study of pharmacovigilance related drug ASPIRIN

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Abstract

Antiplatelet therapy has been documented to reduce risks of cardiovascular disease after acute myocardial infarction, coronary artery bypass graft, and in chronic atrial fibrillation patients, amongst other risk factors. Conventional management of thrombosis-based disorders includes the use of heparin, oral anticoagulants, and the preferred antiplatelet agent aspirin. Interestingly, aspirin was not intended to be used as an antiplatelet agent; rather, after being repurposed, it has become one of the most widely prescribed antithrombotic drugs. To this end, there have been several milestones in the development of antiplatelet agents in the last few decades, such as adenosine diphosphate receptor inhibitors, phosphodiesterase inhibitors, and GPIIb/IIIa inhibitors. However, given some of the limitations of these therapies, aspirin continues to play a major role in the management of thrombotic and cardiovascular disorders and is expected to do so for years to come.
Aspirin (acetylsalicylic acid) is the best-known salicylate and belongs to the non steroid anti-inflammatory drug class. Despite wide use being made since more than 100 years, knowledge about mechanism of action and therapeutic issues continually evolves. The main mechanism of action is prostaglandin synthesis inhibition. This is achieved through inhibition of prostaglandin endoperoxide synthase (PGHS) or cyclooxygenase (COX) synthesis. Most of the therapeutic uses of aspirin are explained by this mechanism. Nevertheless aspirin uses change as time goes by: if the main one during the first fifty years was an analgesic, anti-pyretic and anti-inflammatory one, the last fifty years saw aspirin being used mainly as an anti-thrombotic agent, in primary and secondary thrombo-embolic prevention. Better knowledge of mechanism of action points today at, on one hand, more selective and therefore better tolerated molecules, and, on the other hand, at new therapeutic applications, such as anti-cancer and neurodegenerative diseases prevention.

Clinical Research.

Clinical trials :

- Clinical trials are response. Studies, perform in people that are aimed, at evaluating a medical, surgical or beta Vioxal interventions.
- Clinical trials are a type of research, that studied new test and, treatment, and evaluate that their effect on human.. health outcomes.
- people volunteer to take of clinical trials to text, medical intervention including drugs, cell and, other, biological product, surgical procedures radiological procedure devices behavioural treatment and preventive care.
- Clinical trials are carefully designed reviewed and completed, and need to be approved before they can, stare people or all, ages take part in clinical trials, including children

Reference

- WHO clinical trials overview

Types of clinical trials.

- Clinical trials should be conducted and analysed, according to sound, scientific principle, with due regard to clinical consideration, in under, to achieve, the trial The objective
- Bob foul trials must to reported, fully and objectively and result must be ass visible to those who need them

O phase

- first Human clinical trials. Of an unexamined drug
- Primary goals & to evaluate mechanism of action/target modulation, assess, relation shipoptimise. Target
- Boone involve – 10-15 patient. •No therapeutic intent in Ivalo pre limited dosing)

Phase- I

- clinical pharmacology in small numbers (tens) of healthy non-patient
- Volunteers to asses tolerability, precision 01-biological effect using surrogate. Endpoint or rarely thematic effect.

Phase II

11. Frequently divided into

11a – clinical pharmacology in patient, with target, diseases (small number? To 100-200) to asses pharma co du anomie pharmacokinetic, and, safety, and caudate surrogate end point.. preliminary efficacy and +

11b - Tayler scale (seral hundreds, trial in patient to formally asses dose- response, relationship and continue expand the officially la safety database

Phase-III

formal therapeutic trials Agronomies controlled in hundred, or The as thousand of patient I to Him substantial scale

Phase - IV

Postilion sing studies, in the. Target population, with widening enter critic to brood on experience in clinical,

Lucy practice. Study objective may, marketing formal, Thera the comparator trial. Sunalinse safety.

An approach, to classifying clinical studies according to objective

Types of study

Objective

- Study example
- Human perf Dose tailorbird
- Asset's tolerability studies: pharm Geology Define / describe
- Pak and PD single 2. It explore drug met!
- boils drug interaction
- Multiple. Dose.
- Therapeutic Explore use for earliest exploratory targeted indicia trial of re
- Timely

- Engels estimate dosage
- • short To bait up for subsequent -titan.
- Narrow study
- Therapeutic Demonte/confirm
- Control Studies provide adequate to establish
- Adequate confirmatory efficacy establish and well, safety profile. ROD BLASTS bonds for asses You benefit nick Support licensing
- Assessing efficacy fonder miser relationship to dose-response parallel
- Therapeutic lose & Define under beehive reloading
- Combative. Sepal studies of mortality lectors Reassuming general or. Population/envenom
- Reference blue mays umbers se rating the textbook of pharmaceutical medicine. Edition – TV (John P. Griffin) (de RNO-248-250 (John -D-Grady).

Pre -clinical phase

- Exide Details of non-clinical / pre-Clinical studies are discussed under, ICH, Ms guideline the detail are motioned, below. De
- it include safety pharmacology, studies reported, dose toxicity studies, toxiolotinetic and non-clinical pharmacokinetic studies.
- Animal safety studies, and Human, clinical trials, should be designed, to Cand, ethical.

Represent scientifically. Appropriates approach.

1 Sever pharmacology

To get the core safety pharmacology study include the assessment of effect on condensers; central nervous, and respiratory system consideration should be given. En to spy inclusion of any in vivo, evaluation,

As addition to general toxicity studies case should be taken to reduce number of animal used

2) Toxic kinetic

pharmacokinetic studies & in vitro metabolic data for animal and human and expanse date in animal should be evaluated prior, imitating human clinical trials, further, absorption, gripe distribution, metabolism and excretion, in animal. Should be available Por I treating long ducat A deration.

3) Acute toxicity studies

brose Acute toxicity information has been, contained from single dose toxicity Studies in two moated, species using bath. Clinical and parental route of administration, this available to phase – III clinical trial's for higher risk for over dose.

Eg-depression, pain dementia.

4) Respond dose toxicity studies:

In principle, the duration of animal toxicity studies, Conducted in two, mammalian, species, should equal to exceed the duration, of Homan clinical trials up to maximum, recommended, duration, of repeated

Toxicity studies

5) local tolerance studies –

27 to evaluate local tolerant by o

Invented, therapeutic route as part, a general toxicity studies of nam

Impact tromp entered blinds to limited human and by To the ileitis rang eg-single TV) non

6) Gnotoxicity studies

An assay gone motation,generally considered Suffern to Support all single clinical development

7) corinogenecity studies it should be conducted, marketing

Application to t 1- for pharmaceutical develop, to treat, cream serious diseases, forged adult podiatric patient caxeinegenisty testing

8) Reproduction toxicity & bunt is should be conducted, population that is to exposited, as appropriates •these are following four categories, men, women, not child bearing women' of child bearing in pregnant women.

9) other toxicity. Some sites art non clinical study – e.g. identify potential biomarkers

✓Clinical I phase :-

TCH Es guideline refers to structure and content of clinical study. Reports section 12 of the guideline deal with

Safety evaluation. The definition of other significant,

Adverse event include haematological laboratory abnormalities adverse

Event that lead to intervention including withdrawal of drug treatment dose reduction or therapy. Significant concomitant therapy.

Reference :-

Pharmacovigilance

Dr. S.B Bhise

Mrs. m.s. Bhise P.NO – 4.1 to 4.5.

#function of Drug controller General of India (DCGI) and central drug • standard control organization CDSCO))

DCGI

- Preparation and maintenance of material reference standard. Minority 6 to bring about the unit the informant of the and
- Cosmetic Act. Training of drug Analysts dependent by state • drug controlled laboratories and other institution

Nausea of Cosmetic received as

Survey sample DSCα.

Reference DCGI Article.

CDSCO

Ⓒ Approval of new drug and clinical trials.

© import Registration and licensing

Ⓒ licence approving Blooded Bank, lops, Vaccine, r-DNA product and same medical derivate.

