IMPACT OF TUBERCULOSIS ON DIFFERENT BODY ORGANS AND ITS TREATMENT

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ABSTRACT

Despite the availability of excellent treatment since the 1940s, tuberculosis, an ancient disease caused by the bacteria Mycobacterium tuberculosis, is nevertheless responsible for more fatalities globally each year than any other infectious disease, including the human immunodeficiency virus (HIV). Malnutrition, which weakens the host immune systems; overcrowding, which enhances the likelihood of tubercle bacilli transmission; and disruption of medical and public health services, which hampered control and treatment efforts, were the key risk factors. Although tuberculosis is a treatable disease, its odds of being cured diminish as the disease develops multidrug resistant, and the situation worsens as the disease becomes extensively drug resistant. In the initial treatment period of 6-9 months, medications are given in various combinations of first-line treatments (isoniazid, rifampin, and pyrazinamide), which comprise the core of the therapy regimen. Drug-resistant tuberculosis is a critical barrier for tuberculosis treatment and control initiatives. It is critical to keep up to speed on the mechanisms and molecular bases of drug resistance evolution in Mycobacterium TB. TB has a negative impact on a variety of human organs. It affects not just the lungs, but also the heart, renal system, central nervous system, gastrointestinal tract, and joints, among other organs. This review focuses on the treatment of tuberculosis by discussing the pharmacokinetics and mode of action of antituberculosis medications, as well as the pathophysiology and impact of tuberculosis on various organs of the body (isoniazid, rifampin, and pyrazinamide).

Key words *:Pharmacokinetics,malnutrition,pathophysiology and nervous system*

INTRODUCTION

Tuberculosis (TB) has been a part of human history since the dawn of time, is an ailment that has been well-described as feasting and has historically resulted in considerable morbidity and mortality. The sickness has existed for much of human history, and it has been particularly fatal at times. In fact, tuberculosis can be drawn back more than 5,000 years to early Egypt. In 1882 Robert Koch's discovered the causative agent of tuberculosis [1]. Robert Koch's discovery sparked a revolution by clarifying the disease's infectious aetiology, which had been a mystery for so long. Mycobacterium is an immobile, aerobic, acid-fast bacteria with a diameter of 0.8-4 micron that is sensitive to solar and ultraviolet radiation, heat, and disinfectant but not to drying. Tuberculosis is a chronic disease caused by the Mycobacterium tuberculosis complex, which includes Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium caprae and Mycobacterium africanum. other mycobacteria (also known as non-TB, atypical, or environment mycobacteria) can cause pulmonary or extrapulmonary disease in a marginal of cases [2]. Because Mycobacterium tuberculosis primarily affects the lungs, pulmonary illness is the most predominant symptoms. The respiratory system, gastrointestinal (GI) system, lymphoreticular system, skin, central nervous system, musculoskeletal system, reproductive system, and liver are the organ system most typically impacted Patients with tuberculosis are pragmatically defined as having latent TB infection (LTB), which is an asymptomatic and non-transmissible state, or active TB disease, which manifests as fever, lethargy, lack of appetite, and weight loss [3][4].

1. EPIDEMIOLOGY

From antiquity to today, Mycobacterium tuberculosis, a human disease with no known environmental reservoir, has perfected the art of survival and thrived in human societies. In recent decades, there has been a concentrated global campaign to eradicate tuberculosis (TB). The WHO South-East Asian Region saw the newest cases in 2020, accounting for 43 percent of all new cases, followed by the WHO African Region with 25 percent and the WHO Western Pacific with 18 percent. In 2020, the 30 nations with the highest TB burden accounted for 86 percent of new TB cases. India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa accounted for two-thirds of new TB cases. According to the WHO's global tuberculosis report for 2021, TB is treatable and preventable. About 85% of patients with tuberculosis can be successfully treated with a 6-month treatment regimen, and TB infection can be treated with regimens ranging from 1 to 6 months [3][5]. Multisectoral intervention to address TB factors such as poverty, undernutrition, HIV infection, smoking, and diabetes can also lower the number of people who become infected and develop disease (and consequently the number of people who die from Tuberculosis) [6]. Some countries have already decreased their TB disease burden to less than 10 cases and 1 death per 100,000 people each year. To quickly reduce the number of new cases each year worldwide to the levels already attained in these low-burden countries, research breakthroughs are required [7].

