



WIKIPEDIA
The Free Encyclopedia

Main page
Contents
Featured content
Current events
Random article
Donate to Wikipedia
Wikipedia store

Interaction

Help
About Wikipedia
Community portal
Recent changes
Contact page

Tools

What links here
Related changes
Upload file
Special pages
Permanent link
Page information
Wikidata item
Cite this page

Print/export

Create a book
Download as PDF
Printable version

In other projects

Wikimedia Commons

Languages

Afrikaans
Alemannisch
العربية
Asturianu
Azərbaycanca

Бân-lâm-gú
Беларуская
Български

★ Bosanski
Català
Čeština
Dansk
Deutsch
ދިވެހިބަސް
Eesti
Ελληνικά

★ Español
Esperanto
Euskara
فارسی
Français
Gaeilge
Galego

□□□
Հայերեն
■ ■ ■ ■ ■ ■ ■ ■

Hrvatski
Ido
Bahasa Indonesia
Íslenska
Italiano

Not logged in Talk Contributions Create account Log in

Article **Talk**

Read Edit View history

Search Wikipedia

Aspirin

From Wikipedia, the free encyclopedia

Aspirin, also known as **acetylsalicylic acid** (**ASA**), is a medication used to treat pain, fever, or inflammation.^[3] Specific inflammatory conditions in which aspirin is used include Kawasaki disease, pericarditis, and rheumatic fever.^[3] Aspirin given shortly after a heart attack decreases the risk of death.^[3] Aspirin is also used long-term to help prevent heart attacks, ischaemic strokes, and blood clots, in people at high risk.^[3] Aspirin may also decrease the risk of certain types of cancer, particularly colorectal cancer.^[4] For pain or fever, effects typically begin within 30 minutes.^[3] Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) and works similar to other NSAIDs but it is also an antiplatelet and suppresses the normal functioning of platelets.^[3]

Common side effects include an upset stomach.^[3] More significant side effects include stomach ulcers, stomach bleeding, and worsening asthma.^[3] Bleeding risk is greater among those who are older, drink alcohol, take other NSAIDs, or are on blood thinners.^[3] Aspirin is not recommended in the last part of pregnancy.^[3] It is not generally recommended in children with infections because of the risk of Reye's syndrome.^[3] High doses may result in ringing in the ears.^[3]

Aspirin, in the form of leaves from the willow tree, has been used for its health effects for at least 2,400 years.^[5] In 1853, chemist Charles Frédéric Gerhardt treated sodium salicylate with acetyl chloride to produce acetylsalicylic acid for the first time.^[6] In the second half of the nineteenth century, other chemists established the chemical structure and came up with more efficient methods to make it.^{[6]:69–75} In 1897, scientists at Bayer began studying acetylsalicylic acid as a less-irritating replacement for common salicylate medicines.^{[6]:69–75} By 1899, Bayer had named the drug Aspirin and was selling it around the world.^[7] The word *Aspirin* was Bayer's brand name; however, their rights to the trademark were lost or sold in many countries.^[8] Aspirin's popularity grew over the first half of the twentieth century leading to competition between many brands and formulations.^[8]

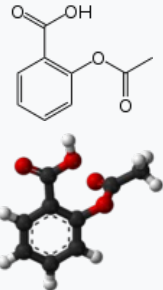
Aspirin is one of the most widely used medications globally with an estimated 40,000 tonnes (50 to 120 billion pills) being consumed each year.^{[9][9]} It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.^[10] Aspirin is available as a generic medication. The wholesale cost in the developing world as of 2014 is 0.002 to 0.025 USD per dose.^[11] As of 2015 the cost for a typical month of medication in the United States is less than US\$25.^[12]

Contents

- Medical use
 - Pain
 - Fever
 - Inflammation
 - Heart attacks and strokes
 - Cancer prevention
 - Other uses
 - Resistance
 - Dosage
- Adverse effects
 - Contraindications
 - Gastrointestinal
 - Central effects
 - Reye's syndrome
 - Skin
 - Other adverse effects
 - Overdose
 - Interactions
- Chemical properties
 - Synthesis
- Physical properties
 - Polymorphism

Aspirin

INN: **acetylsalicylic acid**



Clinical data

Pronunciation acetylˈsælɨsɪˈlɪk/
/əˈsiːtəlˈsæliːsik

Synonyms 2-acetoxybenzoic acid
acetylsalicylate
acetylsalicylic acid
O-acetylsalicylic acid, Aspirin (BAN UK), Aspirin (USAN US)

AHFS/Drugs.com Monograph

MedlinePlus a682878

License data US FDA: Aspirin

Pregnancy category AU: C
US: C (Risk not ruled out) D in the 3rd trimester

Routes of administration bymouth, rectal, lysine acetylsalicylate may be given intravenously or intramuscularly

ATC code A01AD05 (WHO) B01AC06 (WHO), N02BA01 (WHO)

Legal status

Legal status AU: S2 (Pharmacy only) except when given intravenously (in which case it is schedule 4), used in animal medicine (schedule 5/6) or when the dose is higher than usual.
UK: General sales list (GSL, OTC)
US: OTC

Pharmacokinetic data

Bioavailability 80–100%^[2]
Protein binding 80–90%^[1]
Metabolism Liver, (CYP2C19 and possibly CYP3A), some is also hydrolysed to salicylate in the gut wall.^[1]
Biological half-life Dose-dependent; 2 h to 3 h for low doses, 15 h to 30 h for large doses.^[1]
Excretion Urine (80–100%), sweat, saliva, feces^[2]

Identifiers

IUPAC name 2-(ethyloxy)benzenecarboxylic acid
CAS Number 50-78-2 ✓
PubChem CID 2244
IUPHAR/BPS 4139
DrugBank DB00945 ✓

עברית

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Қазақша

Kreyòl ayisyen

Kurdî

Latviešu

Lietuvių

Magyar

Македонски

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Norsk

Norsk nynorsk

Occitan

■ ■ ■ ■ ■

Ўзбекча/Ўзбекча

Polski

Português

Română

Русский

Саха тыла

Scots

Shqip

Simple English

Slovenčina

Slovenščina

کوردی

★ Српски / srpski

Srpskohrvatski / српскохрватски

Suomi

Svenska

Tagalog

■ ■ ■ ■ ■

■ ■ ■ ■ ■ ■ ■

Ἑλληνικά

Tsetsêhestâhese

Türkçe

Українська

اردو

ئۇيغۇرچە / Uyghurche

Tiếng Việt

Walon

Winaray

ייִדיש

粵語

Žemaitėška

★ 中文

Edit links

- 5 Mechanism of action

5.1 Discovery of the mechanism

5.2 Prostaglandins and thromboxanes

5.3 COX-1 and COX-2 inhibition

5.4 Additional mechanisms

6 Pharmacokinetics

7 History

7.1 Trademark

7.2 Compendial status

8 Veterinary medicine

9 References

10 External links

Medical use [edit]

Aspirin is used in the treatment of a number of conditions, including fever, pain, **rheumatic fever**, and inflammatory diseases, such as **rheumatoid arthritis**, **pericarditis**, and **Kawasaki disease**.^[13] Lower doses of aspirin have also been shown to reduce the risk of death from a **heart attack**, or the risk of **stroke** in some circumstances.^{[14][15][16]} There is some evidence that aspirin is effective at preventing **colorectal cancer**, though the mechanisms of this effect are unclear.^[17] In the United States low dose aspirin is deemed reasonable in those between 50 and 70 years old who have a more than 10% risk of cardiovascular disease and are not at an increased risk of bleeding who are otherwise healthy.^[18]

