eggs, vitamin D is found in the yolk
- Swiss cheese
- Fortified cereals

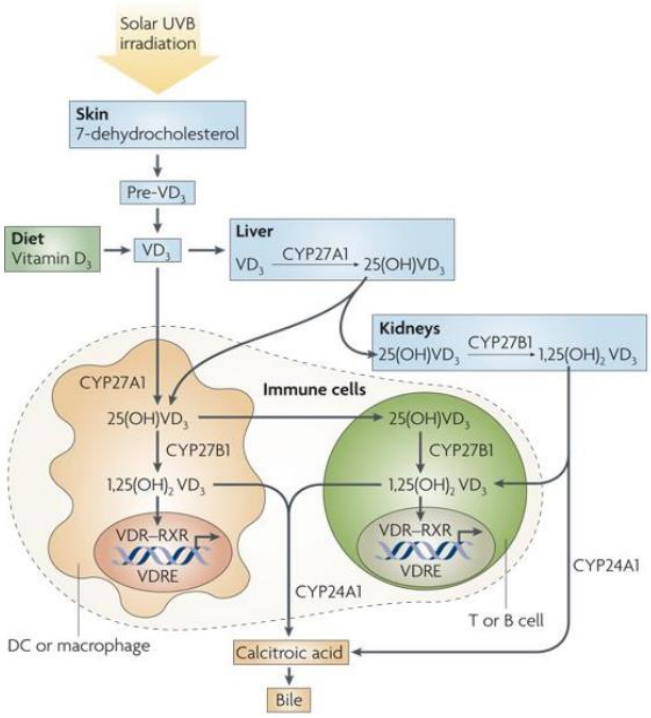
You also can get vitamin D from 10 minutes of mid-day exposure to the sun. However, prolonged sun exposure has been linked to aging skin and skin cancer and is not recommended.

A simple blood test can tell you whether you're deficient in vitamin D. If you're concerned, talk with your doctor.

Metabolic pathway of Vitamin D

Vitamin D_3 (VD_3), the most physiologically relevant form of vitamin D, is synthesized in the skin (Stratum spinosum and Stratum basale) from 7-dehydrocholesterol, a process which depends on sunlight, specifically ultraviolet B radiation (wavelengths of 270–300 nm). Alternatively, it can be acquired in the diet or in vitamin supplements. VD_3 is then converted in the liver by VD_3-25 hydroxylase to 25-dihydroxyvitamin D_3 (25(OH)VD_3), which is the main circulating form of VD_3. Finally, 25(OH)VD_3 is metabolized in the kidneys by the cytochrome P450 protein CYP27B1 (Its enzyme,25-Hydroxy Vit D_3-14,1α Hydroxylase) to 1,25$(OH)_2VD_3$, the most physiologically active VD_3 metabolite.

In addition to being processed in the liver and the kidneys, VD_3 can also be metabolized by cells of the immune system. In this way, 1,25$(OH)_2VD_3$ is concentrated locally in those lymphoid microenvironments that contain physiologically high concentrations of



VD_3, thereby increasing its specific action and also limiting potentially undesirable systemic effects, such as hypercalcaemia and increased bone resorption[7].

Cells of the immune system, including macrophages, dendritic cells (DCs), T and B cells express the enzymes CYP27A1 and/or CYP27B1, and therefore can also hydroxylate $25(OH)VD_3$ to $1,25(OH)_2VD_3$. $1,25(OH)_2VD_3$ acts on immune cells in an autocrine or paracrine manner by binding to the vitamin D receptor (VDR).

Finally, the enzyme 24-hydroxylase, which is most abundant in the kidney and intestine[10], catabolizes $1,25(OH)_2VD_3$ to its inactive metabolite, calcitroic acid, which is then excreted in the bile.

