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DR. D. Y. PATIL COLLEGE OF PHARMACY, AKURDI, PUNE

TECH PHARMA

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EDITORS DESK:

The technological advancements, like media and internet, have surely helped the pharmacist patients as well as the clinicians. However, many traditional disease issues, remain the same. Yet the woes of treating the same continue and the pharmacist try to find and develop better ways to alleviate the sufferings of the patient. The advancements in science and technology continue, and different modes of new treatments and diagnostic modalities continue to emerge. Yet the common diseases, historically seen in the patients, are still the subject of medical research, books, journals and the medical industry as a whole.

The current issue of the journal highlights some of the above mentioned aspects of clinical medicine. In the issue we published the papers about the best front-line treatment on some commonly seen medical problems. Thus, this particular issue will be helpful, for all pharmacist to understand their role better.

-Dr. Sudhir V. Pandya, Professor, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

The current issue focuses upon the topic of utmost priority that is "Health", addressing the current need of an hour and spreading awareness about some common diseases, our students and faculty members have put forward some informative articles. This Pharmacist day we salute our pharmacists for their extraordinary efforts and selfless contribution to the smiles of the globe!

-Miss. Shivani S. Patil, Assistant Professor, Dr. D. Y. Patil College of Pharmacy, Akurdi.

Pharma Tech magazine of current issue emphasize on Global public health days which offer great potential to raise awareness and understanding about health issues and mobilize support for action, from the local community to the international stage. There are many world days observed throughout the year related to specific health issues or conditions. So our students and faculty member wrote article related on Global health public days which would be helpful for Pharmacist to improve awareness regarding Global public health days.

-Mr. Pavankumar P Wankhade. Assistant Professor. Dr D. Y. Patil College of Pharmacy, Akurdi.

"We would like to express our gratitude and heartfelt thanks to our beloved Principal and In-Charge Director Dr. Neeraj Vyawahare for constant support and motivation. We are also grateful to our Vice Principal Dr. (Mrs). Shilpa Chaudhari, all the teaching, non-teaching staff and our students."

Our organisation feels special and privileged in presenting this issue. Thank you all once again.

ACQUIRED HAEMOPHILIA A

Curated by - Mr. Bhavik Gala, Third year B. Pharmacy.
Dr. D.Y. Patil College of Pharmacy Akurdi, Pune-44.

Acquired haemophilia A (AHA) is a rare disease resulting from autoantibodies (inhibitors) against endogenous factor VIII (FVIII) that leads to bleeding, which is often spontaneous and severe. AHA tends to occur in elderly patients with co-morbidities and is associated with high mortality risk from underlying co-morbidities, bleeding, or treatment complications. Treatment, which consists of haemostatic management and eradication of the inhibitors, can be challenging to manage.

Few data are available to guide the management of AHA-related bleeding and the eradication of the disease-causing antibodies. Endorsed by the Haemostasis and Thrombosis Research Society of North America, an international panel of experts in AHA analyzed key questions, reviewed the literature, weighed the evidence, and formed a consensus to update existing guidelines.

AHA is likely underdiagnosed and misdiagnosed in real-world clinical practice. Recommendations for the management of AHA are summarized here based on the available data, integrated with the clinical experience of panel participants.

Introduction:

Acquired haemophilia A (AHA) is a rare, potentially life-threatening autoimmune disorder caused by an autoantibody directed against factor VIII (FVIII). Unlike congenital haemophilia, AHA presents equally in men and women and occurs mainly in older patients than children, with the median age at presentation between 60 and 67 years.[1] Bleeding patterns vary from superficial bruising that requires no haemostatic therapy to fatal internal bleeding, for example intracranial, retroperitoneal, gastrointestinal, and lung bleeding.[2] Patients with acquired haemophilia exhibit increased mortality.[3] Although possibly associated with several underlying pathologies, nearly 50% of reported AHA cases remain idiopathic.[2] AHA diagnosis is confirmed using special laboratory tests, and therapy is challenging due to the difficulty of diagnosis and comorbidities often associated with elderly patients. It has been reported that no demonstrable platelet impairment was observed in AHA patients,[4] and spontaneous joint hem arthrosis is rarely in AHA cases.[5]

Etiology of AHA:

AHA results from the spontaneous emergence of autoantibodies directed against FVIII, which inhibit or neutralize FVIII. In addition, an alloantibody to FVIII develops in 20% to 40% of congenital hemophilia patients who are treated with factor FVIII.[6] Autoantibodies against FVIII occur in approximately 0.2–1.0 cases per million per year in nonhemophilia.[7] The etiology of AHA is complicated and unknown; 46% of AHA patients are labeled idiopathic while more than 50% of cases are potentially associated with illnesses. The most commonly associated illnesses are autoimmune diseases, such as SLE and rheumatoid arthritis.[8] The 2 largest case series showed an autoimmune association of 17% to 18%.[8] Another frequently reported comorbidity is cancer or precancerous states, including solid tumours and lymphoproliferative malignancies.[8,9,10] Skin disorders (such as pemphigus and epidermolysis bullosa), drugs (including penicillin, cephalosporin, and interferon), infections, postpartum, and chronic graft-versus-host disease have also been reported to be associated with AHA.[8,9,11,12] Because the patient in our case study was a woman of child-bearing age and plasma complement C3 and C4 were reduced, a diagnosis of CTD, especially SLE, could not be excluded. However, the results of multiple laboratory tests for CTD were negative and the patient lacked typical CTD symptoms, therefore CTD could not be diagnosed. The work-up of malignancy was also unremarkable. Given her use of cephalosporin before bleeding symptoms, we suspected an association between cephalosporin and AHA in this patient, but this could not be definitively identified.

Clinical presentation of AHA:

Almost 90% of AHA cases manifest as severe haemorrhagic diathesis. Extensive subcutaneous blood extravasations, mucosal haemorrhages, bleeding from postoperative surgical wounds and after tooth extraction procedures, and painful intramuscular hematomas are all typical in AHA patients. In contrast to congenital haemophilia, spontaneous joint hemarthrosis is rarely observed in AHA cases. However, our patient presented with shoulder joint hemarthrosis. We suspect the joint hemarthrosis in this patient was the result of severe prolonged aPTT. Therefore, we consider that joint hemarthrosis was related to the extent of prolonged

aPTT and weight load in the joint and believed that joint hemarthrosis is not specific to congenital haemophilia.

Diagnosis of AHA:

Although rare, AHA should be considered in differential diagnosis, particularly in women and the elderly with a bleeding tendency or prolonged aPTT. When a patient without a hematologic history presents with prolonged aPTT, PT, and a suggestive clinical picture, AHA should be suspected. The most common way to delineate the cause of the prolonged aPTT is to perform a mixing study after heparin contamination is excluded. If aPTT is corrected, this suggests a clotting factor deficiency, and if not, an inhibitor to the factor is likely. The latter can be a lupus anticoagulant or an inhibitor to the clotting factor, commonly FVIII. If only one clotting factor is reduced by the inhibitor, this would suggest the presence of the lupus anticoagulant factor where antibodies can affect the laboratory estimation of more than one factor. The strength of an inhibitor can be quantified using the Bethesda assay, which measures residual FVIII activity after incubation of normal plasma with serial dilutions of patient plasma for 2 hours at 37°C. The inhibitor titer in BU represents the reciprocal of the dilution of the patient's plasma which leads to 50% inhibition in the assay. The patient's clotting test result was consistent with the diagnostic criteria for AHA with a negative autoimmune screen. Given this, the patient was diagnosed as having AHA. Anaemia is also common in AHA patients, but the cause of anaemia is rarely reported. Since this patient also presented with severe anaemia on admission, we performed laboratory tests for anaemia, and noted that serum B12 and red cell folate concentrations were within normal limits. Reticulocyte percentages and serum bilirubin were normal, and the Coombs test was negative. The extent of the patient's anaemia was not further aggravated once the active bleeding was controlled. Therefore, we strongly suspect anaemia in this patient was the result of blood loss and no haemolysis.

It has been reported that no demonstrable platelet impairment is observed in AHA patients.[4] However, the patient in our study did present with severe thrombocytopenia. Further laboratory tests confirmed that the platelet-associated antibody IgG of this patient was positive, and the platelet count could be recovered using immunosuppressant therapy. Therefore, this patient was simultaneously diagnosed with AHA and immune thrombocytopenia. We inferred that autoantibodies could be simultaneously directed against FVIII and platelets in this patient, resulting in a deficiency of FVIII and platelets. This data shows that AHA potentially accompanies other autoimmune disorders besides CTD, which increases the difficulty of diagnosis of the disease and leads to significant mortality.

Therapy of AHA:

The mortality rate of AHA is between 7.9% and 22%. [1] Once a patient is diagnosed with AHA, appropriate therapy directed at arresting haemorrhage and eradicating the inhibitor must be initiated. If plasma FVIII levels can be increased to 30% to 50% in a patient with AHA, haemostasis can generally be achieved. [1] This result can be achieved using either DDAVP or infusion of FVIII. If a patient has severe bleeding and an inhibitor titer >5BU, it is prudent to begin therapy with an agent that bypasses FVIII, either activated prothrombin complex concentrate (aPCC) or recombinant factor VIIα (rVIIα).[1] Aside from treating the bleeding, removal of the inhibitor is critical to achieving long-term, stable AHA control. Presently, immunosuppressive medication plays the most crucial role in inhibitor elimination. Immunosuppressive agents include corticosteroids (prednisone 1 mg/kg/day), cyclophosphamide (1.5–2.0 mg/kg/day), IVIG (total dosing of 2 g/kg over 2 or 5 days), cyclosporine A (4–6 mg/kg/day), [13] and anti-CD20 monoclonal antibodies, which can be used either alone or in combination with other medication. The optimal immunosuppressive regimen is unclear. In the last several years, the anti-CD20 monoclonal antibody has been used for the management of various autoimmune diseases, as well as lymphomas. “Off label” use of anti-CD20 monoclonal antibody has been studied for patients with acquired haemophilia, showing promising results of durable remission. [14–16] The usual dose is 375 mg/m2 each week for 4 weeks. Most responses are observed within the first 2 weeks of therapy, with some clinician's inputs, it should be considered in patients resistant to first-line therapy or for those that cannot tolerate standard immunosuppressive therapy.[9] FVIII: I titer for the patient in the current study was 210 BU/mL, which is much more than 5 BU/mL, therefore the patient was initially transfused with FFP and hPCC to complement clotting factors for the treatment of bleeding, when FVIII, aPCC, and VIIα were unavailable. At the same time, this patient initially accepted corticosteroids combined with IVIG or intravenous cyclophosphamide to eradicate the inhibitor. After 1 month of corticosteroid-based combination treatment, the aPTT of the patient remained severely prolonged. The patient then presented with shoulder joint

hemarthrosis, which was her second episode of bleeding. As a result of the very high inhibitor titer and severe bleeding presented by this patient, we adopted an anti-CD20 monoclonal antibody treatment plan at 375 mg/m2 each week combined with an oral dose of prednisone at 0.8 mg/kg/day. Following 4 weeks of anti-CD20 monoclonal antibody therapy, the patient achieved complete remission. Although rituximab-based regimens showed good results, the current study did not support the use of rituximab alone or, if used as a first-line treatment, which is a better or safer option than other less expensive immunosuppressive agents. [17]

In conclusion, we present a very rare account of a patient with AHA complicated by joint hemarthrosis and immune thrombocytopenia which was successfully managed. We learned that AHA is an immune disease and AHA can co-exist with immune cytopenia in addition to CTD, which often makes patient presentation complicated and increases the difficulty of accurate diagnosis and therapy. As haematological physicians, we should acquire more knowledge on AHA and associated autoimmune diseases, recognize the shared pathophysiology of these associated autoimmune conditions, and make prompt and accurate diagnoses. When the first-line therapy using cyclophosphamide combined with prednisone is not enough to eradicate the inhibitor, especially for a higher inhibitor titer, anti-CD20 monoclonal antibody therapy could be beneficial in these patients.

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PULMONARY ARTERIAL HYPERTENSION TREATMENT: A REVIEW

Curated by – Dr. (Mrs.) Shilpa P. Chaudhari(Vice-Principal), Vivek Y. Jadhav (M. Pharmacy).

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Pulmonary arterial hypertension is a type of high blood pressure that affects arteries in the lungs and the heart. Current treatments of PAH include Prostanoids, Endothelin receptor antagonist, Phosphodiestrerase-5 inhibitors, and soluble guanylate cyclase (sGC) stimulator, available in oral dosage form like (film-coated tablet, suspension) or Intravenous form, but these therapies hinder the patient compliance, have a short half-life and show off-target side effects. Therefore, to overcome these problems various novel drug delivery systems like liposomes, nanoparticles, micelle, nanoerythrosomes, polymeric microspheres have been investigated for PAH treatment. These novel systems were developed by hydration and extrusion method, a solvent evaporation method, double emulsion solvent evaporation method, thin lipid film rehydration method, and many more. These novel delivery systems provide a localized effect to the pulmonary circulation and avoid the systemic side effects. Surface modification of these carriers with a targeting moiety has been shown to improve the specificity of the drug. Therefore, these novel drug delivery systems have been shown to increase patient compliance and improve the half-life of the drug.

Introduction:

Pulmonary hypertension, additionally referred to as pulmonary arterial hypertension, is a disorder marked with the aid of using pulmonary vasoconstriction and growing endothelial proliferation withinside the small and medium pulmonary arteries. It is described as a resting mean pulmonary artery pressure (mPAP) of 25 mm Hg or above.[1] PAH, is an extraordinary ailment of the pulmonary circulation; particularly small pulmonary arteries, which impacts 15-50 people according to million with anticipated annual mortality of 20,000 within side the United States.[2] According to the National Institutes of Health Registry, PAH is an ailment represented with the aid of using excessive suggested pulmonary arterial pressure (mPAP) withinside the variety of 25 mm Hg at relaxation or 30 mm Hg after a workout. PAH has regularly been taken into consideration to be a multi-factorial disease because of the complicated etiology associated, suggesting it to be an own circle of relatives of many sicknesses with not unusual place pathophysiological traits.[3] Despite being diagnosed in 1891, pulmonary hypertension became categorized via way of means for the primary time in 1973 via way of means of World Health Organization (WHO), categorizing it into primary and secondary pulmonary hypertension. This medical class has been up to date for the reason that then at normal periods with the maximum current replace in March/April 2013 on the fifth World Symposium on Pulmonary Hypertension (WSPH) held in France to encompass facts posted because the ultimate meeting (Dana Point, California; 2008). As in step with the modern-day class, Group 1 Pulmonary hypertension is likewise referred to as PAH, having numerous subgroups derived because of complicated pathology of PAH, and additionally PAH being a prognostic pathology of diverse cardiopulmonary disease. [4]

Pulmonary Hypertension: **Group I: Pulmonary Arterial Hypertension:**

A) Idiopathic PAH
B) Heritable PAH

Idiopathic PAH describes a sporadic sickness with neither an own circle of relative's records of PAH nor a recognized hazard issue. When PAH takes place in a familial context, germline mutations withinside the bone morphogenetic protein receptor 2 (BMPR2) gene, a member of the remodeling boom issue beta (TGF- ß) signaling own circle of relatives, may be detected in approximately 70% of cases.[5,6] More rarely, mutations in activin receptors like kinase kind 1 (ACVRL1 or ALK1) or endoglin genes, additionally coding for contributors of the TGF-ß signaling family, had been diagnosed in sufferers with PAH, predominantly with coexistent hereditary hemorrhagic telangiectasia. Some authors advised that mutations of genes encoding for Smads proteins (Smad8, Smad1, and Smad5), which can be different. BMPR2 mutations have additionally been detected in 11–40% of reputedly idiopathic instances without an own circle of relative history contributors of the TGF-ß signaling pathway, or mutations in the caveolin-1 gene can also additionally predispose to PAH. [7-9] BMPR2 mutations have additionally been detected in 11–40% of reputedly idiopathic instances without their own circle of relative history.[10,11] Indeed, the difference among idiopathic and familial PAH with

BMPR2 mutations is artificial, as all sufferers with a BMPR2 mutation have the heritable disease. In addition, BMPR2 mutations have been recognized

in the handiest 70-80% of families with PAH. Thus, it changed into determined to desert the term "familial PAH" in choose of the term "heritable PAH", inclusive of idiopathic PAH with germline mutations and familial instances without or with recognized mutations. [12,13]

Functional classification for pulmonary arterial hypertension as per New York Heart Association (NYHA)/World Health Organization (WHO) [10]

Class I	Patients with pulmonary hypertension who do not have a restriction on their physical activity. Normal physical exercise does not result in excessive dyspnea, weariness, chest pain, or near syncope.
Class II	Patients with pulmonary high blood pressure ensuing in the moderate challenge of bodily interest. They are cushty at rest. Ordinary bodily interest reasons undue dyspnoea or fatigue, chest pain, or close to syncope.
Class III	Patients with pulmonary hypertension have a significant restriction in their physical activities. They feel at ease when they are resting. Excessive dyspnoea or weariness, chest pain, or near syncope are all symptoms of insufficient activity.
Class IV	Patients with pulmonary high blood pressure lack of ability to perform any bodily pastime without symptoms. These sufferers show up symptoms and symptoms of proper coronary heart failure. Dyspnoea and/or fatigue can also additionally be at rest. Discomfort is elevated with the aid of using any bodily pastime.

Currently Available Therapeutic Options for the Treatment of PAH [15]

Delivery system	Drug	Brand name	Excipient	FDA Approval	Advantage	Limitation
	Prostanoids					
Intravenous	Epoprostenol	Flolan	Glycine, sodium chloride, sodium hydroxide, mannitol	Class III Class IV	Easy to titrate, longest experience	Requires permanent I.V catheter, Risk of line infection, risk of syncope or cardiovascular collapse, need for ice packs, mixing every 24 hours
Intravenous	Epoprostenol	Veletri	Sucrose, L-arginine, Sodium hydroxide	Class III Class IV		Short half-life (3-5min), Unstable at acidic pH, cannot be taken orally
Inhalation	Epoprostenol (arginine)	Veletri	Sterile water	Class III Class IV	Non-invasive, reduced dosing frequency, increased accumulation to vascular region	A short half-life, cannot be taken orally.
subcutaneous	Treprostinil	Remodulin	Sodium chloride, metacresol, sodium citrate, WFI	Class II Class III	Smaller pump, no mixing	Pain at the site of infusion

Intravenous	Treprostinil	Remodulin	Sodium chloride, metacresol, sodium citrate, WFI	Class IV	Cassette changed every 48h, no need for ice packs, less risk of cardiovascular collapse	The risk associated with the permanent I.V. catheter
Oral Inhalation	Treprostinil	Tyvaso	Sodium chloride, sodium citrate, Sodium hydroxide, hydrochloride acid in WFI	Class III	It is an alternative to IV and SC and improves patient compliance, delivery of drug to the desired location, the absolute bioavailability of inhaled Treprostinil is greater compared to IV	Dosing errors due to variations in breathing patterns and tolerance issues may limit delivery to below the target treatment dose, frequency and duration of administrations can be an inconvenience to patients
Extended-Release Oral Tablet	Treprostinil	Orenitram	Xylitol, Maltodextrin, SLS, Magnesium Stearate, Cellulose acetate, Triethyl citrate PVA, Titanium dioxide, PEG, talc, Shellac, ferrosoferric oxide, Butyl alcohol, Isopropyl alcohol, PG	Class II Class III	Improved patient compliance, eliminates the risk of blood stream infection and thrombosis, no need of analgesic to suppress pain (like in case of subcutaneous	Complex medication with high side effect burden, very high cost, an unclear role in the current therapeutic armamentarium
Inhaled	Iloprost	Ventavis	Ethanol 96%, WFI, hydrochloric acid, trometamol sodium chloride	Class III Class IV	No need for an IV catheter Local delivery limits side effects	6–9 inhalations per day, more risk of syncope Half-life of 20-25mins
Intravenous	Iloprost	Ventavis	Ethanol 96%, WFI, hydrochloric acid, trometamol, sodium chloride	Class III Class IV	Easy to titrate but has less experience	Requires permanent I.V. catheter, risk of line infection, risk of syncope or cardiovascular collapse, need for ice packs, mixing every 24 hours
Oral Tablet	Beraprost	Beraprost		Class II Class III	Oral delivery hence patient compliance	Gastrointestinal intolerance, unclear efficacy, Elimination half-life is 35-40mins

	Endothelin Receptor Antagonist					
Film-coated tablets, tablets for oral suspension	Bosentan	Tracleer	corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropyl methylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow	Class III	Convenient for patient Tablet for oral suspension has greater compliance for pediatric patients	Liver toxicity causes an increase in hepatic aminotransferase
Tablet for oral delivery	Ambrisentan	Letairis	Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, aluminum oxide, lecithin, soybean, PEG, PVA, talc, titanium dioxide	Class II Class III	Letairis can improve your ability to exercise, help slow down the worsening of your physical condition and symptoms. Safe and effective in children	Teratogenicity, Liver toxicity
Film-coated tablet	Macitentan	Opsumit	Lactose monohydrate, microcrystalline cellulose, povidone, sodium starch glycollate type A, magnesium stearate, polysorbate 80, PVA, titanium dioxide, talc, soya lecithin, xanthan gum	Class II Class III	Increased patient compliance	Teratogenicity
	Phosphodiesterase-5 inhibitors					
Tablet	Sildenafil	Revatio	Microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, Hypromellose, titanium dioxide, lactose	Class II Class III	Improved patient compliance	In some patients it may show loss of vision and hearing, Revatio cannot be given to pediatric patients

			monohydrate, triacetin.			
Injection	Sildenafil	Revatio	dextrose and water for injection.	Class II Class III	Systemic delivery avoids first-pass metabolized	Dose-dependent systematic side effects
Oral Suspension	Sildenafil	Revatio	Sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide, sodium benzoate, colloidal silicon dioxide anhydrous, and grape flavor.	Class II Class III	Improves chemical stability of drug	Discard the suspension after 60days of reconstitution
Film-coated tablet	Tadalafil	Adcirca	Croscarmellose sodium, hydroxypropyl cellulose, Hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, triacetin	Class II Class III	Efficacy has been shown in idiopathic PAH (IPAH) and PAH related to collagen vascular disease	Dose-dependent side effect
	Soluble Guanylate cyclase					
Novel Drug Delivery Systems explored to Increase the Selectivity and Specificity of Conventional and Investigational Drugs for Pulmonary Arterial Hypertension (PAH) Treatment						
Film coated tablet	Riociguat	Adempas	Microcrystalline cellulose, crospovidone, Hypromellose, lactose monohydrate, magnesium stearate, SLS, hydroxypropyl cellulose, PG, Titanium dioxide	Class II Class III	Efficacy has been shown in a PAH population including heritable PAH or PAH associated with connective tissue disease	Reduction in systolic blood pressure

Delivery System	Drug	Ingredients	Method of preparation	Rational	Result	Ref

Liposomes Via. Inhalation	Fasudil	Fasudil monohydrochloride, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), cholesterol (CHOL), monocrotaline (MCT), chloroform, methanol, ammonium sulfate, dimethyl sulfoxide (DMSO), acetonitrile	By hydration and extrusion method	Invasive method of administration, short duration of action, lack of pulmonary selectivity.	Reduced dosing frequency due to 10 folds increase in plasma half-life, non-invasive, controlled release.	14
Liposomes (CAR peptide) Via. Inhalation	Fasudil	Fasudil, 1,2-distearoyl-sn-glycero-3 phosphoethanolamine-N-[methoxy (polyethylene glycol)- 2000] (DSPE-PEG2000), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), N-Succinimidyl 1,3-(2-pyridyldithio)propionate (SPDP), TGF-β, CAR peptide, cell medium containing an extra cysteine for conjugation through the free sulfhydryl	By film-hydration method, and the drug was encapsulated by active loading	This study establishes that CAR-conjugated inhalable liposomal fasudil offers favorable pharmacokinetics and produces pulmonary vasculature-specific dilatation.	Increased specificity to pulmonary region, reduced mPAP without affecting mSAP	15
liposome (CAR peptide) via. Intratracheal	Fasudil and Superoxide Dismutase (SOD)	Fasudil hydrochloride, Superoxide dismutase (SOD), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), Cholesterol (CHOL), dimethyl sulfoxide (DMSO), Phosphate buffer solution (PBS), chloroform, methanol	By the thin-film formation, hydration, and extrusion method	Due to the short duration of action, the feasibility of encapsulation of two drugs into liposomes	Better retention in lungs compared to plain liposomes, targeted delivery, reduced dose, and frequency	16

Nano-erythrosomes Via. Intratracheal	Fasudil	Fasudil monohydrochloride, methanol, phosphate-buffered saline (PBS 1X), acetonitrile, and dimethyl sulfoxide	NERs by hypotonic lysis of erythrocytes followed by extrusion through polycarbonate membranes	To exhibit efficient drug loading, targeting specificity and prolonged biological half-life	Higher in vitro cellular uptake, the half-life of Fasudil increased to 6.8-folds compared to plain drug	17
Nano-erythrosomes (CAR peptide) Via. Inhalation	Fasudil	Fasudil, Hypotonic solution using phosphate-buffered saline (PBS) with water, white unsealed ghosts, hypertonic solution (10× PBS)	by hypotonic lysis 32 and extrusion method	to extend the biological half-life and deploy drugs at a disease site with the help of homing devices like peptides, to produce prolonged pulmonary preferential vasodilation.	1.5 folds higher cellular uptake compared to, plain erythrosomes, 2 folds higher selectivity to the lungs	18
Micelles (CAR peptide) Via. Inhalation	Fasudil	Fasudil hydrochloride, 1,2-Distearoyl-sn-glycero-3phosphoethanolamine–N[methoxy(polyethylene-glycol)-5000], DSPE–PEG2000-maleimide, CAR peptide, monocrotaline, chloroform, methanol, phosphate-buffered saline (PBS), acetonitrile, and dimethyl sulfoxide.	Solvent evaporation method	To improve efficacy, promote specificity, and enhance the safety of encapsulated therapeutic agents.	Cellular uptake and t1/2 increased to 1.7- and 5- folds, respectively compared to plain micelles. Higher lung accumulation, reduced mPAP by ~60% without affecting mSAP.	19