Pain [edit]

Aspirin is an effective analgesic for acute pain, but is generally considered inferior to **ibuprofen** for the alleviation of pain because aspirin is more likely to cause **gastrointestinal bleeding**.^[19] Aspirin is generally ineffective for those pains caused by muscle **cramps**, **bloating**, **gastric distension**, or acute skin irritation.^[20] As with other NSAIDs, **combinations** of aspirin and **caffeine** provide slightly greater pain relief than aspirin alone.^[21] **Effervescent** formulations of aspirin, such as **Alka-Seltzer** or **Blowfish**,^[22] relieve pain faster than aspirin in tablets,^[23] which makes them useful for the treatment of **migraines**.^[24] **Topical** aspirin may be effective for treating some types of **neuropathic pain**.^[25]

Headache [edit]

Aspirin, either by itself or in a combined formulation, effectively treats certain **types of a headache**, but its efficacy may be questionable for others. Secondary headaches, meaning those caused by another disorder or trauma, should be promptly treated by a medical provider.

Among primary headaches, the **International Classification of Headache Disorders** distinguishes between **tension headache** (the most common), migraine, and **cluster headache**. Aspirin or other over-the-counter analgesics are widely recognized as effective for the treatment of tension headache.^[26]

Aspirin, especially as a component of an **aspirin/paracetamol/caffeine combination**, is considered a first-line therapy in the treatment of migraine, and comparable to lower doses of **sumatriptan**. It is most effective at stopping migraines when they are first beginning.^[27]

Fever [edit]

Like its ability to control pain, aspirin's ability to control **fever** is due to its action on the **prostaglandin** system through its irreversible inhibition of **COX**.^[28] Although aspirin's use as an **antipyretic** in adults is well-established, many medical societies and regulatory agencies (including the **American Academy of Family Physicians**, the **American Academy of Pediatrics**, and the U.S. **Food and Drug Administration** (FDA)) strongly advise against using aspirin for treatment of fever in children because of the risk of **Reye's syndrome**, a rare but often fatal illness associated with the use of aspirin or other salicylates in children during episodes of viral or bacterial infection.^{[29][30][31]} Because of the risk of Reye's syndrome in children, in 1986, the FDA required labeling on all aspirin-containing medications advising against its use in children and teenagers.^[32]

Inflammation [edit]

Aspirin is used as an **anti-inflammatory agent** for both acute and long-term **inflammation**,^[33] as well as for treatment of inflammatory diseases, such as **rheumatoid arthritis**.^[13]

Heart attacks and strokes [edit]

Aspirin is an important part of the treatment of those who have had a **myocardial infarction** (heart attack).^[34] One trial found that among those likely having an **ST-segment elevation MI**, aspirin saves the life of 1 in 42 by reducing the 30-day death rate from

ChemSpider

2157

UNII

R16CO5Y76E

KEGG

D00109

ChEBI

CHEBI:15365

ChEMBL

CHEMBL25

PDB ligand

AIN (PDBe, RCSB PDB)

ECHA InfoCard

100.000.059

Chemical and physical data

Formula

C9H8O4

Molar mass

180.157 g/mol

3D model (JSmol)

Interactive image

Density

1.40 g/cm³

Melting point

135 °C (275 °F)

Boiling point

140 °C (284 °F)
(decomposes)

Solubility in water

3 mg/mL (20 °C)

SMILES

O=C(C)Oc1ccccc1C(=O)O

InChI

InChI=1S/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3,(H,11,12)

Key:BSYNRYMUTXBXSQ-UHFFFAOYSA-N

(verify)



Aspirin 325 mg / 5 grains for pain



Uncoated aspirin tablets, consisting of about 90% acetylsalicylic acid, along with a minor amount of inert fillers and binders

11.8% to 9.4%.^[35] There was no difference in major bleeding, but there was a small increase in minor bleeding amounting to roughly 1 in every 167 people given aspirin.^[35]

High risk [\[edit\]](#)

For people who have already had a heart attack or stroke, taking aspirin daily for two years prevented 1 in 50 from having a cardiovascular problem (heart attack, stroke, or death), but also caused non-fatal bleeding problems to occur in 1 of 400 people.^{[36][37][38]}

Lower risk [\[edit\]](#)

Studies have not found an overall benefit in the general population of healthy people, although it is possible that there are small benefits for those at especially high risk, despite never having had a heart attack or stroke in the past.^[39] One study found that among those who have never had a heart attack or stroke, taking aspirin daily for 1 year prevents 1 in 1,667 from having a non-fatal heart attack or stroke, but caused 1 in 3,333 to have a non-fatal bleeding event. However, the study population were at relatively higher risk than those who had never had a heart attack or stroke.^[40]

Aspirin appears to offer little benefit to those at lower risk of heart attack or stroke—for instance, those without a history of these events or with pre-existing disease. Some studies recommend aspirin on a case-by-case basis,^{[41][42]} while others have suggested the risks of other events, such as gastrointestinal bleeding, were enough to outweigh any potential benefit, and recommended against using aspirin for primary prevention entirely.^[43] Aspirin has also been suggested as a component of a [polypill](#) for prevention of cardiovascular disease.^{[44][45]}

Complicating the use of aspirin for prevention is the phenomenon of aspirin resistance.^{[46][47]} For people who are resistant, aspirin's efficacy is reduced.^[48] Some authors have suggested testing regimens to identify people who are resistant to aspirin.^[49]

After surgery [\[edit\]](#)

After [percutaneous coronary interventions](#) (PCIs), such as the placement of a [coronary artery stent](#), a U.S. [Agency for Healthcare Research and Quality](#) guideline recommends that aspirin be taken indefinitely.^[50] Frequently, aspirin is combined with an [ADP receptor inhibitor](#), such as [clopidogrel](#), [prasugrel](#), or [ticagrelor](#) to prevent [blood clots](#). This is called dual [antiplatelet therapy](#) (DAPT). United States and European Union guidelines disagree somewhat about how long, and for what indications this combined therapy should be continued after surgery. U.S. guidelines recommend DAPT for at least 12 months, while EU guidelines recommend DAPT for 6–12 months after a drug-eluting stent placement.^[51] However, they agree that aspirin be continued indefinitely after DAPT is complete.