Terminology:

- **Active TB disease**: Active tuberculosis is a condition in which bacteria multiply rapidly and infiltrate various organs of the body. Cough, phlegm, chest pain, weakness, weight loss, fever, chills, and night sweating are all common symptoms of active tuberculosis. A person with active pulmonary tuberculosis can transfer the disease to others by coughing infectious particles into the air [8].
- **Miliary TB disease**: Miliary tuberculosis is a rare form of active tuberculosis that occurs when TB bacteria enter the bloodstream. The bacteria proliferate throughout the body in microscopic nodules in this form, affecting numerous organs at once. This type of tuberculosis can be lethal in a matter of days [9].
- **Latent TB infection**: Many people who are afflicted with tuberculosis do not exhibit symptoms. They don't have any symptoms, and an X-ray of their chest may be normal. The tuberculin skin test (TST) or the interferon-gamma release assay may be the only signs of this interaction (IGRA). However, there is always the possibility that the latent infection will progress to active disease. Other disorders, such as HIV, or drugs that impair the immune system, enhance the risk [10].
- **Droplet nuclei infection**: This sort of infection occurs when the virus or bacteria-containing liquid element of a cough or sneeze evaporates, scatters as microscopic particles, and floats in the air until inhaled. An infection could spread over a large area depending on how the air containing the droplet nuclei flows [11].
- **Resistant bacteria**: Bacteria that can no longer be destroyed by a particular antibiotic.

- **Tuberculin or PPD**: During a Tb skin test, a liquid is injected beneath the skin on the lower part of the arm. If someone has a latent tuberculosis infection, they will most likely have a positive tuberculin reaction [12].
- **Osteoarticular tuberculosis**: The bones are destroyed when tuberculosis bacteria attach to the bones and joints, forming tuberculous lesions in the skeletal tissue. The most common variety is Pott's illness. In this illness, the bones press against the nerves, causing pain and deforming the back. Osteoarticular TB is a type of tuberculosis that affects the hip and knee joints [13].
- **Pleura:** the membrane that covers the lungs' and chest wall's surfaces. The pleura forms the pleural cavity between the lungs and the chest wall, which aids in the smooth breathing of the lungs.
- Pulmonary tuberculosis: Infection of the lungs or bronchial tube with TB. Pneumococcal tuberculosis accounts for 80% of tuberculosis infections [12]**.**
- **Extrapulmonary tuberculosis (EPTB):** Tuberculosis that occurs outside of the lungs is known as extrapulmonary tuberculosis. Meningitis caused by tuberculosis, abdominal tuberculosis, skeletal tuberculosis, Pott's illness, lymphadenitis, and renal tuberculosis are all examples of EPTB [11][45].

2. PATHOGENESIS OF TUBERCULOSIS

Infection occurs when a person inhales tubercle bacilli-containing droplet nuclei that reach the lungs' alveoli. These tubercle bacilli are ingested by alveolar macrophages, and most of them are destroyed or suppressed When macrophages die, a tiny number of them may multiply intracellularly and be discharged. If alive, these bacilli can move to more distant tissues and organs via lymphatic routes or the bloodstream (including areas of the body in which TB disease is most likely to develop regional lymph nodes, apex of the lung, kidneys, brain, and bone). The immune system is primed for a systemic reaction as a result of this dissemination process [14][15].

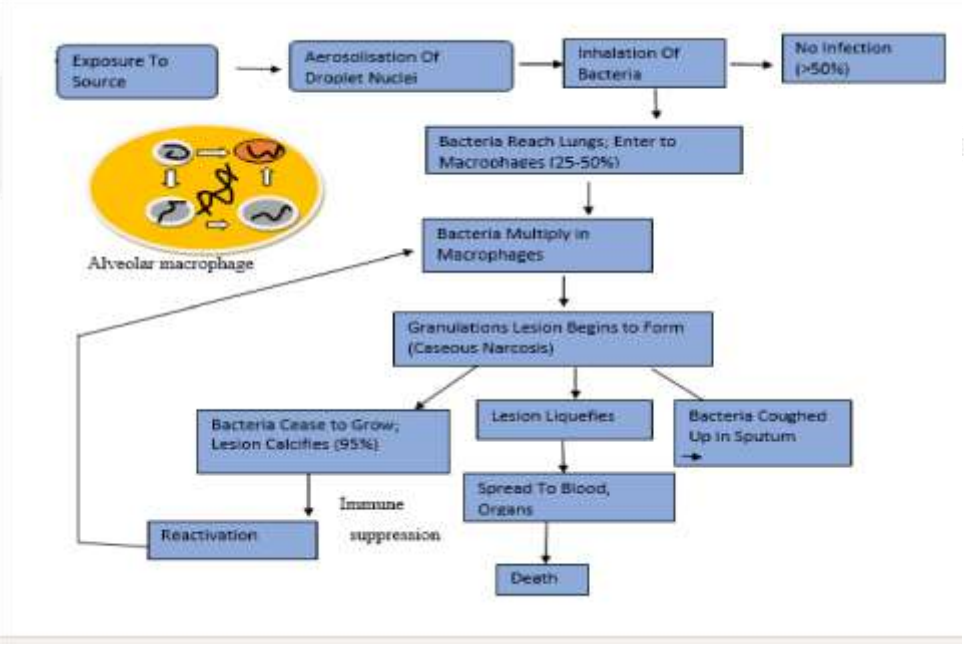

Fig: flow chart showing pathogenesis of tuberculosis**.**

2.1 Types of tuberculosis and their symptoms

A. Pulmonary tuberculosis

- Primary tuberculosis**:** Primary tuberculosis, also known as Ghon's complex or childhood tuberculosis, is an infection that occurs in someone who has never been infected or inoculated.
- Secondary tuberculosis**:** Secondary TB is an infection that occurs after a human has been previously infected or sensitised. It is also known as post-primary tuberculosis, reinfection, or chronic tuberculosis**.**