Micelles Via. Intratracheal	Human ADM gene (Adrenomedullin)	Human ADM gene, poly (ethylene glycol) (PEG)-based block catiomers, which form core-shell polyplex nanomicelles, aqueous media containing serum protein, a poly(aspartamide) derivative bearing an N-(2-aminoethyl)aminoethyl group	Gene therapy approach	AM is indicated for PAH because of its prodilatory effects and the abundance of AM receptors in the lung. AM-based Gene delivery to the lung will avoid immediate nuclease degradation in the bloodstream and the difficulty associated with penetrating endothelial barriers	Right ventricular pressure decreased, ADM mRNA level in lungs enhanced.	20
Liposomes Vis. Inhalation	Iloprost	Iloprost trometamol (ILO), di-palmitoyl-phosphatidyl-choline (DPPC), cholesterol (CH) and polyethyleneglycol-di-palmitoyl-phosphatidyl-ethanolamine (DPPE-PEG), Chloroform, methanol	By thin lipid film rehydration method	The feasibility of liposomes to provide a sustained release formulation to reduce inhalation frequency	Liposomes were found stable during nebulization.	21
Liposome nanoparticle	Iloprost	Anhydrous iloprost, Cationic lipids, stearylamine, 1,2-di-(9Z-octadecenoyl)-3-trimethylammonium-propane (DOTAP), DPPC, 1-palmitoyl-2oleoyl-sn-glycero-3-phosphocholine (POPC)	By thin-film rehydration method	Cationic liposomes can encapsulate iloprost with high efficacy and can serve as potential iloprost carriers to improve its therapeutic efficacy.	2-fold dose reduction, significantly higher vasodilation of pulmonary arteries as compared to free drug	22
Polymeric nanoparticle Via. Intravenous	Alprostadil (Prostaglandin E1)	poly (lactic acid) homopolymer, poly (ethylene glycol)-poly(lactide) block copolymer	Nanoparticles encapsulating PEG1 by solvent diffusion method	Rapid inactivation of PGE1during its first passage through the lungs, severe side effects due to distribution to the whole body.	Increased half-life, increased accumulation to vascular region	23

Microsphere for Inhalation	Alprostadil (Prostaglandin E1)	Prostaglandin E1 (PGE1), Poly (lactic-co-glycolic acid) (PLGA), Polyethyleneimine (PEI), Poly vinyl alcohol (PVA), dichloromethane	Double-emulsion solvent evaporation method	For localized delivery to the lungs, to avoid vital organ damages	Enhance drug payload, provides extended biological half-life, offers protection against metabolic degradation	24
Polymeric nanoparticle Via. Intravenous	Beraprost	Beraprost sodium, poly (lactic acid) homopolymer, and monomethoxy poly(ethylene glycol)–poly(lactide) block copolymer.	the oil-in-water solvent diffusion method	To provide sustained release, to improve the targeting ability	Higher accumulation and prolonged residence time in the pulmonary arteries, effective against MCT- and hypoxia-induced pulmonary arterial remodeling and right ventricular hypertrophy	25
Polymeric nanoparticle Via. Intratracheal	Imatinib	Imatinib, Polylactide-glycolide (PLGA), fluorescein isothiocyanate (FITC), a copolymer ratio of lactide to glycolide	By emulsion solvent diffusion method	A drug delivery system using nanoparticles (NPs) enables the reduction of side effects while maintaining the effects of the drug.	Lung delivery of imatinib nanoparticles suppressed MCT-induced PAH by reducing PAH-pulmonary arterial smooth muscle cells (PASMC) proliferation.	26
Solid lipid nanoparticles for inhalation.	Sildenafil	Sildenafil citrate, Phospholipon-phospholipid, deoiled soya lecithin-phosphatidyl choline, Lysophosphatidylcholine, and tocopherol. Hydrogenated palm oil, macrogol-15-hydroxystearate	A customized microchannel high-pressure hot melt homogenization device	Non-invasive method, to gain both local and systemic delivery of drug	The high surface area with rapid absorption due to high vascularization as well as circumvention of the first-pass effect are evident	27
Polymeric nanoparticle Via. Inhalation	Sildenafil	Sildenafil (free base), Poly(D,L-lactide-co-glycolide) (PLGA), Poly vinyl alcohol (PVA)	Solvent evaporation technique	To improve controlled drug delivery to the lung	Avoids the unwanted systemic side effects, the direct delivery of nanoencapsulation therapeutics to the lung sustained and controlled drug release at the desired site of action	28

Nanodispersion Via. Inhalation (Metered-dose inhalers)	Sildenafil	Sildenafil citrate, Sorbitan monooleate, ethanol, propellant, tetrafluoroethane, poloxamer 188 (P188)	Nano Spray Dryer	For direct delivery to the pulmonary system could help mitigate the adverse system events and improve the onset of response by its direct delivery.	The formulation was stable and well-uniform after 6 months. It was nontoxic to respiratory epithelial cells. A positive correlation between P188 concentration and mass median aerodynamic diameter (MMAD) of the MDIs was observed	29
Liposomal Via. Inhalation	Vasoactive Intestinal Peptide (VIP)	VIP (amino-acid sequence HSDAVFTDNYTRL RK QMAVKKYLNSILN -NH2), Palmitoyl-oleoyl-phosphatidylcholine (POPC), lyso-stearyl-phosphatidylglycerol (lyso-PG), polyethyleneglycol conjugated distearyl-phosphatidylethanolamine (DSPEPEG2000), (Trp-VIP) and EtCy3-VIP	By thin-film rehydration method	To overcome the enzymatic cleavage and rapid degradation of VIP	Significantly higher vasodilation as compared to free VIP	30
Unilamellar nano-sized VIP-loaded liposomes (VLL) Via. Inhalation	Vasoactive Intestinal Peptide (VIP)	VIP (amino acid sequence HSDAVFTDNYTRL RK QMAVKKYLNSILN -NH2), Phospholipids, Krebs–Henseleit buffer (KH), Sodium chloride, Potassium Chloride, Potassium dihydrogen phosphate, Calcium chloride, Magnesium chloride, glucose, Sodium hydrogen carbonate.	By thin-film rehydration method	To overcome the short half-life problem due to rapid enzymatic degradation in the airways	Liposomes are stable during nebulization. The liposomes had the potential to improve VIP inhalation therapy by providing a “dispersible peptide depot” in the bronchi.	31

Nanoparticle Via. Intravenous	AntimiRNA-145 (Antisense therapy)	AntimiR-145 sequence was 5′-CCTGGGAAAACTGGA-3′, Locked nucleic acid (LNA)/DNA oligonucleotides, Star and Star-mPEG, Chloroform, WFI, 5% dextrose	By thin-film rehydration method	For effective delivery of oligonucleotides to target cells and reduced delivery to non-target cells, to achieve significant knockdown of target gene expression for at least 10 days following a single IV dose	Higher lung tissue accumulation and reduced expression of endogenous miRNA-145. Decreased pulmonary remodeling without exhibiting any systemic side effect.	32
Nanoparticle Via. Intravenous	Rapamycin	Rapamycin, Poly (ethylene glycol)-poly-(E-caprolactum), fluorophore BODIPY	By solvent evaporation method	(RAP)-loaded NPs, mTOR inhibitor, accumulate in the diseased lung, selectively targeting mTOR and preventing PAH progression	Monocrotaline-exposed rats showed increased NP accumulation within lungs compared to healthy controls, with NPs present to a high extent within pulmonary perivascular regions.	33
Polymeric microsphere Via. Inhalation	Nifedipine	Nifedipine, Poly vinyl alcohol (PVA-release modifier), Sodium dodecyl sulfate, water, ethanol	By spray drying technique	Controlled release microsphere to minimize the number of doses required	The size and morphology of the microsphere were suitable for inhalation. Prolonged toxicity studies confirmed the biocompatibility of PVA (release modifier)	34
Nanocomposite Microparticles (nCmP) Via. Inhalation (DPI)	Tacroli-mus (TAC)	Tacrolimus, Dextran, pyridinium p-toluene sulfonate, D-mannitol, 2-methoxypropene, triethylamine, anhydrous dimethyl sulfoxide, PVA, dichloromethane, deuterium chloride, Tween 80, potassium phosphate dibasic, potassium phosphate monoxide, acetonitrile, deuterium oxide, PBS	Oil/Water emulsion and solvent evaporation	Due to poor solubility, instability, poor bioavailability, and systemic side effects of tacrolimus	High encapsulation efficacy, desirable aerosol dispersion allows deep deposition into the lungs. Improved solubility, Controlled release.	35

Patches	Borneol-mediated vardenafil hydrochloride	Vardenafil hydrochloride, Sodium polyacrylateNP-700, ethyl paraben, 1,2-propanediol, azone, borneol, glycerin, gelatin, tartaric acid, PVP-K90D, water	By coating method	Due to certain drawbacks of the tablet. Preferable drug delivery for children	Appropriate adhesive force and low skin permeation. The blood concentration within therapeutic window of BO-VarP lasted longer than i.g and BO-VarP could improve symptoms of PPAH.	36
Nanoparticle Via. Intratracheal	Pitavastatin	PLGA, copolymer lactide, and glycolide, Poly vinyl alcohol (PVA)	By emulsion solvent diffusion method	Due to the enhanced ability of Pitavastatin-NP in inhibiting cellular proliferation and inflammation in vitro	In monocrotaline-induced PAH, a single intratracheal instillation of NP resulted in the delivery of NP into alveolar macrophages and small PAs for up to 14 days after instillation	37
Oral Drop Liquid Solution	Sildenafil Citrate	Sodium citrate, phosphate, glycerin, phosphoric acid, sodium hydroxide	Plackett-Burman Design	Due to the non-adaptable form of administration for pediatrics, there is a need for such a suitable dosage form	Type of buffer and glycerin content influence the Sildenafil solubility. The formulation was stable for 6 months under three assayed conditions. Palatability assay showed that formulation diluted with 4.8ml milk had similar palatability to milk alone. No precipitate, No turbidity.	38
Nanocomposite Via inhalation (Dry Powder Inhaler)	Tadalafil	Pure tadalafil, Methylparaben, mannitol, lactose-monohydrate, L-isoleucine, monobasic potassium phosphate, sodium hydroxide, tert-butyl methyl ether, carboxymethyl cellulose, methanol.	Spray Drying Technique	To prepare dry powder formulation for inhalation for increasing bioavailability and treatment efficacy as well as decreasing systemic side effects	The values of fine particle fraction and redispersion for inhalable tadalafil nanocomposite with a particle size of 3.2um can reach the capillaries of the alveoli and redisperse to the primary nanoparticle in the lungs	39

Conclusion:

PAH is a rare disease of pulmonary circulation that affects the small pulmonary arteries. Several Novel therapies have been discussed for the treatment of PAH. Currently, there are several FDA-approved PAH treatments available in the market, but these agents suffer from serious drawbacks including a short half-life and reduction of systemic blood pressure. Therefore, to improve the efficacy of the conventional drugs various novel carriers including liposomes, nanoparticles, micelles, solid lipid nanoparticles have been exploited for therapeutic delivery to the disease site i.e., lungs, via both systemic and local delivery. Surface modification of these carriers (liposomes, nanoerythrosomes, micelles) with a targeting moiety (CAR peptide) having affinity to the receptors present on pulmonary smooth muscle cells or endothelial cells might improve the specificity of the drugs.

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UNDERSTANDING OSTEOPOROSIS, ITS RISK, PREVENTION, AND TREATMENT.

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Definition:
An ailment wherein the bones become weak and delicate, brittle from loss of tissue, typically because of hormonal changes, or lack of calcium or vitamin D.

Introduction:
20th October- Osteoporosis Day, Old individuals are the quickest growing population on the planet and, as individuals age, bone mass decays, and the danger of fractures increases. Subsequently, the social and economic burden of osteoporosis is expanding consistently due to the aging of the total populace.[1] Osteoporosis is a significant general medical condition mainly a skeletal disorder described by low bone mass, permeable bone, and its structural deterioration, which is related to higher fracture risk. It develops when bone density and thickness decrease.[2] The body reabsorbs more bone tissue and creates less to replace it.
The most influenced portions of the body are the bones of the lower arm, the hip, and the vertebrae in the spine. In more terrible conditions, bones might lose solidarity so much that they may break even with little stress.[3]

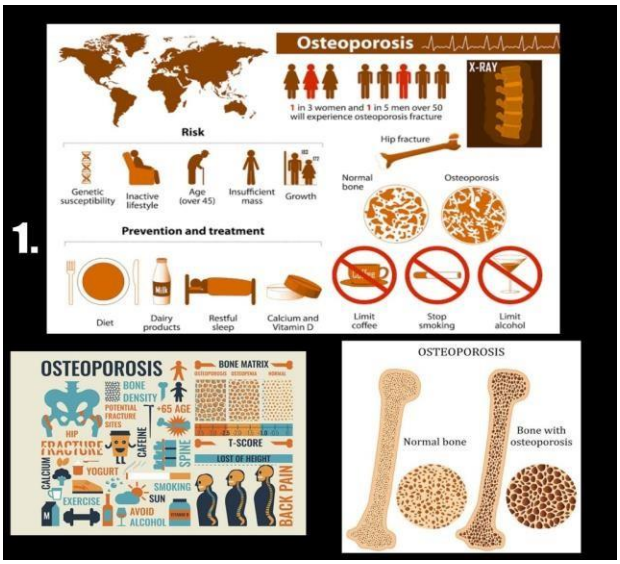
Etiology:
Three main factors responsible for Osteoporosis:

1. Estrogen Deficiencies in Women. Women typically suffer estrogen deficiencies during perimenopause and menopause.
2. Calcium Deficiencies. Bones are constantly losing and replacing minerals.
3. Inactive Lifestyle.

The risk of fracture is high in the following:

- Advanced age
- Prior history of a fracture
- Female gender
- Menopause
- Use of corticosteroids
- Low body mass index
- Smoker
- Secondary osteoporosis
- Intake of alcohol

Having certain medical conditions, such as inflammatory bowel disease, cancer, thyroid problems, rheumatoid arthritis, diabetes, eating disorders, or history of bariatric surgery, etc.



2. 3.
Image: 1) and 2) Explains risk factors, prevention to be taken, and Treatment. 3) Compare pores of normal bone vs bone with Osteoporosis.

Epidemiology:
Osteoporosis affects more than 200 million people worldwide, and its prevalence rises as people get older. Over 70% of persons over the age of 80 suffer from the condition. Females are more likely than males to suffer from this condition. Approximately 2% to 8% of males and 9% to 38% of females in the developed world are afflicted. Osteoporosis causes over 9 million fractures each year worldwide.
An osteoporotic fracture affects one in every three females and one in every five males over 50. In comparison to persons living at lower latitudes, people living in areas of the world with less vitamin D from sunlight had higher fracture rates.

Pathogenesis:
Osteoporosis can result from a combination of factors, including-
1) Inability to reach peak bone mass and
2) Increased bone resorption and/or insufficient bone production during remodeling.
1) Peak Bone Mass- Achieving peak bone mass is critical for avoiding osteoporosis and consequent fractures in age. With a 10% increase in peak bone mass, the risk of hip fracture can be lowered by 30%. According to twin studies, genetic variables play a significant role in peak bone mass and bone loss, accounting for up to 80% of peak bone mass variability. Environmental factors like nutrition, activity, and smoking all play a part in reaching optimal bone mass. It is now known that peak bone mass can be modulated.
2) Imbalance of bone absorption and formation- The bone remodeling process, which heals areas of micro damage, is critical for bone health maintenance in adulthood. This is a biological mechanism in which osteoclasts (bone-resorbing cells) and osteoblasts

(bone-making cells), which make up the multicellular unit of the bone, coordinate their functions. The most prominent mediators of osteoclast activity are OPG/RANK and its ligand (RANKL). Hormones, growth factors (TGF-, IGF-1, BMP2), cytokines (IL-1, IL-6, TNF-, prostaglandins E2), and medications all have an impact on OPG/RANKL expression and, as a result, bone turnover. Oestrogen insufficiency causes an imbalance in bone remodeling during menopause.

Diagnosis:

1. BMD measurement- The gold standard for diagnosing osteoporosis is dual X-ray absorptiometry (DXA). The findings of BMD testing are stated in standard deviations and are compared to a sex-matched young healthy adult (T-score) or a sex-matched and age-matched healthy population (Z-score). A T-score of less than or equal to 2.5 indicates osteoporosis, while a T-score of 1.0 to 2.5 indicates osteopenia.
2. Clinical risk factors and fracture risk assessment- Several clinical risk factors, such as age, falls, and a history of fragility fractures, should be considered. A complete medical history, physical examination, and a variety of investigative procedures depending on the case are all part of differential diagnosis. The WHO task force created and introduced a country-specific Fracture Risk Assessment Tool (FRAX) to aid doctors in their clinical management process, based on data collected from large international cohorts in which clinical risk factors, BMD, and fractures were examined. The technology calculates a 10-year likelihood based on BMD measurements and clinical risk factors.[4]

Different models used in osteoporosis:

Various kinds of animals used in Osteoporosis are Zebrafish, Medaka, OVX rodents, Sheep, Rabbits, Dogs, and Primates, Etc.

1) Glucocorticoid-Induced Osteoporosis (GIOP)- Osteoblasts in glucocorticoid-induced osteoporosis (GIOP) undergo increased apoptosis and have decreased activity and number. In the early stages of GIOP, osteoclast proliferation, longevity, and activity all rise. Longer treatments, on the other hand, reduce the development and function of osteoclasts. The causes underlying osteoporosis are still being studied, and there is currently no effective treatment for GIOP.

2) High glucose and high fat Induced Osteoporosis- Adult zebrafish exposed to glucose showed a decrease in scale matrix mineralization, the presence of bone resorption lacunae associated with intense osteoclast activity, and altered expression of bone regulatory genes 2019b), which is similar to what has recently been reported in diabetic rodents and humans bones.

3) Iron Overload Induced Osteoporosis- Iron overload hindered bone development and lowered the expression of osteoblast marker genes in zebrafish larvae, presumably due to increased ROS generation and oxidative stress.

4) RANKL Overexpression Induced Osteoporosis- Active osteoclasts were produced ectopically in rank transgenic fish and increased bone resorption in mineralized arches and vertebral bodies, similar to what is seen in human osteoporosis.

5) Microgravity Induced Osteoporosis- Adult medaka and transgenic larvae flown to the International Space Station showed decreased osteoblastic activity, increased osteoclastic activity, and a lower BMD as a result of microgravity. Several osteoclast marker genes (e.g., trap, ctsk, and mmp9) had their promoter activity and expression increased during spaceflight, indicating increased osteoclastic activity.

Treatment:

1. Bisphosphonates-
   Bisphosphonates are the most commonly investigated and given BPs for postmenopausal osteoporosis therapy. Alendronate, ibandronate, risedronate, and zoledronic acid are among them, and they are accessible in oral and injectable forms. Blood pressure should be taken 30 to 60 minutes before any food or other fluids after an overnight fast with only water. These synthetic substances help to improve Bone Mineral Density and reduce the risk of vertebral fractures.
2. MHT and SERM-
   i) Menopausal Hormone Therapy (MHT), commonly known as Hormone Replacement Therapy (HRT), is a type of hormone replacement therapy that uses estrogens alone or in combination with progestin. In early and late postmenopausal women, MHT has been found to reduce bone turnover and improve bone mineral density (BMD) at all skeletal locations.
   ii) Selective oestrogen receptor modulators (SERM) or oestrogen agonists/antagonists are nonsteroidal synthetic compounds that can weakly bind to oestrogen receptors throughout the body. Depending on the organ they target, they operate as oestrogen agonists or antagonists. The idea behind SERM is that tamoxifen, which is used to treat breast cancer, acts as a partial oestrogen agonist on bone in postmenopausal women.
3. Denosumab-
   Denosumab is a completely human monoclonal antibody that binds with high affinity and specificity to the receptor activator of nuclear factor-kB ligand (RANKL). It inhibits the proliferation, activation, and survival of osteoclasts by

blocking the interaction of RANKL with the receptor activator of nuclear factor-kB (RANK) on the cells of the osteoclastic lineage, leading to a strong and rapid reduction of bone resorption.

4. Anabolics-

i) Teriparatide-Teriparatide has been found to stimulate bone formation by increasing the number of osteoblasts and their activity on quiescent bone surfaces, largely through bone remodeling and to a lesser extent through bone modeling on quiescent bone surfaces.

ii) Abaloparatide- Abaloparatide is a a synthetic peptide with 34 amino acids. It's a parathyroid hormone-related protein (PTHrP) analog that's been chosen as a parathyroid hormone receptor-selective activator (PTH1R).

iii) Romosozumab- Romosozumab is a sclerostin-specific humanized monoclonal antibody. Sclerostin is a secreted protein by the osteocyte that inhibits bone growth and is expressed by the SOST gene.

Complications:

The most significant effects of osteoporosis are pathological fractures, notably in the hip or spinal column. Hip fractures are commonly caused by falls and can result in disability and even an increased risk of death in the days after the injury. In the absence of patient falls, there are also spinal fractures, with compression fractures causing back pain and a kyphotic posture.[5]

Conclusion:

Osteoporosis prevention should begin early in life and continue throughout one's life with measures that improve or maintain bone health, such as regular physical activity and a well-balanced diet that includes not only an adequate intake of calcium but also other minerals, proteins, and antioxidant-rich foods.

Smoking and binge drinking should be avoided. The avoidance of falls and the maintenance of an appropriate vitamin D status are particularly important in older people who are at risk of fragility fractures. Fracture risk assessment should always be followed by proven non-pharmacological and pharmacological therapy techniques.

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MIGRAINE

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Introduction:

Migraine is the most common multidisciplinary and complex neurologic disorder, characterized by recurring headache attacks. It is defined as a strong throbbing combined with unilateral headache, nausea, photophobia, phonophobia, and vomiting. The name migraine derives from the Greek word hemicranias, which means "half of the skull." This is a notable feature of the condition, as most people experience discomfort in one-half of their heads. Bilateral discomfort, which occurs at the front and back of the head, is also prevalent. The pain is throbbing in character and intensifies with exercise or movement. Migraine attacks are from mild to severe.

The global prevalence of migraine, which affects both men and women, is estimated to be 15–18 percent. Migraine is a disabling disorder that ranks ninth in the globe in terms of burden and fourth in women. During assaults, over half of the affected cases have a 50% reduction in productivity or ability to work. These people are typically absent from school or job once every three months on average.

In this review, we describe recent advances in the treatment of migraine, associated root causes, diagnosis, treatment, management strategies, and preventive measures for migraine. This comprehensive review will briefly describe recent advances in knowledge of this disorder and new formulations relates to this disease.

Migraine can be divided into two types: migraine with aura (MA) and migraine without aura (MA) (MO). Migraine can also be divided into two types: chronic migraine and episodic migraine. Another type of MA is hemiplegic migraine, which is a severe and uncommon illness that affects one side of the body and produces migraine. [1]

Types of migraine headaches:

Frontal migraine headache:

Frontal migraine headaches are distinguished by frontal pain, occur in the late afternoon, and are linked to stress. These headaches are characterized by hypertrophy of the furrowing muscles, notably the corrugator supercili. Other clinical signs of frontal migraines include brow ptosis and eyelid ptosis.

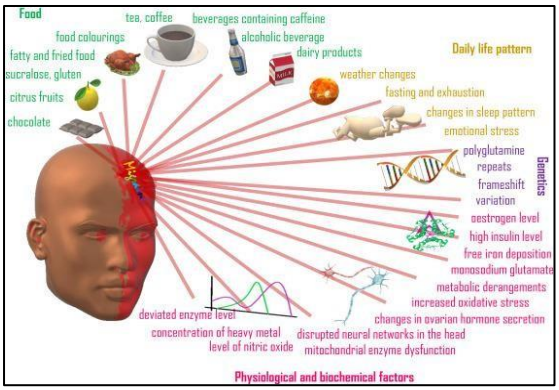


Fig.1 Physiological and biochemical factors affecting the Migraine.

Frontal migraines are caused by irritation of the supraorbital and supratrochlear nerves. The most common trigger site is the frontal 2 Olla et al trigger. The supraorbital nerves are activated by three muscles: the corrugator supercilii, the depressor supercilii, and the procerus. About the corrugator muscle, the supraorbital nerve has four branching kinds. The supraorbital artery and the entrance into the brow via the supraorbital forearm or a narrow supraorbital cleft may also irritate the supraorbital nerve. In comparison to the corrugator muscles, the supratrochlear nerve has three branching patterns.