Cancer prevention [\[edit\]](#)

Aspirin is thought to reduce the overall risk of both getting cancer and dying from cancer.^[52] This effect is particularly beneficial for [colorectal cancer](#) (CRC).^{[17][53][54][55]} It may also slightly reduce the risk of [endometrial cancer](#),^[56] [breast cancer](#), and [prostate cancer](#).^[57]

Some conclude the benefits are greater than the risks due to bleeding in those at average risk.^[52] Others are unclear if the benefits are greater than the risk.^{[58][59]} Given this uncertainty, the 2007 [United States Preventive Services Task Force](#) guidelines on this topic recommended against the use of aspirin for prevention of CRC in people with average risk.^[60]

Other uses [\[edit\]](#)

Aspirin is a first-line treatment for the fever and joint-pain symptoms of [acute rheumatic fever](#). The therapy often lasts for one to two weeks, and is rarely indicated for longer periods. After fever and pain have subsided, the aspirin is no longer necessary, since it does not decrease the incidence of heart complications and residual rheumatic heart disease.^{[61][62]} [Naproxen](#) has been shown to be as effective as aspirin and less toxic, but due to the limited clinical experience, naproxen is recommended only as a second-line treatment.^{[61][63]}

Along with rheumatic fever, [Kawasaki disease](#) remains one of the few indications for aspirin use in children^[64] in spite of a lack of high quality evidence for its effectiveness.^[65]

Low-dose aspirin supplementation has moderate benefits when used for prevention of [pre-eclampsia](#).^{[66][67]} This benefit is greater when started in early pregnancy.^[68]

Resistance [\[edit\]](#)

For some people, aspirin does not have as strong an effect on platelets as for others, an effect known as aspirin-resistance or insensitivity. One study has suggested women are more likely to be resistant than men,^[69] and a different, aggregate study of 2,930 people found 28% were resistant.^[70] A study in 100 Italian people, though, found, of the apparent 31% aspirin-resistant subjects, only 5% were truly resistant, and the others were [noncompliant](#).^[71] Another study of 400 healthy volunteers found no subjects who were truly resistant, but some had "pseudoresistance, reflecting delayed and reduced drug absorption".^{[72][\[verification needed\]](#)}

Dosage [\[edit\]](#)

Adult aspirin tablets are produced in standardised sizes, which vary slightly from country to country, for example 300 mg in Britain and 325 mg (or 5 [grains](#)) in the United States. Smaller doses are based on these standards, e.g., 75 mg and 81 mg tablets. The 81 mg (1 ¼-grain) tablets are commonly called "baby aspirin" or "baby-strength", because they were originally—but no longer—intended to be administered to infants and children.^[73] No medical significance occurs due to the slight difference in

dosage between the 75 mg and the 81 mg tablets.

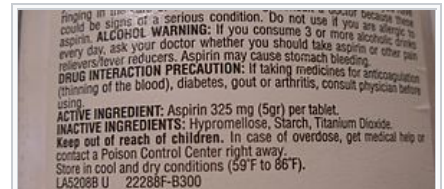
In general, for adults, doses are taken four times a day for fever or arthritis,^[74] with doses near the maximal daily dose used historically for the treatment of [rheumatic fever](#).^[75] For the prevention of [myocardial infarction](#) (MI) in someone with documented or suspected [coronary artery disease](#), much lower doses are taken once daily.^[74]

Recommendations from the USPSTF^[76] on the use of aspirin for the primary prevention of coronary heart disease encourage men aged 45–79 and women aged 55–79 to use aspirin when the potential benefit of a reduction in MI for men or stroke for women outweighs the potential harm of an increase in [gastrointestinal hemorrhage](#).^[77] The WHI study said regular low dose (75 or 81 mg) aspirin female users had a 25% lower risk of death from cardiovascular disease and a 14% lower risk of death from any cause.^[77] Low-dose aspirin use was also associated with a trend toward lower risk of cardiovascular events, and lower aspirin doses (75 or 81 mg/day) may optimize efficacy and safety for people requiring aspirin for long-term prevention.^[77]

In children with Kawasaki disease, aspirin is taken at dosages based on body weight, initially four times a day for up to two weeks and then at a lower dose once daily for a further six to eight weeks.^[78]



Coated 325 mg (5-grain) aspirin tablets



The 5-grain aspirin. The usage guidance label on a bottle of aspirin indicates that the dosage is "325 mg (5 gr)".

Adverse effects [\[edit\]](#)

Contraindications [\[edit\]](#)

Aspirin should not be taken by people who are allergic to [ibuprofen](#) or [naproxen](#),^{[79][80]} or who have [salicylate intolerance](#).^{[81][82]} or a more generalized [drug intolerance](#) to NSAIDs, and caution should be exercised in those with [asthma](#) or NSAID-precipitated [bronchospasm](#). Owing to its effect on the stomach lining, manufacturers recommend people with [peptic ulcers](#), mild [diabetes](#), or [gastritis](#) seek medical advice before using aspirin.^{[79][83]} Even if none of these conditions is present, the risk of [stomach bleeding](#) is still increased when aspirin is taken with [alcohol](#) or [warfarin](#).^{[79][80]} People with [hemophilia](#) or other bleeding tendencies should not take aspirin or other salicylates.^{[79][83]} Aspirin is known to cause [hemolytic anemia](#) in people who have the genetic disease [glucose-6-phosphate dehydrogenase deficiency](#), particularly in large doses and depending on the severity of the disease.^[84] Use of aspirin during [dengue fever](#) is not recommended owing to increased bleeding tendency.^[85] People with [kidney disease](#), [hyperuricemia](#), or [gout](#) should not take aspirin because it inhibits the kidneys' ability to excrete [uric acid](#), thus may exacerbate these conditions. Aspirin should not be given to children or adolescents to control cold or influenza symptoms, as this has been linked with [Reye's syndrome](#).^[86]

Gastrointestinal [\[edit\]](#)

Aspirin use has been shown to increase the risk of gastrointestinal bleeding.^[87] Although some [enteric-coated](#) formulations of aspirin are advertised as being "gentle to the stomach", in one study, enteric coating did not seem to reduce this risk.^[87] Combining aspirin with other [NSAIDs](#) has also been shown to further increase this risk.^[87] Using aspirin in combination with clopidogrel or warfarin also increases the risk of upper gastrointestinal bleeding.^[88]

Blockade of COX-1 by aspirin apparently results in the upregulation of COX-2 as part of a gastric defense^[89] and that taking COX-2 inhibitors concurrently with aspirin increases the gastric mucosal erosion.^[90] Therefore, caution should be exercised if combining aspirin with any "natural" supplements with COX-2-inhibiting properties, such as garlic extracts, curcumin, bilberry, pine bark, ginkgo, fish oil, resveratrol, genistein, quercetin, resorcinol, and others.

In addition to enteric coating, "buffering" is the other main method companies have used to try to mitigate the problem of gastrointestinal bleeding. Buffering agents are intended to work by preventing the aspirin from concentrating in the walls of the stomach, although the benefits of buffered aspirin are disputed. Almost any buffering agent used in antacids can be used; Bufferin, for example, uses [magnesium oxide](#). Other preparations use [calcium carbonate](#).^[91]

Taking it with vitamin C is a more recently investigated method of protecting the stomach lining. Taking equal doses of vitamin C and aspirin may decrease the amount of stomach damage that occurs compared to taking aspirin alone.^{[92][93]}

Central effects [\[edit\]](#)

Large doses of [salicylate](#), a metabolite of aspirin, cause temporary [tinnitus](#) (ringing in the ears) based on experiments in rats, via the action on [arachidonic acid](#) and [NMDA receptors](#) cascade.^[94]

Reye's syndrome [\[edit\]](#)

Main article: [Reye's syndrome](#)

Reye's syndrome, a rare but severe illness characterized by acute [encephalopathy](#) and [fatty liver](#), can occur when children or adolescents are given aspirin for a fever or other illness or infection. From 1981 through 1997, 1207 cases of Reye's syndrome in people younger than 18 were reported to the U.S. [Centers for Disease Control and Prevention](#). Of these, 93% reported being ill in the three weeks preceding the onset of Reye's syndrome, most commonly with a [respiratory infection](#), [chickenpox](#), or [diarrhea](#). Salicylates were detectable in 81.9% of children for whom test results were reported.^[95] After the association between

Reye's syndrome and aspirin was reported, and safety measures to prevent it (including a [Surgeon General's](#) warning, and changes to the labeling of aspirin-containing drugs) were implemented, aspirin taken by children declined considerably in the United States, as did the number of reported cases of Reye's syndrome; a similar decline was found in the United Kingdom after warnings against pediatric aspirin use were issued.^[95] The [U.S. Food and Drug Administration](#) now recommends aspirin (or aspirin-containing products) should not be given to anyone under the age of 12 who has a fever,^[86] and the British [Medicines and Healthcare products Regulatory Agency](#) recommends children who are under 16 years of age should not take aspirin, unless it is on the advice of a doctor.^[96]

Skin [\[edit\]](#)

For a small number of people, taking aspirin can result in symptoms resembling an allergic reaction, including [hives](#), swelling, and headache. The reaction is caused by [salicylate intolerance](#) and is not a true [allergy](#), but rather an inability to metabolize even small amounts of aspirin, resulting in an [overdose](#).