B. Extrapulmonary tuberculosis: Secondary tuberculosis is an infection that develops after a person has already been infected or sensitised. It's also known as chronic TB, reinfection, or post-primary tuberculosis.

- Lymphadenitis TB: In HIV-positive people, this is a common occurrence. Painless swelling of lymph nodes, most typically at the cervical and supraclavicular levels, is one of the most prevalent symptoms.
- Pleural TB**:** Pleural involvement is prevalent in primary tuberculosis and is caused by tubercle bacilli penetrating the pleural space.
- TB of upper airways: The larynx, pharynx, and epiglottis are all involved. Dysphagia and a prolonged productive cough are among the symptoms.
- Genitourinary TB: Infection can occur in any area of the genitourinary tract. Urinary frequency, dysuria, and hematuria are some of the symptoms.
- Skeletal TB: Weight-bearing joints such as the spine, hip, and knee are all involved. Symptoms include pain in the hip joints and knees, as well as swelling and damage**.**
- Gastrointestinal TB: Any section of the gastrointestinal tract is involved. Abdominal pain, diarrhea, and weight loss are some of the symptoms.

- Miliary tuberculosis: It is caused by tubercle bacilli spreading through the bloodstream. It spread because the virus entered the pulmonary vein, causing lesions in various extrapulmonary locations.
- Less common extrapulmonary TB**:** Painful hypersensitivity-related phlyctenular conjuctivitis, often known as pan ophthalmitis [16][17][47].

2.2 Causes of tuberculosis

- Tuberculosis is transmitted from one person to another through the air.
- Undernutrition.
- Bacterial infection
- Smoking
- Close touch with someone who is sick [46].

2.3 Risk factors

1. Weakened immune system

A strong immune system may typically defeat tuberculosis bacteria. However, your immune system can be weakened by a number of illnesses and drugs, including:

- HIV/AIDS,
- Diabetes,
- Severe Kidney Disease,
- and Some Cancers
- Chemotherapy for cancer
- Anti-rejection drugs for transplanted organs.
- Some drugs used to treat rheumatoid arthritis,
- Crohn’s disease psoriasis
- Malnutrition low body weight.
- Very young or advanced age

2. **Travelling or living in certain areas**

The risk of contracting tuberculosis is higher in areas such as

- Africa,
- Asia,

- Eastern Europe,
- Russia, and
- Latin America.

3. **Other factors:**

- **Using substances**: Your immune system is weakened by IV medications or heavy alcohol consumption, making you more susceptible to tuberculosis.
- **Using tobacco**: Tobacco use increases the chances of contracting tuberculosis and dying from it.
- **Working in health care**: Contact with sick persons on a frequent basis increases your chances of contracting tuberculosis. You can drastically lower your risk by wearing a mask and washing frequently.
- **Living or working in a residential care facility**: Due to congestion and poor ventilation, people who live or work in jails, homeless shelters, psychiatric hospitals, or nursing homes are at a higher risk of tuberculosis.
- **Living with someone infected with TB**: Close contact with someone who has tuberculosis raises your risk of contracting the disease [18][19].

3.IMPACT OF TUBERCULOSIS ON VARIOUS ORGANS OF HUMAN BODY

Untreated active TB typically affects lungs, but it can affect other parts of body, as well.

Tuberculosis complication include:

Impact of TB on respiratory system

Although it is unclear whether these disease manifestations occur as a result of primary infection or reactivation locally or elsewhere, Mycobacterium tuberculosis can cause TB manifestations in all compartments of the respiratory tract (i.e., nose, sinuses, pharynx, larynx, trachea, bronchi, bronchioles, and lungs). Mycobacterium tuberculosis must navigate lung anatomy, airway function, and the laws of physics that regulate flow dynamics, size, shape, velocity, and quantity of inhaled particles in order to infect a cell in the alveolar space. Cough reflex arcs, airway geometry, humidity, mucociliary clearance, and mucosal bactericidal chemicals, for example, must all be avoided by Mycobacterium tuberculosis-containing droplets. M. tb droplets can be deposited in the lungs in four different ways, depending on their size, shape, and speed. In the case of

larger particles, centrifugal force causes droplets to collide against the upper bronchial walls. Larger, elongated particles (e.g., M. tb clumps) are intercepted as soon as they come into contact with the airway and are normally removed by mucus and ciliary activity. These mucus-coated bacilli are usually evacuated and/or delivered into the stomach, which represents another possible entry point. Sedimentation happens when smaller particles stay in the airways longer and are deposited in the lower bronchi, where air flow is slower, due to gravity. Finally, for particles smaller than 0.5 microns, Brownian motion is dominant, and deposition in the lungs is ineffective. It's currently unclear how intrinsic (size, charge, viscosity, surface tension, density) and extrinsic (speed, concentration, clumping/agglomeration, humidity, temperature) features of M. tb droplets influence infection and transmission. M. tb infection, on the other hand, is thought to necessitate close contact with someone who has active tuberculosis [9][20][21][22].