©Testing new drug

© grant of test licence For export personal knots

Reference :- http ulsco gove.in.

Type In commination new drug (TWD) New drug application, (NDA) and Activate New Drug Application (ANDA).

1)Investigational new during Application :

- To identify and contact information of and are phase of trials Sponsor and one phase of trials.
- A commitment that in IRB coil be Represent for initial and Continuing review of trials.
- The name of the doug list of ingredient and it's dosage and route of administration
- The objective planned deviation, of the proposed clinical trials.

2) Nuevo dug Application (NDA)

- An application submitted by the manufacture, of a drug to the FDA of other clinical trials, have been completed for a licence, to the market, the drug for specified.
- New drug application (NDA) vehicles in the united, State, through which drug sponsors, normally propose OPDA. Appeen & a new
- The data gathered, the during the animal, Studies and Homan clinical of an investigate ted and new dog (IND) become of NDA part o

3) Abbreviated, new dog Application, (ANDA) -

- An application, of Ifence, liersion of drug that has, already been drug that, has already been, granted, an apple voted under an fall NDA. je- drug has already met the Saturday. standard, for safety, and effective
- A generic drug produce, is one that is, comparable, to an innovator, drug product in dosage form, strength of administration, quality performance, characteristic, intended use.

Reference & NDA ppt from google.

Sagar savale Jan 19-2016. AL

Duration.

Duration of Investigational New drugs Application & 80 days

An Ind application

Effect 30 days after FDA receiver the Application Unless POA notified the sponsor that go into the invers ligations described in the application. subject to a clinical that the clinical

Investigation in the IND may begin.

Duration of New drug Application :

Submission of an NDA, is the formal stop asking the PDA to consider, a drug marketing approval After an NDA is received, the FDA has 60 days to decide weather, to fe it so it can be reviewed.

Duration of Abbreviated New drug Application:

This Act also permits fond home companies, to apply for exclusive patent right to cover their new drug op to 5 years.

1) Phase-o-trial

Objective : Measure pk1 toxicity in humans before phase 1 : Improve preclinical condiale selation.

Therapy : Any indication.

Dosage : Subtherapeutic dosing

were (normally micro-closing)

Trial length : usually less than one week

Patient : phase- o- of a clinical trial is done with a very small number foot/ pot people, usually fewer

2)phase- 1- trial.

Objective : The main aim of phase I trial is to find out about doses and si

Trial length & patient : Phase I clinical trials, con such. last several month, to a year, they usually have 10, to so volunteers, the treatment might help the cancer-

purpose : safety & dosage.

3) Phase II clinical trials

Objective : An phase II clinical trials tells doctor, more about, how safe the treatment is and how well. it works

- Doctor also test, weather, a new, treatment works for a specific cancer
- They might measure the tumour, take blood sample, or check how well you can do certain activities.

Length of Study : Several months to 2 years

Purpose : efficacy and side effects Approximately 33% of drugs move to next phase

4)Phase III-clinical Trials

Objective : The main objective of phase III is to verify the therapeutic action of a new. Substance in a large number of patient essentially to determine the risk | benefit ration

Length of study : 1 to 4 years.

Study participants: 300 to 3000 volunteers,

Who have the discase or conditions.

Purpose : Efficacy and monitoring of adverb Reaction Approximately 25-30% 01 Drug move to next phase.

5)Phase- V

Objective : A type of clinical trial that, studies the side effect count overtime by a new. Treatment, afters, it has, bee approved,And is an on marker, this trials look sideffect that not seen in earlier, trials, that may Stud how, well a new treatment work, over a long period.

Study participants : Several thousand volunteers who have the diseases /condition.

Purpose : Safety & efficacy

length of study : Typically they are conducted for a minimum of two years.

Reference:

Clinical trials Pda.gov.in.

Good clinical practice

- **ICH GCP:-**

In the middle part of the last century drug developement, experiences several event t that gave weight to greater homonisatio within Initially and then International In theUSA terrible mistake, in the form

ICH - Good clinical practice

1. Quality data + ethics + GCP (Good clinical practice)
    - The Good clinical practice cover
    1. Design
    2. Performance
    3. Monitoring
    4. Avditing
    5. Analysis
    6. Reporting.

- **Objective**

1. To provide an overview of history of good clinical practice (international conference hormonization)
2. To emphasize importance of ICH CACP Compliance when conducting clinical trial
3. To recognise implication of non- complicance
4. To review positive and negative case studies
5. Protect and patient
6. Avoid trials duplication
7. Therical requirement for medicainal product containing new
    - **Scope of GCP**

Good clinical laboratory should be used by all laboraties where test are done on biological diagnosis patient cover diseases control

- Micro- biological and serology
- Hematology and blood boating
- Molecular biology and molecular pathology
- Clinical pathology
- Histopathology

Key change in2019 new drug and clinical trial rules

In new rule 2019 such research has been defined to include studies on basic applied and operational research or clinical research designed primarily to increase scientific knowledge about diseases and condition (physico - sociobehavioral) their and cause evolving strategy health promotion

Prevention amelioration diseases rehabilitation does not include (T study type include)

- Lnvitro diagnosis (. INDS) performance testing for research
- New sergical intervention
- Assisted reproductive technology (PRT)
- epilmiological and non- interventional study of old drug

There type studies should be approves ethics comities constituted under pulele registered under rule 17 with cosco office as ethics comities for Biomedical and health research

- **Academic clinical trial:-**

  New rule 2019 deseribed acedemic clinical trial as clinical trial of drug already approved for certain claim and initiated by inpestigator academic research institution for new indication or now route of administration or new close or new dosage form .
- **Some important point for acedemic clinical trial include :-**
- Only for approved drug

- CT initiatated investigator acedemic or, research authority (CLR) and CIA must respond in indication new route new dose or new dosage
- EC can seek clarity from central licensing authority (CLA) and (LA) respond in 30 days or deemed that no approve needed medical management and comlnmpensation application as per ICMR guideline biomedical research on human paticies pant academic CTS required conduct accordance with CT protocall approval Ec Guideline for biomedical research human participant

- **Ethics committee (ECS) :-**

As delineated inthe 2019 CT rule and additional resource CA India has decentralised process for the etnical review committee (EC) approval for each trial use

In accordance with 2019 CT rules and additional recourse (A) all ethics comities (ECS) that review drug clinical trial are required to register with new drug controller general of India (DCGI) Head of drug general standard control organization (CDSCO) Prior to reviewing and approving clinical trial protocol

1. In addition the 2019 CT rules established a separate registration and monitoring system for ECS that overuse bio- medical and health research studies .
2. PCR notice 15 Sept 2019 and chapter IV of the 3019 CT rules any institutions and organization that plane to conduct bio - medical and health research involving number participant is not expired to have EC to review overcast conduct such research before study

- **EC Composition :-**

Pursuant to the 2019 CT rules and ICMR guideline institutional lindcpedant EC should be multi disciplinary multisectional representing mixed gender ,age, composition.

As per 2019 CT rules ICMR guideline composition should involve following:-

- Chair person from out side of the institute
- One (1) to two (2) basic medical scientist preferably one (1) pharmacologist
- One (1) to two (2) clinical from various institution
- Legal expert or retired judge
- One (1) social scientist / expresentatibe non- government voluntary agents
- One (1) philosopher / ethics / thecologic
- One (1) lay person from community
- Member secratory

Phase 4. And postmarketic studies (PMS)

Previously there was ambiguity definition requirement phase 4. And PMS

New fule 2019 was differentional requirement conducting phase - a CT and post marketic surveillance for new drug

New rule 2019 phase 4. Study :-

- Drug - drug interaction
- Dose - response or safety studies
- Trials designed to support use under approved indication

Post marketing survilance studies :-

Such studies are conducted with new drug approved condition of its use with scientific objective approved by **CLA**

- **Ofphan drug registration :-**

New rule 2019 define orphan drug as drug intended treat condition which affects not more than five laks (5,00,000 person in India.