Temporal migraine headache:

Temporal migraine headaches occur in the temple region, lateral and superior to the lateral canthus. They are most common in the morning, are related to stress, and are associated with teeth clenching. Patients frequently wake up in the morning in agony after grinding their teeth while sleeping, and inspection may reveal damaged dental facets. Migraine headaches in this area are also linked to triggering point discomfort and temporomandibular joint pain.

Temporal migraine headaches are produced by compression or traction of the trigeminal nerve's zygomaticotemporal branch (ZTBTN). The nerve exit point via the zygomatic bone, 17 mm lateral to and 7 mm superior to the lateral canthus, is a trigger site. Furthermore, the ZTBTN may be squeezed by the temporalis muscle, deep temporal fascia, or superficial temporal artery. The second most prevalent trigger location is the temporal trigger.

Migraines in the temporal region are occasionally triggered by irritation of the auriculo-temporal nerve (ATN) as it goes superior to the ear. Migraine migraines in the occipital region Occipital migraines cause discomfort in the upper neck and occipital region. These headaches are linked to stress, upper neck and occipital pain, muscle tightness, and trigger point tenderness, and they may be caused by

strenuous exercise. Patients may have a whiplash history.

Migraine headaches at this region are hypothesized to be caused by semispinalis apitis compression of the greater occipital nerve. As it passes through the semispinalis capitis muscles, the occipital nerve is squeezed. Mosser and colleagues conducted an anatomic examination of the nerve's relationship to the muscle, demonstrating that the nerve may be located 3 cm inferior to the occipital protuberance and 1.5 cm lateral to the midline with reliability. The nerve may also be squeezed by the trapezius, obliquus capitis, and nuchal fascia muscles.

Rhinogenic migraine headaches:

Retrobulbar pain behind the eye is a symptom of a rhinogenic migraine headache. They are most common in the early morning and are caused by weather, allergens, and hormones. The headaches are frequently cyclical in character. Nasal sprays can be tried as a test. 10 Intranasal triggers cause impingement and irritation of the terminal trigeminal branches and can be identified on an intranasal examination by evidence of nasal septum deviation, turbinate hypertrophy, and/or mucosal inflammation. Computed tomography (CT) of the face with evidence of contact points, such as septal spurs or septal deviation, may provide additional diagnostic support for these. [2]

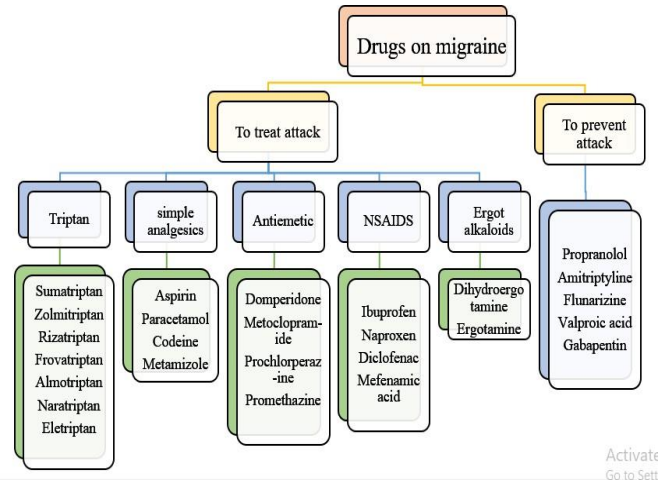
Diagnostic criteria for migraine headaches:

The International Headache Society's Headache Classification Committee published the International Classification of Headache Disorders, 3rd edition, providing diagnostic criteria for migraine headaches in 2018. This distinguishes diagnosed with migraine headaches, at least 5 attacks must match the following criteria:

- Headache attacks lasting 4 hours to 72 hours (when untreated or unsuccessfully treated).
- Headaches having 2 of the following 4 characteristics:
- Unilateral location
- Pulsating quality
- Moderate/severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) During headache at least 1 of the following:
    - ✓ Nausea and/or vomiting
    - ✓ Photophobia and phonophobia
- Not better accounted for by another diagnosis. [2]

Treatment:

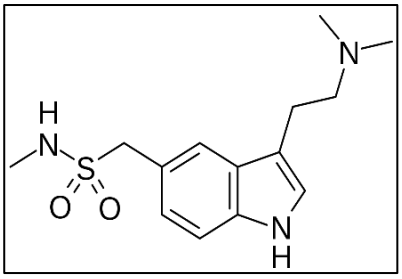
Medication therapy is the mainstay of acute treatment of migraine. [3]



To treat attack:

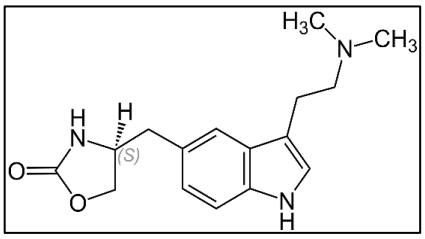
A] Selective 5 HT agonist (Triptans):

1. Sumatriptan[4] :



Properties	
IUPAC Name	1-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-*N*-methyl-methanesulfonamide
Chemical formula	$C_{14}H_{21}N_3O_2S$
Molar mass	295.40 g·mol^{-1}
Solubility	2.14X10+4 mg/L at 25 °C
BCS class	Class – III
Medicinal uses	Migraine, cluster headache, post-dural puncture headache.
Formulations still now	Tablet, injection, suppository, patch, noisome, etc.

2. Zolmitriptan[10] :

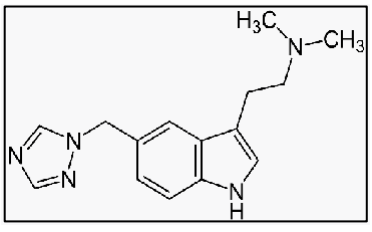


Properties	
IUPAC Name	(*S*)-4-({3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl}methyl)-1,3-oxazolidin-2-one
Chemical formula	$C_{16}H_{21}N_3O_2$
Molar mass	287.363 g·mol^{-1}
Solubility	1.3 mg/ml
BCS class	Class – III
Medical uses	Migraine.
Formulations till now	Nasal spray, tablet, patch, sublingual tablet, etc.

Sr. No.	Title of paper	Type of formula-tion	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Influence of formulation variables in transdermal drug delivery system containing zolmitriptan [11]	Patch	International Journal of Pharmaceutics	Polyglyceryl-3 oleate, propylene glycol mono laurate, polyoxy glycerate, Tween 80, Span 80, oleic alcohol, IPP, PEG12, PEG20, etc. Analysed by HPLC & UV detector.	Zolmitriptan was formulated into a transdermal patch for better mode of drug delivery. Permeation of zolmitriptan from the matrix was influenced by different formulation variables like the nature of adhesive, enhancer, thickness of matrix, drug load and the solvent system used. Stable formulations were identified through stability testing. The present study suggests that, matrix based transdermal dosage form of zolmitriptan could be explored for the management of migraine.	Robhash Kusam Subedi, Je-Phil Ryoo, Cheol Moon, Hoo-Kyun Choi, (2011)
2.	Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation[12]	Subling ual Tablet	European Journal of Pharmaceutics and Biopharmaceu tics	HPMC, chitosan, CMCNa, sodium starch glycolate, polyethylene glycol, Microcrystalline cellulose, Spray-dried alpha-lactose monohydrate FlowLac.	In this study the zolmitriptan sublingual tablet formulated. It is found that, sublingually zolmitriptan is well absorbed, and its bioavailability by this route is significantly enhanced with the addition of chitosan at the ratio of 5. As a result, sublingual tablet administration of zolmitriptan appeared to be a promising alternative to traditional drug administration routes.	Ziya Bayrak, Cetin Tas, Umut Tasdemir, Halil Erol, Cansel Kose Ozkan, Ayhan Savaser, Yalcin Ozkan.

3.	Brain targeting efficiency of antimigraine drug loaded mucoadhesive intranasal nano-emulsion[13]	Intranasal Nano-emulsion	International Journal of Pharmaceutics	Capryol PGMC, Capmul MCM EP, Maisine 35-1, and Captex 200-P, Polyoxyl 35 hydrogenated castor oil, Chitosan, Tween 80, Brij 35, Ploxamer 188, Oleic acid, IPM, and Olive oil. Detected by UV Visible spectrophotometer.	Zolmitriptan mucoadhesive nanoemulsion was prepared and characterized to be suitable for use by the intranasal delivery. It showed no abnormality in the nasal mucosa of mice after 14-day application. From the results, it seems that this is a promising drug delivery system to enhance bioavailability and treatment efficacy.	Ebtsam M. Abdou, (2017)
4.	Pullulan based oral thin film formulation of zolmitriptan: Development and optimization using factorial design[14]	Oral Thin Film (OTF)	International Journal of Biological Macromolecules.	Pullulan based, by using solvent casting method.	An oral thin film of zolmitriptan using pullulan as a natural biodegradable film former, PEG 400 as a plasticizer and sucralose as a sweetener was successfully formulated at lab-scale by solvent casting method. This types of OTF can be commercially processed easily with consideration of factors influencing on the formulation of OTF.	Vipul D. Prajapati, Anita M. Chaudhari, Abhishek K. Gandhi, Pankaj Maheriya. (2018)
5.	Preparation of zolmitriptan –chitosan microparticles by spray drying for nasal delivery[15]	Microparticle	European Journal of Pharma-ceutical Sciences	Chitosan, By spray drying method	Spray drying is a suitable technique for preparing spherical microparticles of zolmitriptan and chitosan with a narrow particle size range and high drug loading. The powders were chemically stable during processing and amorphous in nature. Hydrogen bonds were formed between the carbonyl stretching of Zolmitritan and the amino group of the Chitosans.	Amjad Alhalaweh, Staffan Andersson, Sitaram P. Velaga. (2009)

3. Rizatriptan[16] :



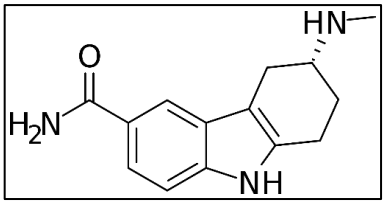
Properties	
IUPAC Name	*N*,*N*-dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine
Chemical formula	$C_{15}H_{19}N_5$
Molar mass	269.352 g·mol^{-1}
Solubility	42 mg/mL (for free base)
BCS class	Class – III
Medical uses	Acute migraine attacks with or without auro
Formulations till now	Tablet

Formulations of Rizatriptan :

Sr. No.	Title of paper	Type of formula-tion	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Intranasal Spray Formulation Containing Rizatriptan benzoate for the Treatment of Migraine.[17]	Intranasal spray	International Journal of Pharmac-eutics	Ethanol, water, propylene glycol and polyethylene glycol. HPLC	The objective of developing rizatriptan intranasal spray formulation is to achieve quick onset of action. Composition#1,2,3 and 4 have Median Tmax of 60 min, Geo mean Cmax in range of 9.9-15.8 ng/mL and Geo mean AUC in 1506-1993 ng*min/mL. While a spray containing 20% ethanol elicits a significantly faster median Tmax (5 min) and much higher Cmax and AUC. Further studies will be conducted to optimize the dose in order to be bio-equivalent with marketed product PK profile.	Ashish Chokshi, Ravi Vaishya, Rachana Inavolu, Thrimoorthy Potta. (2019)
2.	Formulation and evaluation of Rizatriptan Benzoate Orally Disintegrating Tablets[18]	Orally Disintegrating Tablets	International Journal of Drug Development & Research	Crospovidone, Croscarmellose sodium, Sodium starch glycolate. Factorial design technique, Direct compression.	The goal of the study was to identify the optimum combination of superdisintegrants for the development of orally disintegrating tablets of Rizatriptan benzoate. 22 full factorial design was used for a set of two superdisagreements and totally twelve formulations were made by direct compression method. The compounds were evaluated for their hardness, friability and key parameters like invitro dispersion time, wetting time and water absorption ratio.	Mothilal. M (2012)
3.	Design and optimization of kollicoat ® IR based mucoadhesive buccal film for co-delivery of rizatriptan benzoate and propranolol hydrochloride[19]	Mucoadhesive Buccal film for co-delivery	Materials Science & Engineering C	Hydroxypropyl methylcellulose (HPMC K4M), polyvinyl alcohol-polyethylene glycol graft-copolymer (Kollicoat ® IR) (Mw = 45000 Da), stevia, Polyethylene oxide, Glycerol, Disodium hydrogen phosphate, sodium chloride, (KCl), and potassium dihydrogen phosphate, Formalin, chloroform, hematoxylin, and eosin. solvent casting method.	-	Sahar Salehi, Soheil Boddohi (2018)

4.	Preparation And Characterization Of Rizatriptan Benzoate Loaded Solid Lipid Nanoparticles For Brain Targeting[20]	Solid lipid nanoparticles	Materials Today: Proceedings(2)	Glyeceryl monosterate (GMS), Lecithine, Pluronic F127. solvent diffusion method.	Intranasal drug delivery provides a route of direct entry of drug to the brain that circumvents the blood–brain barrier. Rizatriptan benzoate loaded solid lipid nanoparticles could be a promising approach to delivering the drug. The half life of optimized formulation was found to be increases as compared to the drug solution administered intravenously.	Anjita Singh (2015)
5.	Formulation of rizatriptan benzoate sublingual tablets prepared by direct compression with different bioadhesive polymer: in vitro and ex vivo evaluation[21]	Sublingual tablet	Asial journal of pharmaceutical and clinical research.	sodium carboxymethyl cellulose, hydroxyl propyl methyl cellulose-K4M, and chitosan, sodium starch glycolate (SSG) or cross carmellose sodium (CCS). Direct compression method.	The results obtained from the study showed that the bioavailability problem of the drug has been solved as the drug is given by sublingual route and it directly enters into systemic circulation. Furthermore, the formulation overcomes the problems associated with migraine attack as fast disintegrating technology is used.	HARMANPREET SINGH (2017)

4. Frovatriptan[22] :

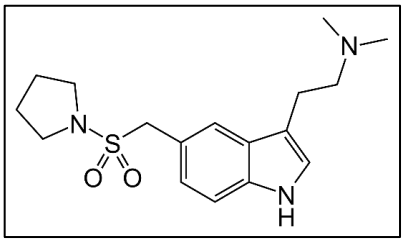


Properties	
IUPAC Name	(+)-(*R*)-3-Methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole
Chemical formula	$C_{14}H_{17}N_3O$
Molar mass	243.310 g·mol^{-1}
Solubility	1.9X10+4 mg/L at 25 °C
BCS class	Class – III
Medical uses	Migraine
Formulations till now	Tablets

Formulation of Frovatriptan:

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	TPGS stabilized sublingual films of frovatriptan for the management of menstrual migraine: Formulation, design and antioxidant activity[23]	Sublingual films	Journal of Drug Delivery Science and Technology	Frovatriptan succinate monohydrate (FSM), Transcutol®HP and Hydroxyethylcellulose, , Gattefose, TPGS (D-alfa-Tocopherol PEG 1000 succinate), chitosan, Polysorbate 80 and Tri- chloroacetic acid, potassium feericyanide, Acetonitrile and methanol. Method : conventional solvent casting method.	HEC, FSM and TPGS were used to develop films for sublingual delivery of hydrophilic drugs such as FSM in migraine patients with nausea or swallowing difficulties during an attack. The films have satisfactory physico-mechanical properties, good mucoadhesive strength, fast drug release and maximum permeation without causing any damage to the mucosa. Further work is in progress to support the obtained results by pharmacokinetic and pharmacodynamic studies in suitable animal model.	Harmanpreet Singh (2017)
2.	Intranasal Drug Delivery of Frovatriptan SuccinateeLoaded Polymeric Nanoparticles for Brain Targeting [24]	Intranasal polymeric nanoparticles	Journal of Pharmaceutical Sciences	Polyvinyl alcohol, PLGA 50:50 (lactide:glycolide ratio), Span80. Method : Double emulsion (w/o/w) method.	FS PNPs were formulated successfully, and various characterization techniques like SEM, AFM confirmed spherical nature. Hydrophillic molecule of FS was entrapped in PNP to achieve burst action followed by controlled and targeted delivery. Brain targeting was effectively achieved by intranasal delivery using PNI.	Deepika Deepika (2018)
3.	Development Of Frovatriptan Succinate Microemulsion For Nasal Delivery: Optimization, In Vitro And In Vivo Evaluation [25]	Microemulsion for nasal delivery.	Asian journal of pharmaceutical and clinical research.	Frovatriptan succinate, Capmul MCM, Cremophor EL and Cremophor RH 40, Labrafil M 2125 CS, Maisine 35–1, and Plurol Oleique, Tween 80, propylene glycol, and PEG 400,	Microemulsion of said composition was found to be enhancing delivery of frovatriptan succinate to brain tissues through nasal route.	Upendra C Galgatte1, Pravin D Chaudhari (2019)

5. Almotriptan[26] :



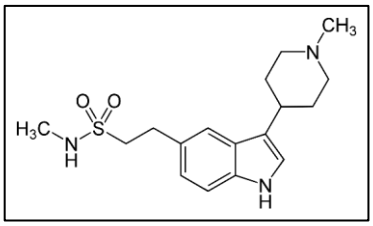
Properties	
IUPAC Name	*N*,*N*-dimethyl-2- [5-(pyrrolidin-1-ylsulfonylmethyl)- 1*H*-indol-3-yl]-ethanamine
Chemical formula	$C_{17}H_{25}N_3O_2S$
Molar mass	335.47 g·mol^{-1}
Solubility	1.21e-01 g/L
BCS class	Class – III
Medical uses	Migraine
Formulations till now	Tablet

Formulation of Almotriptan:

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1	Mucoadhesive buccal film of almotriptan improved therapeutic delivery in rabbit model[27]	Buccal film	Saudi Pharmaceutical Journal	Proloc 15, Eudragit RL 100 and Eudragit RS 100, Propylene glycol, polyvinylpyrrolidone, polyethylene glycol 400 (PEG 400), methanol, ethyl cellulose, acetone, isopropyl alcohol, dibutyl phthalate and polyvinyl pyrrolidone. onventional solvent casting technique.	A study has shown the feasibility of the buccal delivery of almotriptan. Physicomechanical properties, mucoadhesion and percentage hydration exhibited by FA1-FA4 films were found ideal for the treatment of migraine. The study demonstrated the benefit of trans-mucosal administration for the pharmacotherapeutic management of migraines..	Anroop B Nair (2019)
2	Flash Dissolving Sublingual Almotriptan Malate Lyotabs For Management Of Migraine[28]	Flash dissolving sublingual tablet	International Journal of Pharmacy and Pharmaceutical Sciences	Polyvinyl pyrrolidone (PVP K25), chitosan, sodium alginate, Polyvinyl alcohol (PVA), Mowiol® 40-88:, Mannitol, etc. Lyophilization (freeze-drying technique)	Almolyotab (F8) is a promising formulation, prepared easily by lyophilization technique, utilising safe polymers. In vitro disintegration time within 1.85 sec, and complete drug release within one minute. F8 formulation would be an alternative to conventional almotriptan oral formulations, owing to instant absorption in the sublingual area.	Abeer Ahmed Kassem (2017)

3	Effect of iontophoresis on in vitro transdermal absorption of almotriptan[29]	Trasderm -al patch	International Journal of Pharmaceutics	Acetonitrile, ammonium di-hydrogen phosphate, Orto-phosphoric acid, HEPES (N-[2-Hydroxiethyl] piperazine-N -[2-ethanesulfonic acid]), NaOH, HCl analytical grade and silver chloride (99%), silver, and platinum wire 1 mm (both 99.9%), agarose, etc.	The application of a current density of 0.50 mA/cm2 produces a statistically significant increment with respect to a passive control (411-fold). The results obtained in vitro are promising, but further work in vitro should be carried out to ensure that therapeutic blood levels of almotriptan can be achieved using iontophoresis.	M.A. Calatayud-Pascual(2011)
4	Formulation and evaluation of almotriptan chewable tablets[30]	Chewabl e tablet	International journal of pharmacy and analytical research	Crospovidone, Croscarmellose, Sodium starch glycollate, etc.	The above results suggest that the formulated immediate release tablets of Almotriptan exhibited good physical parameters. The overall results indicated that formulation F6 with croscaramellose (7.5%) had a higher edge compared to other formulations containing super disintegrants and palatability is good. They satisfy all the criteria for chewable release tablets. This direct compression process is simple, reproducible and robust to prepare chewable release tablets of almotriptan and other anti-migraine drugs.	V. Anil kumar (2016)
5	A novel nasal almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: Preparation, characterization and in vivo evaluation[31]	Gel	International Journal of Pharmaceutics		SLNs are a good candidate for ALM nose to brain targeting, as it showed obvious fast ALM brain delivery. Tmax /brain was 10 min., Cmax/brain was double that of ND (Free ALM based) and I.V. The achieved out comings are encouraging for further clinical trials of the developed system in humans.	Nancy Abdel Hamid Abou Youssef (2018)

6. Naratriptan[32] :



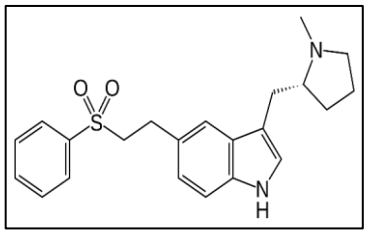
Properties	
IUPAC Name	N-methyl-2-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]ethanesul fonamide
Chemical formula	$C_{17}H_{25}N_3O_2S$
Molar mass	335.47 g·mol^{-1}
Solubility	35 mg/mL
BCS class	Class – III
Medical uses	Migraine
Formulations till now	Tablet

Formulation of Naratriptan:

SR. No.	Title of paper	Type of formulat-ion	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Oral transmuco-sal delivery of naratriptan [33]	Oral tablet	International Journal of Pharma-ceutics	Transcutol P1 (TC), ethanol, Methocel1 60 HG (MC), and polyethylene glycol 400 (PEG 400), Dipropylene glycol (DPG),	The study builds on our previous work which characterised NAR base and investigated its permeation in excised porcine buccal tissue. The combination of TC with MG did result in significantly enhanced permeation of NAR compared with TC alone. These findings underline the importance of monitoring vehicle components in the development of optimal formulations for oral transmucosal delivery.	Mohammed Sattar (2016)
2.	Formulation and evaluation of thermo-reversible mucoadhesiv e in situ gel for intranasal delivery of Naratriptan hydrochlorid e[34]	Intranasa l Gel	Journal of Drug Delivery Science and Technology	NH, Poloxamer 407, Carbopol 934 and cellophane membrane (12,000–14,000 M.W), etc.	Intranasal gel of NH could be a better alternative to existing conventional dosage form to improve drug bioavailability and patient compliance. In-vitro release and ex-vivo permeation studies suggest that carbopol not only acts as mucoadhesive agent, but also as a penetration enhancer.	Mr. Santosh Shelke (2015)

3.	Formulation and evaluation of sublingual strips of naratriptan [35]	Sub-lingual strips	Indo American Journal of pharmaceutical sciences	hydroxyl propyl methyl cellulose like HPMC E5, HPMC E15 and HPMC E50, etc. solvent-casting method.	the film, based on data obtained from in-vitro dissolution, that B1 is a promising formulation for the immediate release of the drug. It can be accomplished that sublingual films can be possible novel drug dosage form for pediatric, geriatric, and general people. Hence fast dissolving films of naratriptan were found to be suitable for better therapeutic effect in the treatment of migraine.	Naresh Kshirasagar (2019)
4.	Formulation development and optimization of fast orodispersible tablets of naratriptan hydrochloride by using factorial design[36]	Orodispersible tablet	Int J Res Med	: Naratriptan hydrochloride, sodium starch glycolate (SSG), croscarmellose sodium (CCS), polacrellin potassium (kyron-T314), talc, citric acid, mannitol, avicell pH 102, mannitol magnesium stearate, sodium steryfumret, etc. Factorial design.	Superdisintegrating tablets can accelerate disintegrating of tablets under their ability to absorb a large amount of water when exposed to an aqueous environment. The disintegrating is reported to affect dissolution characteristics as well. There was no difference observed in release profile and drug content after the accelerated Stability study for 1 month.	N.A. Oza (2013)

7) Eletriptan[37] :



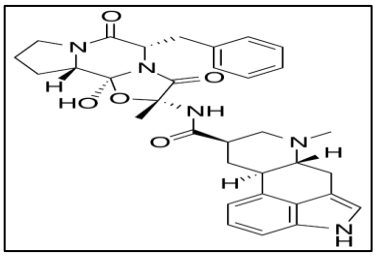
Properties	
IUPAC Name	3-{[(2*R*)-1-methylpyrrolidin-2-yl]methyl}-5-[2-(benzenesulfonyl)ethyl]-1*H*-indole.
Chemical formula	$C_{22}H_{26}N_2O_2S$
Molar mass	382.52 g·mol^{-1}
Solubility	1.18e-03 g/L
BCS class	Class – III
Medical uses	Migraine
Formulations till now	Tablet

Formulation of **Eletriptan:**

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Nose to brain delivery of eletriptan hydrobromide nanoparticles: Preparation, in vitro/in vivo evaluation and effect on trigeminal activation[38]	Nasal Nanoparticle	Journal of Drug Delivery Science and Technology	Eletriptan Hydrobromide (EH), PLGA (lactide: glycolide, Polyvinyl alcohol, Dialysis membrane. W/O/W emulsion–solvent evaporation method.	In this study, preparation, P-gp inhibition, and antimigraine efficacy of polymeric nanoparticles of EH were investigated. As the pH of the water phase is changed, different drug encapsulations were observed ($p < 0.05$). Intranasal administration was found to be more effective than intravenous injection in the treatment of migraine.	Ozgur Esim (2020)