Impact of TB on kidney:

Kidneys aid in the removal of waste and pollutants from the bloodstream. Tuberculosis in these organs might cause them to stop working properly. The kidneys can get contaminated as a result of infection spreading from other regions of the body, particularly the lungs, through the bloodstream. Renal TB is tuberculosis that affects the kidneys and is caused by Mycobacterium tuberculosis, a major cause of respiratory illness in impoverished and developing countries. Other bacteria, such as Mycobacterium bovis, can also cause it. When the BCG vaccine is directly injected into the bladder, the mycobacterium in the vaccine can develop primary renal tuberculosis. Babies are usually given the BCG vaccine to protect them from tuberculosis. A newer application is for the treatment of superficial bladder cancer, in which the vaccine is injected into the bladder. Some cases of kidney TB have resulted from this method. Reduced

immunity, such as in HIV patients, diabetics, and those on immunosuppressive medicines after organ transplantation, raises the chance of developing renal tuberculosis.

Risks and Complications of renal tuberculosis include the following

- Calcium deposits in the kidney, which suggest that kidney function is deteriorating.
- Hypertension.
- The occurrence of cellular alterations known as keratinizing squamous metaplasia, which predisposes to squamous cell carcinoma.
- The creation of an abscess that spreads around the kidney.
- Tuberculosis spreads to the ureters, which transport urine from the kidney to the urinary bladder. Ulceration and narrowing of the tube might occur as a result of the infection, blocking urine flow into the bladder.
- Tuberculosis spreading to the urinary bladder. Thimble bladder is a condition in which the bladder shrinks and contracts. In males, tuberculosis infection spreads to the urinary bladder through the epididymis, or when the BCG vaccination is injected into the bladder.
- Hydronephrosis is the swelling of the kidney.
- Renal failure that has progressed to the end stage [23][24].

Impact of TB on joint damage:

The disease can affect any bone or the joint, but most common bones affected are spinal vertebra, knee, hip, shoulder and elbow bones and joints. Following are the main clinical manifestations of tuberculosis of bone:

- **Pain:** The weight-bearing bones are primarily affected. It's possible that pain will develop at the point of involvement. The thoracic spine is usually more afflicted than the rest of the bones. The patient may experience back pain. In certain circumstances, the pain may spread to the front of the ribs**.** Tuberculosis of the joints can cause pain, oedema, and stiffness in the joint. It limits the actions of the patient.
- **Arthritis**: Tuberculosis of the joints damages the synovial tissue and bones of a joint, primarily the hip and knee joint, over time. The injured joint has oedema, redness, and stiffness.
- **Spinal deformity**: If untreated, tuberculosis of the spine can lead to the growth of a hump on the back. The slow degeneration of the spinal vertebra causes this malformation. The spinal bone may get displaced and lose its alignment as a result of the damage. At the back, it may appear as a hump or a gibbus.
- **Paraplegia:** The vertebra may collapse on another vertebra as a result of the destruction. This could cause damage to the spinal cord, resulting in paralysis of the lower limbs.
- **Constitutional symptoms**: Other general symptoms may include moderate fever, night sweats, weight loss, decreased appetite, weariness, and so on (causes of tb).
- Tissue damage from tuberculosis arthritis can be severe. It's critical to keep the infection from spreading to other joints. Joint degradation, nerve compression, spinal cord compression, and vertebral collapse leading to kyphosis are all possible sequelae of TB arthritis [25][26][27][45].

Impact of TB on heart:

Tuberculosis can infect the tissues surrounding the heart on rare occasions, causing inflammation and fluid accumulations that can impair the heart's capacity to pump adequately. Tamponade is a potentially lethal disorder. As soon as the infection is severe enough to induce clinical symptoms, the first changes in the heart and circulatory system are noticed. This is an increase in the rate of the pulse. It is most likely toxic in nature and is linked to a decrease in blood pressure due to the effect of tubercle toxins on vasodilators. As the condition worsens and the toxins' effects become more visible, widespread muscular atrophy occurs, with the heart muscle bearing a share of the burden. Then there are the most significant variations in blood pressure. Early in the disease, hypertrophies changes in the right ventricle, and later, fairly typically, a thickening of the artery walls, oppose the failure in pressure [9] [28][29][45].