Aspirin and other NSAIDs, such as ibuprofen, may delay the healing of skin wounds.^[97] Aspirin may however help heal venous leg ulcers that have not healed following usual treatment.^[98]

Other adverse effects [\[edit\]](#)

Aspirin can induce [swelling of skin tissues](#) in some people. In one study, angioedema appeared one to six hours after ingesting aspirin in some of the people. However, when the aspirin was taken alone, it did not cause angioedema in these people; the aspirin had been taken in combination with another NSAID-induced drug when angioedema appeared.^[99]

Aspirin causes an increased risk of cerebral microbleeds having the appearance on [MRI](#) scans of 5 to 10 mm or smaller, hypointense (dark holes) patches.^{[100][101]} Such cerebral microbleeds are important, since they often occur prior to [ischemic stroke](#) or [intracerebral hemorrhage](#), [Binswanger disease](#), and [Alzheimer's disease](#).^[original research?]

A study of a group with a mean dosage of aspirin of 270 mg per day estimated an average absolute risk increase in [intracerebral hemorrhage](#) (ICH) of 12 events per 10,000 persons.^[102] In comparison, the estimated absolute risk reduction in myocardial infarction was 137 events per 10,000 persons, and a reduction of 39 events per 10,000 persons in ischemic stroke.^[102] In cases where ICH already has occurred, aspirin use results in higher mortality, with a dose of about 250 mg per day resulting in a [relative risk](#) of death within three months after the ICH around 2.5 (95% [confidence interval](#) 1.3 to 4.6).^[103]

Aspirin and other NSAIDs can cause [abnormally high blood levels of potassium](#) by inducing a [hyporeninemic hypoaldosteronic state](#) via inhibition of prostaglandin synthesis; however, these agents do not typically cause hyperkalemia by themselves in the setting of normal renal function and euvolemic state.^[104]

Aspirin can cause prolonged bleeding after operations for up to 10 days. In one study, 30 of 6499 people having elective surgery required reoperations to control bleeding. Twenty had diffuse bleeding and 10 had bleeding from a site. Diffuse, but not discrete, bleeding was associated with the preoperative use of aspirin alone or in combination with other NSAIDs in 19 of the 20 diffuse bleeding people.^[105]

On 9 July 2015, the [FDA](#) toughened warnings of increased [heart attack](#) and [stroke](#) risk associated with [nonsteroidal anti-inflammatory drugs](#) (NSAID). Aspirin is an NSAID but is not affected by the new warnings.^[106]

Overdose [\[edit\]](#)

Main article: [Aspirin poisoning](#)

Aspirin overdose can be acute or chronic. In acute poisoning, a single large dose is taken; in chronic poisoning, higher than normal doses are taken over a period of time. Acute overdose has a [mortality rate](#) of 2%. Chronic overdose is more commonly lethal, with a mortality rate of 25%;^[107] chronic overdose may be especially severe in children.^[108] Toxicity is managed with a number of potential treatments, including [activated charcoal](#), intravenous dextrose and normal saline, [sodium bicarbonate](#), and [dialysis](#).^[109] The diagnosis of poisoning usually involves measurement of plasma salicylate, the active metabolite of aspirin, by automated spectrophotometric methods. Plasma salicylate levels in general range from 30–100 mg/l after usual therapeutic doses, 50–300 mg/l in people taking high doses and 700–1400 mg/l following acute overdose. Salicylate is also produced as a result of exposure to [bismuth subsalicylate](#), [methyl salicylate](#), and [sodium salicylate](#).^{[110][111]}

Interactions [\[edit\]](#)

Aspirin is known to [interact](#) with other drugs. For example, [acetazolamide](#) and [ammonium chloride](#) are known to enhance the intoxicating effect of salicylates, and alcohol also increases the gastrointestinal bleeding associated with these types of drugs.^{[79][80]} Aspirin is known to displace a number of drugs from protein-binding sites in the blood, including the [antidiabetic drugs](#) [tolbutamide](#) and [chlorpropamide](#), [warfarin](#), [methotrexate](#), [phenytoin](#), [probenecid](#), [valproic acid](#) (as well as interfering with [beta oxidation](#), an important part of valproate metabolism), and other NSAIDs. Corticosteroids may also reduce the concentration of aspirin. Ibuprofen can negate the antiplatelet effect of aspirin used for cardioprotection and stroke prevention.^[112] The pharmacological activity of [spironolactone](#) may be reduced by taking aspirin, and it is known to compete with [penicillin G](#) for renal tubular secretion.^[113] Aspirin may also inhibit the absorption of vitamin C.^{[114][115]}^[unreliable medical source?]^[116]

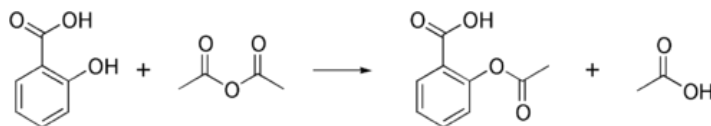
Chemical properties [\[edit\]](#)

Aspirin decomposes rapidly in solutions of [ammonium acetate](#) or the [acetates](#), [carbonates](#), [citrates](#), or [hydroxides](#) of the [alkali metals](#). It is stable in dry air, but gradually [hydrolyses](#) in contact with moisture to [acetic](#) and [salicylic acids](#). In solution with alkalis, the hydrolysis proceeds rapidly and the clear solutions formed may consist entirely of acetate and salicylate.^[117]

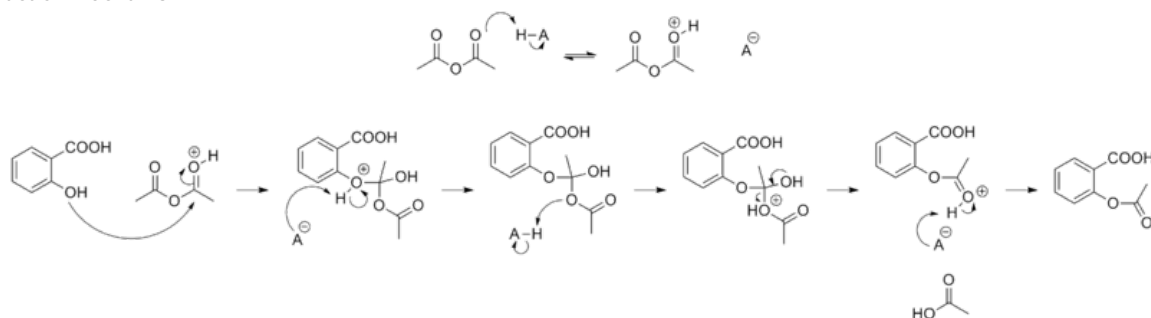
Like [flour mills](#), factories that make aspirin tablets must pay attention to how much of the powder gets into the air inside the building, because [the powder-air mixture can be explosive](#). The [National Institute for Occupational Safety and Health](#) (NIOSH) has set a [recommended exposure limit](#) in the United States of 5 mg/m³ (time-weighted average).^[118] In 1989, the [Occupational Safety and Health Administration](#) set a legal [permissible exposure limit](#) for aspirin of 5 mg/m³, but this was vacated by the [AFL-CIO v. OSHA](#) decision in 1993.^[119]