- Provision for fast- tract approval process special states orphan during include complete free wajver CT filling
- Prevision expecuities review process in situation where evidence for clinical safety efficacy have been established

study and phase 4 on satisfaction of CLA

- **Post trial Access:-**
  New rule 2019 defines post trial Access as making new drug investigation new drug available to trial subject after complection of clinical trial through which said drug has been formed beneficial to a trial subject during clinical trials
- There are still some gap in understanding questions raised about issues needed to addressed CDSCO include .
- How long post trial acess medicines should provide to patient this is of special importance there is chronic diseq with long treatment
- How is safety signal monitored for this period should sponsor / continue providing drug under post - trial Access marketing Authorization approved and drug available in market

Other significant updates :-

Condition for generating stability data have been revised for drug substance and formulation intended to be stored under general condition have been revised as per zone in for long term from **30°C +2°C/**

New clinical trial approved timeline also have been included for the clinical trials of drug developed outside of the India there ,0.5a go working day limit of CLA to respond

Concept of pharmacovigilance

1. **Define objective types and components pharmacovigilance**

- **Definition**

pharmacovigilance is the science and activity relating to the detection assesment , understanding and prevention of adverse effect or any other medicinal, urine related problems for patient safety .

- **Objective**
  - Improvement of patient charcoal safety in relation to the use of medicines with medical and paramedical important parameter
  - The main objective of pharmacovigilance involve exhibiting the efficacy of drug by monitoring their adverse effect profile for many years from the lab to the pharmacy tracking and drastic effect of drug improving public health and safety.relation to the use of medicines eniovraging the safety radiation and cost - effective use of drug.
  - Promotion understanding education and clinical training in pharmacovigilance to the generic public
  - In addition providing information consumers particitieness and regulators on the effect use of drug along with designing programs and procedure for collecting and analysing report to the object of pharmacovigilance

    Reference:-. Review article of pharmacovigilance needs and objectives by Antur Rohilla, Nishant Singh, Vipin Kumar, Mohit Kumar Sharma.
    Journal of advanced pharmacy education research Oct- Dec- 2012 .

- **Type**

There are four important types of pharmacovigilance.

1. Passive survilance
2. Active survilance
3. Cohort event monitoring
4. Targeted clinical investigation

1. Passive serveilance

Passive serveilance methods involve the use of spontaneous advances event report volunteering sent by healthcare professionals or patient to the marketing Authorization regulatory authority
The data related to the adheravation are collected in a central or regional data base.

2. Active serveilance

This method aims to monitor cortain specific drug related and secks to ascertain the number of ADR entering through a pre planned process
It is commonly known as toxicity monitoring or safety monitoring.

3. **Cohort event monitoring:-**
   In this method the study if planed prior to begining the treatment with the medication A group of people are exposed to a drug for a defined period and activity followed up during treatment.
   Ade of the target drug or the event with one or more medicine taken with that drug are monitored.
4. **Targeted clinical investigation:-**
   These kind of investigation are performed to identify the characterize the advance reaction related to a drug among special population like people with same genetic disorder, pregnant women and older people.

Reference some as defination.

2. Constitutional object of pharmacovigilance of India.

The purpose of the PV program of India is to collect and analysis data to arnive at an intranet to recommend regulatory intervention besides communicating risks to healthcare pro.

- **PVPI**
  the central drug standard control organization (CDSCO) dicetrate general of health services under the aegic of ministers of health and family welfare Government of India collaboration with department of pharmacology all india institute of medical science.(AIIMS).
  New delhi launched the nation wide PV program for protecting the health of the patient by assuring drug safety
- **Objective**
  - To monitor adr in India population
  - To create awareness among helath care professionals about the imp of ADR.
  - to monitor benefit filter profile to monitor
  - Generate independent evidence based recommendation on the safety of medicines
  - Support the classes ofr formulating safety related regulatory decisions for medicines.
  - Communicate finding with all key stakeholders
  - Create a national centre of excellence at pre with global drug safety monitoring standards .

  Reference:- WWW. airms.cdv.pupi.

3. Lust of national adverse drug monitoring centre and their functions:-

- **National co-ordinating centre (NCC).**
  1. Department of pharmacology all india institute of medical science New Delhi.
     Co-ordinators- Dr Y.K.Gupta National co-ordinater.
- **ADR monitoring centre (AMC).**
  1. Department of pharmacology and ADS and NBSBSP: theropeutics and toxicology GOVT medical College Bakshi nagar Jammu.
     Co-ordinators-Dr Vishal tandon.
  2. Department pharmacology PGIMER Chandigarh
     Co-ordinators-. Dr Bakshi medhi
  3. Department of pharmacology RG kar medical College Kolkata
     Co-ordinators-Dr Anjan Adhikari.
  4. Department of pharmacology body hording medical College New Delhi.
     Co-ordinators-Dr H.S Rehan
  5. Department of clinical pharmacology Saint GS medical College of KEM hospital Mumbai
     Co-ordinators-Dr. Urmila Matte .
  6. Department of clinical Exp pharmacology school of hospital medicine Chandigarh.
     Co-ordinators-Dr. Santanu tripati
  7. Department of pharmacology J I M P E R Pondicherry.
     Co-ordinators-Dt. C. Adithan.
  8. Department of clinical pharmacy TSI medical College hospital Karnataka.

Co-ordinators-Dr. Prashant. G

9. Department of pharmacology medical College Guwahati.
   Co-ordinators-Dr. Mangala. lonkar
10. Institute of pharmacology Madras medical College Chennai.
    Co-ordinators-Dr. R. Nandani.
11. Department of pharmacology GSVM medical College Swaroop Nagar.
    Co-ordinators-Dr. S.P. Singh.
12. Department of pharmacology s a i m s medical College Indore
    Co-ordinators-Dr. Chnaya .goyal .
13. Department of pharmacology pandit Bhagwat Dayal Sharma post graduate institute of medical science Rohtak Haryana.
    Co-ordinators-Dr. M.C Gupta.
14. Department of pharmacology Dayanand medical college Ludhiana and Punjab.
    Co-ordinators-Dr. Sandeep Kasuhal.
15. Department of clinical pharmacology Shri I Krishna of medical science Srinagar Jammu and Kashmir.
    Co-ordinators-Dr. Z.A. Wafal.
16. Himalayan institute of medical Dehradun Uttarakhand.
    Co-ordinators-Dr. D.C Dhasmana.
17. Department of pharmacology Santosh medical university Santosh Nagar Ghaziabad.
    Co-ordinators-Dr V.C Chopra .
18. Department of pharmacology s m s medical College Jaipur.
    Co-ordinators-Dr. Mukul. Mathur.
19. Department of clinical pharmacology Christian medical College vellore Tamilnadu.
    Co-ordinators-Dr. Sujith. Chandy.
    Reference:-. PharmaBiz.com.