Impact of TB on gastrointestinal:

Gastrointestinal tuberculosis can affect any part of the digestive tract, but it mostly affects the small and large intestine. The most common site of the gastrointestinal TB is ileocecal location (ileocecal TB), followed by jejunum and colon. The oesophagus, stomach and duodenum are rarely involved.

Oesophageal TB: Although oesophageal involvement is uncommon in immunocompetent patients, accounting for approximately 0.2 percent to 1% of all gastrointestinal TB cases, it is more common in AIDS patients. Retrosternal discomfort, dysphagia, and odynophagia are the most common symptoms

Gastric TB: The presence of gastric involvement is frequently linked to pulmonary tuberculosis or an immunocompromised state. Because of the bactericidal property of gastric acid, the lack of lymphoid tissue in the gastric wall, and the thick intact gastric mucosa, primary stomach involvement is uncommon (0.4 percent -2 percent). Other modes of transmission include hematogenous spread and lymph node spread from nearby lymph nodes. Patients may have nonspecific symptoms such as vague epigastric discomfort, weight loss, and fever, or they may have symptoms of gastric outlet obstruction. Many different forms of gastric involvement can be recognised morphologically. The ulcerative lesion along the lesser curvature and pylorus is the most prevalent kind. Hypertrophic variation, numerous miliary tubercles, and tubercular pyloric stenosis in late stages are the other forms. In most cases, tubercular lymphadenitis is observed. These lesions can present on imaging as benign ulcers or erosions. Features of pyloric stenosis, such as a deformed antropyloric area, can appear in the late stages. Gastric TB has a wide differential diagnosis that includes cancer, lymphoma, and other infections such as syphilis.

Jejunal and ileocecal TB: The ileocecal area is the most common site of GI involvement, accounting for 64 percent of all cases with gastrointestinal TB. Because of several contributing factors such as stasis, the presence of extensive lymphoid tissue, the greater rate of absorption at this region, and the closer contact of the bacilli with the mucosa, the terminal ileum is more usually affected. Concomitant jejunal involvement can manifest itself as one or more short or long segment strictures. Isolated jejunal involvement is uncommon, but if it occurs, it can be mistaken for Crohn's disease. Small intestine TB has a wide range of symptoms, but the most common ones are colicky abdominal pain, borborygmi, and vomiting. Bowel obstruction is the most common consequence, which might be caused by hyperplastic mural thickening, stricture development, or adhesions. Tuberculosis is the second most common cause of minor intestinal perforations in India, accounting for 5% to 9% of all cases after typhoid fever [29][30][44][45].

Impact of TB on CNS

CNS TB is linked to immunodeficiency, malnutrition, alcoholism, and malignancies in people with active TB. Tuberculomas are unusual TB symptoms in which composite caseous foci develop in the brain from coalescing tubercles acquired during earlier hematogenous bacillaemia. Patients with miliary TB might develop silent, numerous nodular enhancing lesions, which are more prevalent in meningitis. The presence of M. tuberculosis in the sputum and gastric aspirate, as well as particular CSF and brain MRI abnormalities, led to the diagnosis of CNS tuberculoma in this patient. Miliary tuberculosis is caused by the lymphatic and hematologic spread of tuberculosis from a TB focus and is potentially fatal if not treated. Miliary tuberculosis has become more common as a result of the human immunodeficiency virus/acquired immunodeficiency syndrome pandemic and the use of immunosuppressive medicines [31][42][43][45].

4.ROLE OF ISONIAZIDE IN TREATMENT OF TUBERCULOSIS

Isoniazid (INH): Isonicotinic Acid Hydrazide: One of the most important medications in the treatment of tuberculosis is isoniazid. Since 1952, it has been in use. Isoniazid has a straightforward structure. A pyridine ring and a hydrazine group are present. Isoniazid has a minimum inhibitory concentration of 0.02-0.20 g/mL against Mycobacterium TB**.** Isoniazid has a limited bactericidal impact on slow growing (usually intracellular) and occasionally growing (typically extracellular) bacteria. [anti tb drug]

Isoniazid is commonly used to treat tuberculosis infections, both latent and active. When people with isoniazid +9/sensitive Mycobacterium TB infection follow the indicated treatment, isoniazid-based medication regimens are frequently effective. Drug regimens based on isoniazid, on the other hand, have a significant failure rate in people with isoniazid-resistant Mycobacterium tuberculosis infection. For the treatment of latent tuberculosis, isoniazid can be used alone or in combination with Rifampin, or as part of a four-drug regimen for the treatment of active tuberculosis. The medicine is usually taken orally once a day or once a week for three to nine months, usually under the supervision of Directly Observed Therapy (DOT) [33][34].