Synthesis [[edit](#)]

The synthesis of aspirin is classified as an [esterification](#) reaction. [Salicylic acid](#) is treated with [acetic anhydride](#), an acid derivative, causing a chemical reaction that turns salicylic acid's [hydroxyl](#) group into an [ester](#) group (R-OH → R-OCOCH₃). This process yields aspirin and [acetic acid](#), which is considered a [byproduct](#) of this reaction. Small amounts of [sulfuric acid](#) (and occasionally [phosphoric acid](#)) are almost always used as a [catalyst](#). This method is commonly employed in undergraduate teaching labs.^[120]



Reaction mechanism



Formulations containing high concentrations of aspirin often smell like [vinegar](#)^[121] because aspirin can decompose through hydrolysis in moist conditions, yielding salicylic and acetic acids.^[122]

Physical properties [[edit](#)]

Aspirin, an [acetyl](#) derivative of salicylic acid, is a white, crystalline, weakly acidic substance, with a [melting point](#) of 136 °C (277 °F), and a boiling point of 140 °C (284 °F).^[123] Its acid dissociation constant ([pK_a](#)) is 3.5 at 25 °C (77 °F).^[124]

Polymorphism [[edit](#)]

[Polymorphism](#), or the ability of a substance to form more than one [crystal structure](#), is important in the development of pharmaceutical ingredients. Many drugs are receiving regulatory approval for only a single crystal form or polymorph. For a long time, only one crystal structure for aspirin was known. That aspirin might have a second crystalline form was suspected since the 1960s. The elusive second polymorph was first discovered by Vishweshwar and coworkers in 2005,^[125] and fine structural details were given by Bond *et al.*^[126] A new crystal type was found after attempted cocrystallization of aspirin and [levetiracetam](#) from hot [acetonitrile](#). The form II is only stable at 100 K and reverts to form I at ambient temperature. In the (unambiguous) form I, two salicylic molecules form centrosymmetric [dimers](#) through the acetyl groups with the (acidic) [methyl](#) proton to [carbonyl hydrogen bonds](#), and in the newly claimed form II, each salicylic molecule forms the same hydrogen bonds with two neighboring molecules instead of one. With respect to the hydrogen bonds formed by the [carboxylic acid](#) groups, both polymorphs form identical dimer structures.^[*citation needed*]

Mechanism of action [[edit](#)]

Main article: [Mechanism of action of aspirin](#)

Discovery of the mechanism [[edit](#)]

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](#).^{[127][128]} For this discovery he was awarded the 1982 [Nobel Prize in Physiology or Medicine](#), jointly with [Sune Bergström](#) and [Bengt Ingemar Samuelsson](#).^[129] In 1984, he was made a [Knight Bachelor](#).

Prostaglandins and thromboxanes [[edit](#)]

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](#) and [ibuprofen](#)), which are reversible inhibitors ([Suicide inhibition](#)).

Low-dose aspirin use irreversibly blocks the formation of [thromboxane A₂](#) 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 in people who have had a heart attack, unstable angina, ischemic stroke or transient ischemic attack.^[130] 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A₂ release provoked acutely, with the prostaglandin I₂ synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition.^[131]

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 [\[edit\]](#)

At least two different types of cyclooxygenases, COX-1 and COX-2, are acted on by aspirin. 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.^{[132]^[verification needed]} 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.^[9]

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.^{[133]^[134]} 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.

Furthermore, aspirin, while inhibiting the ability of COX-2 to form pro-inflammatory products such as the [prostaglandins](#), converts this enzyme's activity from a prostaglandin-forming cyclooxygenase to a [lipoyxygenase](#)-like enzyme: aspirin-treated COX-2 metabolizes a variety of [polyunsaturated fatty acids](#) to hydroperoxy products which are then further metabolized to [specialized proresolving mediators](#) such as the aspirin-triggered [lipoxins](#), aspirin-triggered [resolvins](#), and aspirin-triggered [maresins](#). These mediators possess potent anti-inflammatory activity. It is proposed that this aspirin-triggered transition of COX-2 from cyclooxygenase to lipoyxygenase activity and the consequential formation of specialized proresolving mediators contributes to the anti-inflammatory effects of aspirin.^{[135]^[136]^[137]}

Additional mechanisms [\[edit\]](#)

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.^[138] Aspirin buffers and transports the protons. When high doses 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 have been shown in mice to have an independent mechanism of reducing inflammation. This reduced leukocyte adhesion is an important step in the immune response to infection; however, evidence is insufficient to show aspirin helps to fight infection.^[139] More recent data also suggest salicylic acid and its derivatives modulate signaling through [NF-κB](#).^[140] 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.^{[141]^[142]} 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.^{[143]^[144]} These acetylation reactions may explain many hitherto unexplained effects of aspirin.

Pharmacokinetics [\[edit\]](#)

Acetylsalicylic acid is a [weak acid](#), and very little of it is [ionized](#) in the [stomach](#) after oral administration. Acetylsalicylic acid is quickly absorbed through the cell membrane in the [acidic](#) conditions of the stomach. The increased [pH](#) and larger surface area of the [small intestine](#) causes aspirin to be absorbed more slowly there, as more of it is ionised. Owing to the formation of concretions, aspirin is absorbed much more slowly during overdose, and [plasma](#) concentrations can continue to rise for up to 24 hours after ingestion.^{[145]^[146]^[147]}

About 50–80% of salicylate in the blood is bound to [albumin protein](#), while the rest remains in the active, ionized state; protein binding is concentration-dependent. Saturation of binding sites leads to more free salicylate and increased toxicity. The volume of distribution is 0.1–0.2 L/kg. Acidosis increases the volume of distribution because of enhancement of tissue penetration of salicylates.^[147]

As much as 80% of therapeutic doses of salicylic acid is [metabolized](#) in the [liver](#). [Conjugation](#) with [glycine](#) forms [salicyluric acid](#), and with [glucuronic acid](#) to form two different glucuronide esters. The conjugate with the acetyl group intact is referred to as the *acyl glucuronide*; the deacetylated conjugate is the *phenolic glucuronide*. These metabolic pathways have only a limited capacity. Small amounts of salicylic acid are also hydroxylated to [gentisic acid](#). With large salicylate doses, the kinetics switch from first-order to zero-order, as [metabolic pathways](#) become saturated and [renal](#) excretion becomes increasingly important.^[147]

Salicylates are excreted mainly by the kidneys as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%), and

acyl glucuronides (5%), [gentisic acid](#) (< 1%), and [2,3-dihydroxybenzoic acid](#).^[148] When small doses (less than 250 mg in an adult) are ingested, all pathways proceed by first-order kinetics, with an elimination half-life of about 2.0 h to 4.5 h.^{[149][150]} When higher doses of salicylate are ingested (more than 4 g), the half-life becomes much longer (15 h to 30 h),^[151] because the biotransformation pathways concerned with the formation of salicylic acid and salicyl phenolic glucuronide become saturated.^[152] Renal excretion of salicylic acid becomes increasingly important as the metabolic pathways become saturated, because it is extremely sensitive to changes in [urinary pH](#). A 10- to 20-fold increase in renal clearance occurs when urine pH is increased from 5 to 8. The use of urinary alkalinization exploits this particular aspect of salicylate elimination.^[153]