International Conference on Harmonization (ICH) E2e Guideline

Aspirin

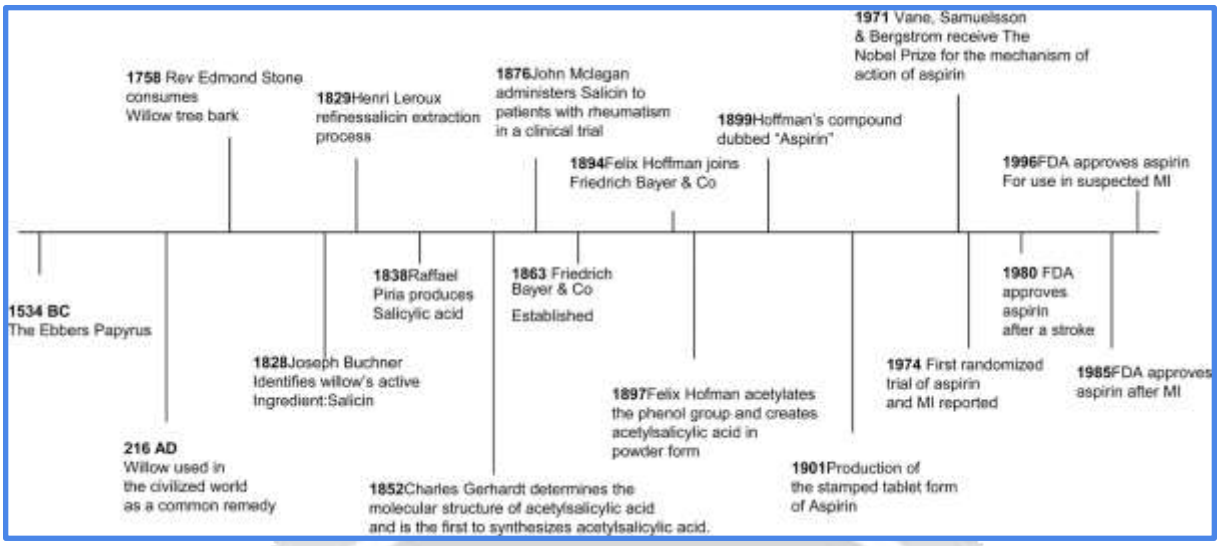
Discovery & development:

- **Discovery:**

A Dundee physician, Thomas Maclagan, used salicin to treat patients who had rheumatism, and he reported its beneficial effects in The Lancet in 1876. In 1897, Felix Hoffman, a German chemist working for the Bayer company, was able to modify salicylic acid to create acetylsalicylic acid, which was named aspirin .
Aspirin has long been established as a useful analgesic and antipyretic. Even in ancient times, salicylate-containing plants such as the willow were commonly used to relieve pain and fever.

- **Development**

A Dundee physician, Thomas Maclagan, used salicin to treat patients who had rheumatism, and he reported its beneficial effects in The Lancet in 1876. In 1897, Felix Hoffman, a German chemist working for the Bayer company, was able to modify salicylic acid to create acetylsalicylic acid, which was named aspirin .
History of aspirin :



Clinical trial of aspirin :

Aspirin also known as actylsaticalic acid is has an analogist to relieve minor acnes and pains has an anti hypotic to reduce fever and has an anti inflamentary medication it was first isolated by Arthur Sichengrim achemist with the German company bears

Today Aspirin is one of the most widely used medications in the world with an estimated 40000 turns

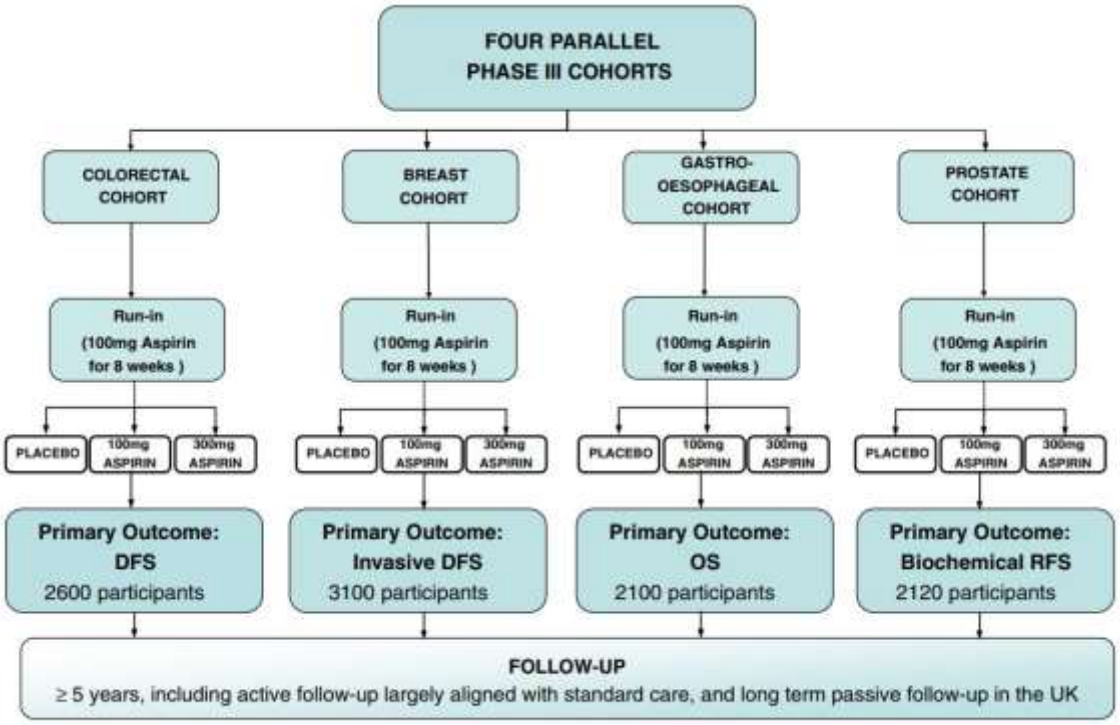
The risk and benefit of Aspirin in relation to cardiovascular problem through clinical trials and the interesting results got are influencing clinical business with in divisible patient in routine clinical practice this studies have been standard to include the effect of aspirin and non vascular outcomes such as cancer and asthma

Using this scientific strategies data obtained was critically analysed and the following tentative conclusion have been reached.

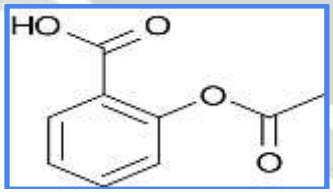
1. **Taking logos of Aspirin for 5 years reduce the risk of death from cancer**
2. **Regularly aspirin conception reduce the risk of asthma 22%**
3. **Who take aspirin on at least one day for month have and 26% lower risk of developing pancreatic cancer than people who do not take as print on that list one day per month**
4. **People who take adult strength Aspirin regularly for at least 5 years and 30% less at risk of developing colorated cancer then people who do not take aspirin regularly**
5. **Aspirin one at least one day per month has 33% less at risk of developing heart disease than people who do not take aspirin one at least one day per month**
    - **Indeed side effect of aspirin stomach urination and gastronalous bleeding Aspirin e even in low dose may not be suitable for everyone so everyone should not just start taking it in spite of short coming this result shows that the Aspirin is very important to the principal presence**

Preliminary research of aspirin

The physicians health study is a randomised double bind plateau controlled trial testing to primary prevention hypothesis weather 325 mg of aspirin as bufferin every after day reduces martinating from cardiovascular disease and weather 50 mg of taken on a ultimate days decreases the increase of cancer at a specific meeting on December 18 1987 the external data monitoring board of the physician health study to the conclusional step of recommending the early termination of the recommendised aspirin department of the trial preliminary because of a static flee extreme beneficial effect.



Brand name :
Aggrenox, Alka-seltzer, Alka-seltzer Fruit Chews, Anacin, Arthriten Inflammatory Pain, Ascomp, Aspi-cor, Aspir-low, Bayer Aspirin, Bayer Womens, Bc Arthritis, Bc Original Formula, Bufferin, Duoplavin, Durlaza, Ecotrin, Ecpirin, Endodan Reformulated May 2009, Equagesic, Exaprin, Excedrin, Excedrin PM Triple Action, Fasprin, Fiorinal, Fiorinal With Codeine, Goody's Body Pain, Goody's Extra Strength
Generic name :
Acetylsalicylic acid
Commonly known or available as Aspirin
Type :
Small Molecule
Groups :
Approved, Vet approved
Structure :



Weight :
Average: 180.1574
Monoisotopic: 180.042258744
Chemical formula :
C9H8O4
Synonyms:
Acetylsalicylate
Acetylsalicylsäure
Acide acétylsalicylique

Acidum acetylsalicylicum
Aspirin
Aspirina
Azetylsalizylsäure
Polopiryna
Salicylic acid acetate

Pharmacology:

Indication :

Pain, fever, and inflammation

Acetylsalicylic acid (ASA), in the regular tablet form (immediate-release), is indicated to relieve pain, fever, and inflammation associated with many conditions, including the flu, the common cold, neck and back pain, dysmenorrhea, headache, tooth pain, sprains, fractures, myositis, neuralgia, synovitis, arthritis, bursitis, burns, and various injuries. It is also used for symptomatic pain relief after surgical and dental procedures .