4.1 **Mechanism of Action:**

Isoniazid is a prodrug that prevents mycobacterial cell walls from forming. KatG, a bacterial catalase-peroxidase enzyme found in Mycobacterium TB, is required for isoniazid activation. KatG catalyses the production of the isonicotinic acyl radical, which combines with NADH spontaneously to create the nicotinoyl-NAD adduct. This complex binds strongly to the InhA enoyl-acyl carrier protein reductase, preventing the natural enoyl-AcpM substrate and fatty acid synthase activity. The formation of mycolic acids, which are necessary components of the mycobacterial cell wall, is inhibited by this mechanism. KatG activation of isoniazid produces a variety of radicals, including nitric oxide, which has also been demonstrated to play a role in the activity of another antimycobacterial prodrug, pteromalid [TB12]. Isoniazid is bactericidal against rapidly dividing mycobacteria but bacteriostatic against slow-growing mycobacteria. It functions as a source of free radicals by inhibiting the cytochrome P450 system. Isoniazid is a monoamine oxidase inhibitor with a low potency (MAO-I) [32][34].

4.2 Pharmacokinetics of Isoniazid

Absorption: Isoniazid is usually administered orally, but if the patient is critically ill, the drug can be delivered intramuscularly or intravenously as a slow 5-minute bolus in 25 ml of normal saline. If INH is taken with food, INH may be reduced to hydrazine due to the presence of fatty substances, thus decreasing INH's bioavailability and absorption. Although early clinical trials from the 1970s suggested that antacids, such as aluminium hydroxide, could reduce medication bioavailability, more recent investigations have found no such effect. INH will enter the gastrointestinal tract, be absorbed by the small intestine, and transported to the liver through the hepatic portal system without the use of transporters due to its high permeability. Although early clinical trials from the 1970s suggested that antacids, such as aluminium hydroxide, could reduce medication bioavailability, more recent investigations have found no such effect. INH will enter the gastrointestinal tract, be absorbed by the small intestine, and transported to the liver through the hepatic portal system without the use of transporters due to its high permeability. Patients who took INH orally, on the other hand, exhibited considerably varied INH blood concentrations, with rapid acetylators having significantly lower INH concentrations than slow acetylators. The prodrug's plasma concentrations normally peak 1-3 hours after intake of INH. The quick acetylators boosted acetylation activity, causing a larger first pass metabolic effect in the liver, according to the researchers. Because of this premature metabolism, a smaller proportion of the medication reaches systemic circulation, potentially lowering INH efficacy. Despite the fact that this evidence implies that the rapid acetylator phenotype is associated with a larger first pass effect and hence poorer INH bioavailability, current research suggests that slow acetylators are more susceptible to INH-mediated hepatotoxicity. Previous research has suggested that these various metabolic phenotypes are caused by genetic polymorphisms in acetylating enzymes, which are expressed in mucosal cells lining the small intestine, implying that the first pass effect can also occur in the digestive tract.

Distribution: INH is transported throughout the body, including the placenta, after undergoing some first-pass metabolism in the liver. INH is a prodrug that must be cleaved, and bio transformed into an INH-NAD+ adduct before it can be activated and used to kill bacteria. In the presence of nicotinamide adenine dinucleotide, this reaction happens within Mtb via KatG, a catalase peroxidase (NADH). In KatG deletion tests, INH was found to be ineffective against Mtb, suggesting that the mycobacterial catalase peroxidase is required for the antibiotic's bactericidal efficacy. INH can passively diffuse into macrophage cells and Mtb due to its tiny size. KatG cleaves INH's hydrazine group, generating a free radical, and subsequently oxidises NADH to NAD+ within Mtb. The INH-NAD+ adduct is formed when the positively charged NAD+ has a strong affinity for and binds to the free radical generated. The activated INH-NAD+ adduct competitively inhibits InhA, a carrier protein reductase in the Fatty Acid Synthase (FAS) II Cycle, according to substantial evidence. The NAD component of the INH-NAD+ adduct binds to the NADH binding site in InhA, while the nicotinoyl moiety binds to the substrate binding site. This prevents NADH from binding to the enzyme, rendering it inactive. Alternatively, the INH-NAD+ adduct can be produced via attaching to the NADH substrate inside InhA's active site. Mammalian peroxidases, such as lactoperoxidase and human neutrophil myeloperoxidase NAD+, can also activate INH in the host. The positively charged NAD+ has a great affinity for the free radical formed and attaches to it, generating the INH-NAD+ adduct. The activated INH-NAD+ adduct competitively inhibits InhA, a carrier protein reductase in the Fatty Acid Synthase (FAS) II Cycle, according to substantial evidence. The NAD component of the INH-NAD+ adduct binds to InhA's NADH binding site, while the isonicotinoyl moiety binds to the substrate binding site. This prevents NADH from binding to the enzyme, rendering it inactive. Alternatively, the INH-NAD+ adduct can be produced via attaching to the NADH substrate inside InhA's active site. Mammalian peroxidases, such as lactoperoxidase and human neutrophil myeloperoxidase, can likewise activate INH in the host.