History ^[edit]

Main article: [History of aspirin](#)



1923 advertisement

Medicines made from [willow](#) and other [salicylate](#)-rich plants appear in clay tablets from ancient [Sumer](#) as well as the [Ebers Papyrus](#) from ancient Egypt.^{[6]:8–13[8]} Hippocrates referred to their use of salicylic tea to reduce fevers around 400 BC, and were part of the pharmacopoeia of Western medicine in [classical antiquity](#) and the [Middle Ages](#).^[8] Willow bark extract became recognized for its specific effects on fever, pain and inflammation in the mid-eighteenth century.^[154] By the nineteenth century pharmacists were experimenting with and prescribing a variety of chemicals related to [salicylic acid](#), the active component of willow extract.^{[6]:46–55}

In 1853, chemist [Charles Frédéric Gerhardt](#) treated [acetyl chloride](#) with [sodium salicylate](#) to produce [acetylsalicylic acid](#) for the first time.^{[6]:46–48} In the second half of the nineteenth century, other academic chemists established the compound's chemical structure and devised more efficient methods of synthesis. In 1897, scientists at the drug and dye firm [Bayer](#) began investigating acetylsalicylic acid as a less-irritating replacement for standard common salicylate medicines, and identified a new way to synthesize it.^{[6]:69–75} By 1899, Bayer had dubbed this drug Aspirin and was selling it around the world.^{[7]:27} The word *Aspirin* was Bayer's brand name, rather than the

generic name of the drug; however, Bayer's rights to the trademark were lost or sold in many countries. Aspirin's popularity grew over the first half of the twentieth century leading to fierce competition with the proliferation of aspirin brands and products.^[8]

Aspirin's popularity declined after the development of [acetaminophen/paracetamol](#) in 1956 and [ibuprofen](#) in 1962. In the 1960s and 1970s, [John Vane](#) and others discovered the basic mechanism of aspirin's effects,^{[6]:226–231} while clinical trials and other studies from the 1960s to the 1980s established aspirin's efficacy as an anti-clotting agent that reduces the risk of clotting diseases.^{[6]:247–257} The initial large studies on the use of low-dose aspirin to prevent heart attacks that were published in the 1970s and 1980s helped spur reform in [clinical research ethics](#) and [guidelines for human subject research](#) and US federal law, and are often cited as examples of clinical trials that included only men, but from which people drew general conclusions that did not hold true for women.^{[155][156][157]}

Aspirin sales revived considerably in the last decades of the twentieth century, and remain strong in the twenty-first with widespread use as a preventive treatment for [heart attacks](#) and [strokes](#).^{[6]:267–269}

Trademark ^[edit]

Due to allowing the use of "Aspirin" for years by other manufacturing chemists, despite the trademark-infringing nature of the use, and its own failure to use the name for its own product when it began selling direct, Bayer lost its trademark in the United States in 1918, affirmed by court appeal in 1921.^[158] Today, aspirin is a [generic word](#) in Australia, France, India, Ireland, New Zealand, Pakistan, Jamaica, Colombia, the Philippines, South Africa, Ghana, the United Kingdom and the United States.^[159] Aspirin, with a capital "A", remains a registered trademark of Bayer in Germany, Canada, Mexico, and in over 80 other countries, where the trademark is owned by Bayer, using acetylsalicylic acid in all markets, but using different packaging and physical aspects for each.^{[160][161]}

Compendial status ^[edit]

- [United States Pharmacopeia](#)^[162]
- [British Pharmacopoeia](#)^[163]

Veterinary medicine ^[edit]

Aspirin is sometimes used for pain relief or as an anticoagulant in veterinary medicine, primarily in dogs and sometimes horses, although newer medications with fewer side effects are generally used instead.

Both dogs and horses are susceptible to the gastrointestinal side effects associated with salicylates, but it is a convenient treatment for arthritis in older dogs, and has shown some promise in cases of [laminitis](#) in horses.^{[citation needed][164]} It is no longer commonly used for cases of laminitis, as it could be counterproductive for treatment. Aspirin should be used in animals only under the direct supervision of a [veterinarian](#); in particular, cats lack the [glucuronide](#) conjugates that aid in the excretion of aspirin, making it potentially toxic.^[165] No clinical signs of toxicosis occurred when cats were given 25 mg/kg of aspirin every 48 hours for 4 weeks.^[166] The dose recommended in cats for relief of pain and fever is 10 mg/kg every 48 hours.^[167]

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158. [^] [Bayer Co. v. United Drug Co.](#), 272 F. 505, p.512 (S.D.N.Y. 1921) ("Disregarding this, however, it was too late in the autumn of 1915 to reclaim the word which had already passed into the public domain. If the consuming public had once learned to know 'Aspirin' as the accepted name for the drug, perhaps it is true that an extended course of education might have added to it some proprietary meaning, but it would be very difficult to prove that it had been done in 17 months, and in any case the plaintiff does not try to prove it. [...] Yet, had it not been indifferent to the results of selling to the consumer, it could have protected itself just as well at the time when consumers began to buy directly as in 1915. Nothing would have been easier than to insist that the tablet makers should market the drug in small tin boxes bearing the plaintiff's name, or to take over the sale just as it did later. Instead of this, they allowed the manufacturing chemists to build up this part of the demand without regard to the trademark. Having made that bed, they must be content to lie in it. Hence it appears to me that nothing happening between October 1915, and March 1917, will serve to turn the word into a trademark.").
159. [^] CBE Style Manual Committee; Huth, Edward J. (1994). *Scientific style and format: the CBE manual for authors, editors, and publishers*. Cambridge University Press. p. 164. ISBN 978-0-521-47154-1. Archived from the original on 15 October 2015.
160. [^] "Aspirin: the versatile drug". *CBC News*. 28 May 2009. Archived from the original on 6 November 2016.
161. [^] Cheng, Tsung O. (2007). "The history of aspirin". *Texas Heart Institute Journal*. **34** (3): 392–393. PMC 1995051. PMID 17948100.
162. [^] Sigma Aldrich. "Aspirin". Archived from the original on 18 August 2011. Retrieved 13 July 2009.
163. [^] British Pharmacopoeia. "Index BP 2009" (PDF). Archived from the original (PDF) on 11 April 2009. Retrieved 13 July 2009.
164. [^] Cambridge H, Lees P, Hooke RE, Russell CS (1991). "Antithrombotic actions of aspirin in the horse". *Equine Veterinary Journal*. **23** (2): 123–7. PMID 1904347. doi:10.1111/j.2042-3306.1991.tb02736.x.
165. [^] Lappin, Michael R, ed. (2001). *Feline internal medicine secrets*. Philadelphia: Hanley & Belfus. p. 160. ISBN 1-56053-461-3.
166. [^] "Analgesics (toxicity)". Merck. Archived from the original on 11 April 2015. Retrieved 3 March 2016.
167. [^] "Plants poisonous to livestock". Cornell University Department of Animal Science. Archived from the original on 16 August 2015. Retrieved 3 March 2016.