Other indications :

ASA is also indicated for various other purposes, due to its ability to inhibit platelet aggregation. These include:

Reducing the risk of cardiovascular death in suspected cases of myocardial infarction (MI) Label.

Reducing the risk of a first non-fatal myocardial infarction in patients, and for reducing the risk of morbidity and mortality in cases of unstable angina and in those who have had a prior myocardial infarction .

Contra indication :

Bleeding disorders like hemophilia and others, active peptic ulcer, asthmatics, impaired renal or liver function and G6PD deficiency. Not recommended in children till the age of 15 years if feverish. It should be avoided in patients with dengue fever to prevent bleeding and in viral fevers for risk of precipitating Reye's syndrome.

Monitoring:

Therapeutic drug monitoring (TDM) is used in drug therapy for selected drugs with narrow therapeutic index, or a broad range of kinetics variation, or drugs with strong correlation between plasma concentration and clinical effects or toxicity. Aspirin is one of the widely used old generation drugs, with a broad range of activity spectrum: analgesic, antipyretic, anti-inflammatory, and antiplatelet. As antiâ€inflammatory drug, aspirin directed as therapy for many of chronic inflammation, such as rheumatoid arthritis.

Dosing:

Anti-inflammatory, antipyretic, analgesic:
<12 years: 10-15 mg/kg orally every 4 hours;
maximum of 60-80 mg/kg/day.
212 years: 325-650 mg orally/rectally every 4-6 hours, as when needed.
Kawasaki disease:
80-100 mg/kg/day orally, 4 times/day. After the fever resolves decrease dose to 3-6 mg/kg/day given orally in single dose as for maintenance.
Juvenile Rheumatoid Arthritis:
<25 kg: 60-100 mg/kg/day orally, every 6-8 hours (Maintain serum salicylate at 150-300 mcg/mL).
225 kg: 2.4-3.6 g/day.
Anti-platelet:
3-5 mg/kg/day OD, maximum 75 mg.
Rheumatic fever:
100 mg/kg/day divided into 4 to 5 doses; if response inadequate, may increase dose to 125 mg/kg/day; continue for 2 weeks; then decrease dose to 60 to 70 mg/kg/day in divided doses for an additional 3 to 6 weeks.

Pharmacodynamics :

- **Effects on pain and fever**

Acetylsalicylic acid disrupts the production of prostaglandins throughout the body by targeting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COx-2)

- **9,10,11. Prostaglandins are potent, irritating substances that have been shown to cause headaches and pain upon injection into humans**

.

Effects on platelet aggregation :

- **The inhibition of platelet aggregation by**

ASA occurs because of its interference with thromboxane A2 in platelets, caused by COX-1 inhibition.

- **Thromboxane A2 is an important lipid responsible for platelet aggregation, which can lead to clot formation and future risk of heart attack or stroke .**

A note on cancer prevention :

- **ASA has been studied in recent years to determine its effect on the prevention of various malignancies 15. in general, acety salicylic acid is involved in the interference of various cancer signaling pathways, sometimes inducing or upregulating tumor suppressor genes .**

Mechanism of action :

- **Acetyisalicylic acid (ASA) blocks**

prostaglandin synthesis. It is non-selective for COX-1 and COX-2 enzymes 9,10,11
Inhibition of COX-1 results in the inhibition of platelet aggregation for about 7-10 days (average platelet lifespan).

- **The acetyl group of acetylsalicylic acid binds with a serine residue of the cyclooxygenase-1 (COX-1) enzyme, leading to irreversible inhibition. This prevents the production of pain-causing prostaglandins.**
- **This process also stops the conversion of arachidonic acid to thromboxane A2 (TXA2), which is a potent inducer of platelet aggregation Label Platelet aggregation can result in clots and harmful venous and arterial thromboembolism, leading to conditions such as pulmonary embolism and stroke.**

Absorption :

- **Absorption is generally rapid and complete following oral administration but absorption may be variable depending on the route, dosage form, and other factors including but not limited to the rate of tablet dissolution, gastric contents, gastric emptying time, and gastric pH**
- **When ingested orally, acetylsalicylic acid is rapidly absorbed in both the stomach and proximal small intestine. The non-ionized acetylsalicylic acid passes through the stomach lining by passive diffusion. Ideal absorption of salicylate in the stomach occurs in the pH range of 2.15 - 4.10. Intestinal absorption of acetylsalicylic acid occurs at a much faster rate. At least half of the ingested dose is hydrolyzed to salicylic acid in the first-hour post-ingestion by esterases found in the gastrointestinal tract. Peak plasma salicylate concentrations occur between 1-2 hours post-administration .**

Volume of distribution:

- **This drug is distributed to body tissues shortly after administration. It is known to cross the placenta. The plasma contains high levels of salicylate, as well as tissues such as spinal, peritoneal and synovial fluids, saliva and milk.**
- **The kidney, liver, heart, and lungs are also found to be rich in salicylate concentration after dosing. Low concentrations of salicylate are usually low, and minimal concentrations are found in feces, bile, and sweat .**

Protein binding :

- **50% to 90% of a normal therapeutic concentration salicylate (a main metabolite of acetylsalicylic acid Label) binds plasma proteins, particularly albumin, while acetylsalicylic acid itself binds negligibly .**

Metabolism:

- **Acetylsalicylic acid is hydrolyzed in the plasma to salicylic acid. Plasma concentrations of aspirin following after administration of the extended-release form are mostly undetectable 4-8 hours after ingestion of a single dose. Salicylic acid was me inasured at 24 hours following a single dose of extended-release acetylsalicylic acid .**

- **Acetylsalicylic acid**
  - **Phenolic glucuronide + Salicylic acid acyl glucuronide**
  - **Salicylic acid**
  - **Gentisic acid**
  - **Salicyluric acid**

Route of elimination:

- **Excretion of salicylates occurs mainly through the kidney, by the processes of glomerular filtration and tubular excretion, in the form of free salicylic acid, salicyluric acid, and, additionally, phenolic and acyl glucuronides .**
- **Salicylate can be found in the urine soon after administration, however, the entire dose takes about 48 hours to be completely eliminated. The rate of salicylate is often variable, ranging from 10% to 85% in the urine, and heavily depends on urinary pH .**

Half life :

- **The half-life of ASA in the circulation ranges from 13 - 19 minutes. Blood concentrations drop rapidly after complete absorption. The half-life of the salicylate ranges between 3.5 and 4.5 hours .**

Clearance :

- **The clearance rate of acetylsalicylic acid is extremely variable, depending on several factors 6. Dosage adjustments may be required in patients with renal impairment .**

Adverse effects:

- **Abdominal or stomach pain, cramping, or burning**
- **black, tarry stools**
- **bloody or cloudy urine**
- **change in consciousness**
- **chest pain or discomfort**
- **confusion**
- **constipation**
- **convulsions, severe or continuing**
- **dark urine**
- **decreased frequency or amount of urine**
- **diarrhea**
- **difficult breathing**
- **drowsiness**
- **fainting**
- **fast breathing**
- **feeling that something terrible will happen**
- **fever**

Toxicity :

Lethal doses :

Acute oral LD50 values have been reported as over 1.0 g/kg in humans, cats, and dogs, 0.92 g/kg - 1.48 g/kg in albino rats, 1.19 g/kg in guinea pigs, 1.1 g/kg in mice, and 1.8 g/kg in rabbit models Labe

Acute toxicity :

- **Salicylate toxicity is a problem that may develop with both acute and chronic salicylate exposure 7.**
- **Multiple organ systems may be affected by salicylate toxicity, including the central nervous system, the pulmonary system, and the gastrointestinal system.**
- **Severe bleeding may occur.**

Use in pregnancy and lactation :