Metabolism: Metabolism is the process of converting a medicine into a more hydrophilic substance so that it can be eliminated from the body through the kidneys. This occurs largely in the liver and is divided into four phases: phase 0, phase I, phase II, and phase III. Phase 0 starts the process by allowing the drug ingredient to pass through the liver's plasma membrane via basolateral hepatic uptake transporters that utilise a variety of different mechanisms. However, because INH is very permeable, these transporters have only a minor impact on INH absorption by hepatocytes. Metabolism occurs after phase 0 and involves enzymes that break down or chemically alter the medication to a more polar molecule. Oxidative enzymes are found in Phase I metabolism, while conjugative catalysts are found in Phase II metabolism. INH is first changed by phase II enzymes before being subjected to phase enzyme processes. As a result, these phases are not always in chronological order. Finally, energy-dependent efflux pumps known as ATP-binding cassette (ABC) transporters remove the polar molecule from hepatocytes during Phase III of INH metabolism. A little quantity of INH may penetrate the bile into the intestines and be expelled in the faeces after it is released from the liver, while a considerable portion reaches the glomerulus and is eliminated through urine.

Elimination: Most INH metabolites (AcINH, AcHz, DiAcHz) are eliminated in urine to the tune of 80 percent. Isonicotinic acid, for example, can be eliminated as a free acid metabolite or as a conjugated species with glycine (isonicotinyl glycine). In stools, less than 10% of oral INH is eliminated, and it can also be excreted in breast milk. INH, pyruvic hydrazine, and alpha-ketoglutaric hydrazine are all important urinary excretion products of INH. As previously reported, a urine product of an INH-NAD+ metabolite, 4-INN, has been discovered in INH-treated TB patients, but in lower relative abundance than other key INH metabolites. Due to a decline or absence of function, patients with kidney or liver disorders have a lower elimination efficiency [34].

4.3 Adverse Effect of Isoniazid

Minor adverse effect

- Nausea, vomiting, and epigastric pain: When isoniazid is administered in isolation for tuberculosis chemoprophylaxis, nausea, vomiting, and epigastric pain might occur at the beginning of treatment. Symptoms can be relieved by taking the pill 2 hours after the first meal and utilising symptomatic medication (metoclopramide, ranitidine, or omeprazole).
- Temporary and asymptomatic increase in hepatic enzyme levels: In 10-20% of patients who take isoniazid in isolation, serum levels of the enzyme alanine aminotransferase (formerly known as glutamic-pyruvic transaminase), which is more specific for liver damage than aspartate aminotransferase, rise up to threefold above normal (formerly known as glutamic-oxaloacetic transaminase). As the treatment progresses, their levels will return to normal.
- Arthralgia: Arthralgia is a rare side effect of isoniazid therapy that can be treated with nonsteroidal anti-inflammatory medications.
- Changes in behaviour: Arthralgia is a rare side effect of isoniazid therapy that can be treated with nonsteroidal anti-inflammatory medications.
- Acne: Acne on the face and chest is a typical symptom that goes away after isoniazid is stopped.
- Cutaneous pruritus or fever: After using isoniazid, patients report having cutaneous pruritus or fever.

Major adverse effect

- Psychosis, convulsive seizures, mental confusion, and coma: Neurological and psychiatric signs are less prevalent, more severe, and often harder to diagnose in patients taking isoniazid. It's important to rule out tuberculous meningitis and hepatic encephalopathy as possibilities. Suicide attempts have been documented among patients taking isoniazid.
- Hematological alterations or vasculitis: Hypersensitivity causes haematological changes and vasculitis, which are uncommon side effects of isoniazid treatment.
- Peripheral neuropathy: Approximately 20% of people treated with isoniazid develop peripheral neuropathy. It is dose dependant, and at a dose of 5 mg • kg1 • day1, it is uncommon. It occurs more frequently at doses greater than 300 mg per day. The risk of polyneuritis increases in the presence of associated conditions, such as advanced age, diabetes mellitus, alcoholism, nutritional deficiency, slow acetylator phenotype, HIV infection, kidney failure, pregnancy, and

breastfeeding. Patients can be treated prophylactically with pyridoxine, at a dose of 25-50 mg/day. Patients who develop polyneuritis should be treated with 100-200 mg/day of pyridoxine.