- Jeffreys, Diarmuid (11 August 2005). *Aspirin: the remarkable story of a wonder drug*. Bloomsbury. ISBN 1-58234-600-3.
- Sheldon Peter (2007). *The fall and rise of aspirin the wonder drug*. Brewin Books. ISBN 978-1-85858-403-4.

External links [edit]

- Aspirin at DMOZ
- U.S. National Library of Medicine: Drug Information Portal – Aspirin
- CDC – NIOSH Pocket Guide to Chemical Hazards – Acetyl salicylic Acid
- Take two: Aspirin, New uses and new dangers are still being discovered as aspirin enters its 2nd century. Shauna Roberts, American Chemical Society
- Ling, Greg (2005). "Aspirin". *How Products are Made*. **1**. Thomson Gale.



v · t · e		Antithrombotics (thrombolytics, anticoagulants and antiplatelet drugs) (B01)	
Antiplatelet drugs	Glycoprotein IIb/IIIa inhibitors	Abciximab · Eptifibatide · Orbofiban · Roxifiban · Sibrafiban [§] · Tirofiban	
	ADP receptor/P2Y ₁₂ inhibitors	Thienopyridines (Clopidogrel · Prasugrel · Ticlopidine) · Nucleotide/nucleoside analogs (Cangrelor · Elinogrel · Ticagrelor)	
	Prostaglandin analogue (PGI ₂)	Beraprost · Iloprost · Prostacyclin · Treprostinil	
	COX inhibitors	Acetylsalicylic acid/Aspirin[#] · Aloxiprin · Carbasalate calcium · Indobufen · Triflusal	
	Thromboxane inhibitors	Thromboxane synthase inhibitors (Dipyridamole (+ aspirin) · Picotamide · Terbogrel) · Receptor antagonists (Terbogrel · Terutroban [§])	
	Phosphodiesterase inhibitors	Cilostazol · Dipyridamole · Triflusal	
	Other	Cloricromen · Ditazole · Vorapaxar	
Anticoagulants	Vitamin K antagonists (inhibit II, VII, IX, X)	Coumarins: Acenocoumarol · Coumatetralyl · Dicoumarol · Ethyl biscoumacetate · Phenprocoumon · Warfarin [#] · 1,3-Indandiones: Clorindione · Diphenadione · Phenindione · Other: Tiodomarol	
	Factor Xa inhibitors (with some II inhibition)	Heparin group/ glycosaminoglycans/ (bind antithrombin)	Low molecular weight heparin (Bemiparin · Certoparin · Dalteparin · Enoxaparin · Nadroparin · Pamaparin · Reviparin · Tinzaparin [‡]) · Oligosaccharides (Fondaparinux · Idraparinux [§]) · Heparinoids (Danaparoid · Dermatan sulfate · Sulodexide)
		Direct Xa inhibitors ("xabans")	Apixaban · Betrixaban · Darexaban [§] · Edoxaban · Otamixaban [§] · Rivaroxaban
	Direct thrombin (IIa) inhibitors	Bivalent: Hirudin (Bivalirudin · Desirudin · Lepirudin) · Univalent: Argatroban · Dabigatran · Efegatran · Inogatran [§] · Melagatran [‡] · Ximelagatran [‡]	
	Other	Antithrombin III · Defibrotide · Protein C (Drotrecogin alfa [‡]) · Ramatroban · REG1	
Thrombolytic drugs/ fibrinolytics	Plasminogen activators: r-tPA (Alteplase · Reteplase · Tenecteplase) · UPA (Saruplase · Urokinase) · Anistreplase · Montepulse · Streptokinase [#] · Other serine endopeptidases: Ancrod · Brinase · Fibrinolysin		
Non-medicalinal	Citrate · EDTA · Oxalate		
[#] WHO-EM · [‡] Withdrawn from market · Clinical trials: ([†] Phase III · [§] Never to phase III)			

v · t · e	Nonsteroidal anti-inflammatory drugs (NSAIDs) (primarily M01A and M02A, also N02BA)	
	Pyrazolones / Pyrazolidines	Aminophenazone · Ampyrone · Azapropazone · Clofezone · Difenamizole · Famprofazone · Feprazone · Kebuzone · Metamizole · Mofebutazone · Morazone · Nifenazone · Oxyphenbutazone · Phenazone · Phenylbutazone · Propyphenazone · Sulfinpyrazone · Suxibuzone [‡]
	Salicylates	Aspirin (acetylsalicylic acid)[#] · Aloxiprin · Benorylate · Carbasalate calcium · Diflunisal · Dipyracetyl · Ethenzamide · Guacetisal · Magnesium salicylate · Methyl salicylate · Salsalate · Salicin · Salicylamide · Salicylic acid (salicylate) · Sodium salicylate
	Acetic acid derivatives and related substances	Acetofenac · Acemetacin · Aldofenac · Amfenac · Bendazac · Bromfenac · Bumadizone · Bufexamac · Diclofenac · Difenpiramide · Etodolac · Felbinac · Fenclozic acid · Fentiazac · Indomethacin · Indomethacin farnesil · Isoxepac · Ketorolac · Lonazolac · Oxametacin · Prodolic acid · Proglumetacin · Sulindac · Tiopinac · Tolmetin · Zomepirac [‡]
	Oxicams	Ampiroxicam · Droxicam · Isoxicam · Lomoxicam · Meloxicam · Piroxicam · Tenoxicam
	Propionic acid derivatives (profens)	Alminoprofen · Benoxaprofen [†] · Carprofen [‡] · Dexibuprofen · Dextetoprofen · Fenbufen · Fenoprofen · Flunoxaprofen · Flurbiprofen · Ibuprofen[#] · Ibuproxam · Indoprofen [†] · Ketoprofen · Loxoprofen · Mroprofen · Naproxen · Oxaprozin · Pirprofen · Suprofen · Tarenflurbil · Tepoxalin [‡] · Tiaprofenic acid · Vedaprofen [‡] · <i>COX-inhibiting nitric oxide donor</i> : Naproxinod
	N-Arylanthranilic acids (fenamates)	Azapropazone · Clonixin · Etofenamate · Flufenamic acid · Flunixin · Meclofenamic acid · Mefenamic acid · Morniflumate · Niflumic acid · Tolfenamic acid · Flutiazin
	Coxibs	Apricoxib · Celecoxib · Cimicoxib [‡] · Deracoxib [‡] · Etoricoxib · Firocoxib [‡] · Lumiracoxib [‡] · Mavacoxib [‡] · Parecoxib · Robenacoxib [‡] · Rofecoxib [‡] · Valdecoxib [‡]
	Other	Aminopropionitrile · Benzylamine · Chondroitin sulfate · Diacerein · Fluproquazone · Glucosamine · Glycosaminoglycan · Hyperforin · Nabumetone · Nimesulide · Oxaceprol · Proquazone · Superoxide dismutase/Orgotein · Tenidap
Items listed in bold indicate initially developed compounds of specific groups. [#] WHO-EM [†] Withdrawn drugs. [‡] Veterinary use medications.		
v · t · e	Analgesics (N02A, N02B)	
	Opiates/opium	Codeine [#] (+paracetamol, +aspirin) · Morphine[#] (+naltrexone) · Opium · Laudanum · Paregoric
		Acetyldihydrocodeine · Benzylmorphine · Buprenorphine (+naloxone) · Desomorphine · Diamorphine (heroin) · Dihydrocodeine (+paracetamol) · Dihydromorphine · Ethylmorphine ·