B) Ergot Alkaloids :

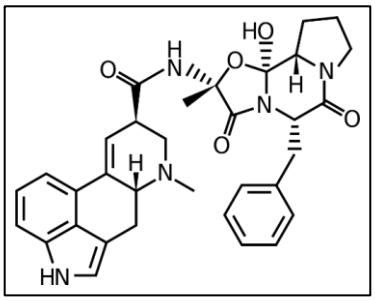
1) Dihydroergotamine[39] –



Properties	
IUPAC Name	(2*R*,4*R*,7*R*)-*N*-[(1*S*,2*S*,4*R*,7*S*)-7-benzyl-2-hydroxy-4-methyl-5,8-dioxo-3-oxa-6,9-diazatricyclo[7.3.0.$0^{2,6}$]dodecan-4-yl]-6-methyl-6,11-diazatetracyclo[7.6.1.$0^{2,7}$.$0^{12,16}$]hexadeca-1(16),9,12,14-tetraene-4-carboxamide.
Chemical formula	$C_{33}H_{37}N_5O_5$
Molar mass	583.689 g·mol^{-1}
Solubility	2.29g/L
Formulations till now	Transdermal patch

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Dihydroergotamine mesylate-loaded dissolving microneedle patch made of polyvinylpyrrolidone for management of acute migraine therapy[40]	Microneedle patch	Journal of Controlled Release	DHE, caroverine HCI, polyvinylalcohol, Sucrose, Gentian violet, Optical Microscope, etc.	DHE delivery using MNPs had a pharmacokinetic profile similar to SC injection, as determined by no statistically significant difference in tmax and AUC. DHE delivery was facilitated by formulation with PVP, which is believed to enable rapid dissolution of microneedles due to the high water solubility of PVP.	Cetin Tas (2017)
2.	Influence of oleic acid and other permeation promoters on transdermal delivery of dihydroergotamine through rabbit skin[41]	Transdermal Delivery DHE	International Journal of Pharmaceutics	Dihydroergotamine mesylate, propylene glycol, oleic acid, lauric acid, urea, procaine hydrochloride, propyl hydroxy-4-benzoate, sodium chloride, glycine and hydrochloric acid, methanol, acetonitrile.	In conclusion, this investigation provides useful information about penetration enhancers, which could be utilized in the development of clinically acceptable transdermal therapeutic systems for DHE in the future. Additional studies are currently underway to investigate various transdermal formulations of DHE in vivo.	Esmail M. Niazy (1990)

2) Ergotamine[42] -



Properties	
IUPAC Name	(6a*R*,9*R*)-*N*-((2*R*,5*S*,10a*S*,10b*S*)-5-Benzyl-10b-hydroxy-2-methyl-3,6-dioxooctahydro-2*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-2

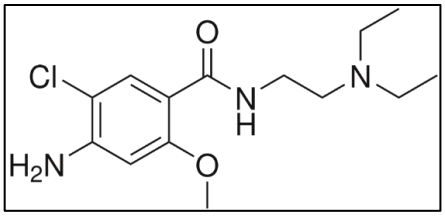
	-yl)-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide.
Chemical formula	$C_{33}H_{35}N_5O_5$
Molar mass	581.673 g·mol^{-1}
Solubility	2.91 mg/L at 25 °C
Medical uses	Acute migraine headache
Formulations till now	Buccal tablet

Formulation of **Ergotamine** -

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Buccal absorption of ergotamine tartrate using the bioadhesive tablet system in guinea-pigs[43]	Buccal tablet	International Journal of Pharmaceutics	ET, Sodium caprate (CA) and glycocholic acid sodium salt (GC), polyoxyethylene octylphenyl, carboxy vinyl polymer, Polyoxyethylene hydrogenated castor oil, Cod-liver oil extract (CLOE), white petrolatum 25%, stearyl alcohol 20%, propylene glycol 12%, HCO 60 4%, glycerine monostearate 1%, p-methyl hydroxybenzoate 0.1%, p-propyl hydroxybenzoate 0.1%, purified water 37.8%;, macrogol 1500, polyethylene glycol 1500 100%, caprylic acid and stearic acid,	The in vitro buccal ET absorption was significantly greater than that of oral administration in guinea pigs. Although many kinds of purified fatty acid have strong potency of enhancing drug permeation in various membranes, their harmfulness remains too problematic. CLOE derived from a natural marine product with absorption enhancing capability is feasible to fulfill this requirement.	Keiko Tsutsumi (2002)

C. Other drugs

1. Metochlopramide[44] -

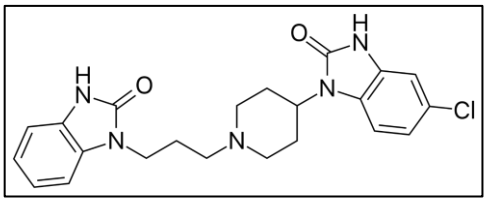


Formulations of Metoclopramide:

Properties	
IUPAC Name	4-Amino-5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxybenzamide
Chemical formula	$C_{14}H_{22}ClN_3O_2$
Molar mass	299.80 g·mol^{-1}
Solubility	0.02 g/100 mL at 25 °C
BCS class	Class III
Medical uses	Nausea, Migraine, Gastroparesis, Lactation
Formulations till now	Gel, Nasal solution

Sr. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Metoclopramide hydrochloride thermally sensitive rectal in situ gelling system, a novel out-patient treatment for vomiting in pediatric age[45]	Rectal in-situ gel	Journal of Drug Delivery Science and Technology	Metoclopramide HCL, Poloxamer 407 (P407) and Hydroxypropylmethylcellulose (HPMC K15 M), Polyvinylpyrrolidone (PVP) and Hydroxyethylcellulose (HEC), Disodium hydrogen phosphate and Potassium dihydrogen phosphate, rtho phosphoric acid (OPA) and triethylamine (TEA), Acetonitrile (HPLC grade), etc. cold method.	MET HCL loaded LSs were formulated, characterized and examined for their effectiveness in delivering MET HCL via rectal route. The pharmacokinetic parameters and statistical analysis showed a significant increase in the Tmax, AUC0–24 and MRT, and decrease in the Cmax of the optimized formula ($p < 0.05$) compared to oral administration.	Amal M. Abd El Razek (2019)
2.	Rapid-onset intranasal delivery of metoclopramide hydrochloride Part I. Influence of formulation variables on drug absorption in anesthetized rats[46]	Nasal solution	International Journal of Pharmaceutics	Metoclopramide hydrochloride, hydroxypropyl methylcellulose, urethane, sodium cholate, sodium deoxycholate, protamine sulphate, poly-l-arginine, chitosan disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, benzalkonium chloride.	In conclusion, the results of this study suggest that the rate of nasal absorption of MCP HCl can be enhanced by: adjusting the pH of the drug solution at 8, incorporation of 0.01% BAC and/or absorption enhancers. Of the various absorption enhancers tested, SDC gave the highest promoting effect and might represent a viable approach to achieving rapid systemic delivery of the antiemetic drug in emergency situations. The possible irritation effect of the different enhancers in addition to a bioavailability study are performed in subsequent work (Part II).	N.M. Zaki (2006)

2. Domperidone[47]



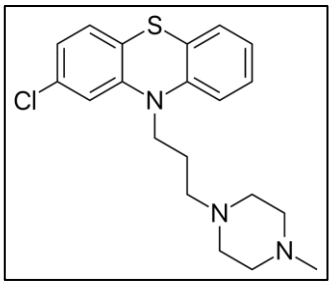
Properties	
IUPAC Name	5-Chloro-1-(1-[3-(2-oxo-2,3-dihydro-1*H*-benzo[*d*] imidazol-1-yl)propyl] piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one
Chemical formula	$C_{22}H_{24}ClN_5O_2$
Molar mass	425.92 g·mol^{-1}
Solubility	0.986 mg/L
BCS class	Class III
Medical uses	Nausea and Vomiting, Gastroparesis, Parkinson's disease, Functional dyspepsia, Lactation, Reflux in children.
Formulations till now	Tablet, gel, pellets, etc.

Formulation of Domperidone :

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Chitosan-ethyl cellulose microspheres of domperidone for nasal delivery: Preparation, in-vitro characterization, in-vivo study for pharmacokinetic evaluation and bioavailability enhancement[48]	Intranasal Microsphere	Journal of Drug Delivery Science and Technology	DOM, sodium hydroxide & sodium chloride, Chitosan, Ethylcellulose, methanol, ethanol, and hexane, Acetonitrile and methanol, etc. emulsion solvent evaporation technique.	Microspheres formulation was developed by the solvent evaporation technique using CH as a mucoadhesive and EC as a drug release controlling polymer. Findings of in-vivo studies confirmed the enhanced bioavailability of DOM in form of microspheres administered nasally as compared to DOM-Sol administered orally and Com-tab administered orally.	Ameeduzz afar Zafar (2021)
2.	Development of nanostructured lipid carriers for intaoral delivery of domperidone[49]	Intraoral lipid carriers	International Journal of Pharmaceutics	Domperidone, NLC isopropylpalmitate, glycerol monostearate, isopropylmyristate, palmitic acid, oleic acid, sesame oil and soybean oil, tween 20 & 80, methanol, ammonium acetate, fetal bovine serum (FBS), penicillin streptomycin, and phosphate buffered saline, etc. Lipid screening.	Tween 80 in the concentration of 2% (w/w) was found to be the most appropriate stabilizer for the preparation of NLC. A mean diameter of around 280 nm was obtained for Domperidone NLC and a zeta potential higher than -30 mV was observed over a period of 28 days indicating physical stability over the investigated time. In-vitro and ex vivo studies showed that NLC were actively internalized by the cells without causing adverse side effects and were able to penetrate/permeate the tissue of the buccal epithelium. This leads to the conclusion they are suitable drug delivery systems for the transport of poorly soluble active candidates into/across the oral mucosa.	Carolin Tetyczka (2017)

3.	Development and in vitro evaluation of domperidone/Dowex resinate embedded gastro-floatable emulgel and effervescent alginate beads[50]	Floatable emulgel	Journal of Drug Delivery Science and Technology	Millipore deionized water, Domperidone maleate, Dowex 50WX2, HPLC grade acetonitrile solvent, Sodium chloride, sodium bicarbonate, monopotassium phosphate, hydrochloric acid, sodium phosphate dibasic dodecahydrate, sodium alginate, light mineral oil, calcium chloride, and tween 20. Single batch process used.	Gastro-floatable beads embedded with domperidone/Dowex 50WX2 resinate complex. Developed effervescent alginate beads containing 10% NaHCO3 and emulgel beads with 10% light mineral oil showed excellent buoyancy behavior. Resinate complex appears to be more beneficial in achieving sustained drug release with no burst.	Baher A. Daihom (2020)
4.	In vitro and in vivo characterization of domperidone-loaded fast dissolving buccal films[51]	Fast dissolving buccal film	Saudi pharmaceutical journal	Domperidone, Polyvinyl pyrrolidone K-90, PEG 400, Ethyl alcohol and tween 80, etc. Solvent casting method.	In this work, we designed and successfully produced fast dissolving flexible buccal films containing DMP using highly water soluble excipients. The film showed short Tmax, high Cmax, large absorption rate constant (Ka) and enhanced relative bioavailability. Fast dissolving oral film stands as a promising dosage form for the transmucosal delivery of DMP.	Gamal M. Zayed (2020)
5.	Multiple Unit Pellet System (MUPS) based fast disintegrating sustained release tablets for Domperidone delivery[52]	Sustained release pellets	Journal of Drug Delivery Science and Technology	Domperidone Maleate, Avicel® and Ac-Di-Sol®, Lactose monohydrate, Magnesium stearate, isopropyl alcohol, methanol, Acetonitrile and Hydrochloric acid. Domperidone loaded pellets were prepared by Extrusion-spheronization, drug layering on sugar sphere and MCC sphere were prepared.	Multiple Unit Pellet System (MUPS) of Domperidone shows great potential in terms of hardness, rapid disintegration property, unaltered release profile and in converting them to suitable tablet dosage form. Different types of tableting excipients were combined to get better compressibility of pellets. Combination of Ceolus granules with Ludipress found to be having great potential to function as tablets excipient for MUPS. Various factors like property of pellets to be compressed, coating type & level, type and composition of tabletting excipient and ratio of drug loaded pellets to tablets were identified and optimized.	Sandipkumar A. PateL (2018)

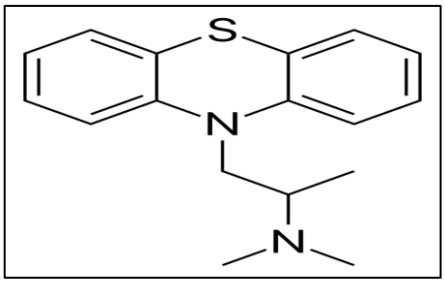
3. Prochlorperazine[53]



Properties	
IUPAC Name	2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10*H*-phenothiazine
Chemical formula	$C_{20}H_{24}ClN_3S$
Molar mass	373.94 g·mol^{-1}
Solubility	1.496X10-2 g/L (14.96 mg/L) at 24 ℃
BCS class	Class II
Medical uses	Nausea, Vomiting, Schizophrenia, Anxiety, Migraine, Labyrinthitis.
Formulations till now	Tablets, injection, etc.

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	In vitro and in vivo characteristics of prochlorperazine oral disintegrating film[54]	Oral disinter-grating film	International Journal of Pharmaceutics	Prochlorperazine maleate, Microcrystalline cellulose, polyethylene glycol, polysorbate 80, hydroxypropyl cellulose, hydroxypropylmethyl cellulose.	The film preparation met the criteria of AV in the dosage uniformity test for JP15 and USP27. In rats, plasma concentration of prochlorperazine increased after the topical application of the film preparation to the oral cavity (5 mg). Pharmacokinetic parameters were not significantly different between the two groups, although the bioequivalence was not shown.	Misao Nishimura (2009)
2.	Intramuscular Prochlorperazine Versus Metoclopramide as Single-Agent Therapy for the Treatment of Acute Migraine Headache[55]	IM Injection	American Journal Of Emergency Medicine		Intramuscular prochlorperazine was found to be significantly more effective than metoclopramide for the treatment of acute migraine headache. Therapy with prochlorperazine also provided greater relief from associated nausea and vomiting. However, the need for rescue analgesia in the majority of our study population does not recommend intramuscular prochlorperazine or metoclopramide as singleagent therapy for acute migraine headache.	Jeffrey Jones (1995)

4. Promethazine[56] :



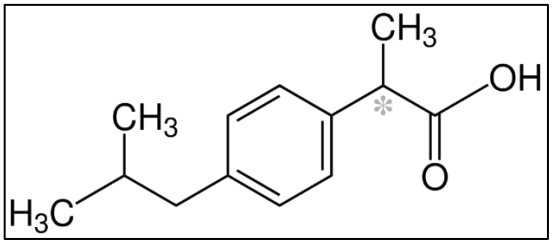
Properties	
IUPAC Name	(*RS*)-*N*,*N*-Dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine
Chemical formula	$C_{17}H_{20}N_2S$
Molar mass	284.42 g·mol^{-1}
Solubility	1.56X10-2 g/L (15.6 mg/L) at 24 °C
BCS class	Class I
Medical uses	Nausea, Allergies, Difficulty in sleeping, Migraine.
Formulations till now	Tablets, suppository, orodispersible film, etc.

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion
1.	Biophysical investigation of promethazine hydrochloride binding with micelles of biocompatible gemini surfactants: Combination of spectroscopic and electrochemical analysis[57]	Micelles	Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy	Dichloride, 2,2′-[(oxybis(ethane-1,2-diyl))bis(oxy)]bis(N-tetradecyl-N,N-dimethyl-2-oxoethanaminium) dichloride (C14-E2O-C14, CMC = 0.0078 mM) and 2,2′-[(oxybis(ethane-1,2-diyl)) bis(oxy)]bis(N-hexadecyl-N,N-dimethyl-2-oxoethanaminium) dich loride (C16-E2O-C16, CMC = 0.0062 mM, Promethazine hydrochloride, etc.	Cationic gemini surfactants with varying alkyl chains (Cm-E2O-Cm, m = 12, 14 and 16) have relatively lower toxicity and far better biodegradability, which make them a strong potential tunable contender for drug carriers. The binding interactions were found to be endothermic, spontaneous and primarily controlled by hydrophobic forces as manifested through thermodynamic parameters. These new cationics can serve the required purpose in biological, pharmaceutical and other related fields.
2.	Morphological evolution of nanosheets-stacked spherical ZnO for preparation of GO-Zn/ZnO ternary nanocomposite: A novel electrochemical platform for nanomolar detection of	Nanosheets	Journal of Alloys and Compounds	Promethazine hydrochloride, sodium hydroxide (NaOH), sulfuric acid (H2SO4), 30% hydrogen peroxide (H2O2), and 37% hydrochloric acid (HCl), glucose ($C_6H_{12}O_6$), ascorbic acid (C6H8O6), hydroquinone (C6H6O2), tryptophan (C11H12N2O2), sodium dihydrogen phosphate (NaH2PO4), disodium monohydrogen phosphate (Na2HPO4) and cysteine (C3H7NO2S), Phosphoric acid	An economical and efficient electrochemical sensor to detect the antihistaminic drug PMTZ was developed based on a novel GO-Zn/ZnO ternary nanocomposite. Morphologically varied ZnO nanostructures were successfully obtained using an aqueous solution approach by regulating the molar concentration of the base. This study may offer new insights into development of highly

	antihistamine promethazine hydrochloride[58]			(H3PO4), potassium permanganate (KMnO4), zinc nitrate hexahydrate (Zn(NO3)2·6H2O), sodium chloride (NaCl), magnesium nitrate hexahydrate (Mg(NO3)2·6H2O), sodium nitrate (NaNO3), anhydrous ethanol (C2H5OH), acetonitrile (C2H3N), and anhydrous ether (C4H10O), etc.	sensitive electrochemical sensors.
3.	Nano-engineering chitosan particles to sustain the release of promethazine from orodispersables[59]	Oro-dispersible film	Carbohydrate polymer	Promethazine hydrochloride, chitosan, Sodium tripolyphosphate, Polyethylene glycol PEG, Polyvinylpyrrolidone, polyethylene co acrylic acid, Magnesium stearate fluka, D (+)-Lactose Monohydrate, hydroxypropoxy content, etc. ionotropic gelation method	The properties of CS nanoparticles was engineered using Minitab in order to manufacture a new formulation of SR-ODTs. The nanoparticles were further characterised using SEM which revealed that all the samples were spherical in shape with smooth surface and had particle size ranging between 100- 200 nm. All tablets had passed the friability test and showed good tensile strength despite disintegrating in less than 40sec. The drug release profile was studied in 0.01M HCL solution showing that tablets containing PVP and PEG coated nanoparticles managed to sustain the drug release over 24hr, yet showed a slight toxic effect on Caca-2 cell lines at high concentrations.
4.	Formulation of sublingual promethazine hydrochloride tablets for rapid relief of motion sickness[60]	Sublingual tablet	Saudi Pharmaceutical Journal	Promethazine hydrochloride, Sodium stearyl fumarate, spray-dried mannitol, MannogemTM EZ, Spray-dried lactose monohydrate, crospovidone, etc. direct compression method.	High drug solubility stands as an obstacle because of the drug's bitter taste. Eudragit E100 was added to improve drug taste, in addition to SSF as a lubricant and taste-masking agent. The analysis of variance revealed that all the independent variables had a significant effect on the hardness, disintegration time, and dissolution efficiency.
5.	Bioequivalence and Pharmacokinetic Profile of Promethazine Hydrochloride Suppositories in Humans[61]	Suppositories	Journal of Pharmaceutical Sciences	Promethazine hydrochloride, phenothiazine monohydrochloride, trifluopromethazine, etc.	The promethazine polyethylene glycol suppositories evaluated appeared to have rapid dissolution in vivo. They produce serum promethazine concentrations comparable to an oral promethazine solution, and the relative bioavailability is approximately the same as the oral solution. Thus, in practice, these suppositories would act as a reliable dosage form for rectal promethazine administration.

D) NSAIDS :

1. Ibuprofen[62]



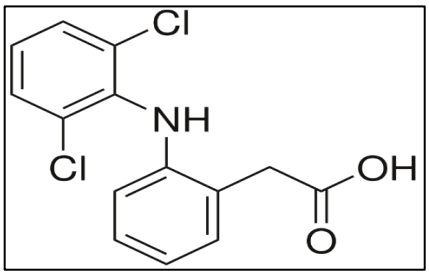
Properties	
IUPAC Name	(*RS*)-2-(4-(2-Methylpropyl)phenyl)propanoic acid
Chemical formula	$C_{13}H_{18}O_2$
Molar mass	206.285 g·mol^{-1}
Solubility	0.021 mg/mL (20 °C)
BCS class	Class II
Medical uses	Lysine, Painful menstrual periods, Migraine, Rheumatoid Arthritis.
Formulations till now	Tablet, Capsule, Emulsion, Nanogel, Patch, etc.

Formulations of Ibuprofen:

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen[63]	Mucoadhesive tablet	International Journal of Pharmaceutics	Chitosan, ibuprofen, Pig gastric tissue, Acetic acid, acetic anhydride, ethanol, acetone, etc.	Formulation of such a carrier–drug complex may have beneficial effects on the absorption of poorly water soluble drugs. Chitosan is known to enhance permeation in the gastrointestinal tract by opening tight junctions and by prolonging the contact of the drug with the membrane through its mucoadhesive nature. In this work, drug formulations were prepared by spray-drying and by physical co-grinding. Drug loading in microparticles was 41%, close to the theoretical load of 50% and was higher than HACHI (32%) due to the higher charge density.	Ioannis A(2012)
2.	Comparison of ibuprofen release from minitablets and capsules containing ibuprofen: b-Cyclodextrin complex[64]	Mini tablet and capsule	European Journal of Pharmaceutics and Biopharmaceutics	Ibuprofen, lactose, MCC, b-cyclodextrin, Hydroxypropylmethyl cellulose capsule shells, Hydrochloric acid, phosphate buffer, etc.	Inclusion complexes between a model drug, ibuprofen and b-cyclodextrin was possible. The complex can be formed with different amounts of water: from small amounts (30%, w/w) to a solution, remaining stable after drying. All mixtures of powder have shown poor flow abilities (Carr's index and angle of repose), implying that glidants must be added to these powders.	P.J. Salústio (2011)

3.	Colloidal nanodispersions for the topical delivery of Ibuprofen: Structure, dynamics and bioperformances[65]	Nano-emulsion	Journal of Molecular Liquids	Propionic acid, Polyoxyethylene sorbitan monoolate, 5-Doxyl stearic acid, chitosan, ethanol, 2-propanol, methanol and acetonitrile, etc.	Two O/W colloidal nanodispersions, a microemulsion and a nanoemulsion, were developed and studied as delivery vehicles for the topical administration of ibuprofen. The nanoemulsions showed a good stability profile for 2 months while their droplet size was not altered after the addition of the drug. Both systems can be used for topical administration of ibuprofen but the hydration level and droplet size can be correlated to the effective penetration of the formulations through skin. Microemulsions provide better storage conditions for the encapsulated compound due to its thermodynamic stability and an increased release rate from the droplets.	I. Thech ari (2021)
4.	Ex vivo skin permeation and retention studies on chitosan–ibuprofen–gellan ternary nanogel prepared by in situ ionic gelation technique—a tool for controlled transdermal delivery of ibuprofen[66]	Nanogel	International Journal of Pharmaceutics	Ibuprofen, chitosanand pytagel, double distilled water, polymers, etc.	Strong interaction between the carboxylate ion of ibuprofen and the protonated amino group of chitosan leads to formation of a new eutectic product with remarkable decrease in particle size. This simplicity of the technique used in this study has demonstrated the potential application of ternary nanogels for drug delivery.	Amos Oluseg un Abioye (2015)
5.	Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen[67]	Transdermal patch	European Journal of Pharmaceutics and Biopharmaceutics	Ibuprofen, Cremophor, poly[butyl methacrylate, (2-dimethylaminoethyl)methacrylate methyl methacrylate], poly(ethyl acrylate, methyl methacrylate, trimethy lammonioethyil methacrylate chloride), etc. The patches were prepared by using a laboratory-coating unit Mathis LTE-S(M) (Mathis, Switzerland) equipped with a blade coater.		Francesco Ciluzzo (2005)

2. Diclofenac[68]



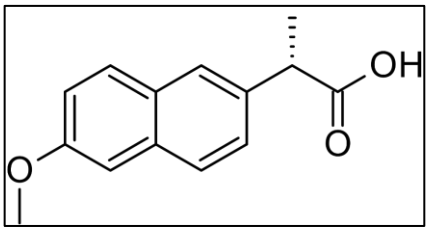
Properties	
IUPAC Name	[2-(2,6-Dichloroanilino)phenyl]acetic acid
Chemical formula	$C_{14}H_{11}Cl_2NO_2$
Molar mass	296.15 g·mol^{-1}
Solubility	2.37 mg/L at 25 °C
BCS class	Class II
Medical uses	Pain reliever, Gout, Migraine.
Formulations till now	Tablet, Patch, Hydrogel, etc.