Dosage

The following doses have been studied in scientific research:

By Mouth:

- For preventing osteoporosis and fractures: 400-1000 IU per day has been used for older adults. Some experts recommended higher doses of 1000-2000 IU daily.
- For preventing falls: 800-1000 IU/day has been used in combination with calcium 1000-1200 mg/day.
- For preventing multiple sclerosis (MS): long-term consumption of at least 400 IU per day, mainly in the form of a multivitamin supplement, has been used.
- For preventing all cancer types: calcium 1400-1500 mg/day plus vitamin D3 (cholecalciferol) 1100 IU/day in postmenopausal women has been used.
- For muscle pain caused by medications called "statins": vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) 50,000 units once a week or 400 IU daily.
- For preventing the flu: vitamin D (cholecalciferol) 1200 IU daily.

→ Most vitamin supplements contain only 400 IU (10 mcg) vitamin D.

→ The Institute of Medicine publishes recommended daily allowance (RDA), which is an estimate of the amount of vitamin D that meets the needs of most people in the population. The current RDA was set in 2010. The RDA varies based on age as follows: 1-70 years of age, 600 IU daily; 71 years and older, 800 IU daily; pregnant and lactating women, 600 IU daily. For infants ages 0-12 months, an adequate intake (AI) level of 400 IU is recommended.

→ Some organizations are recommending higher amounts. In 2008, the American Academy of Pediatrics increased the recommended minimum daily intake of vitamin D to 400 IU daily for all infants and children, including adolescents. Parents should not use vitamin D liquids dosed as 400 IU/drop. Giving one dropperful or mL by mistake can deliver 10,000 IU/day. The US Food and Drug Administration (FDA) will force companies to provide no more than 400 IU per dropperful in the future.

→ The National Osteoporosis Foundation recommends vitamin D 400 IU to 800 IU daily for adults under age 50, and 800 IU to 1000 IU daily for older adults.

→ The North American Menopause Society recommends 700 IU to 800 IU daily for women at risk of deficiency due to low sun (e.g., homebound, northern latitude) exposure.

→ Guidelines from the Osteoporosis Society of Canada recommend vitamin D 400 IU per day for people up to age 50, and 800 IU per day for people over 50. Osteoporosis Canada now recommends 400-1000 IU daily for adults under the age of 50 years and 800-2000 IU daily for adults over the age of 50 years.

→ The Canadian Cancer Society recommends 1000 IU/day during the fall and winter for adults in Canada. For those with a higher risk of having low vitamin D levels, this dose should be taken year round. This includes people who have dark skin, usually wear clothing that covers most of their skin, and people who are older or who don't go outside often.

→ Many experts now recommend using vitamin D supplements containing cholecalciferol in order to meet these intake levels. This seems to be more potent than another form of vitamin D called ergocalciferol.

Effective for:

- Low levels of phosphate in the blood due to an inherited disorder called familial hypophosphatemia. Taking vitamin D (calcitriol or dihydrotachysterol) by mouth along with phosphate supplements is effective for treating bone disorders in people with low levels of phosphate in the blood.
- Low levels of phosphate in the blood due to a disease called Fanconi syndrome. Taking vitamin D (ergocalciferol) by mouth is effective for treating low levels of phosphate in the blood due to a disease called Fanconi syndrome.
- Low blood calcium levels due to low parathyroid hormone levels. Low levels of parathyroid hormone can cause calcium levels to become too low. Taking vitamin D (dihydrotachysterol, calcitriol, or ergocalciferol) by mouth is effective for increasing calcium blood levels in people with low parathyroid hormone levels.
- Softening of the bones (osteomalacia). Taking vitamin D (cholecalciferol) is effective for treating softening of the bones. Also, taking vitamin D (calcifediol) is effective for treating softening of the bones due to liver disease. In addition, taking vitamin D (ergocalciferol) is effective for treating softening of the bones caused by medications or poor absorption syndromes.
- Psoriasis. Applying vitamin D or calcipotriene (a synthetic form of vitamin D) to the skin treats psoriasis in some people. Applying vitamin D to the skin together with cream containing drugs called corticosteroids seems to be more effective for treating psoriasis than using just vitamin D or the corticosteroid creams alone.
- A bone disorder called renal osteodystrophy, which occurs in people with kidney failure. Taking vitamin D (calcifediol) by mouth manages low calcium levels and prevents bone loss in people with kidney failure. However, vitamin D does not appear to reduce the risk of death or bone pain in people with kidney failure.
- Rickets. Vitamin D is effective for preventing and treating rickets. A specific form of vitamin D, calcitriol, should be used in people with kidney failure.
- Vitamin D deficiency. Vitamin D is effective for preventing and treating vitamin D deficiency.
- Bone loss in people taking drugs called corticosteroids. Taking vitamin D (calcifediol, cholecalciferol, calcitriol, or alfacalcidol) by mouth prevents bone loss in people taking drugs called corticosteroids. Taking vitamin D alone or with calcium seems to improve bone density in people with existing bone loss caused by using corticosteroids.