- **While teratogenic effects were observed in animals nearly lethal doses, no evidence suggests that this drug is teratogenic in humansl.**
- **It is advisable, however, to avoid ASA use the first and second trimester of pregnancy, unless it is clearly required.**
- **If acetylsalicylic acid containing drugs are ingested by a patient attempting to conceive, or during the first and second trimester of pregnancy, the lowest possible dose at the shortest possible duration should be taken Label This drug is contraindicated in the 3rd trimester of pregnancy .**

Drug drug interactions :

Drug	Intractions
Abacavir	Acetylsalicylic acid may decrease the excretion rate of Abacavir which could result in a higher serum level.
Abatacept	The metabolism of Acetylsalicylic acid can be increased when combined with Abatacept.
Abciximab	Acetylsalicylic acid may increase the antiplatelet activities of Abciximab.
Abrocitinib	The risk or severity of bleeding and thrombocytopenia can be increased when Acetylsalicylic acid is combined with Abrocitinib.
Acamprosate	The excretion of Acamprosate can be decreased when combined with Acetylsalicylic acid

Food intraction :

- **Avoid alcohol. Alcohol increases the risk of gastrointestinal bleeding.**
- **Avoid herbs and supplements with anticoagulant/antiplatelet activity. Examples include garlic, ginger, bilberry, danshen, piracetam, and ginkgo biloba.**
- **Take after a meal. This reduces irritating gastrointestinal effects.**
- **Take with a full glass of water.**

Drug monitoring :

- **Therapeutic drug monitoring (TDM) is used in drug therapy for selected drugs with narrow therapeutic index, or a broad range of kinetics variation, or drugs with strong correlation between plasma concentration and clinical effects or toxicity.**
- **Aspirin is one of the widely used old generation drugs, with a broad range of activity spectrum: analgesic, antipyretic, anti-inflammatory, and antiplatelet.**
- **As anti-inflammatory drug, aspirin directed as therapy for many of chronic inflammation, such as rheumatoid arthritis.**

Safety & efficacy :

Safety pharmacology :

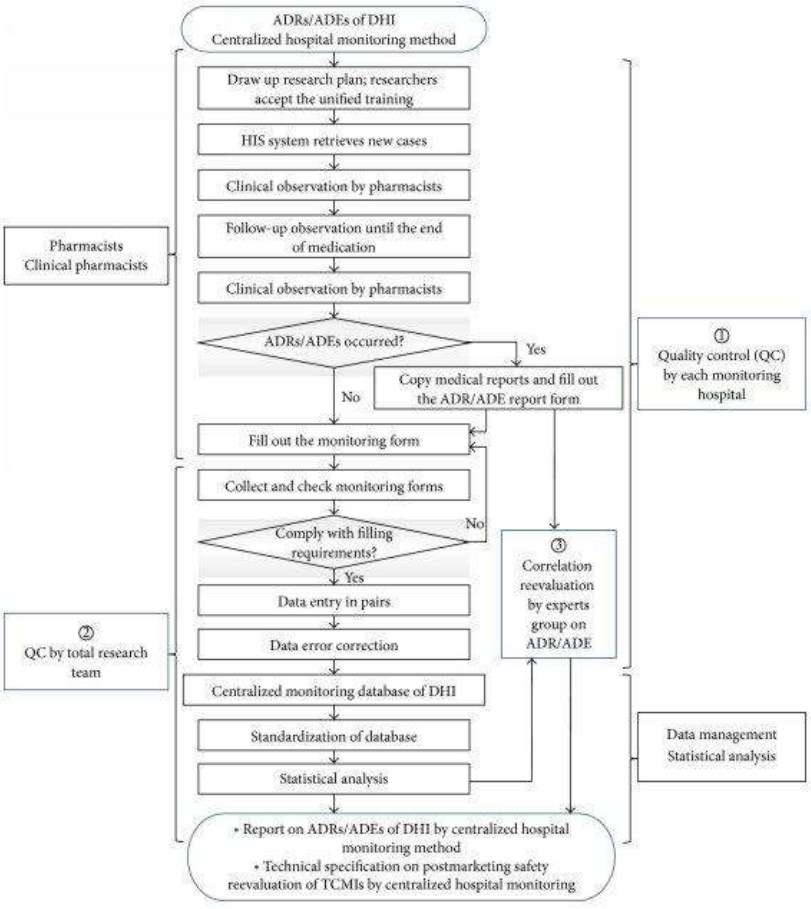
- **Objective: To assess the association between low-dose aspirin and the incidence of colorectal cancer (CRC), gastric cancer (GC), oesophageal cancer (EC) and gastrointestinal bleeding (GIB) in adults without established atherosclerotic cardiovascular disease.**
- ***Design*: Cohort study with propensity score matching of new-users of aspirin to non-users.**
- **Setting: Clinical Data Analysis and Reporting System database, Hong Kong.**

- **Participants: Adults ≥40 years with a prescription start date of either low-dose aspirin (75-300 mg/daily) or paracetamol (non-aspirin users) between 1 January 2004 to 31 December 2008 without a history of atherosclerotic cardiovascular disease.**
- **Main outcome measures: The primary outcome was the first diagnosis of gastrointestinal cancer (either CRC, GC or EC) and the secondary outcome was GIB. Individuals were followed from index date of prescription until the earliest occurrence of an outcome of interest, an incident diagnosis of any type of cancer besides the outcome, death or until 31 December 2017**
- **Results: After matching, 49 679 aspirin and non-aspirin users were included. The median (IQR) follow-up was 10.0 (6.4) years. HRs for low-dose aspirin compared with non-aspirin users were 0.83 for CRC (95% CI, 0.76 to 0.91), 0.77 for GC (95% CI, 0.65 to 0.92) and 0.88 for EC (95% CI, 0.67 to 1.16).**

Efficacy of drug :

- **Aspirin is an effective medicine for prevention of heart attacks in patients with coronary artery disease and works by preventing clots from forming.**

Postmarketing & monitoring of drug aspirin :



Selection of drug class :

- **Selection of drug class for pharmacovigilance study using different critrial**

Eg.. Commerical availability , seeling of drug.

Availability :

Aspirin :

- **Aspirin can be administered via the oral , rectal and intravenous (lV) soute.**
- **It is available in different doses , the lowest being 18 mg , also called a baby aspirin.**

- **Tablet : 325 mg , 500 mg.**
- **Delayed-relase tablet : 81 mg , 325 mg , 500 mg , 659 mg .**
- **Chewable : 81 mg**
- **Suppository : 60 mg , 120 mg , 200 mg ,**
  300 mg , 600 mg .
- **Intravenous : 250 mg , 500 mg .**

Brand Names :

1) **Anacin® Aspirin Regimen**
2) **Bayer® Aspirin**
3) **Buffering®**
4) **Buffex®**
5) **Easpirin**

Available :

- **Aspirin is also available in combination with other medications such as**
  1)antacids
  2)Pain relievers
  3)Cough
  4)Coldmedications
- **This monographs only includes information about the use of aspirin alone**
- **If you are taking a combination product , read the information on the package or prescription on the package or prescription label or ask your doctor or pharmacist for more information.**

Selling :

- **The global aspirin market size is estimated to augment at a CAGR of 2.40% increasing from US $ 2.167 billion in 2020 to reach US $ 2.2558 billion by 2027**
- **The growing active pharmaceutical ingredient industry , will contribute to propelling the market growth of acetylsalicylic acid as an active ingredient in drug formulations china , from the APAC region is estimated to hold a significant market shares in the global APL industry .**
- **The presence of companies offering acetylsalicylic acid products is propagataing market growth during the forecast period .**
- **Baby aspirin has been an essential medicine for over 100 years .**
- **It helps alleviate pain and cardiovascular events prevention and has stood the test of time .**
- **Aspirin T is among the highest trusted products by a range of customers worldwide compared to any other over the country medicine for reducing pain.**
- **Based on it's pain relief and anti platelet effects , aspirin is listed as one of the essential.**
- **The company's products portfolio includes aspirin and aspirin cardio as it's products .**
- **Aspirin T falls under the category of consumer health and pharmaceuticals .**
- **On the other hand , aspirin for consumer health includes the following application namely headache , bodypain , muscle pain & fever .**