Formulations of Diclofenac:

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	A novel diclofenac-hydrogel conjugate system for intraarticular sustained re- lease: Development of 2-pyridylamino-substituted 1-phenylethanol (PAPE) and its derivatives as tunable traceless linkers[69]	Sustained release hydrogel	International Journal of Pharmaceutics	Phosphate buffered saline, Bovine synovial fluid, methoxypoly(ethyleneglycol), succinimidyl carboxy methyl ester, hexa-glycerine, octa-poly(ethylene glycol) ether, succinimidyl valerate, p-nitrophenyl carbonate, etc.	A novel class of aminopyridine based diclofenac esters (PAPE), was successfully developed. PAPE can be released from the PAPE system by a tunable self-immolative process. Release rate can be modulated to afford half-lives ranging from 120 to 840 hours in PBS at 37 ºC.	Toshio Kawanami (2020)
2.	Prolonged release from orodispersible films by incorporation of diclofenacloaded micropellets[70]	Micropellets	International Journal of Pharmaceutics	diclofenac sodium, MCC, carmellose sodium, anhydrous colloidal silica, ammonio methacrylate copolymer type B, triethylcitrate, talc, Hypromellose, anhydrous glycerol, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, phosphoric acid 85%, ethanol, etc. wet-extrusion and spheronization.	MPs containing DS, a freely water-soluble drug, were produced by application of a functional film coating consisting of Eudragit RS and RL. The degree of DS release prolongation depended on the applied coating thickness. ODFs with different DS dosages and varying release profiles were realized by incorporating different amounts of either thin-coated or thickcoated MPs into the ODF matrix.	Isabell Speer (2019)

3.	Surfactant-modified natural zeolites as carriers for diclofenac sodium release: A preliminary feasibility study for pharmaceutical applications[71]	Zeolite	Materials Chemistry and Physics	Chabazite, Clinoptilolite, sodium chloride - NaCl (99.5%, Merck); silver nitrate - AgNO3 (99%, Merck); sodium hydroxide - NaOH (99.5%, Merck); monopotassium phosphate - KH2PO4 (99.5%, Merck); cetyltrimethylammonium bromide - CTAB (98%, BDH Chemicals); diclofenac sodium - DS (CAS [15307-79-6], 98%, Alfa Aesar); and distilled water.	DS adsorption tests reveal that an increase in the concentration of CTAB is accompanied by an adsorbed amount of DS. Modifying the surface of natural zeolites provides benefits that promote their use in drug administration. It is necessary to carry out future studies focused on innovation in optimizing the modification process with surfactants.	Adriana M. Vargas (2020)
4.	Characterisation and optimisation of diclofenac sodium orodispersible thin film formulation[72]	Orodispersible thin film	International Journal of Pharmaceutics	Diclofenac sodium, glycerol, spearmint mild flavour, pearmint mild flavour, sucralose, hydroxypropyl methyl cellulose, etc.	Here, we have succusfuly formulated an oral thin films fo diclofenac sodium which dissolved rapidly with excellent taste masking of diclofenac sodium. The film was strong enough to withstand any mechanical handling. This formulated OTF was able to achieve rapid release of diclofenac sodium within 15 minuts after administration. This OTFs are ideal for patients with swallowing difficulties such as elderly and pediatric patients.	Ibrahim Khadra (2019)
5.	Topical Diclofenac Patch Relieves Minor Sports Injury Pain: Results of a Multicenter Controlled Clinical Trial[73]	Transdermal patch	Journal of Pain and Symptom Management		In conclusion, this multicenter controlled clinical trial demonstrates the efficacy and safety of a topical diclofenac epolamine patch for the treatment of pain due to acute minor sports injury over a 2-week treatment period. This novel pharmacotherapeutic delivery system has several important clinical advantages over currently available drug treatments, including its ease of use and lack of systemic activity and systemic side effects.	Bradley S. Galer (2000)

3. Naproxen[74]



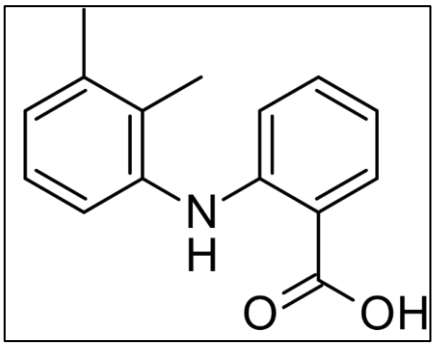
Properties	
IUPAC Name	(+)-(*S*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid
Chemical formula	$C_{14}H_{14}O_3$
Molar mass	230.263 g·mol^{-1}
Solubility	15.9 mg/L at 25 °C
BCS class	Class II
Medical uses	Menstrual cramps, Rheumatoid arthritis, Gout, Fever, etc.
Formulations till now	Tablet, powder, etc.

Formulations of Naproxen -

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Formulation of co-amorphous systems from naproxen and naproxen sodium and in situ monitoring of physicochemical state changes during dissolution testing by Raman spectroscopy[75]	Co-amorphous system	International Journal of Pharmaceutics	Crystalline naproxen, crystalline anhydrate, crystal forms of naproxen, etc. Ball milling.	A study aimed at designing and characterizing a co-amorphous system utilizing naproxen (NAP) and its sodium salt, NAP(Na) It found that an excess amount of each form of the drug led to crystallization of the respective component during preparation or storage. Further formulation studies should be pursued in order to advance this promising strategy.	Hiroshi Ueda (2020)
2.	Tablets and minitablets prepared from spray-dried SMEDDS containing naproxen[76]	Tablets and minitablets	International Journal of Pharmaceutics	Naproxen (NPX), maltodextrin, Hypromellose, MCC, Aerosil® 200, croscarmellose sodium, nausilin, glycerol monooleates (type 40), lauroyl, macrogol-32 glycerides, polyethylene glycol, etc.	Spray-drying process and maltodextrin (MD) exhibited the best self-microemulsifying properties, comparable with liquid SMEDDS. Pressure and pump speed had a major and significant influence on mean droplet size and PDI. DoE can be successfully used for method optimization.	Katja Cerpnjak Alenka Zvonar Pobirk Franc Vreˇcer ˇ Mirjana Gasperlin (2015)

3.	Proniosomal vesicles as an effective strategy to optimize naproxen transdermal delivery[77]	Niosomal vesicles	Journal of Drug Delivery Science and Technology	Naproxen, Soya lecithin, and cholesterol, spans (20, 40, 60, 80), tweens (20, 40, 60, 80), hydroxypropyl methylcellulose (HPMC) K100, potassium dihydrogen orthophosphate, sodium chloride, sodium hydroxide, etc.	Naproxen encapsulated proniosomal gel formulation (F3) contributed highest EE, stability and permeation efficiency, demonstrating 5.3-fold enhancement. Naproxen proniosome gel formulation showed comparable therapeutic efficacy in both anti-inflammatory and antinociceptive effects, as that of oral marketed naproxen tablets at same dose.	Hiral Shah (2021)
4.	The effect of sonication time on the surface morphology and dissolubility of naproxen sodium powders [78]	Powder	Applied Surface Science	Water, ethanol, stearic acid, etc.	Crystalline nature of drug particles was reduced as a result of sonication. Reduction in crystalline status and increased surface of drug would improve its saturation solubility. But, a several of sonicated agglomerates has shown shallow pits on the surface there by decreased dissolubility profile.	Gokhan Savaroglu (2019)
5.	Bioequivalence of 2 Naproxen Sodium Tablet Formulations in Healthy Male and Female Volunteers[79]	Tablet	Current Therapeutic Research		Results support the use of RB naproxen sodium tablets as an alternative to the popular tablet formulation. Both formulations were well tolerated and the incidence of treatment emergent adverse effects was low during the study. There was little difference between the test and reference IMPs in terms of the treatment-related adverse effects profile.	Dalma Sugár (2019)

4. Mefenamic acid[80]



Properties	
IUPAC Name	2-(2,3-dimethylphenyl)aminobenzoic acid
Chemical formula	$C_{15}H_{15}NO_2$
Molar mass	241.290 g·mol^{-1}
Solubility	0.0041 G/100 ML at 25 °C, 0.008 G/100 ML at 37 °C
BCS class	Class II
Medical uses	Rheumatoid arthritis, Osteoarthritis, Menorrhagia, Menstrual pain, Migraine headache.
Formulations till now	Tablet, gel, emulsion, etc.

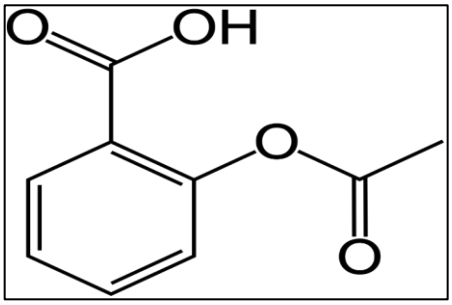
Formulations of Mefanamic acid -

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Formulation and evaluation of mefenamic acid emulgel for topical delivery[81]	Emulgel	Saudi Pharmaceutical Journal	Mefenamic acid, Carbopol 940, dialysis membrane, etc.	In this study, topical emulgels of mefenamic acid were formulated and subjected to physicochemical studies i.e. rheological studies, spreading coefficient studies and bioadhesion strength, in vitro release studies and ex vivo release studies through rat skin. From the in vitro studies, formulation F4 showed maximum release of 56.23% in 240 min.	Rachit Khullar (2012)
2.	In-situ dissolution and permeation studies of nanocrystal formulations with second-derivative UV spectroscopy[82]	In-situ gel	International Journal of Pharmaceutics	MFA, sodium dodecyl sulfate (SDS), and trifluoroacetic acid (TFA), HPMC (Hydroxypropyl methylcellulose TC-5E), GIT-0 lipid (20% w/w phospholipid dissolved into dodecane) and acceptor sink buffer (ASB), etc.	The improved dissolution rate of nanosuspension compared to that of microsuspension could be confirmed with second-derivative UV spectroscopy. The enhanced MFA solubility was evaluated by filtration-HPLC techniques. This combination would be a useful in vitro tool to confirm the superiority of nanocrystal formulations.	Masaaki Imono (2019)
3.	Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology[83]	Oral disintegrating tablets	Journal of Drug Delivery Science and Technology	Mefenamic acid, Eudragit® E PO and Aerosil®, Avicel® 200, Polyplasdone™ crospovidone, Magnesium stearate, etc.	Mefenamic acid was successfully extruded with the various concentrations of Eudragit® E PO using HME technology. The optimized formulations produced very promising solid dispersions for both taste masking and solubility enhancement. The dissolution rate of MA was improved with the increase in the concentration of Euadragit E PO, indicating that MA's solubilization was enhanced.	Sultan M. Alshehri (2015)

4.	A new self-emulsifying formulation of mefenamic acid with enhanced drug dissolution[84]	Self emulsifying formulation	Asian journal of pharmaceutical science	Mefenamic acid, clove oil, olive oil and rice bran oil, Caprylic/capric triglycerides, caprylic/capric glyceride, polyoxy ethylene 20 sorbitan monolaurate (Tween® 20), Polyoxyethylene (20) sorbitan monostearate (Tween® 60 polyoxyethylene 20 sorbitan monooleate (Tween® 80), sorbitan monolaurate (Span® 20) and sorbitan monostearate (Span® 60), etc.	SEF composing of oil, surfactant and co-surfactant was used to improve the dissolution of mefenamic acid. The optimal concentration of components that provided high drug loading was determined using ternary phase diagram. The formulation containing Imwitor, Tween and Transcutol (10:30:60) demonstrated the highest drug dissolution in 45 min, resulting from a fast spontaneous emulsion formation and small droplet size.	Pornsak Sriamornsak (2014)
5.	Investigations on mefenamic acid sustained release tablets with water-insoluble gel[85]	Sustained release tablets	Il Farmaco	Mefenamic acid, Sodium alginate, Calcium gluconate (CaGL), magnesium stearate and talc, Avical pH 101, etc.		S. Gungor (2003)

D) SIMPLE ANALGESICS:

1. Aspirin[86]

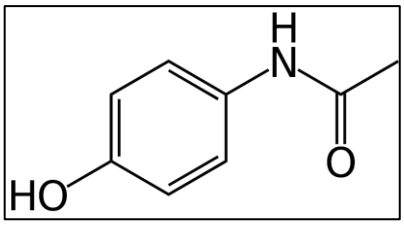


Properties	
IUPAC Name	Aspirin
Chemical formula	$C_9H_8O_4$
Molar mass	180.159 g/mol
Solubility	1 g sol in: 300 mL water at 25 °C
BCS class	Class II
Medical uses	Pain , Fever, Inflammation, Heart attack and stroke, Cancer prevention, Bipolar disorder, Dementia, etc
Formulations till now	Tablet, capsule, injection, hydrogel, emulsion, etc.

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	An injectable and thermosensitive hydrogel: Promoting periodontal regeneration by controlled-release of aspirin and erythropoietin[87]	Injectable hydrogel	Acta Biomaterialia	Chitosan, b-sodium glycerophosphate, gelatin, aspirin, Anti-rat cyclooxygenase-2, anti-rat matrix metalloproteinase-9, Erythropoietin, hydrochloric acid, and NaOH, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphe nyl-2-H-tetrazolium bromide, etc.	CS/b-GP/gelatin hydrogel loaded with aspirin/EPO was successfully prepared and proved to be applicable in periodontium regeneration. Most of the aspirin and EPO in the hydrogels were released in the first 8 days, and continued a sustained release till 21st day. It did not cause any toxicity or side effects either in vitro or in vivo.	Xiaowei Xu (2019)
2.	Anti-inflammatory and analgesic activity of novel oral aspirin-loaded nanoemulsion and nano multiple emulsion formulations generated using ultrasound cavitation[88]	Nano-emulsion	International Journal of Pharmaceutics	propylene glycol monolaurate Type II (LauroglycolTM90), diethylene glycol monoethyl ether (Transcutol HP®), aspirin, . -carrageenan and polyoxy 35 castor oil (Cremophor EL®), etc.	Nanoemulsion and nano multiple emulsion containing aspirin exerts anti-inflammatory and analgesic activity in the above three experimental animal models. This is evidenced by pronounced decrease of paw edema induced by carreegenan as well as significant reduction in the number of writhes and reaction latency respectively.	Siah Ying Tang (2012)
3.	Preparation and characterization of aspirin-loaded polylactic acid/ graphene oxide biomimetic nanofibrous scaffolds[89]	Scaffolds	Polymer	PLA, Natural flake graphite, etc.	A series of ASA-loaded 3D PLA/GO porous biomimetic nanofibrous composite scaffolds was successfully prepared by phase separation. A thin layer of GO covered the surface of the PLA nanofibers, thereby mproving the hydrophilicity and performance of the latter. Improvements in water absorption were beneficial to the bioactivity, cytocompatibility and sustained-release performance of the ASA-loaded composite scaffolds. The prepared	Shuqiong Liu (2020)

					PLA/GO/ASA PBNCSs revealed good sustained drug-release performance and, thus, may have potential applications in drug-loaded bone tissue engineering scaffolds.	
4.	Sustained release of aspirin and vitamin C from titanium nanotubes: An experimental and stimulation study[90]	Nanotubes	Materials Science and Engineering C	Titanium sheets, Stannous octoate (Sn(Oct)2), dichloromethane and Hexane, aspirin tablets, vit C tablet, etc.	Aspirin and vitamin C as model drugs were loaded into TiO2 nanotubes. Low molecular weight PLA was synthesized to act as an embedding material. PLA could retard the release rate of drugs. Only when PLA micelles degrade gradually in bodily fluids, aspirin can be released slowly.	Weihu Yang (2016)

3. Paracetamol [91]



Properties	
IUPAC Name	*N*-(4-hydroxyphenyl)acetamide
Chemical formula	$C_8H_9NO_2$
Molar mass	151.165 g·mol^{-1}
Solubility	10 mg/mL
BCS class	Class II
Medical uses	Pain, Fever, Patent ductus arteriosus, etc.
Formulations till now	Tablet. Oily suspension, solid dispersion, etc.

SR. No.	Title of paper	Type of formulation	Journal name	Material & methods	Conclusion	Author and year of publication
1.	Correlating gastric emptying of amphotericin B and paracetamol solid lipid nanoparticles with changes in	Solid lipid nano-particles	International Journal of Pharmaceutics	Paracetamol, simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), beeswax, Theobroma oil, amphotericin B, Lecithin soy and sodium cholate, Chloroform, ethyl acetate and methanol, etc.	The data obtained indicate that the SLNs after oral ingestion may aggregate in the stomach. However, on reaching the small intestine, both the size and surface charge of the particles would be optimal for absorption. The AmB	Hilda Amekyeh (2017)

	particle surface chemistry[92]			emulsification solvent diffusion technique.	SLNs are therefore a very suitable carrier of AmB for oral delivery.	
2.	In vitro dissolution testing of parenteral aqueous solutions and oily suspensions of paracetamol and prednisolone[93]	Oily suspension	International Journal of Pharmaceutics	paracetamol, prednsiolone and sodium hydroxide, prednisolone-21 hemisuccinate sodium salt, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, medium-chain triglycerides, polyethylengylcol 400, etc.	The choice of dissolution test setup can have a major influence on the obtained test results. In the membrane adapter setup a directed perfusion alongside the adapter is induced. The reciprocating holder offers the opportunity of working with very low media volumes. Sedimentation processes influence the release behavior of drugs applied as oily suspensions.	Mareike Probst (2017)
3.	Fast dissolving paracetamol/caffeine nanofibers prepared by electrospinning[94]	Nanofibers	International Journal of Pharmaceutics	Paracetamol, caffeine, polyvinylpyrrolidone, Ethanol, etc.	Physicists have produced fast-dissolving drug delivery systems for the simultaneous release of paracetamol and caffeine. This was achieved by processing them into electrospun fibers using polyvinylpyrrolidone as the filament forming agent. A flavoring agent can easily be incorporated into the fibers to overcome problems with bitterness.	U. Eranka Illangakoon (2014)
4.	Fabrication of polypyrrole/Au nanoflowers modified gold electrode for highly sensitive sensing of paracetamol in pharmaceutical formulation[95]		Applied Surface Science Advances	Au electrode, chloroauric acid, pyrrole, dimethyl sulfoxide (DMSO), cetrimonium bromide (CTAB), N,O-bis(trimethylsilyl) trifluoroacetamide (BSTFA), trimethylchlorosilane, phosphate-buffered saline, Ammonium persulphate, ethanol, etc.	This paper studied the fabricated PPy/Au nanoflowers modified Au electrode to detect PC and 4AP. Modified electrode offered the advantages of a susceptible electrochemical sensor for detecting PC in real samples. It also offered a promising tool for detecting the presence of 4AP in the paracetamol-based drugs and for quality control application.	Waleed Ahmed El-Said (2020)

5.	Systems biology approach to study permeability of paracetamol and its solid dispersion[96]	Solid dispersion	International Journal of Pharmaceutics	Paracetamol, phosphate buffered saline (PBS)tablets, potassium bromide, ethylenediaminetetraacetic acid (EDTA), agarose, trypan blue, albumin from bovine serum (BSA V), sodium citrate, sodium chloride, formamide, sodium carbonate and sodium bicarbonate, Sodium hydroxide, polyrthylene glycol, etc.	Solid dispersion in PEG 8000 is regarded as highly effective means of increasing the bioavailability of model drug paracetamol. Permeability data analysis showed that drug permeability was higher from solid dispersion when compared to drug alone. The study demonstrated a chemical interaction between the drug and the carrier through hydrogen bonding.	Sheraz Khan (2011)

Conclusion:

Migraine is the most common multidisciplinary and complex neurologic disorder, characterised by recurring headache attacks. Globally, approximately 15% of people are affected by migraine. In this review, we describe recent advances in the treatment of migraine, associated root causes, diagnosis, treatment for migraine. This comprehensive review will briefly describe recent advances in knowledge of this disorder and new formulations relates this disease.

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A REVIEW OF PSYCHOTIC DISORDER: SCHIZOPHRENIA

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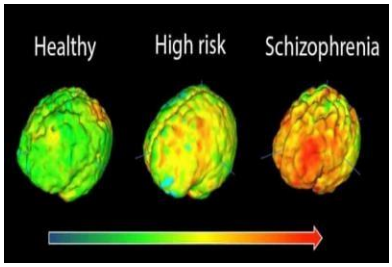
SCHIZOPHRENIA is a psychotic disorder which includes three types predominant public fitness implications. According to diverse sources, it influences as much as 0.3% to 0.7% of the population. The schizophrenia is triggered because of numerous elements including abnormalities in a couple of neurotransmitters, genetic abnormalities and environmental elements which elevate the risk of disease. Antipsychotic drugs are used to cure acute as well as chronic schizophrenia, however they've extra common aspect consequences. Therefore, in current years researchers cantered on maximizing advantages and minimizing negative consequences of drug treatments. Now a days the Ayurvedic drug treatments and nutritional dietary supplements may be introduced to a medicinal-drugs as adjuvant therapy, in order that the healing impact is optimized, without growing the side-effects load. At gift all strategies to the remedy of affected person continue to be experimental, and similarly studies on this region is important. In India, there are numerous rehabilitation centres for diverse sicknesses such as schizophrenia, It includes making use of psychosocial interventions to help people with the contamination to achieve their maximum stage of impartial functioning, most powerful stage of symptom control, and best stage of subjective existence satisfaction.

Introduction:

SCHIZOPHRENIA is psychotic disorder characterized by hallucinations, delusions and disturbances in thoughts, perception and behavioural changes. Traditionally, positive symptoms of schizophrenia are hallucinations, disturbance in thoughts and perception. It has some negative symptoms, such as poverty of speech, lack of motivation and anhedonia. Risk factors includes severe maternal influenza malnutrition, the season of birth, birthing complications, family history, childhood trauma, urbanization, social isolation and cannabis use. The diagnosis of schizophrenia is clinical and made exclusively after obtaining full psychiatric history and excluding other causes of psychosis.[1][2]

To increase the awareness about disorder and educate peoples about this "The World Schizophrenia Day" commemorated on 24th May.[3]

The brain's immune cells are hyperactive in people who are at risk of developing schizophrenia, as well as during the earliest stages of the disease. Microglia are the brain's resident immune cells, which form its first line of defence against infection and injury.



PET imaging in healthy volunteers, high-risk subjects and patients with schizophrenia shows a stepwise elevation in microglial activity (in orange) as the severity of the illness increases.

In such an event, broken neurons emit a misery sign which turns on microglial cells and draws them to the broken or inflamed site, where they continue to engulf and neutralize pathogens, cell debris, and something else this is doubtlessly dangerous or now not needed.[4]

History:

Schizophrenia is a Greek word derived from 'schizo' means splitting and 'phren' means mind, and the term first coined by Eugen Bleuler in in 1908.

Schizophrenia is functional psychotic disorder characterized by presence of delusional beliefs, hallucinations, disturbances in thoughts and behaviour. Due to relative complexity and heterogenicity, the etiology and pathophysiological mechanisms are not fully understood. Due to low prevalence, schizophrenia's global burden of disease is massive. Over half of the patients have co-morbidities, both psychiatric and medical, making it one of the leading causes of disability worldwide. The diagnosis correlates with a 20% reduction in life expectancy, with up to 40% of death attributed to suicide.[5]

About 0.3% to 0.7% of peoples are recognized with schizophrenia at some stage in lifetime. In 2017, there have been an anticipated 1.1 million new instances and in 2019 a complete of 20 million instances globally. In 2015, an anticipated 17000 deaths have been connected to schizophrenia.[6]

Etiology:

The schizophrenia is caused due to several factors such as abnormalities in multiple neurotransmitters, genetic abnormalities and environmental factors associated with enhance the risk of developing disease. The neurotransmitters such as serotonergic, dopaminergic and alpha-adrenergic hyperactivity or GABA hypoactivity causes schizophrenia.

Genetically there is a 46% concordance rate in monozygotic twins and a 40% risk of developing schizophrenia if both parents are affected. The gene neuregulin [NGR1] which is involved in glutamate signalling and brain development, has been implicated and alongside dysbindin [DTNBP1], which helps glutamate release and catecholamine O-methyl transferase polymorphism, which regulate dopamine function.[7]

There are several other factors which enhances the risk of developing the disease are; Gestational diabetes, emergency caesarean section and other birthing complications, abnormal fatal development and low birth weight, winter births (10%high er relative risk) and urban residence (which increase the risk of developing schizophrenia by 2 to 4%).[8]

Diagnosis:

Diagnosis of schizophrenia involves ruling out other mental health disorders and determining that symptoms are not due to substance abuse, medication or a medical condition.