- Preventing falls in older people. Researchers have observed that people who do not have enough vitamin D tend to fall more often than people who do. Taking a vitamin D supplement seems to reduce the risk of falling by up to 22%. Higher doses of vitamin D are more effective than lower doses. One study found that taking 800 IU of vitamin D reduced the risk of falling, but lower doses did not.
- Also, vitamin D, in combination with calcium, but not calcium alone, may prevent falls by decreasing body sway and blood pressure. Taking vitamin D plus calcium seems to prevent falls more significantly in women than men and in older people living in hospitals or residential care facilities than those living in community dwellings.
- Osteoporosis (weak bones). Taking a specific form of vitamin D called cholecalciferol (vitamin D3) along with calcium seems to help prevent bone loss and bone breaks.

Possibly effective for:

- Cancer. Some research shows that people who take a high-dose vitamin D supplement plus calcium might have a lower risk of developing certain types of cancer. However, taking vitamin D alone does not appear to reduce the risk of cancer.
- Cavities. Research suggests that taking vitamin D3 (cholecalciferol) reduces the risk of cavities by 49% and vitamin D2 (ergocalciferol) reduces the risk by 36% in infants, children and adolescents.
- Bone loss caused by having too much parathyroid hormone (hyperparathyroidism). Taking vitamin D (cholecalciferol) by mouth seems to reduce parathyroid hormone levels and bone loss in women with a condition called hyperparathyroidism.
- Multiple sclerosis (MS). Research shows that taking vitamin D can reduce the risk of developing MS in women by up to 40%. Taking at least 400 IU daily, the amount typically found in a multivitamin supplement, seems to work the best.
- Respiratory infections. Research in school aged children shows that taking a vitamin D supplement during winter might reduce the chance of developing seasonal flu. Other research suggests that taking a vitamin D supplement might reduce the chance of an asthma attack triggered by a cold or other respiratory infection. Some additional research suggests that children with low levels of vitamin D have a higher chance of developing a respiratory infection such as the common cold or flu. However, most research suggests that vitamin D might only have an effect on respiratory infections in children. It does not appear to provide the same benefits in adults.

- Rheumatoid arthritis. Research suggests that older women who consume more vitamin D from foods or supplements tend to have a lower risk of developing rheumatoid arthritis.
- Tooth loss. Taking calcium and vitamin D by mouth appears to prevent tooth loss in elderly people.
- Weight loss. Research shows that people with lower vitamin D levels are more likely to be obese than those with higher levels. Women taking calcium plus vitamin D are more likely to lose weight and maintain their weight. However, this benefit is mainly in women who did not consume enough calcium before they started taking supplements.

Side effects

Special Precautions & Warnings:

Pregnancy and breast-feeding: Vitamin D is **likely safe** during pregnancy and breast-feeding when used in daily amounts below 4000 units. do not use higher doses. vitamin d is **possibly unsafe** when used in higher amounts during pregnancy or while breast-feeding. Using higher doses might cause serious harm to the infant.

Kidney disease: Vitamin D may increase calcium levels and increase the risk of "hardening of the arteries" in people with serious kidney disease. This must be balanced with the need to prevent renal osteodystrophy, a bone disease that occurs when the kidneys fail to maintain the proper levels of calcium and phosphorus in the blood. Calcium levels should be monitored carefully in people with kidney disease.