Opioids	Semisynthetic	Hydrocodone (+paracetamol, +ibuprofen, +aspirin) · Hydromorphenol · Hydromorphone · Nicocodeine · Nicodicodeine · Nicomorphine · Oxycodone (+paracetamol, +aspirin, +ibuprofen, +naloxone, +naltrexone) · Oxymorphone · Thebacon
	Synthetic	Alfentanil · Alphaprodine · Anileridine · Butorphanol · Carfentanil · Dextromoramide · Dextropropoxyphene · Dezocine · Fentanyl (+fluanisone) · Ketobemidone · Levorphanol · Lofentanil · Meptazinol · Methadone · Nalbuphine · NFEPP · Pentazocine · Pethidine (meperidine) · Phenadoxone · Phenazocine · Piminodine · Piritramide · Propiram · Remifentanyl · Sufentanyl · Tapentadol · Tilidine · Tramadol
Paracetamol-type	Acetanilide [‡] · Bucetin [‡] · Butacetin[‡] · Paracetamol (acetaminophen) [#] · Parapropamol[‡] · Phenacetin [‡] · Propacetamol [‡]	
NSAIDs	Propionates	Fenoprofen · Flurbiprofen · Ibuprofen [#] · Ketoprofen · Naproxen · Oxaprozin
	Oxicams	Meloxicam · Piroxicam
	Acetates	Didofenac · Indometacin · Ketorolac · Nabumetone · Sulindac · Tolmetin
	COX-2 inhibitors	Celecoxib · Etoricoxib · Lumiracoxib · Parecoxib · Rofecoxib [‡] · Valdecoxib [‡]
	Fenamates	Meclofenamic acid · Mefenamic acid
	Salicylates	Aspirin (acetylsalicylic acid)[#] (+paracetamol/cafeine) · Benorylate · Diflunisal · Ethenzamide · Magnesium salicylate · Salicin · Salicylamide · Salsalate · Wintergreen (methyl salicylate)
	Pyrazolones	Aminophenazone [‡] · Ampyrone · Metamizole (dipyrone) · Nifenazone · Phenazone · Propyphenazone (+paracetamol/cafeine)
	Others	Glafenine
Cannabinoids	Cannabidiol · Cannabis · Nabilone · Nabiximols · Tetrahydrocannabinol (dronabinol)	
Ion channel modulators	Calcium blockers	Gabapentin · Gabapentin enacarbil · Pregabalin · Ziconotide
	Sodium blockers	Carbamazepine · Lacosamide · Local anesthetics (e.g., cocaine, lidocaine) · Mexiletine · Nefopam · Tricyclic antidepressants (e.g., amitriptyline [#]) <i>Na_v1.7/1.8-selective</i> : DSP-2230 [§] · Funapide [§] · PF-05089771 [§] · Raxatrigine [§]
	Potassium openers	Flupirtine
Myorelaxants	Carisoprodol · Chlorzoxazone · Cyclobenzaprine · Mephenoxalone · Methocarbamol · Orphenadrine	
Others	Analgesic adjuvant · Analgesine · Camphor · Capsaicin · Clonidine · Ketamine · Menthol · Methoxyflurane · Nefopam · Proglumide · Tricyclic antidepressants (e.g., amitriptyline [#])	

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([‡]Phase III · [§]Never to phase III)

Acne-treating agents (D10)		
Antibacterial	Azelaic acid · Benzoyl peroxide [#] · 8-Hydroxyquinoline · Blue light therapy · Tea tree oil	
Keratolytic	Glycolic acid · Salicylic acid [#] · Sulfur · Benzoyl peroxide [#]	
Anti-inflammatory	Nicotinamide · Ibuprofen [#] · Aspirin[#] · Red light therapy	
Antibiotics	Clindamycin · Dapsone · Erythromycin · Sulfacetamide · Tetracyclines (Lymecycline · Mncycline · Doxycycline)	
Hormonal	Antiandrogens (Bicalutamide · Cyproterone acetate · Drospirenone · Flutamide · Spironolactone)) · Estrogens (Estradiol · Ethinylestradiol)	
Retinoids	Adapalene · Isotretinoin · Mtretinide · Tazarotene · Tretinoin	
Other	Benzamycin · Epristeride · Mesulfen · Pelretin · Stridex · Tioxolone	
Combinations	Adapalene/benzoyl peroxide · Benzoyl peroxide/clindamycin · Clindamycin/tretinoin · Erythromycin/isotretinoin · Sulfacetamide/sulfur	

[#]WHO-EM · [‡]Withdrawn from market · Clinical trials: ([‡]Phase III · [§]Never to phase III)

Salicylates	
Salicylic acid · Aspirin · Aloxiprin · Methyl salicylate · Magnesium salicylate · Ethyl salicylate · Bismuth subsalicylate · Sodium salicylate · Salicylamide · Salicin · Benorilate · Salsalate · Ethenzamide · Diflunisal · Trolamine salicylate · Homosalate · Salicylmethylecgonine · Octyl salicylate · Aluminon · Benzyl salicylate · Copper aspirinate · Potassium salicylate	

Prostanoid signaling modulators			
Receptor (ligands)	DP (D ₂)	DP ₁	Agonists: Prostaglandin D ₂ · Treprostinil Antagonists: Asapiprant · Laropiprant · Vdupiprant
		DP ₂	Agonists: Indometacin · Prostaglandin D ₂ Antagonists: ADC-3680 · AZD-1981 · Bay U3405 · Fevipiprant · MK-1029 · MK-7246 · QAV-680 · Ramatroban · Setipiprant · Timapiprant · TM80089 · Vdupiprant
	EP (E ₂)	EP ₁	Agonists: Beraprost · Enprostil · Iloprost (ciloprost) · Latanoprost · Lubiprostone · Msoprostol · Prostaglandin E ₁ (alprostadi) · Prostaglandin E ₂ (dinoprostone) · Sulprostone Antagonists: AH-6809 · ONO-8130 · SC-19220 · SC-51089 · SC-51322
		EP ₂	Agonists: Butaprost · Msoprostol · Prostaglandin E ₁ (alprostadi) · Prostaglandin E ₂ (dinoprostone) · Treprostinil Antagonists: AH-6809 · PF-04418948 · TG 4-155
		EP ₃	Agonists: Beraprost · Carbacyclin · Cicaprost · Enprostil · Iloprost (ciloprost) · Isocarbacyclin · Latanoprost · Msoprostol · Prostaglandin D ₂ · Prostaglandin E ₁ (alprostadi) · Prostaglandin E ₂ (dinoprostone) · Remiprostol · Sulprostone Antagonists: L-798106
		EP ₄	Agonists: Lubiprostone · Msoprostol · Prostaglandin E ₁ (alprostadi) · Prostaglandin E ₂ (dinoprostone) · TCS-2510 Antagonists: Grapiprant · GW-627368 · L-161982 · ONO-AE3-208
		Unsorted	Agonists: 16,16-Dimethyl Prostaglandin E₂ · Aganepag · Carboprost · Evatanepag · Gemeprost ·

Categories: Aspirin | Acetate esters | Antiplatelet drugs | Bayer AG | Brands that became generic | Equine medications | German inventions | Hepatotoxins | Nonsteroidal anti-inflammatory drugs | Salicylates | World Health Organization essential medicines | Covalent inhibitors | Chemical substances for emergency medicine | Phenol esters

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