The diagnosis of schizophrenia may include:

- **Physical Exam:** This can be performed to assist rule out different issues that might be inflicting symptoms.
- **Tests and Screenings:** These can also additionally encompass exams that assist rule out situations with comparable symptoms, and screening for alcohol and drugs.
- **Psychiatric evaluations:** A physician or intellectual fitness expert tests the intellectual fitness of sufferers through watching look and asking approximately thoughts, moods, hallucinations, delusions and capability for suicide. Also talk approximately own circle of relatives and private history.[9]

Treatment / management:

- Schizophrenia requires a psychological therapy for lifelong which can help to manage the conditions, even when symptoms have subsided.
- Medications: Most frequently antipsychotic drugs are used for schizophrenia treatment and the main aim to use these drugs are to effectively manage the symptoms. Following medications are prescribed in schizophrenia:

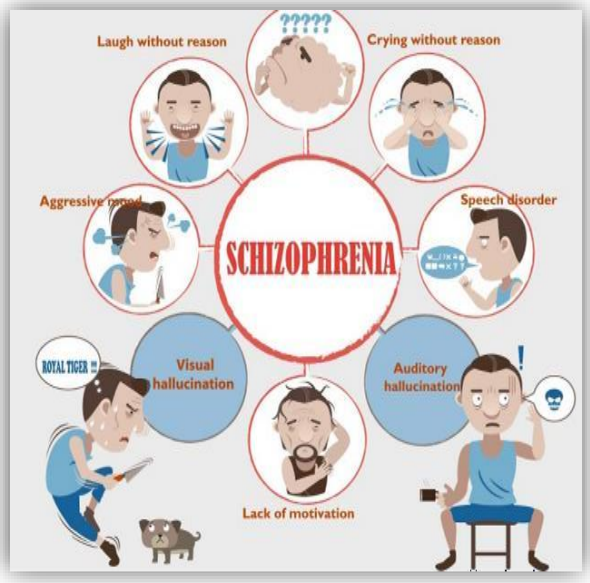


Fig. 1. : Symptoms of Schizophrenia

1. **First-generation antipsychotics:**

The first-generation antipsychotic medications have more frequent and potentially significant neurological side effects. They are also known as typical antipsychotics. They have equal or more affinity for D2 receptors than 5HT 2 receptors. Antagonism of D2 receptors in mesolimbic pathway supress the positive symptoms of schizophrenia and also reduce the dopaminergic neurotransmission in four dopaminergic pathways. [10,11]

2. **Second generation antipsychotics:**

Second generation antipsychotic medications are generally preferred because they pose a lower risk of serious effects than first generation antipsychotic medications. These are also known as **Atypical Antipsychotics.** Second generation antipsychotics have least D2 blocking activity and have potent 5HT 2 Blocking activity. Extrapyramidal side effects are minimal and they improve impaired cognitive function in psychotics. [10,11]

Alternative treatments for schizophrenia:

Dietary supplements:

Most commonly the antipsychotic medicines are given to the patients for schizophrenia, along with that some alternative therapies are also present. An alternative treatment is Nonmainstream approach which are used along with antipsychotic drugs.

Drug name 1st Generation	Brand name	Dosage form and strength	MOA	Side Effects	BCS class
Chlorpromazine	1. Thorazine 2. Clozine plus	1. Tablet (10- 200mg) 2. Spansule- SRC (30-150mg) 3. Suppositories(25-100mg) 4. Syrup (10mg) 5. Multi dose vial (25mg) 1. Tablet (100mg) 2. Capsule (100mg)	Chlorpromazine acts as Dopamine antagonist, Anti-serotonergic and Anti-histaminic.	Agranulocytosis, Skin pigmentation, Pseudo-parkinsonism, ocular change, tardive dyskinesia, drowsiness. Orthostatic hypotension, Dryness in mouth, Constipation, muscle stiffness, weight gain.	Class-2
Haloperidol	1. Agidol 2. benzydol-P 3. Halopidol 4. Triperidol	Tablet (0.25-20mg) Tablet (1.5-10mg) Syrup (2mg/ml) Injection (2.5mg)	Dopaminergic D1 and D2 receptor antagonist.	Dry burn, constipation, Blurred vision, loss of appetite Heartburn, Nausea, Increased saliva.	Class-2
Fluphenazine	1. Prolinate 2. Anatensol 3.F-tensil	Injection (25mg/ml) 1. Tablet (1mg) 2. Injection (25mg/ml) Injection	Postsynaptic Dopamine D2 receptor blockers.	Restlessness, Involuntary movement, tremors and rigidity	-
Perphenazine	1. Trilafon	Tablet 5-10mg)	Blocks the Dopamine receptors	Dizziness, Blurred vision, Breast swelling, Stuffy nose.	Class-2

Drug name 2nd Generation	Brand name	Dosage form and Strength	MOA	Side effects	BCS class
Aripiprazole	1. Asprito 2. Arip MT 3. Arpizole	Tablet (5mg) Tablet (5mg) Tablet (5mg)	Acts as a partial agonist at D2 and 5HT1A receptors and as an antagonist at 5HT2A receptors.	Insomnia, Agitation, Dyspepsia, Orthostatic- hypotension, Dry mouth, Anxiety, Vomiting.	Class-4
Asenapine	1. SAPHRIS	Sublingual Tablet (10mg)	5HT2A and D2 receptor antagonist	Dry mouth, Stomach pain, heartburn, Constipation, Increased appetite, Change In taste**.**	Class-2
Clozapine	1. Sizopine 2. Soloquin	Tablet (25mg) Tablet (25mg)	It blocks 5HT2A and 5HT2C serotonin receptors, And also Dopamine D1 to D4 receptors.	Sudden illness, Swollen glands, Mouth sores, Body aches, Spinning sensation and fast heart rate.	Class-2
Lurasidone	1. Luramax 2. Lurafic 3. luratrend 4. Tablura 5. Atlura	Tablets (40mg)	Exact mechanism not known but may block receptors of several neurotransmitters.	Somnolence, panic attack, Nausea, parkinsonism, anxiety, dyspepsia, Dystonia, Fatigue, Akathisia.	Class-2

Risperidone	1. Risperdal 2. Sizodon 3. Rozidol 4. Risnia	1. tablet (4mg) 2. Film coated tablet (1mg-4mg) 3. Oral solution (1mg/ml) Tablet (2mg) Tablet (2mg) 1. Tablet (1-2mg) 2. Mouth dissolving tablet (1-4mg) 3. Film coated tablet(1-4mg)	Antagonist of dopamine D2 and Serotonin 5HT2A receptors	Rash, Hives, Itching, Difficulty in breathing, Confusion, Fainting, Muscle stiffness, Discoloured skin, Vision problems.	Class-2
Olanzapine	1. Jolyon MD 2. Jolyon Md 3. Olandus 4. Olanex 5. Olanzotic	Tablet (5-15mg) Dispersible tablet (10mg) Tablet/capsule (2.5-10mg) Dispersible tablet(10mg) Tablet/capsule (10mg)	It binds to alpha-1, dopamine, histamine H1, Serotonin type 2 receptors.	Restlessness, Unusual behaviour, Depression, Weakness, Constipation.	Class-2
Paliperidone	1. Paliris 2. Palip XR 3. Palido OD	Tablet (6mg) Tablet (6mg) Tablet (6mg)	Acts as Dopamine, serotonin, Histamine and alpha-adrenergic receptor antagonist.	Tachycardia, headache, somnolence, orthostatic hypotension, AV block, bundle branch block, akathisia**.**	Class-2

Following are some supplements used to reduce symptoms of schizophrenia:

Amino acids:

Mostly the Glycine is used in high dose to enhance the efficacy of antipsychotic drugs. Glycine is a protein building block of our body, It works with glutamine, which aids in brain function. It also decreases the negative symptoms of schizophrenia.

Melatonin:

Some people claim that the amount of sleep they obtain has an impact on the severity of their schizophrenia symptoms. Melatonin, a hormone that regulates sleep-wake cycles, may help you have more restful sleep. persons with schizophrenia take melatonin, it appears that their "sleep efficiency" improves. In other words, they spend the majority of their time in bed sleeping. They may also be able to sleep for longer periods of time.

Deep Brain Stimulation:

It's similar to ECT in concept, but it's more targeted and precise, with less side effects. You will require surgery to implant a matchbox-sized electrical stimulator in your chest for DBS. The nucleus acumens, which helps manage motivation and logical reasoning, is activated by electric signals sent via wires from this gadget.

B Vitamins:

Recent research backs up what some psychiatrists have been saying for years: B vitamins, which can be found in meat, eggs, and nuts, can help with schizophrenia symptoms.

People who took vitamin supplements with their antipsychotic medication (containing B6, pyridoxine; B9, folate; and B12) had fewer symptoms than those who merely took medicine. The vitamins were more likely to help if someone had symptoms for a shorter period of time.

Some people believe that niacin (vitamin B3) can aid with paranoia and delusions, and there may be some scientific evidence to support this notion. However, no studies have yet shown that such a benefit exists, thus more research is required

Omega-3 Fatty Acids:

These nutrients are important components of brain cell membranes. They assist cells in communicating with one another. People who suffer from schizophrenia may be deficient in omega-3 fatty acids. Some people claim

that omega-3 supplements, such as fish oil, help them manage their symptoms. People who consumed fish oil were less likely to develop psychosis in one study of people at risk of schizophrenia.[12]

Cannabinoids:

Cannabinoids is obtained from Marijuana plant, one of the important ingredients in this is cannabidiol, which is used to relieve psychotic symptoms.

Cannabinoids has been shown in small studies to assist persons with schizophrenia stop having hallucinations and delusions. When animals were administered CBD in lab studies, their learning abilities and working memory increased. Researchers aren't sure what cannabinoids does to the brain to manage symptoms and sharpen intellect, although anti-anxiety and anti-inflammatory qualities are suspected. [12]

Herbal supplements:

Unlike prescription pharmaceuticals, herbal supplements can be sold without being examined to ensure that they are safe and effective. Herbal remedies were employed in traditional medical systems (such as Ayurveda)

1. Kava:

Kava is an herbal medicine in which the main ingredient is kavapyrones which acts as a muscle relaxant and anti-convulsant, it also inhibits voltage dependent sodium channels and increase GABA(A) receptor densities. Kava act by increasing GABA(A) receptor densities and suppressing the release of glutamate, this mechanism might explain its usefulness in schizophrenia.

3. Ashwagandha:

Ashwagandha consists of dried root and stem bases of Withania somnifera, belonging to family Solanaceae. Withianine alkaloids and steroidal lactones are the major ingredients of ashwagandha. Ashwagandha has sedative and hypnotic effects immune-modulatory agent and have been shown to possess anti-stress activity. Indians have prescribed ashwagandha as a treatment for cerebral disorders in the elderly, including memory loss and hallucinations. They found that extracts of the shrub had activity that was similar to GABA, which could explain Ashwagandha's effects were also studied by researchers at the University of Texas Health Science Century the plant is effective in reducing anxiety. Another study from 2002 discovered that ashwagandha promotes the formation of axons and dendrites. In 2001, another study discovered that the herb can improve memory. [12,13]

4. Ginkgo:

Ginkgo (Ginkgo biloba) generally found in East Asia and Europe. Ginkgo extracts contain a large number of substances that have been found to have a variety of pharmacological effects. The ginkgo flavonoids are thought to be antioxidants, and the ginkgolides, especially ginkgolide B, inhibit platelet activating factor. There is also evidence that ginkgo extracts can improve vascular perfusion by modulating vessel wall tone. It also reduces the symptoms of schizophrenia. [12,14]

5. Rhodiola Rosea:

(Golden Root, Roseroot, Aaron's Rod) is a Crassulaceae family plant that grows in colder climates. Adaptogen Rhodiola Rosea Root is currently widely used. This describes how it exerts a general body-stabilizing impact without interfering with other functions. Its capacity to balance hormones in the body led researchers to believe it could be useful in the treatment of sadness and anxiety. This herbal supplement, when taken with antipsychotic medicine, can lower the likelihood of adverse effects while also increasing the drug's therapeutic efficacy. [12]

6. Ginseng:

Ginseng is the dried root of various species of panax, like P. ginseng, P. japonica, P. notoginseng, and P. quinquefolium. Ginseng is an immunomodulatory drug. It increases the natural resistance and enhances the power to overcome the illness. It has both stimulant and sedative properties. Ginsenosides appear to modulate neurotransmission through - aminobutyric acid (GABA), and by inhibiting neurotransmitter reuptake.[14]

Jain's cow urine therapy:

Jain's cow urine therapy is patented and scientifically established with pharmacological activities. This therapy has proved effective in reducing the suffering of patients by natural and safe medicines in form of capsule and syrups in schizophrenia treatment by natural ayurvedic remedies.

Cow urine is scientifically proven to reinforce the anti-microbial effects. The invention relates to a completely unique use of cow urine as activity enhancer. It reduce the dosage of antibiotics and other psychotic medicines and enhance the bioavailability and improve the quality of life. [15]

Rehabilitation centres for schizophrenia:

Psychosocial therapies are used to help people with schizophrenia achieve their highest degree of independent functioning, strongest level of symptom control, and highest level of subjective life

satisfaction through rehabilitation. During recovery, not only the addict, but also others who are helping him or her, must deal with the circumstances with considerable tolerance. No matter how difficult the situation may be, one should never give up hope of making positive changes in one's life. For an addict, this can be accomplished at one of the best rehabilitation centres, which are usually abstinence-based and provide an intensive programme of support and care that is aimed at helping them overcome their addiction.

1. Safe House Wellness Retreat, Delhi.

Safe House is one of Delhi's premier rehabilitation centres. They treat men and women from all over the world, starting at the age of 15 years old. They have the best amenities and provide a safe, secure environment with comfortable settings that make you feel at ease. Their team of highly qualified specialists puts themselves in the shoes of the patients and ensures that they are as comfortable and safe as possible.

2. Alpha Healing centre, Gujarat.

In Vadodara, Gujarat, Alpha Healing Centre is a well-known private rehabilitation centre. They have excellent service and all of the latest conveniences. They not only cure schizophrenia, but also alcoholism, gambling addiction, smoking addiction, and a variety of other disorders. They provide a complete treatment with a 96 percent completion rate.

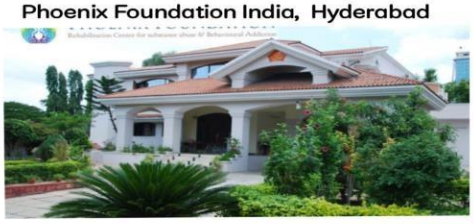
3. Phonix Foundation India, Hyderabad.

Phoenix Foundation India is one of India's leading substance abuse and behavioural addiction treatment centres. They offer courses in cognitive behavioural therapy, rational emotive behaviour therapy, and various therapies for alcoholism, cocainism, heroinism, gamblingism, and other addictions.

4. Cadabam's Amitha, Bengaluru.

Cadabam's Amitha is a short- and long-term rehabilitation centre for those who are addicted to any type of drug, including cigarettes, marijuana, cocaine, LSD, and even painkiller and sleeping pill addiction. They provide individual, group, and family treatment, as well as counselling, yoga, meditation, psychotherapy, and a 12-step programme aimed at enhancing an individual's quality of life. [16]

Phoenix Foundation India, Hyderabad



Pioneer Rehabilitation Centre, Chennai.

5. Zorbacare, Pune

6. Anatta Humanversity, Mumbai.

7. Pioneer Rehabilitation Centre, Chennai.

Conclusion:

Schizophrenia is a complicated multi-factor condition, and it does not appear likely that all symptoms of the disease can be treated with a single-target therapy, based on current knowledge. More possible antipsychotic chemicals are being developed currently than at any time in the last several decades. Further advancements in basic and clinical neurosciences are also expected to lead to dramatically enhanced treatment techniques. There are also countless cases of pharmacologic and psychosocial treatments being combined with herbal or ayurvedic remedies. The present understanding and treatment of schizophrenia is still centred on the disease's dopaminergic theory. We continue to make significant progress in our capacity to employ current medicines in the most effective way feasible with the fewest possible side effects. Simultaneously, it is clear that current medicines have a number of flaws, and that the need for new treatments is obvious to all of us.

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GOUT

Curated by- Prathamesh Jambhulkar, Chaitrali Gosavi.
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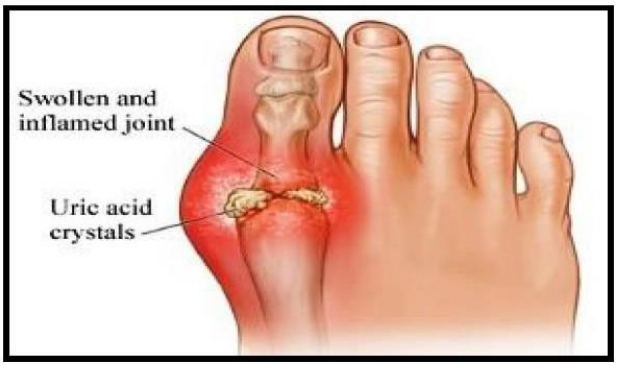
Gout is a visually appealing manifestation of uric acid imbalance. It is the most well-known and well described type of arthritis. Its epidemiology is being researched. New insights into pathophysiology of hyperuricemia and gouty arthritis, both acute and chronic, provide a deeper understanding of the disease. The Importance of genetic predisposition is becoming clearer. Gout is classified into four clinical stages: asymptomatic hyperuricemia, acute gouty arthritis, the intercritical period, and chronic tophaceous gout. Laboratory and radiological findings are used to diagnose gout. The identification of characteristic MSU crystals in synovia fluid using polarized light microscopy is the Gold standard of Diagnosis. Conventional CT Dual-energy CT, Magnetic Resonance imaging, conventional radiography and positron emission tomography are all imaging modalities. Gout management includes flare management, chronic gout management, flare prevention and comorbidity management. Newer drugs in the pharmacological arsenal are effective and are supplementing older ones. Other important aspects of its management include patient education, dietary and lifestyle changes, and the discontinuation of hyperuricemic medications

Introduction: The deposition of monosodium urate crystals (MSU) in tissues causes gout, a systemic illness. The formation of uric acid crystals requires an increase in serum uric acid (SUA) above a certain threshold. Many patients with hyperuricemia do not develop gout or even create UA crystals, despite the fact that hyperuricemia is the most common pathogenic defect in gout. Only 5% of persons with hyperuricemia of more than 9 mg/dL develop gout. As a result, additional factors, such as genetic predisposition, are thought to have a role in the occurrence of gout.[1,2]

MSU crystals can be found in all tissues, most notably in and around joints like shown in Fig.1, where they form tophi. Gout is primarily diagnosed through the identification of pathognomonic MSU crystals via joint fluid aspiration or in tophi aspirate. Gout begins with an acute joint inflammation that is quickly relieved by NSAIDs or colchicine. Renal stones and tophi are examples of late manifestations.

Lowering SUA levels below the deposition threshold, either through dietary changes or by using serum uric acid lowering drugs, is the primary goal in gout management. This causes MSU crystals to dissolve, preventing further attacks.[3,4]



Diagnosis:

1. Joint fluid test. A needle may be used by your doctor to draw fluid from your affected joint. When the fluid is examined under a microscope, ureate crystals may be visible.[5]

2. Blood test. A blood test to measure the levels of uric acid in your blood may be recommended by your doctor. However, blood test results can be deceptive. Some people have high uric acid levels but do not have gout. And some people have gout symptoms but no abnormal levels of uric acid in their blood.[6]

3. X-ray imaging. Joint X-rays can help to rule out other potential causes of joint inflammation.

4. Ultrasound. Sound waves are used in this test to detect urate crystals in joints or tophi.[7]

5. Dual-energy computerized tomography (DECT). To visualise urate crystals in joints, this test combines X-ray images taken from various angles.[7] Treatment Gout medications are classified into two types that address two distinct issues. The first type aids in the reduction of inflammation and pain associated with gout attacks. The second type works by lowering the amount of uric acid in your blood, which helps to prevent gout complications.[8]

Medications to treat gout attacks:

1. Nonsteroidal anti-inflammatory medications (NSAIDs). Over-the-counter NSAIDs include ibuprofen (Advil, Motrin IB, and others) and naproxen sodium (Aleve), as well as stronger prescription NSAIDs like indomethacin (Indocin, Tivorbex) or celecoxib (Celebrex). NSAIDs have the potential to cause stomach pain, bleeding, and ulcers.[8]

2. Colchicine. Colchicine (Colcrys, Gloperba, Mitigare), an anti-inflammatory drug that effectively relieves gout pain, may be prescribed by your doctor. The drug's effectiveness, however, may be offset by side effects such as nausea, vomiting, and diarrhoea.

3. Corticosteroids. Prednisone and other corticosteroid medications may help to control gout inflammation and pain. Corticosteroids can be taken orally or injected into your joint. Corticosteroids can cause mood changes, increased blood sugar levels, and high blood pressure.[8]

Medications to prevent gout complications:

1. Medications that block uric acid production. Allopurinol (Aloprim, Lopurin, Zyloprim) and febuxostat (Uloric) are medications that help limit the amount of uric acid your body produces. Allopurinol side effects include fever, rash, hepatitis, and kidney problems. Rash, nausea, and decreased liver function are some of the side effects of fuxostat. Febuxostat may also increase the risk of heart failure.[8,9]

2. Medications that improve uric acid removal. Probenecid (Probalan) and other drugs help improve your kidneys' ability to remove uric acid from 3 your body. A rash, stomach pain, and kidney stones are some of the side effects.[8,9]

Lifestyle and home remedies[10] :

1. Choose healthier beverages. Drinks sweetened with fruit sugar and alcoholic beverages should be avoided (fructose). Instead, drink plenty of water and other nonalcoholic beverages.

2. Avoid foods high in purines. Purines are particularly abundant in red meat and organ meats such as liver. Anchovies, sardines, mussels, scallops, trout, and tuna are examples of purine-rich seafood. Low-fat dairy products may be a better source of protein for gout sufferers.

3. Exercise regularly and lose weight. Maintaining a healthy weight lowers your risk of gout. Low-impact activities, such as walking, bicycling, and swimming, are better for your joints.

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WORLD IMMUNIZATION DAY

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Every year, 10th November is celebrated as World Immunization Day. The aim this day is to highlighting vaccination as a low-tech, cost effective, high impact solution to preventing illness and disease in individuals of all ages. This day is celebrated to make people aware about the importance of getting timely vaccinations against vaccine preventable diseases. Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine. Vaccinations prevent susceptibility to illnesses which can result in serious complications and even death.[1]

Each World Immunization Week focuses on a theme. The themes have included the following:

2021: "Vaccines bring us closer"

2020: "Vaccines Work for All".

Introduction:

According to the WHO, immunization prevents between 2 and 3 million deaths every year and now protects children not only against diseases for which vaccines have been available for many years, such as Diphtheria, Tetanus, Polio and Measles, but also against diseases such as Pneumonia and Rotavirus Diarrhoea, two of the biggest killers of children under age of five. But there are still nearly 20 million unvaccinated and under-vaccinated children in the world today.[1]

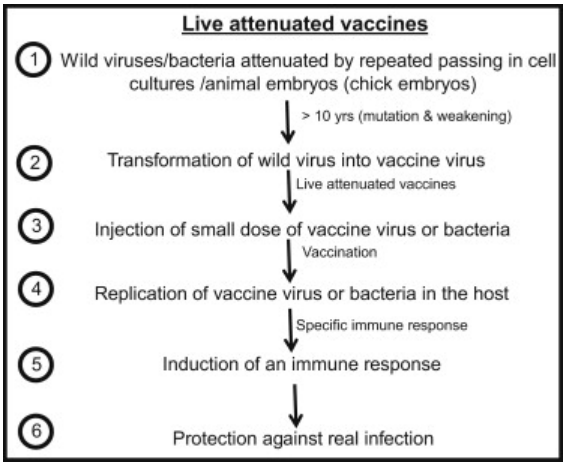
Some diseases that once killed thousands of children, have been eliminated completely. Polio is a prime example of the great impact that vaccines have had in India. Polio was once India's most-feared disease, causing death and paralysis across the country, but today, because of vaccination, as of 2014, India has been declared polio-free by the WHO, and has been removed from the list of endemic countries.

Vaccine :

A vaccine is a type of medicine that helps train the body's immune system to fight a disease which has not come in contact with before. Vaccination is in fact the most effective method to prevent any highly infectious diseases. With the help of vaccination, we could eradicate smallpox and restraint diseases such as measles, polio and tetanus from the large amount of the world. As per the WHO, with the help of licensed vaccines that are currently available, we can prevent and control around twenty five preventable infections.[2]

vaccination necessity:

Vaccination is necessary as the immunity system through immunization provides the strength to fight diseases that are dangerous in nature. Hence, parents are always advised to get their children vaccinated. A timely vaccination is essential for your child's good health. Vaccination is safe and effective as all vaccines undergo strenuous review by doctors scientists and the government to make sure that they are safe & effective.



Principle of immunization:

Immunity is the biological state of being able to resist disease or a toxin: the primary objective of vaccination is to induce an immunological memory against specific diseases, so that if exposure to a disease-causing pathogen occurs, the immune response will neutralise the infection or toxins .[1]

Challenges to immunization:

1. Limited capacities of staff, particularly in poor-performing states and at the field level.
2. Gaps in key areas such as predicting demand.
3. Logistics and cold chain management.

India also still lacks a robust system to track vaccine-preventable diseases. Vaccination coverage varies considerably from state to state, with the lowest rates in India's large central states. Differences in uptake are geographical, regional, rural-urban, poor-rich and gender-related. On average, girls receive fewer immunizations than boys and higher birth order infants have lower vaccination coverage.

Immunization is one of the most cost-effective health investments and vaccination does not require any major lifestyle change.

Five facts on vaccination:

• Vaccines are safe and effective

• Vaccines prevent deadly diseases

• Vaccines provide better immunity than natural infections

• Combined vaccines are safe and beneficial

Vaccines to babies:

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins.

If the babies get antibodies from mother, but it is important to give immunization because the antibodies received from mother do not last long, leaving the infant vulnerable to disease. Moreover, immunization gives extra protection against deadly diseases.

A child can be immunized in a nearby government health centre. Vaccinations are also provided by the private hospitals and private doctors.Immunization is free of cost in government hospitals against the vaccine preventable diseases under the Universal Immunization Program (UIP).