High levels of calcium in the blood: Taking vitamin D could make this condition worse.

"Hardening of the arteries" (atherosclerosis): Taking vitamin D could make this condition worse, especially in people with kidney disease.

Sarcoidosis: Vitamin D may increase calcium levels in people with sarcoidosis. This could lead to kidney stones and other problems. Use vitamin D cautiously.

Histoplasmosis: Vitamin D may increase calcium levels in people with histoplasmosis. This could lead to kidney stones and other problems. Use vitamin D cautiously.

Over-active parathyroid gland (hyperparathyroidism): Vitamin D may increase calcium levels in people with hyperparathyroidism. Use vitamin D cautiously.

Lymphoma: Vitamin D may increase calcium levels in people with lymphoma. This could lead to kidney stones and other problems. Use vitamin D cautiously.

Laxatives

Introduction

Laxatives (**purgatives**, **aperients**) are substances that loosen stools and increase bowel movements. They are used to treat and prevent constipation. Laxatives vary based on how they work and the side effects they have. Certain stimulant, lubricant and saline laxatives are used to evacuate the colon for rectal and bowel examinations, and may be supplemented by enemas under certain circumstances. Sufficiently high doses of laxatives may cause diarrhea.

Some laxatives combine more than one active ingredient. Laxatives may be oral or suppository in form.

Uses

- Acute and chronic constipation
- Bowel preparation
- Chronic immobility

Types of laxatives

Bulk-forming agents

Bulk-forming laxatives, also known as roughage, are substances, such as **fiber** in food and **hydrophilic agents** in over-the-counter drugs, that add bulk and **water to stools** so that they can pass more easily through the intestines (lower part of the digestive tract).

Properties

- Site of action: small and large intestines
- Onset of action: 12–72 hours
- Examples: Dietary Fiber, Metamucil, Citrucel, FiberCon

Bulk-forming agents absorb water and should be taken with plenty of water. Bulk-forming agents generally have the gentlest of effects among laxatives and can be taken for long-term maintenance of regular bowel movements.

Dietary fiber

Foods that help with laxation include fiber-rich foods. Dietary fiber includes insoluble fiber and soluble fiber, such as:

- Fruits, such as bananas, kiwifruits, prunes, apples (with skin), pears (with skin), and raspberries.
- Vegetables, such as broccoli, string beans, kale, spinach, cooked winter squash, cooked green peas, and baked potatoes (with skin).
- Whole grains
- Bran products.
- Nuts
- Legumes, such as beans, peas, and lentils.

Emollient agents (stool softeners)

Emollient laxatives, also known as stool softeners, are anionic surfactants that enable **additional water and fats** to be incorporated in the stool, making it easier for them to move through the gastrointestinal tract.

Properties

- Site of action: small and large intestines
- Onset of action: 12–72 hours
- Examples: Docusate (Colace, Diocto), Gibs-Eze

Emollient agents should be taken with plenty of water. Emollient agents prevent constipation rather than treat long-term constipation.

Lubricant agents

Lubricant laxatives are substances that coat the stool with **slippery lipids** and **retard colonic absorption of water** so that the stool slides through the colon more easily. Lubricant laxatives also increase the weight of stool and decrease intestinal transit time.

Properties

- Site of action: colon
- Onset of action: 6–8 hours
- Example: mineral oil

Mineral oil is the only nonprescription lubricant. Mineral oil may **decrease the absorption of fat-soluble vitamins and some minerals.**

Hyperosmotic agents

Hyperosmotic laxatives are substances that cause the intestines to hold more water within and create an **osmotic effect that stimulates a bowel movement**.

Properties

- Site of action: colon
- Onset of Action: 12–72 hours (oral) 0.25 - 1 hour (rectal)
- Examples: glycerin suppositories, sorbitol, lactulose, and PEG (Colyte, MiraLax).