- **The global branded generics market is projected to grow in the porecast period with the marketing approval by the FDA for several generic drug products in 2019 .**
- **The generic version of aspirin will continue to soar the market growth in the forecast period .**
- **As per the USFDA , generic medicines are around 80 to 85% cheaper than branded versions .**

Aspirin

Drug Usage Statistics, United States, 2013 - 2020

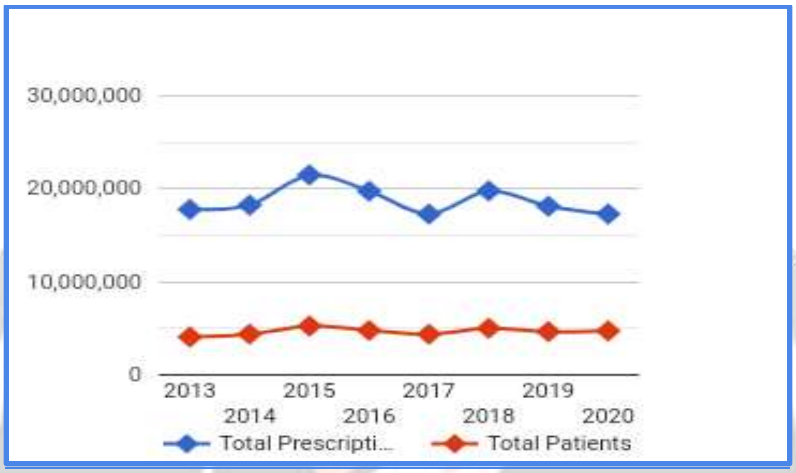
- *Aspirin Summary for 2020*

Top drug rank #36 (2)

Estimated number of prescriptions in the United States (2020) *17,287,372*
Estimated number of patients in the United States (2020) *4,741,732*

Average total drug cost (USD)
Per prescription *$4.54*
Per day of therapy *$0.13/day*
Average out-of-pocket cost (USD)
Per prescription *$1.97*
Per day of therapy *$0.04/day*

Total Prescriptions and Patients Per Year (2013 - 2020)



Rank of Top Drugs Over Time

"Rank" refers to the frequency that a given medication is prescribed within a calendar year compared to all other medications. A rank of "4" would indicate that the medication was the fourth most commonly prescribed medication.
9763253400

Year	***Rank***	***Change***
2013	*45*	*9*
2014	*45*	*0*
2015	*38*	*7*
2016	*37*	*1*

Year	Rank	Change
2017	41	↓ 4
2018	38	↑ 3
2019	38	0
2020	36	↑ 2

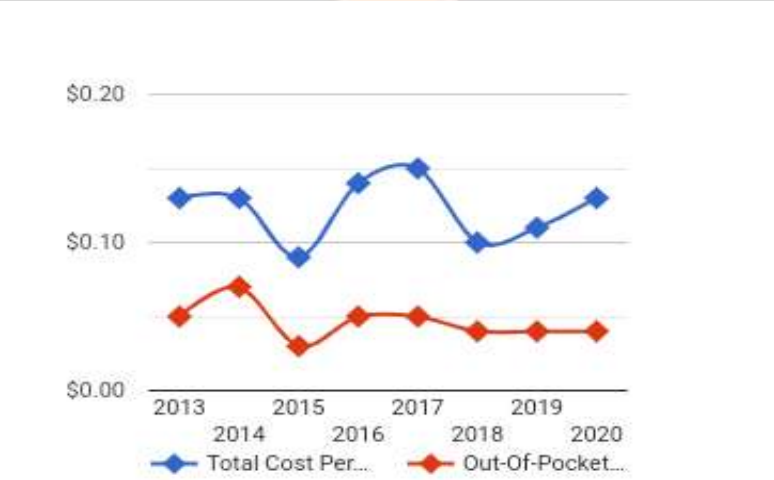
Drug Cost Over Time (2013 - 2020)

▶ ***Cost Per Prescription Fill: Average cost per filled prescription regardless of how many days of therapy the prescription is filled for (e.g. 10 days, 30 days, 90 days, etc.)verage cost per filled prescription regardless of how many days of therapy the prescription is filled for (e.g. 10 days, 30 days, 90 days, etc.)***

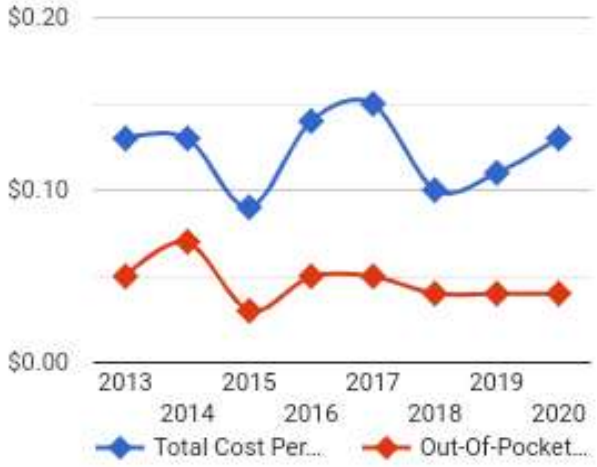
▶ ***Cost per Day of Therapy: The average cost per prescription fill divided by the days of therapy. For example, a 10-day antibiotic course costing $30 would be $3 per day. Similarly, a 30-day supply of an oral antihypetensive costing $30 would be $1 per day.***

▶ ***Total cost: The average total cost of the medication including the out-of-pocket cost (see below) plus the amount paid by other parties (Medicare, Medicaid, private insurance, Veterans Administration, TRICARE, other state/federal sources, Worker's compensation, and other miscellaneous sources)***

▶ ***Out-of-pocket cost: The average payment made by the patient which may include deductibles, coinsurance, copayments, or the cash price paid without insurance coverage.***



Cost Per Day of Therapy (USD/day)

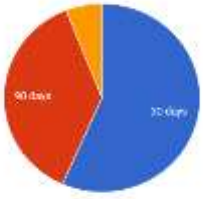


Distribution of Dispensed Dosage Forms (2020)

Dosage form	Strength	% of Dispensed Products
Tablet/Capsule	81 mg	90.2%
Tablet/capsule	325 mg	9.0%

Distribution of Days Supplied (2020)

"Days supply" is defined as the number of days that a prescription should last. For example, a prescription of 60 tablets that is taken twice daily has a day supply of 30 days.



Related drug

Drug	Total prescriptions
Meloxicam	**19,808,582**
Aspirin	**17,287,373**
Ibuprofen	**16,533,209**
Diclofenac	**9,926,750**
Naproxen	**8,184,639**

Drug Synonyms

- **Drug synonyms are used during the sanitation and standardization process of "cleaning" the original data source (MEPS).**

Brand Name Synonyms

- **8-hour Bayer**
- **WeBayer Extra Strength Aspirin For Migraine Pain**
- **Durlaza**
- **Measurin**
- **Vazalore**