Reasons to delay immunization:

There are very few medical reasons (contra indications) to delay immunization:

• The one has a high fever

• A bad reaction to another immunization

• Severe reaction after eating eggs

• Past history of convulsion(fits)

• Cancer or any illness which affects the immune system, for example, HIV or AIDS.

Vaccination provides a shield against the disease before it develops. If you wait to get vaccinated after the disease, it might get too late. Prevention is better than cure.

Side effects:

Vaccines are mostly safe. Only some individuals may develop side effects such as swelling, redness or a minor fever. These side effects last only for a couple of day.If any one miss the dose then it is still advisable to follow the immunization schedule.

Safe Injection Practices are require such as:

It is very essential for patients to be aware that unsafe injection practices can cause a serious threat to their health. It is the duty of healthcare providers (doctors, nurses, and anyone providing injections) to be alert while giving an injection to the patient.

• Ensure that one needle; one syringe is used only one time.

• Make sure that both needle and syringe must be discarded once they have been used. It is very unsafe to change the needle and reuse the syringe as this practice can transmit disease.

• Follow the immunization schedule as per the guidelines. Keep a track of your immunization record and carry it along before getting any subsequent vaccination done.

• Always consult your doctor before getting any type of vaccination done.

Importance of immunization:

Immunisation saves lives.

Immunisation helps protect future generations by eradicating diseases.

Many infectious diseases are rare or eradicated now as a result of immunisation programs, but new infectious diseases are appearing around the world

Immunisation is one of the best ways you can protect yourself, your children and future generations from infectious diseases.

In other words, if you vaccinate, you help wipe out disease that could spread now and into the future.

By making sure you and your family are fully vaccinated. The more people who are vaccinated, the fewer people will be infected, and the less widely a disease can spread.

Immunisation saves lives.[5]

How do vaccinations work:

All immunisations work in the same way. The vaccination uses your body's immune system to increase protection to an infection before one come into contact with that infection. In other words, it is like being infected with the disease without suffering the actual symptoms.

If one come into contact with an infection after one've been vaccinated, your body works to stop you from getting the disease, or one may get just a mild case. Unlike other proposed approaches to immunisation (such as homeopathy), vaccinations have been rigorously tested to demonstrate their safety and effectiveness in protecting against infectious disease.

Some people in our community cannot be vaccinated. This might be because they are too young or too sick. You can help protect these vulnerable people by keeping your family's vaccinations up to date.[3]

Modern outbreaks of infectious diseases:

Many infectious diseases are rare or not around anymore, thanks to vaccination. But there are still infectious disease outbreaks happening around the world today:

1. COVID-19 – a new disease that the world is still learning about. New research is happening all the time so we can understand more about the disease, including the long-term effects.

2. Flu, chicken pox, whooping cough, measles – these diseases still have occasional outbreaks in Australia, mainly when introduced from overseas. They could make a strong comeback if people stop vaccinating. In January 2019, 62,225 measles cases were notified globally compared to the same period in 2018 when only 23,535 cases were notified.

3. Zika – in February 2016 the World Health Organization (WHO) declared the Zika virus an international public health emergency following outbreaks in Central and South America. There is ongoing evidence of transmission throughout the Americas, Africa and other regions of the world. As of 2018, a total of 86 countries and territories have reported evidence of mosquito-transmitted Zika infection.

4. Ebola – the latest outbreak of Ebola virus disease started in Democratic Republic of Congo in August 2018, and is ongoing.

5. HIV/AIDS – the first cases of HIV/AIDS were identified in the gay community in America in 1981 and, by 1985, at least one case had been reported from each region of the world. In 2019, more than 38 million people around the world were living with HIV/AIDS. There is still no cure, but current treatments allow patients to live long and healthy lives.

No vaccines exist for Zika, Ebola or HIV/AIDS, but research is underway.[3]

Immunisation surveillance:

To keep you, your family and your community safe, governments need a complete picture of immunisation. That is where immunisation surveillance comes in. Immunisation surveillance involves researching and collating information on immunisation programs.

Many countries have an official immunisation surveillance body (for example, the CDC in the United States). Australia has one too, called the National Centre for Immunisation Research and Surveillance (NCIRS). [1]

How new vaccines are developed:

It can take a long time to develop a new vaccine. The development process is rigorous, and the vaccine is constantly monitored – even after it is being used – to make sure it is safe and effective.

A new vaccine goes through many phases of development, including research, discovery, pre-clinical testing, clinical testing, and regulatory approval. Once the vaccine is approved, the vaccine is then manufactured and shipped to where it's needed. In certain circumstances, increased resources, concurrent clinical trials and funding can fast-track development, such as in the case of the COVID-19 vaccines.

After vaccines are introduced into immunisation schedules, they are closely monitored through trials and surveillance to see if they are effective and safe. In Australia, there are regional and national surveillance systems actively looking for any adverse events following immunisation. This is necessary, as sometimes unexpected side effects occur after vaccines are registered for use.

Some vaccines, such as the flu vaccination, need to be updated every year to respond to changing infection strains and conditions. For these updates, the process is compressed to ensure the vaccine is available as needed.

Who needs to be vaccinated:

almost everyone needs vaccination.There are some exceptions – usually people with a serious medical condition (for example, a weak immune system). But don't ever decide against immunisation without checking with your GP first. Your doctor will advise which vaccinations you need based on your HALO: health condition, age, lifestyle and occupation.[3]

If 95% of us are vaccinated, the spread of disease is reduced, which helps to protect everyone.

Vaccination is particularly recommended if:

- It is a newborn or young child (as per the NIP schedule).
- Have a newborn baby.
- Are pregnant or planning for a baby.
- Are caring for very young babies (for example, parents, grandparents and carers).
- Are an older person.
- Are an Aboriginal or Torres Strait Islander child or adult.
- Have plans to travel outside Australia (ask your travel agent or check on the Smart Traveller website).
- Are medically at risk due to certain conditions (such as asthma) or treatment.

As COVID-19 is a new disease, it is important to check the latest information on who can get

vaccinated when considering getting a COVID-19 vaccine.

Conclusion of immunization:

The availability of new and underutilized vaccines against Hib, rotavirus, pneumococcus, meningococcus, and human papilloma virus provides an opportunity to increase the impact of immunization activities in terms of prevented morbidity and mortality and represents substantial health benefits for populations of all ages.[3,4]

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WORLD AIDS DAY

Curated by - Ashwini Makta Gavit**,** M.Pharmacy Second year (pharmacology)**.**

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World AIDS Day, celebrated on 1 December every year since 1988, [1] is an international day dedicated to raising awareness of the AIDS pandemic caused by the spread of HIV infection and mourning those who have died of the disease. The acquired immunodeficiency syndrome (AIDS) is a life-threatening condition caused by the human immunodeficiency virus (HIV). The HIV virus attacks the immune system of the patient and reduces its resistance to other diseases.[2] Government and health officials, non-governmental organizations, and individuals around the world observe the day, often with education on AIDS prevention and control.

Introduction:

Acquired immunodeficiency syndrome (AIDS) is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV). By damaging your immune system, HIV interferes with your body's ability to fight infection and disease.

HIV is a sexually transmitted infection (STI). It can also be spread by contact with infected blood or from mother to child during pregnancy, childbirth or breast-feeding. Without medication, it may take years before HIV weakens your immune system to the point that you have AIDS.

There's no cure for HIV/AIDS, but medications can dramatically slow the progression of the disease. These drugs have reduced AIDS deaths in many developed nations.
White blood cells are an important part of the immune system. HIV infects and destroys certain white blood cells called CD4+ cells. If too many CD4+ cells are destroyed, the body can no longer defend itself against infection.

The last stage of HIV infection is AIDS (acquired immunodeficiency syndrome). People with AIDS have a low number of CD4+ cells and get infections or cancers that rarely occur in healthy people. These can be deadly.

But having HIV doesn't mean you have AIDS. Even without treatment, it takes a long time for HIV to progress to AIDS—usually 10 to 12 years.

When HIV is diagnosed before it becomes AIDS, medicines can slow or stop the damage to the immune system. If AIDS does develop, medicines can often help the immune system return to a healthier state.
With treatment, many people with HIV are able to live long and active lives.

There are two types of HIV:

HIV-1, which causes almost all the cases of AIDS worldwide
HIV-2, which causes an AIDS-like illness. HIV-2 infection is uncommon in North America.

Causes:
HIV can transmit when body fluids containing the virus come into contact with a permeable barrier in the body or small breaks in moist tissues of areas such as the genitals.

Specifically, HIV can transmit via:

- Blood
- Semen
- pre-seminal fluid
- vaginal fluids
- rectal fluids
- breast milk

The virus cannot transmit through saliva, so a person cannot contract HIV through open-mouthed kissing, for example.

One of the main causes of HIV transmission in the U.S. is anal or vaginal intercourse. For the transmission to happen, the people must not be using barrier protection, such as a condom, or taking pre-exposure prophylaxis (PrEP), a treatment that aims to prevent HIV transmission among people with known risk factors.

Another main cause of HIV transmission in the country is sharing equipment for injecting drugs.

Less commonly, HIV transmits to babies during pregnancy, childbirth, or breastfeeding.

Also, there is a chance of transmission in blood transfusions, though the risk is extremely low when blood donations are effectively screened.

Symptoms:

Common early symptoms include:

- Fever.
- Sore throat.
- Headache.
- Muscle aches and joint pain.
- Swollen glands (swollen lymph nodes).
- Skin rash.

Symptoms may appear from a few days to several weeks after a person is first infected. The early symptoms usually go away within 2 to 3 weeks.

After the early symptoms go away, an infected person may not have symptoms again for many years. After a certain point, symptoms reappear and then remain. These symptoms usually include:

- Swollen lymph nodes.
- Extreme tiredness.
- Weight loss.
- Fever.
- Night sweats.

Transmission:
HIV can be transmitted via the exchange of a variety of body fluids from infected people, such as blood, breast milk, semen and vaginal secretions. HIV can also be transmitted from a mother to her child during pregnancy and delivery. Individuals cannot become infected through ordinary day-to-day contact such as kissing, hugging, shaking hands, or sharing personal objects, food or water.

It is important to note that people with HIV who are taking ART and are virally suppressed do not transmit HIV to their sexual partners. Early access to ART and support to remain on treatment is therefore critical not only to improve the health of people with HIV but also to prevent HIV transmission.

Risk factors:
Behaviours and conditions that put individuals at greater risk of contracting HIV include:

- having unprotected anal or vaginal sex;
- having another sexually transmitted infection (STI) such as syphilis, herpes, chlamydia, gonorrhoea and bacterial vaginosis;
- sharing contaminated needles, syringes and other injecting equipment and drug solutions when injecting drugs;
- receiving unsafe injections, blood transfusions and tissue transplantation, and medical procedures that involve unsterile cutting or piercing; and
- experiencing accidental needle stick injuries, including among health workers

Diagnosis:
HIV can be diagnosed through rapid diagnostic tests that provide same-day results. This greatly facilitates early diagnosis and linkage with treatment and care. People can also use HIV self-tests to test themselves. However, no single test can provide a full HIV diagnosis; confirmatory testing is required, conducted by a qualified and trained health or community worker at a community centre or clinic. HIV infection can be detected with great accuracy using WHO prequalified tests within a nationally approved testing strategy.

Most widely-used HIV diagnostic tests detect antibodies produced by the person as part of their immune response to fight HIV. In most cases, people develop antibodies to HIV within 28 days of infection. During this time, people experience the so-called “window” period – when HIV antibodies haven’t been produced in high enough levels to be detected by standard tests and when they may have had no signs of HIV infection, but also when they may transmit HIV to others. After infection, an individual may transmit HIV transmission to a sexual or drug-sharing partner or for pregnant women to their infant during pregnancy or the breastfeeding period.

Following a positive diagnosis, people should be retested before they are enrolled in treatment and care to rule out any potential testing or reporting error. Notably, once a person diagnosed with HIV and has started treatment they should not be retested.

While testing for adolescents and adults has been made simple and efficient, this is not the case for babies born to HIV-positive mothers. For children less than 18 months of age, serological testing is not sufficient to identify HIV infection – virological testing must be provided as early as birth or at 6 weeks of age. New technologies are now becoming available to perform this test at the point of care and enable same-day results, which will accelerate appropriate linkage with treatment and care.

Prevention:
Individuals can reduce the risk of HIV infection by limiting exposure to risk factors. Key approaches for HIV prevention, which are often used in combination, include:

- ✓ male and female condom use;
- ✓ testing and counselling for HIV and STIs;
- ✓ testing and counselling for linkages to tuberculosis (TB) care;
- ✓ voluntary medical male circumcision (VMMC);
- ✓ use of antiretroviral drugs (ARVs) for prevention;
- ✓ harm reduction for people who inject and use drugs; and
- ✓ Elimination of mother-to-child transmission of HIV.

Treatment:
HIV disease can be managed by treatment regimens composed of a combination of three or more antiretroviral (ARV) drugs. Current antiretroviral therapy (ART) does not cure HIV infection but highly suppresses viral replication within a person's body and allows an individual's immune system

recovery to strengthen and regain the capacity to fight off opportunistic infections and some cancers.

Since 2016, WHO has recommended that all people living with HIV be provided with lifelong ART, including children, adolescents, adults and pregnant and breastfeeding women, regardless of clinical status or CD4 cell count.

By June 2021, 187 countries had already adopted this recommendation, covering 99% of all people living with HIV globally. In addition to the treat all strategy, WHO recommends a rapid ART initiation to all people living with HIV, includes offering ART on the same day as diagnosis among those who are ready to start treatment. By June 2021, 82 low- and middle-income countries reported that they have adopted this policy, and approximately half of them reported country-wide implementation.

Globally, 27.5 million [26.5–27.7 million] people living with HIV were receiving ART in 2020. This equates to a global ART coverage rate of 73% [56–88%]. However, more efforts are needed to scale up treatment, particularly for children and adolescents. Only 54% [37–69%] of children (0–14 years old) were receiving ART at the end of 2020.

Conclusion:

The conclusion that the AIDS agent was blood-borne rested on two findings. First, AIDS was occurring in transfusion recipients and individuals with haemophilia who had received AHF concentrate; these AIDS patients did not belong to any other known high-risk group for contracting AIDS. World AIDS Day is important because it reminds the public and government that HIV has not gone away – there is still a vital need to raise money, increase awareness, fight prejudice and improve education.

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WORLD PNEUMONIA DAY

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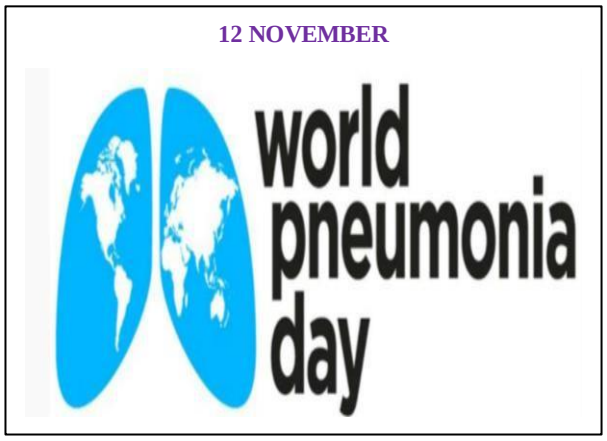
Every year on November 12th, WHO, UNICEF, and a number of other international organizations commemorate World Pneumonia Day. The first World Pneumonia Day was held in 2009 with the goal of raising awareness, promoting prevention and treatment, and generating action to battle the disease. Since then, the day has served as a yearly rallying point for people all across the world to fight the disease. Various events and activities linked to pneumonia are held all around the world to celebrate the day. [1]



Importance of World Pneumonia Day:

1. To promote awareness about the condition, which is fast becoming the leading cause of death among children under the age of five.
2. To strengthen, expedite, and sustain pneumonia prevention and treatment initiatives.
3. To inspire people to develop ways for reaching 'harder-to-reach' populations in order to increase access to available solutions.
4. To encourage students and scientists to come up with novel ways to lower the prevalence of pneumonia. [2]

Pneumonia:

Pneumonia is a lungs illness caused by an acute respiratory tract infection. It inflames the air sacs in one or both lungs, causing them to fill with fluid and pus and solidify. Double pneumonia refers to inflammation that affects both lungs, while single pneumonia refers to inflammation that affects only one lung. Infection can be fatal to anyone, but it is especially dangerous to newborns, children, and individuals over the age of 65.

When a healthy person breathes, tiny sacs called alveoli in the lungs fill up with air. When a person develops pneumonia, the alveoli swell with pus, making breathing difficult and limiting oxygen intake. [3,4]

Pathophysiology of Pneumonia:

Infectious organisms that reach to the alveoli are likely to be particularly pathogenic since they have previously eluded the host's physical defense. As a result, the macrophages may be overwhelmed, leading in the creation of a fibrin-rich exudate that fills the infected and adjacent alveolar spaces, causing them to cling together and become airless. Neutrophils proliferate as a result of the inflammatory reaction. This can cause lung tissue damage, resulting in fibrosis and pulmonary oedema, as well as a reduction in lung expansion. An inflammatory response can also result in the formation of a pleural effusion, which is considered to aggravate up to 40% of pneumonia cases. Gaseous exchange is diminished as a result of these alterations. As a result of the disruption in normal physiology, important organs will be deprived of oxygen, and the respiratory effort required with each breath will increase. In reaction to decreased oxygen and increased carbon dioxide levels, the respiratory and cardiac rates will increase. [5]

Epidemiology: Worldwide:

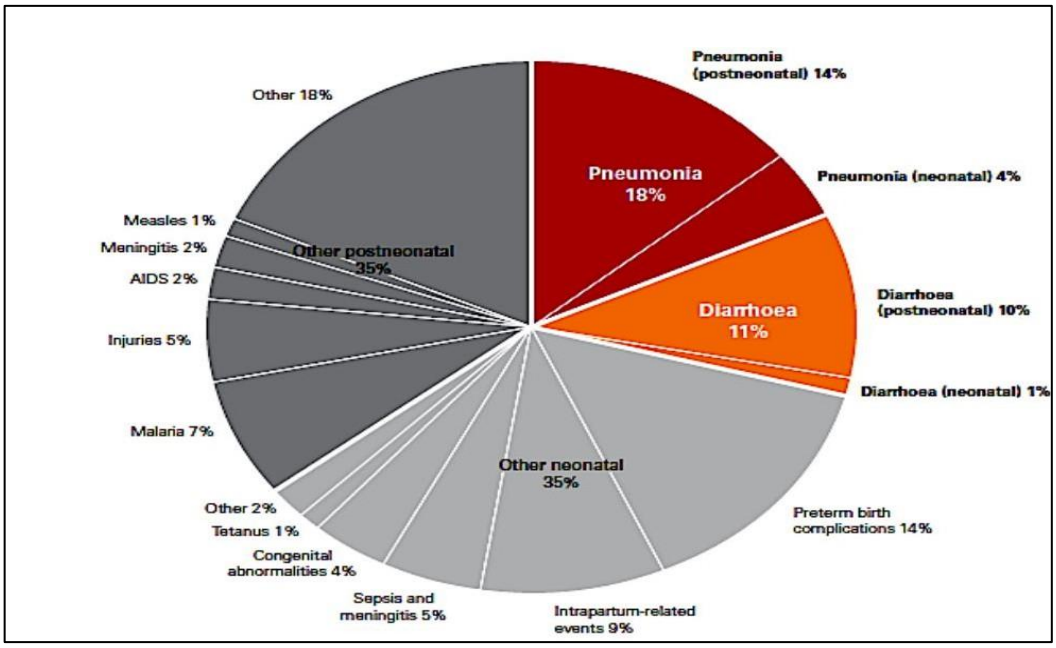
Pneumonia, diarrhoeal infections, preterm birth problems, and birth asphyxia are the four leading causes of death in children under the age of five worldwide. Pneumonia is still the most common cause of death, leading cause of death among children under the age of five. Of the estimated 6.9 million children in the world, each year, pneumonia kills between 1.3 and 1.6 million people in the United States. Around 18% of deaths among children under the age of five occur in this age range.

The trend in global mortality due to pneumonia and pneumonia-related deaths has decreased between 1990 and 2010, along with deaths under five due to pneumonia.[6]

European Countries:

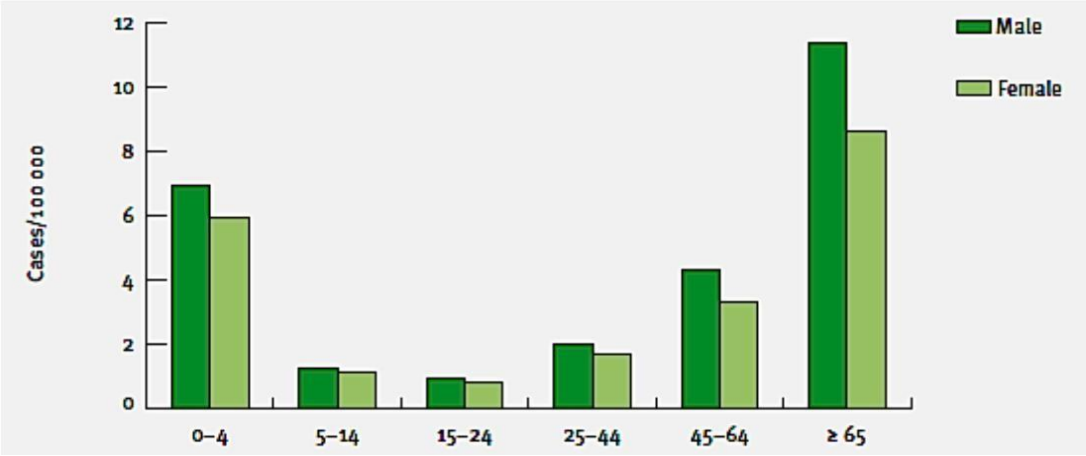
In Europe, pneumonia mortality rates are significantly higher in children under the age of four and individuals aged 75 and older than in most other age groups.

Invasive pneumococcal disease (IPD) is a type of pneumonia in which the bacteria S. pneumoniae enters the blood, cerebrospinal fluid, pleural fluid, joint fluid, or pericardial fluid, and can lead to various problems and infections such as pneumococcal sepsis.



Global distribution of deaths among children under age five by cause, 2009.

Non-invasive pneumococcal illness, on the other hand, can cause otitis media, sinusitis, and bronchitis when germs are aerosolized from the nasopharynx to the aveoli. In comparison to non-invasive pneumococcal disease, IPD is the primary cause of mortality and morbidity in children and adults.



Rates of reported cases of confirmed invasive pneumococcal disease, by age and gender, in EU and EEA/EFTA countries, 2009.[6]

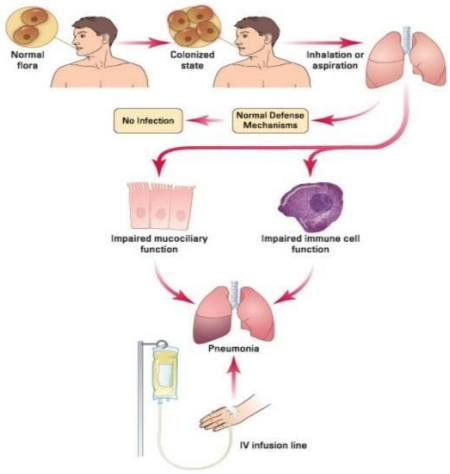
Causes: Pneumonia is caused by a number of infectious agents, including viruses, bacteria and fungi. The most common are:

- *Streptococcus pneumoniae* – the most common cause of bacterial pneumonia in children;
- *Haemophilus influenzae* type b (Hib) – the second most common cause of bacterial pneumonia;
- respiratory syncytial virus is the most common viral cause of pneumonia;
- in infants infected with HIV, *Pneumocystis jiroveci* is one of the most common causes of pneumonia, responsible for at least one quarter of all pneumonia deaths in HIV-infected infants.

Pneumonia can be caused by a parasite or fungus in rare cases. Aspiration pneumonia occurs when a foreign object, generally food or vomit, enters the lungs through the mouth, irritating the airways and lung tissue and increasing the risk of bacterial infection.[7,8]

Transmission:

1. Direct touch (typically the hands) or inhaling droplets in the air from coughing or sneezing can spread infection between people. Eg- Viruses like SARS-CoV-2 (that causes COVID-19) and influenza viruses can cause severe pneumonia.
2. Sometimes a person who has a viral infection, such as influenza virus, will also develop a secondary infection from bacteria such as Staphylococcus aureus or Streptococcus
pneumoniae while they are sick.
3. Pneumonia can be passed from person to person in a variety of ways. If viruses and bacteria frequently found in a child's nose or throat are inhaled, they can infect the lungs. Coughs and sneezes can potentially spread them through airborne droplets.
4. Pneumonia can also spread through the blood, especially during and shortly after birth. More research is needed on the various microorganisms that cause pneumonia and the mechanisms in which they are transmitted, as this is crucial for treatment and prevention.[7,8]



Risk factors:

Pneumonia can strike anyone at any time. However, elderly people and young children are particularly susceptible.

While most healthy children can fight the virus with their natural defences, children with weakened immune systems are more likely to get pneumonia. Malnutrition or undernourishment can decrease a child's immune system, especially in new borns who are not exclusively breastfed.