Glycerin suppositories

Lactulose works by the osmotic effect, which retains water in the **colon, lowering the pH through bacterial fermentation to lactic, formic and acetic acid, and increasing colonic peristalsis.** Lactulose is also indicated in portal-systemic encephalopathy. Glycerin suppositories work mostly by **hyperosmotic action,** but the **sodium stearatein** in the preparation also causes local irritation to the colon.

Solutions of polyethylene glycol and electrolytes (sodium chloride, sodium bicarbonate, potassium chloride, and sometimes sodium sulfate) are used for whole bowel irrigation, a process designed **to prepare the bowel for surgery or colonoscopy** and to treat certain types of poisoning. Brand names for these solutions include GoLytely, GlycoLax, CoLyte, Miralax, Movicol, NuLytely, Suprep, and Fortrans. Solutions of sorbitol (SoftLax) have similar effects.

Saline laxative agents

Saline laxatives are **non-absorbable osmotic substances** that attract and retain water in the intestinal lumen, **increasing intraluminal pressure** that mechanically stimulates evacuation of the bowel. **Magnesium-containing agents** also cause the release of **cholecystokinin,** which increases intestinal motility and fluid secretion. Saline laxatives may alter a patient's fluid and electrolyte balance.

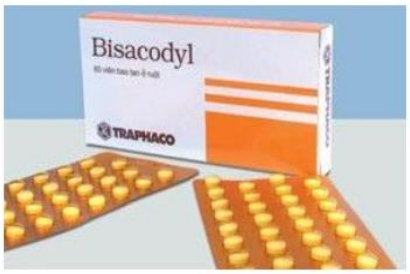
Properties

- Site of action: small and large intestines
- Onset of action: 0.5–3 hours (oral), 2–15 minutes (rectal)
- Examples: sodium phosphate (and variants), magnesium citrate, magnesium hydroxide (milk of magnesia), and magnesium sulfate (Epsom salt)

Saline laxatives should be taken with plenty of water.

Stimulant agents

Stimulant laxatives are substances that act on the intestinal mucosa or nerve plexus, altering water and electrolyte secretion. They also stimulate peristaltic action and can be dangerous under certain circumstances.



Properties

- Site of action: colon
- Onset of action: 6–10 hours
- Examples: senna, bisacodyl

They are the most powerful among laxatives and should be used with care. Prolonged use of stimulant laxatives can create drug dependence by damaging the colon's haustral folds, making a user less able to move feces through the colon on their own. A study of patients with chronic constipation found that 28% of chronic stimulant laxative users lost haustral folds over the course of one year, while none of the control group did.

Miscellaneous

Castor oil is a glyceride that is hydrolyzed by pancreatic lipase to ricinoleic acid, which produces laxative action by an unknown mechanism.

Properties

- Site of action: colon
- Onset of action: 2–6 hours
- Examples: castor oil

Long-term use of castor oil may result in loss of fluid, electrolytes, and nutrients.

Serotonin agonist

These are motility stimulants that work through activation of **5-HT_4 receptors of the enteric nervous system** in the gastrointestinal tract. However, some have been discontinued or restricted due to potentially harmful cardiovascular side-effects.

Tegaserod (brand name Zelnorm) was removed from the general U.S. and Canadian markets in 2007, due to reports of increased risks of heart attack or stroke. It is still available to physicians for patients in emergency situations that are life-threatening or require hospitalization.

Prucalopride (brand name Resolor) is a current drug approved for use in the EU October 15, 2009 and in Canada (brand name Resotran) on December 7, 2011. It has not been approved by the Food and Drug Administration for use in the United States, but it is in development by Shire PLC.

Chloride channel activators

Lubiprostone is used in the management of **chronic idiopathic constipation** and **irritable bowel syndrome**. It causes the intestines to produce a **chloride-rich fluid secretion** that softens the stool, increases motility, and promotes spontaneous bowel movements (SBM).