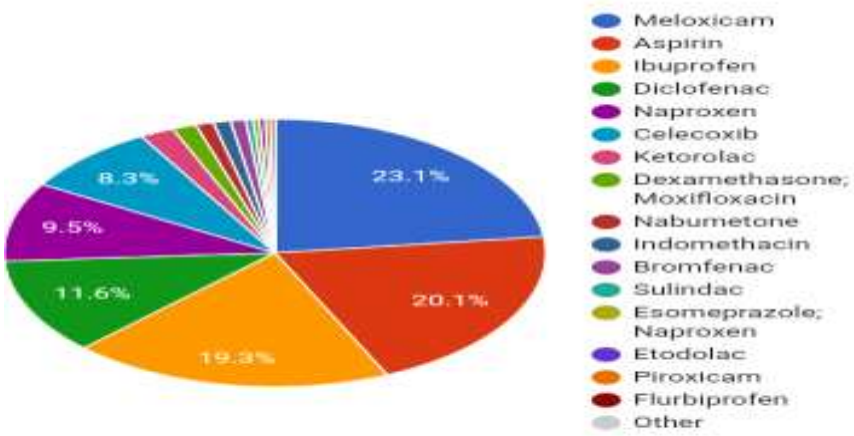
Generic Drug Synonyms

- **Aspirin**

FDA Approval Information

Established Pharmacologic Class (EPC):	**Nonsteroidal Anti-inflammatory Drug, Platelet Aggregation Inhibitor.**
Initial FDA approval date:	**Prior to January 1, 1982**
First FDA applicant:	**Discn**
First dosage form:	**Tablet, Extended Release (oral)**

Total Prescriptions in (2020)



Identification of Adverse Effects of a Selected Drug

- **Identification of adverse effects of a selected drug using different search engines .**
- **(e.g. Medscape.com, drugs.com, rxlist.com, etc.)**

▶ Adverse effects :

- **Abdominal or stomach pain, cramping, or burning**
- **bloody or cloudy urine**
- **chest pain or discomfort**
- **confusion**
- **constipation**
- **dark urine**
- **decreased frequency or amount of urine**
- **diarrhea**
- **difficult breathing**
- **drowsiness**
- **fast breathing**
- **feeling that something terrible will happen**
- **fever**
- **general tiredness and weakness**
- **headache**
- **heartburn**
- **increased thirst**
- **indigestion**
- **irregular heartbeat**
- **lower back or side pain**

Incidence not known :

- **Acid or sour stomach**
- **anxiety**
- **belching**
- **dizziness**
- **dry mouth**
- **hyperventilation**

- **irritability**
- **shaking**
- **stomach discomfort, upset, or pain**
- **trouble sleeping**
- **unusual drowsiness, dullness, tiredness, weakness, or feeling of sluggishness.**

(By the reference www.mayoclinic.org)

▶ **Adverse effects :**

- **confusion**
- **hallucinations**
- **rapid breathing**
- **seizure (convulsions)**
- **severe nausea**
- **vomiting**
- **stomach pain**
- **bloody or tarry stools**
- **coughing up blood**
- **vomit that looks like coffee grounds**
- **fever lasting over 3 days**
- **swelling or pain lasting over 10 days**

The most common side effects of Bayer Aspirin include:

- **upset stomach**
- **heartburn**
- **drowsiness**
- **mild headache**

(By the reference www.Rxlist.com)

▶ **Adverse effects :**

- **Aspirin may cause serious side effects. Stop using this medicine and call your doctor at once if you have:**
- **ringing in your ears, confusion, hallucinations, rapid breathing, seizure (convulsions);**
- **severe nausea, vomiting, or stomach pain;**
- **bloody or tarry stools, coughing up blood or vomit that looks like coffee grounds;**
- **fever lasting longer than 3 days; or**

swelling, or pain lasting longer than 10 days.

- **Common side effects of aspirin may include:**
  - **upset stomach**
  - **heartburn**
  - **drowsiness**
  - **mild headache.**

(By the reference www.drug.com)

Adverse Drug Reaction (ADR) Monitoring Form :
Preparation of ADR monitoring form as per guidelines given by AMCs
(e.g. Indian Pharmacopoeia Commission)

1)Adverse drug reactions monitoring form:-

Sr no	Indian pharmacopoeia commission	For AMC/NCC use only
	Report type clinical follow up -	AMC report no. -
		world wide unique no -
A)	Patient Information	12.Relevent test/laboratory date with date
1)	Patient initial	13.Relevebt medical history eg.. pregnancy allergy
2)	Age at time event	
3)	M- F- Other-	
4)	weigh. Kg/s	
B)	Suspect adverse reactions	14.serious relations
5)	Date of started	• Death • Congited
6)	Date of recovery	• Life threatening
7)	D described reaction problem	• Disability
		15.outcome • Recove • Rp covering

Suspected medication:

Sr no.	Name brand generic	Manufacturers	Batch no.	Exp date	Dose used	Frequency		
1)								
2)								
3)								

2) Concentration comitant medical products including medication and herbal remedies with date (exclude those and treatment)

Additional information:	**D. Reporter details** **16. Name and professional adress-** **Pin-** **E-mail -** **Help no. (With STD code)-** **Occupation-** **Sign-** **17. Date this report-**

- **Common side effect**
- Get emergency medical help if you have signs of an allergic reaction to aspirin: hives; difficult breathing; swelling of your face, lips, tongue, or throat.

- Aspirin may cause serious side effects. Stop using this medicine and call your doctor at once if you have:

- ringing in your ears, confusion, hallucinations, rapid breathing, seizure (convulsions);

- severe nausea, vomiting, or stomach pain;

- bloody or tarry stools, coughing up blood or vomit that looks like coffee grounds;

- fever lasting longer than 3 days; or

- swelling, or pain lasting longer than 10 days.

- upset stomach;
- heartburn;
- drowsiness; or
- mild headache.

- **Serious side effect**
- Along with its needed effects, aspirin may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

- Check with your doctor immediately if any of the following side effects occur while taking aspirin:
- restlessness
- seizures
- skin rash
- stomach cramps
- swelling of the face, fingers, or lower legs
- unusual bleeding or bruising
- unusual tiredness or weakness
- vomiting of blood or material that looks like coffee grounds
- weakness or heaviness of the legs
- weight gain
- yellow eyes and

,

- **Serious allergic reaction**
  Symptoms include flushing, itchy rashes (hives), blocked and runny nose and asthma (sometimes severe), usually within an hour of taking a tablet. If you have hives (urticaria), nasal polyps or asthma, your risk of aspirin allergy is 10-30% compared to 1% in people without these conditions.

Patient interview :-
Interview of patients for under -standing & identification of Adr.
Hospital name:-Sahyadri super specialist hospital Hadapsar Pune

Patient name :- Shaikh ahmead
Age :- 21
Gender:- Male
Disease:- hemolysis
Drug :-aspirin

Drug ADR:-

- Abdominal or stomach pain, cramping, or burning
- bloody or cloudy urine
- chest pain or discomfort
- confusion
- constipation
- dark urine
- decreased frequency or amount of urine
- diarrhea
- difficult breathing
- drowsiness
- fast breathing
- feeling that something terrible will happen
- fever
- general tiredness and weakness
- headache
- heartburn
- increased thirst
- indigestion
- irregular heartbeat
- lower back or side pain

Dosage :- 0.75mg
Routes of administration:- orally

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      review article of pharmacovigilance newdsand objective by Antur Rohilla, Nishant Singh , Vipin Kumar,Mohit Kumar Sharma
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      volume issue 4.
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    - Safety monitoring during clinical trials
    - Discovery development https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1119266/
    - Preclinical trials of aspirin https://dccg.nl/trial/aspirin-trial

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- History of aspirin https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1894700/#:~:text=A%20Dundee%20physician%2C%20Thomas%20Maclagan,in%20The%20Lancet%20in%201876.&text=In%201897%2C%20Felix%20Hoffman%2C%20a,which%20was%20named%20aspirin%20(Fig.
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- Drug usage statistics in USA https://clincalc.com/DrugStats/Drugs/Aspirin
- Adverse effect of drug aspirin https://www.drugs.com/aspirin.html#:~:text=Common%20side%20effects%20of%20aspirin,mild%20headache.
- Common side effects of aspirin https://www.mayoclinic.org/drugs-supplements/aspirin-oral-route/side-effects/drg-20152665
- Alergic reaction of aspirin https://www.allergy.org.au/patients/drug-allergy/allergic-reactions-to-aspirin-and-other-pain-killers#:~:text=Aspirin%20and%20allergy&text=Symptoms%20include%20flushing%2C%20itchy%20rashes,in%20people%20without%20these%20conditions