Some individuals Because they have a history of pneumonia, they are at a higher risk. Existing lung disorders, such as symptomatic HIV infections and measles, as well as poor nutrition and swallowing difficulties Other chronic health issues or immune system. People who smoke and people who are around tobacco smoke are at higher risk of developing pneumonia.

People who have not had the yearly influenza vaccine or who have not been immunized for Streptococcus pneumoniae- Bacteria (Prevnar 13® and/or Pneumovax 23® pneumococcal Vaccines) are also at higher risk for lung infections.

The following environmental factors also increase a child's susceptibility to pneumonia:

-Indoor air pollution caused by cooking and heating with biomass fuels (such as wood or dung)
-Living in crowded homes
-Parental smoking.[7,8]

Signs and symptoms:

The symptoms of bacterial pneumonia include:
-Bluish color to lips and fingernails
-Confused mental state or delirium, especially in older people
-Cough that produces green, yellow, or bloody mucus
-Fever
-Heavy sweating
-Loss of appetite
-Low energy and extreme tiredness
-Rapid breathing
-Rapid pulse
-Shaking chills
-Sharp or stabbing chest pain that's worse with deep breathing or coughing.
-Shortness of breath that gets worse with activity.

Early symptoms of viral pneumonia are the same as those of bacterial pneumonia, which may be followed by:
-Headache
-Increasing shortness of breath
-Muscle pain
-Weakness
-Worsening of the cough.

Stages of Pneumonia:

Bronchopneumonia

It affects both lungs in different ways. It's usually found close to or around the bronchi.

Lobar pneumonia

One or more lobes of lungs are affected by lobar pneumonia. Lungs are divided into lobes, which are distinct regions of the lung.

Stage 1- congestion - It happens within the first 24 hours of infection. Although there are many germs in the lungs, there

are few white blood cells available to fight the illness. The blood flow in the lungs rises, and fluid containing infectious organisms accumulates in the air sacs, causing the lungs to expand. As a result, the lung tissue seems thick and clogged.

Stage 2 -Red hepatization

It takes 48 to 72 hours to appear and lasts for 2 to 4 days. RBCs and immune cells enter the lungs as a result of increased blood flow, giving the lungs a pure red and solid appearance. The diseased lung becomes more dry, granular, and airless, with a consistency similar to that of liver. The airways in the lungs can get clogged with red cells, white cells, germs, and cellular debris.

Stage 3- Grey hepatization

Starts between days 4 and 6 and lasts for 4 to 8 days. As red blood cells begin to break down, the colour of the blood changes from red to grey. The lung is grey or yellow in colour, yet its substance is similar to that of the liver. The breakdown of fibrin, hemosiderin, and red blood cells results in a more fluid-like discharge. The formation of macrophages, a type of big white blood cell, begins.

Stage 4 – Resolution

It is the last stage of recuperation and takes place between days 8 and 10. Cell death fluids and breakdown products are reabsorbed. Macrophages (large white blood cells) are present and assist in the removal of dead white blood cells (neutrophils). This debris may be coughed up. The function of the airways and air sacs (alveoli) in the lungs returns to normal. Lung edoema that persists can lead to chronic lung disease (such as airway narrowing or pleural adhesions).

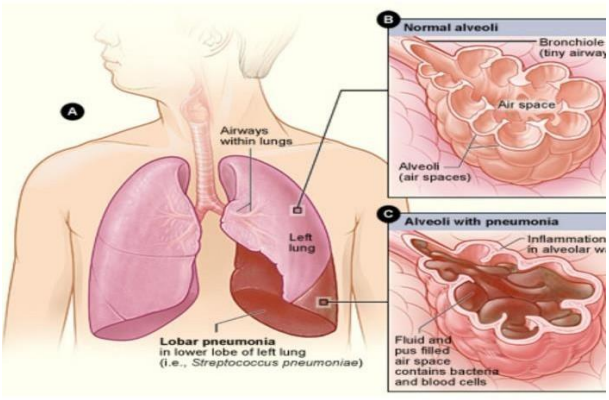


Diagram showing difference between healthy and infected part of lungs.
Figure A- Pneumonia affecting part of the lower lobe.
Figure B- Shows healthy alveoli.
Figure C- represents alveoli filled with pus/ mucus.

Types of pneumonia-

1) **HAP- Hospital Acquired Pneumonia-** Pneumonia obtained in a hospital (HAP). This kind of bacterial pneumonia is contracted while in the hospital. Because the bacteria implicated may be more resistant to drugs than other varieties, it can be more dangerous than other types of pneumonia.
2) **CAP-Community Acquired Pneumonia-** This refers to pneumonia that's acquired outside of a medical or institutional setting.
3) **VAP- Ventilator-associated pneumonia** When people who are using a ventilator get pneumonia, it's called VAP.
4) **Aspiration pneumonia**. Inhaling bacteria into your lungs from food, drink, or saliva can cause aspiration pneumonia. It's more likely to occur if you have a swallowing problem, or if you're too sedated from the use of medications, alcohol, or other drugs.
5) **Walking pneumonia** Walking pneumonia is a milder case of pneumonia. People with walking pneumonia may not even know they have pneumonia. Their symptoms may feel more like a mild respiratory infection than pneumonia. However, walking pneumonia may require a longer recovery period.

The symptoms of walking pneumonia can include things like:
-mild fever
-dry cough lasting longer than a week
-chills
-shortness of breath
-chest pain
-reduced appetite.

WHO response:

The WHO and UNICEF integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) aims to accelerate pneumonia control with a combination of interventions to protect, prevent, and treat pneumonia in children with actions to:

Protect children from pneumonia including promoting exclusive breastfeeding and adequate complementary feeding;
prevent pneumonia with vaccinations, hand washing with soap, reducing household air pollution, HIV prevention and cotrimoxazole prophylaxis for HIV-infected and exposed children;
treat pneumonia focusing on making sure that every sick child has access to the right kind of care -- either from a community

based health worker, or in a health facility if the disease is severe -- and can get the antibiotics and oxygen they need to get well.

Control Strategy:

Pneumonia is caused by a combination of a variety of factors, including pathogens, the environment, health systems, and health-seeking behaviour. Therefore, no single intervention can effectively prevent, treat, or control pneumonia. As such, a confluence of key interventions to control pneumonia would include immunization against specific pathogens, early diagnosis and treatment of the disease, and improvements in nutrition and environmental living conditions (e.g. safe drinking water, sanitation, hygiene, low household air pollution).

Care-seeking behavior:

The Multiple Indicator Cluster Surveys (MICS) and Demographic Household Survey (DHS) provide information on caregivers' knowledge of symptom of pneumonia and on the extent to which caregivers seek appropriate provider for their children with suspected pneumonia. recent data from MICS and DHS between 2000 to 2010 showed that care-seeking for children with symptoms of pneumonia has increased slightly in developing countries, from 54% in 2000 to 60% in 2010.[6]

Early Diagnosis:
Your doctor will begin by gathering information about your medical history. They'll inquire about the onset of your symptoms as well as your overall health.

They'll then conduct a physical examination on you. This will include using a stethoscope to listen to your lungs for any unusual noises, such as crackling.

Your doctor may also prescribe one or more of the following tests, depending on the severity of your symptoms and your risk of complications:

X-ray of the chest- Your doctor can use an X-ray to check for symptoms of inflammation in your chest. If inflammation is present, the X-ray can also tell your doctor where it is and how severe it is.

Blood culture - The blood sample is used in this test to confirm an infection. Culturing can also help you figure out what's causing your problem.

sputum culture -
After you've coughed deeply, a sample of mucus is taken during a sputum culture. The sample is then sent to a lab to be tested in order to determine the source of the infection.

Pulse oximetry -
A pulse oximetry measures the amount of oxygen in your blood. A sensor placed on one of your fingers can indicate whether your lungs are moving enough oxygen through your bloodstream.

CT scan -
CT scans provide a clearer and more detailed picture of your lungs.

Fluid sample -
If your doctor suspects there's fluid in the pleural space of your chest, they may take a fluid sample using a needle placed between your ribs. This test can help identify the cause of your infection.

Bronchoscopy -
A bronchoscopy looks into the airways in your lungs. It does this using a camera on the end of a flexible tube that's gently guided down your throat and into your lungs.

Treatment:
Treatment for pneumonia mainly depends on the type of pneumonia, its severity, and the causative organism. The treatment is mainly focused on relieving the symptoms, resolve the infection and to prevent the development or worsening of complications.
Viral pneumonia usually resolves itself within one or three weeks. Antiviral medications may be prescribed by physician. In case of bacterial pneumonia, an antibiotic treatment is given. The symptoms may get relieved soon after starting the medications. However, it is recommended to take the antibiotics for the prescribed period of time to completely resolve the infection, failing to do so has a high chance of getting relapse of pneumonia.
Most people with Community Acquired Pneumonia are treated at home.[6,9]

Treatment	Dosage	Form
Amoxycillin	250 mg, 500 mg	Tablets
Ampicillin	500 mg, 1 g	Powder for injection
Ceftriaxone	250 mg, 1 g	Powder for injection
Gentamicin	20 mg/ml, 40 mg/ml	Injection
Procaine benzylpenicillin	1 g, 3 g	Powder for injection
Oxygen	-	Medicinal gas

Animal model	Model of human pathology	Primary endpoints	Animal species	Important considerations	Relevant characteristics
One-hit acute model	Acute pneumonia, hospital-acquired pneumonia (depending on the choice of pathogen)	Histopathology: multi-lobar confluent pneumonia Mortality: high	Rat Mouse	High bacterial dose used Aerosol, intranasal, intra-tracheal or endotracheal inoculation	Rapid clearance and risk for sepsis development Different accuracy for dose delivery depending on method
VAP model	Ventilator-associated pneumonia model using MV as additional insult	Histopathology: multi-lobar confluent pneumonia Mortality: very high	Piglet Rat Mouse	MV parameters (protective or injurious) have major impact on model Bacterial inoculation before or after MV Prolonged MV is challenging in rodents	Spontaneous pneumonia (piglet): polymicrobial etiology of common airway colonizing organisms Induced oropharyngeal aspiration model (Piglet) MV itself causes inflammation that impacts the disease pathogenesis
Pa agar bead model	Cystic fibrosis (chronic) pneumonia using agar beads to mimic biofilm matrix	Histopathology: bronchopneumonia Mortality: moderate	Rat Mouse	Bacteria loaded beads or Free-living bacteria mixed with sterile beads Use of mucoid strains	Sterile beads induce infiltration of neutrophils and eosinophils Airway obstruction can occur in mice

Vaccination:

Vaccination is a safe, effective, and cost-effective tool for preventing pneumonia. There are vaccines against major infectious diseases that can cause pneumonia –the flu (influenza virus), measles, pertussis, Hib, and pneumococcus. The WHO recommends that all routine childhood immunization programs include vaccines that protect against these disease.[7]

Comparison of relevant mouse models of acute pneumonia:

Parameter	*Streptococcus pneumoniae*	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Acinetobacter baumannii*	*Legionella pneumophila*	*Escherichia coli*	Middle East respiratory syndrome coronavirus	Influenza A virus (IAV)	IAV + *Streptococcus pneumoniae*
Infectious dose	5×10^6 CFU	5×10^7 CFU	3.5×10^5 CFU	5×10^8 CFU	1×10^6 CFU	5×10^8CFU	7×10^4 $TCID_{50}$	100 PFU	H1N1: 40 PFU, ST3: 1×10^3CFU
Route of infection	Transnasal	Transnasal	Intratracheal	Transnasal	Transnasal	Intraperitoneal	Transnasal	Transnasal	Transnasal
Examination post infection at	48h	48h	48h	48h	48h, 6d	12h	4d	7d	8d + 24h
Distribution of lesions	Multifocal	Multifocal	Multifocal	Multifocal	Multifocal	Diffuse	Multifocal	Diffuse	Diffuse
Expansion to lung periphery	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Type of pneumonia	Broncho-pneumonia	Broncho-pneumonia	Broncho-pneumonia	Broncho-pneumonia	Interstitial pneumonia	Interstitial pneumonia	Interstitial pneumonia	Bronchointerstitial pneumonia	Broncho-pneumonia
Main character	Suppurative	Suppurative	Suppurative	Suppurative	Histiocytic at 48h, granulomatous at 6d	Suppurative	Necrotizing	Necrotizing	Suppurative
Dominant inflammatory cell type	Neutrophils	Neutrophils / macrophages	Neutrophils	Neutrophils / macrophages	Macrophages	Neutrophils	Macrophages / lymphocytes	Lymphocytes / macrophages	Neutrophils / lymphocytes / macrophages

Pneumococcal pneumonia vaccine-
This type of vaccination is particularly recommended for:
Children less than five years of age. Children older than five years old and suffering from lung ailments, heart diseases or cancer.
Adults more than 65 years of age
o Smokers
o People who have chronic diseases, such as diabetes, HIV/AIDS, asthma, or a weak immune system.

Flu (influenza) vaccine-
Many times, people who get the flu are more prone to getting pneumonia than their healthy counterparts. Thus, getting vaccinated every year can help prevent contracting the disease. The flu vaccine is usually administered in the months of September to November, i.e., just before the time when it is most frequently spread.

Hib vaccine-
Heamophilus influenzae type b (H1b) (a bacteria) causes pneumonia and meningitis. Thus, to prevent these two infections, this vaccine is administered in children. It is usually recommended for all kids less than five years old and is often given to babies starting at six months of age.

Animal Models for pneumonia- Summary of animal models of pneumonia-[10]

Animal models for VAP Pneumonia-
Few studies of experimental aspiration pneumonia have been conducted, and the majority of them were conducted in the 1970s using cats and dogs to investigate the pathogenesis of lung injury [5]. Tilson et al. 6 investigated the quantitative bacteriology and pathology of the lung in experimental Pseudomonas aeruginosa pneumonia treated with positive end expiratory pressure (PEEP), and Moser et al. 7 compared the yield of different diagnostic procedures in experimentally induced Streptococcus pneumoniae pneumonia using a canine model of pneumonia. The research carried out by Johanson and coworkers 8-10 in the 1980s, which employed a baboon model to explore the bacteriological diagnosis of pneumonia, were the first attempts to use an animal model for the investigation of different features of nosocomial pneumonia following mechanical ventilation. Cultures of tracheal secretions, bronchoalveolar lavage (BAL), protected specimen brushes (PSB), and direct lung aspirates were compared to cultures of lung homogenates and histological findings in investigations by Johanson and coworkers 8-10.

Marquette et al. used 22+2 kg Landrace-White piglets to create a model of experimental pneumonia in mechanically ventilated individuals. The authors decided to conduct a study comparing the histological and bacteriological findings in previously healthy pigs infected with bacterial pneumonia while free of antibiotic therapy after discovering that piglets mechanically ventilated for 4 days with experimentally created tracheal stenosis consistently developed spontaneous pneumonia.[11]

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WORLD DIABETES DAY

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The 14th of November is World Diabetes Day. World Diabetes Day (WDD) was established in 1991 by the International Diabetes Federation (IDF) and the World Health Organization (WHO) in response to growing concerns about diabetes's growing health hazard. With the approval of United Nations Resolution 61/225 in 2006, World Diabetes Day became an official United Nations Day.[1]

Introduction:

Diabetes is a condition in which your blood glucose, often known as blood sugar, is abnormally high. Your main source of energy is blood glucose, which comes from the food you eat. Insulin, a hormone produced by the pancreas, aids glucose absorption into cells for use as energy. Sometimes your body doesn't produce enough — or any — insulin, or it doesn't use it properly. Glucose remains in your circulation and does not reach your cells as a result. Having too much glucose in your blood might lead to health issues over time. Although there is no cure for diabetes, you may take efforts to manage it and stay healthy. Diabetes is also referred to as "a touch of sugar" or "borderline diabetes." These words imply that someone does not have diabetes or has a milder form of the disease, however diabetes affects everyone.[2]

A blood sugar level of 140 mg/dL or less at 2 hours is considered normal, 140 mg/dL to 199 mg/dL indicates prediabetes, and 200 mg/dL or above implies diabetes.[3]

Types of diabetes:

Type 1 diabetes

An autoimmune disease is one in which your body attacks itself. The insulin-producing cells in your pancreas are damaged in this situation. Type 1 diabetes affects up to 10% of patients with diabetes. It's most commonly found in children and young adults (but can develop at any age). It used to be called "juvenile" diabetes. People with Type 1 diabetes must take insulin on a daily basis. It's also known as insulin-dependent diabetes because of this.[4]

Type 2 diabetes

This type occurs when your body either does not produce enough insulin or when your body's cells do not respond to insulin properly. Diabetes mellitus is the most frequent form of the disease. Type 2 diabetes affects up to 95% of diabetics. It mainly affects persons in their forties and fifties. Type 2 diabetes is also known as adult-onset diabetes or insulin-resistant diabetes. It was probably referred to as "having a touch of sugar" by your parents or grandparents.[4]

Prediabetes

This is the stage prior to the onset of Type 2 diabetes. Your blood glucose levels are higher than normal, but not high enough for Type 2 diabetes to be diagnosed.[4]

Gestational diabetes

Some women develop this kind during pregnancy. Gestational diabetes normally disappears after the baby is born. If you have gestational diabetes, however, you are more likely to develop Type 2 diabetes later in life.[4]

Less common types of diabetes include:

Monogenic diabetes syndromes

These are rare hereditary diabetes types that account for up to 4% of all cases. Neonatal diabetes and young-onset diabetes are two such examples.[4]

Cystic fibrosis-related diabetes

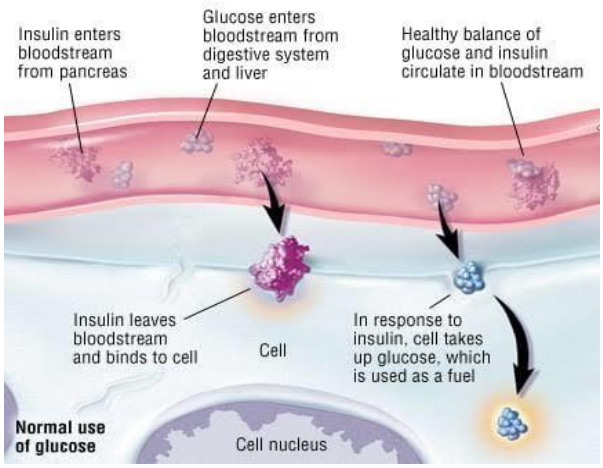
This is a type of diabetes that only affects persons who have it.

Drug or chemical-induced diabetes: Examples of this type happen after organ transplant, following HIV/AIDS treatment or are associated with glucocorticoid steroid use.

Diabetes insipidus is an uncommon disease in which your kidneys create an excessive amount of urine.[4]

Pathophysiology of Diabetes mellitus

Type 1 diabetes is an autoimmune illness in which beta cells are destroyed over a long period of time before clinical diabetes is identified. Type 2 diabetes is caused by a combination of insulin resistance and relative insulin shortage or a malfunction in insulin release.[5]



Etiology:

Causes

To comprehend diabetes, you must first comprehend how glucose is regularly handled in the human body.

How Insulin works?

Insulin is a hormone produced by a gland below and beneath the stomach (pancreas). Insulin is released into the bloodstream by the pancreas. Insulin circulates in your body, allowing sugar to enter your cells. Insulin is a hormone that reduces the quantity of sugar in your blood. The amount of insulin secreted by your pancreas decreases as your blood sugar level drops.[6]

Role of glucose

Glucose — a sugar — is a source of energy for the cells that make up muscles and other tissues. Glucose comes from two major sources: food and liver. Sugar is absorbed into the bloodstream, where it enters cells with the help of insulin. Liver stores and makes glucose. When your glucose levels are low, such as when you haven't eaten in a while, the liver breaks down stored glycogen into glucose to keep your glucose level within a normal range.

Causes of Type 1 diabetes:

Type 1 diabetes has an aetiology that is unknown. What is known is that your immune system, which is generally responsible for fighting harmful bacteria and viruses, assaults and destroys your pancreas' insulin-producing cells. You will have very little or no insulin as a result of this. Sugar builds up in your bloodstream instead of being delivered to your cells.

Type 1 diabetes is assumed to be caused by a mix of genetic predisposition and environmental factors, however the exact nature of those variables is unknown. Weight isn't thought to play a role in type 1 diabetes.

Causes of Prediabetes and Type 2 diabetes:

Cells become resistant to the action of insulin in prediabetes — which can lead to type 2 diabetes — and type 2 diabetes, and the pancreas is unable to create enough insulin to overcome this resistance. Sugar builds up in your bloodstream instead of going into cells where it is needed for energy.

It's unclear why this happens, while genetic and environmental variables are thought to play a role in the development of type 2 diabetes. Although being overweight is significantly connected to the development of type 2 diabetes, not everyone who has the disease is obese.

Causes of gestational diabetes:

The placenta generates hormones to keep the pregnancy going during pregnancy. Insulin resistance is increased by these hormones.

The pancreas normally responds by generating enough additional insulin to overcome resistance. However, the pancreas can't always keep up. When this occurs, too little glucose enters cells while too much remains in the circulation, resulting in gestational diabetes.[6]

Diagnosis and treatment:

Blood sugar testing is a reasonably inexpensive way to make an early diagnosis.

Diabetes is treated through a combination of diet and exercise, as well as reducing blood glucose and other recognised blood vessel-damaging risk factors. Tobacco abstinence is also necessary to avoid problems.

In low- and middle-income nations, interventions that are both cost-effective and practical include:

Controlling blood glucose levels, especially in people with type 1 diabetes. Type 1 diabetes requires insulin, while type 2 diabetes can be managed with oral medications but may require insulin as well as blood pressure control and foot care (patient self-care by maintaining foot hygiene; wearing appropriate footwear; seeking professional care for ulcer management; and regular examination of feet by health professionals).[7]

Other cost saving interventions include:

Retinopathy (which causes blindness) screening and treatment; blood lipid control (to keep cholesterol

levels in check); and early detection and treatment of diabetes-related kidney disease.

Prevention:

It is impossible to prevent type 1 diabetes. However, the same healthy lifestyle choices that aid in the treatment of prediabetes, type 2 diabetes, and gestational diabetes can also aid in the prevention of these conditions:

Consume nutritious foods. Reduce your fat and calorie intake while increasing your fibre intake. Fruits, vegetables, and whole grains should be prioritised. To avoid boredom, strive for variety.

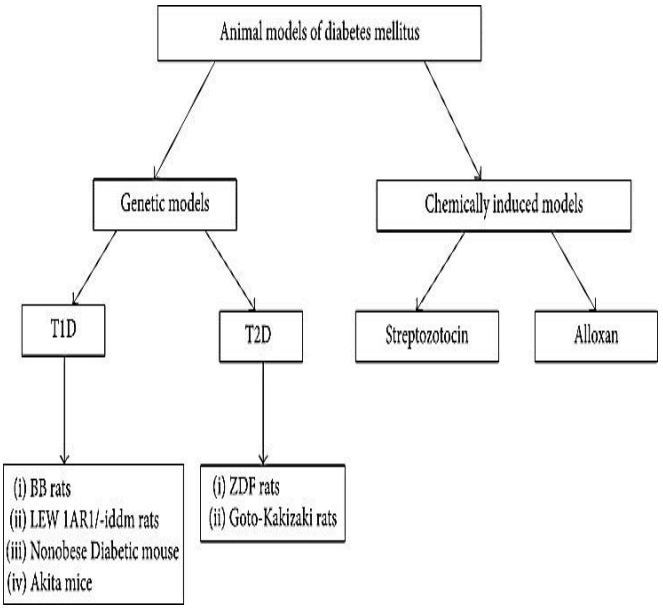
Increase your physical activity. Aim for at least 150 minutes of moderate aerobic activity per week, or roughly 30 minutes of moderate aerobic activity on most days of the week. Get rid of the extra pounds.

However, don't strive to lose weight when pregnant. Consult your doctor about how much weight you should gain during your pregnancy.

Focus on long-term improvements to your food and activity habits to maintain a healthy weight. Remember the advantages of losing weight, such as a healthier heart, greater energy, and improved self-esteem, to keep yourself motivated.

Medication is sometimes an option as well. Metformin (Glumetza, Fortamet, and others) and other oral diabetes medications can help reduce the risk of type 2 diabetes, although good lifestyle choices are still important. Check your blood sugar at least once a year to be sure you don't have type 2 diabetes.[8]

Animal models of Diabetes are depicted in via a tree diagram:



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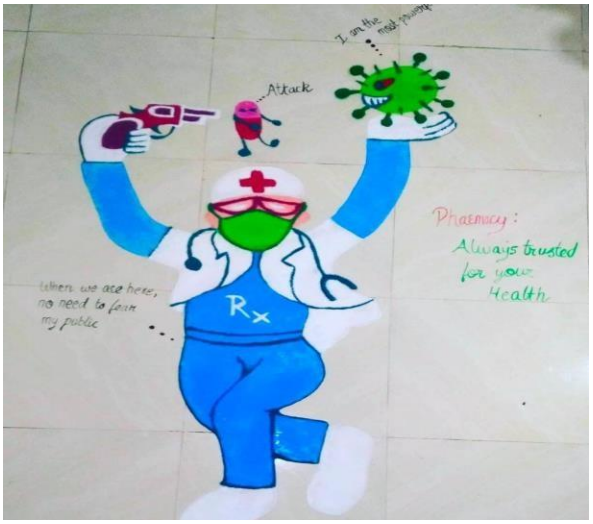
THANK YOU!!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Always trusted
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Health
When we are here,
no need to fear
my public