Problems with use

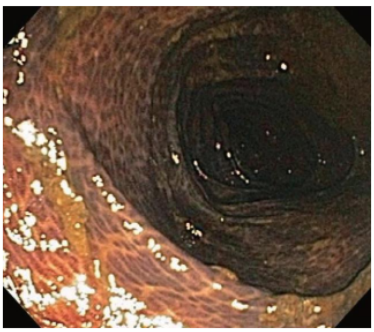
Laxative abuse

Laxative abuse can lead to potentially fatal fluid and electrolyte imbalances (especially dehydration, hypokalaemia and a metabolic acidosis) as well as intestinal paralysis, irritable bowel syndrome (IBS), pancreatitis, renal failure, factitious diarrhea and other problems.

Although patients with eating disorders such as **anorexia nervosa and bulimia nervosa** frequently abuse laxatives in an attempt to lose weight, laxatives act to speed up the transit of feces through the large intestine, which occurs subsequent to the absorption of nutrients in the small intestine. Thus, studies of laxative abuse have found that effects on body weight reflect primarily temporary losses of body water rather than energy (calorie) loss.

Laxative gut

Physicians warn against the chronic use of stimulant laxatives due to concern that chronic use causes the colonic tissues to get worn out over time and not be able to expel feces due to long-term overstimulation. A common finding in patients having used stimulant laxatives is a **brown pigment deposited in the intestinal tissue,** known as **melanosis coli**.



Typical alligator or snake-like appearance of melanosis coli

Note

Suppository - A **suppository** is a drug delivery system that is inserted into the rectum (rectal suppository), vagina (vaginal suppository) or urethra (urethral suppository), where it dissolves or melts and is absorbed into the blood stream. They are used to deliver both systemically and locally acting medications.

Melanosis coli, also **pseudomelanosis coli**, is a disorder of pigmentation of the wall of the colon, often identified at the time of colonoscopy. It is benign, and may have no significant correlation with disease. The brown pigment is lipofuscin in macrophages, not melanin.

Colonoscopy or **coloscopy** is the endoscopic examination of the large bowel and the distal part of the small bowelwith a CCD camera or a fiber optic camera on a flexible tube passed through the anus. It can provide a visual diagnosis (e.g. ulceration, polyps) and grants the opportunity for biopsy or removal of suspected colorectal cancer lesions. Colonoscopy can remove polyps as small as one millimetre or less. Once polyps are removed, they can be studied with the aid of a microscope to determine if they are precancerous or not. It can take up to 15 years for a polyp to turn cancerous.

Anorexia nervosa, often referred to simply as **anorexia**, is an eating disorder characterized by a low weight, fear of gaining weight, a strong desire to be thin, and food restriction. Many people with anorexia see themselves as overweight even though they are underweight. If asked they usually deny they have a problem with low weight. Often they weigh themselves frequently, eat only small amounts, and only eat certain foods. Some will exercise excessively, force themselves to vomit, or use laxatives to produce weight loss. Complications may include osteoporosis, infertility and heart damage, among others. Women will often stop having menstrual periods.

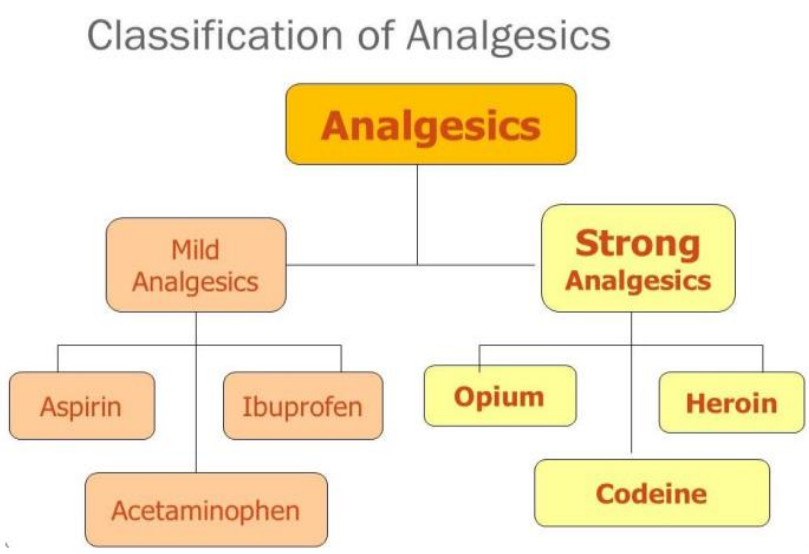
Bulimia nervosa, also known as simply **bulimia**, is an eating disorder characterized by binge eating followed by purging. Binge eating refers to eating a large amount of food in a short amount of time. Purging refers to attempts to rid oneself of the food consumed. This may be done by vomiting or taking a laxative. Other efforts to lose weight may include the use of diuretics, stimulants, fasting, or excessive exercise. Most people with bulimia have a normal weight. The forcing of vomiting may result in thickened skin on the knuckles and breakdown of the teeth. Bulimia is frequently associated with other mental disorders such as depression, anxiety, and problems with drugs or alcohol. There is also a higher risk of suicide and self-harm.

ANALGESICS

An **analgesic** or **painkiller** is any member of the group of drugs used to achieve analgesia, relief from pain.

Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which reversibly eliminate sensation.

Analgesics include paracetamol (known in North America as acetaminophen or simply APAP), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and oxycodone.



Mild analgesics

1. Aspirin

Aspirin, also known as **acetylsalicylic acid** (**ASA**), is a medication, often used to treat

- Pain,
- Fever, and
- Inflammation.

Aspirin is also used long-term, at low doses, to help prevent **heart attacks, strokes, and blood clot** formation in people at high risk of developing blood clots.

Low doses of aspirin may be given immediately after a heart attack to reduce the risk of another heart attack or the death of heart tissue. Aspirin may be effective at preventing certain types of cancer, particularly **colorectal cancer.**

Mechanism of action

Discovery of the mechanism

In 1971, **British pharmacologist John Robert Vane**, then employed by the Royal College of Surgeons in London, showed aspirin suppressed the production of **prostaglandins** and **thromboxanes**. For this discovery he was awarded the **1982 Nobel Prize in Physiology or Medicine**, jointly with Sune K. Bergström andBengt I. Samuelsson.

Suppression of prostaglandins and thromboxanes

- Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its **irreversible inactivation** of the **cyclooxygenase** (COX; officially known as prostaglandin-endoperoxide synthase, PTGS) enzyme required for prostaglandin and thromboxane synthesis. Aspirin acts as an **acetylating agent** where an **acetyl group is covalently attached** to a **serine residue** in the active site of the **PTGS enzyme**. This makes aspirin different from other NSAIDs (such as diclofenac andibuprofen), which are reversible inhibitors.
- Low-dose aspirin use **irreversibly blocks the formation of thromboxane A_2 in platelets**, producing an **inhibitory effect on platelet aggregation** during the lifetime of the affected platelet (8–9 days). This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks. 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition.
- Prostaglandins, local hormones produced in the body, have diverse effects, including the **transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation**. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are caused primarily by blood clots, and **low doses of aspirin** are seen as an effective medical intervention for **acute myocardial infarction.**

COX-1 and COX-2 inhibition

At least two different types of cyclooxygenase occur: COX-1 and COX-2. Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are proinflammatory. Aspirin-modified PTGS2 produces lipoxins, most of which are anti-inflammatory. Newer NSAID drugs, COX-2 inhibitors (coxibs), have been developed to inhibit only PTGS2, with the intent to reduce the incidence of gastrointestinal side effects.

However, several of the new COX-2 inhibitors, such as rofecoxib (Vioxx), have been withdrawn in the last decade, after evidence emerged that PTGS2 inhibitors increase the risk of heart attack and stroke. Endothelial cells lining the microvasculature in the body are proposed to express PTGS2, and, by selectively inhibiting PTGS2, prostaglandin production (specifically, PGI2; prostacyclin) is downregulated with respect to thromboxane levels, as PTGS1 in platelets is unaffected. Thus, the protective anticoagulative effect of PGI2 is removed, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new PTGS once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

Additional mechanisms

Aspirin has been shown to have at least three additional modes of action.

→ It **uncouples oxidative phosphorylation in cartilaginous (and hepatic) mitochondria,** by diffusing from the inner membrane space as a proton carrier back into the mitochondrial matrix, where it ionizes once again to release protons. In short, **aspirin buffers and transports the protons**. When **high doses** of aspirin are given, it may actually cause **fever**, owing to the heat released from the electron transport chain, as opposed to the antipyretic action of aspirin seen with lower doses.

→ In addition, aspirin induces the formation of **NO-radicals** in the body, which has been shown in mice to have an independent mechanism of reducing inflammation. This reduced leukocyte adhesion, which is an important step in immune response to infection; however, evidence is insufficient to show aspirin helps to fight infection.

→ More recent data also suggest **salicylic acid** and **its derivatives** modulate signaling through **NF-κB**. NF-κB, a transcription factor complex, plays a central role in many biological processes, including inflammation.

→ Aspirin is readily **broken down** in the body to **salicylic acid**, which itself has anti-inflammatory, antipyretic, and analgesic effects. In 2012, salicylic acid was found to activate AMP-activated protein kinase, which has been suggested as a possible explanation for some of the effects of both salicylic acid and aspirin. The acetyl portion of the aspirin molecule has its own targets. Acetylation of cellular proteins is a well-established phenomenon in the regulation of protein function at the post-translational level. Aspirin is able to acetylate several other targets in addition to COX isoenzymes. These acetylation reactions may explain many hitherto unexplained effects of aspirin.

Aspirin dosage

1. Aspirin comes as a regular tablet, a **delayed-release tablet, a chewable tablet, a powder, a gum, and a rectal suppository**.
2. It's typically taken every four to **six hours** to treat **fever and pain**. It's usually taken once a day to lower the risk of a heart attack or stroke. Typical dosages range from **50 milligrams** (mg) to **6,000 mg**, daily.
3. You should swallow the delayed-release tablets with a full glass of water. These tablets don't work immediately after they are taken, so you shouldn't use them for quick pain relief.
4. The chewable tablets can be crushed, chewed, or swallowed whole. You should drink a full glass of water right after taking this form of the medication.

Medical uses

Aspirin is used in the treatment of a number of conditions, including

- Rheumatic fever, and
- Fever,
- Pain,
- Inflammatory diseases, such as
  - ✓ rheumatoid arthritis,
  - ✓ pericarditis, and
  - ✓ Kawasaki disease.

Lower doses of aspirin have also shown to reduce the risk of death from a heart attack, or the risk of stroke in some circumstances. There is some evidence that aspirin is effective at preventing colorectal cancer, though the mechanisms of this effect are unclear

Side effects

The main side effects of aspirin are gastric ulcers, stomach bleeding, and ringing in the ears, especially with higher doses. While daily aspirin can help prevent a clot-related stroke, it may increase risk of a bleeding stroke (hemorrhagic stroke). In children and adolescents, aspirin is not recommended for flu-like symptoms or viral illnesses, because of the risk of Reye's syndrome.

Aspirin Warnings

Before taking aspirin, tell your doctor if you have or have ever had:

- Asthma
- Frequent stuffed or runny nose
- Nasal polyps (growths on the linings of the nose)
- Frequent heartburn, upset stomach, or stomach pain
- Ulcers
- Anemia
- Gout
- Diabetes
- Liver or kidney disease
- Hemophilia (a bleeding disorder) or any other bleeding conditions

You should ask your doctor before giving aspirin to a child or teenager. The medicine can cause a serious and sometimes fatal condition known as Reye's syndrome.

Note

Reye syndrome or **Reye's syndrome** is a rapidly progressive encephalopathy which usually begins shortly after recovery from an acute viral illness, especially influenza and varicella (chickenpox). It is a potentially fatal syndrome that has numerous detrimental effects on many organs, especially the brain and liver, as well as causing hyperammonemia(elevated blood ammonia level) and low blood sugar. The classic features are a rash, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use. The disease causes fatty liver with minimal inflammation and cerebral edema (swelling of the brain). The liver may become slightly enlarged and firm, and there is a change in the appearance of thekidneys. Jaundice is not usually present.