- Clinical hepatitis: Recent research has revealed that the incidence of clinical hepatitis in isoniazid patients is lower than previously thought. According to a meta-analysis of six trials on the use of isoniazid in isolation, the incidence of hepatitis was 0.6 percent. Hepatitis was found to be 2.7 percent when isoniazid was administered in combination with Rifampin. The risk of getting hepatitis in persons using isoniazid alone rises with age. In people under the age of 20, the condition is quite rare. The chance of getting hepatitis in people aged 50–64 years old, on the other hand, can be as high as 2%. Individuals with a history of liver illness, those who consume alcohol on a regular basis or who are strong drinkers, and women in the immediate postpartum period are all at higher risk. Hepatitis that results in death is extremely uncommon, occurring in fewer than 0.023 percent of cases. The medication must be stopped, and the causal medicine must be identified in patients who are on multiple-drug regimens.
- Lupus-like syndrome: During the course of treatment with isoniazid, patients may generate antinuclear antibodies. Systemic lupus erythematosus affects less than 1% of people, and it affects both men and women equally. Isoniazid treatment can exacerbate pre-existing lupus [38][39].

4.4 Contraindications of Isoniazid

Use During Pregnancy: Isoniazid is classified as a category C drug. Isoniazid is deemed safe to take during pregnancy. In the postpartum period, however, there is a danger of hepatitis. All pregnant women taking isoniazid should also take pyridoxine (25-50 mg/day), according to the WHO. Isoniazid-treated moms have a higher chance of giving birth to babies who experience convulsive seizures**.**

Use in patients with liver failure: In people with liver failure, it's a good idea to use it. Isoniazid is a hepatotoxic medicine, and its side effects are more noticeable in those who have liver disease, are alcoholics, or are over 50 years old. The half-life of isoniazid is longer in these patients, and the drug's serum levels are higher. Those with liver disease should be continuously followed and should have clinical examinations and laboratory tests performed more regularly than patients without liver disease.

Use during breastfeeding: Although isoniazid and nursing are thought to be compatible, the infant should be checked for jaundice.

Use in patients with kidney failure: Isoniazid doses do not need to be adjusted in individuals with renal failure or those on haemodialysis.

INTERACTIONS

Foods: Isoniazid should be taken on an empty stomach since it needs to be absorbed in an acidic environment. Foods, particularly carbs, can reduce medication absorption by as much as 57 percent and lower drug plasma levels by as much as 30 percent. The medication should not be taken with fluids that are high in glucose or lactose**.** Isoniazid inhibits the monoamine oxidase enzyme, which is why it shouldn't be used with foods high in tyramine and histamine, such as Swiss and Cheshire cheeses, fish (tuna and herring), and alcohol, particularly red wine. Palpitation, perspiration, flushing of the face, chills, headache, diarrhoea, erythema, and itching are all signs of these interactions. **Antacids**: Isoniazid absorption is slowed by drugs that raise the stomach ph. Antacids containing aluminium hydroxide or ranitidine should be taken 1 hour after the isoniazid has been taken.

Other drugs: Isoniazid inhibits the cytochrome P450 (CYP450) system families CYP2C9, CYP2C19, and CYP2E1, but has only a minor impact on the CYP3A family.

Isoniazid's inhibitory effect can cause certain medicines' plasma concentrations to rise to dangerous levels. When anticonvulsants like phenytoin and carbamazepine are used with isoniazid, the plasma concentrations of these medicines can rise. Theophylline, valproic metabolised by oxidation (e.g., diazepam and triazolam), as well as theophylline, valproic acid, disulfiram, acetaminophen, and oral anticoagulants. Hypertension, palpitation, and flushing of the face can occur when isoniazid and levodopa are taken together [38][39].

5. ROLE OF RIFAMPIN IN TUBERCULOSIS

Rifampin is an antibiotic that is used to treat or prevent tuberculosis(TB). Rifampin may also be used to reduce certain bacteria in your nose and throat that could

cause meningitis or other infections. Rifampin prevents you from spreading these bacteria to other people, but rifampin will not treat an active meningitis infection. Rifampin is the most important drug in the treatment of tuberculosis. The drug has been used since 1966 and the MIC of rifampin for M. tuberculosis is 0.05-0.50 µg/mL. Rifampin is a bactericidal drug that kills growing, metabolically active bacilli, as well as bacilli in the stationary phase, during which metabolism is reduced. When rifampin is used in combination with pyrazinamide, tuberculosis treatment duration can be reduced to six months [40].

5.1 MECHANISM OF ACTION

Rifampin produces bactericidal antimicrobial activity by inhibition of DNA-dependent RNA polymerase (RNAP) either by sterically blocking the path of the elongating RNA at the 5′ end or by decreasing the affinity of the RNAP for short RNA transcripts. It specifically inhibits the microbial RNAP, halting further RNA synthesis. Rifampin has no action on the mammalian RNAP enzyme, thereby decreasing the number of potential adverse effects in humans. Elevated levels of bile acids are primarily responsible for the pruritis seen with cholestatic diseases like primary biliary cirrhosis (PBC). The antipruritic effect of rifampin, which has been described to be of most benefit in cholestatic disorders, is mediated by the upregulation of the microsomal enzymes cytochrome P3A (CYP3A), which subsequently induces hydroxylation of bile acids. The hydroxylation of bile acids decreases their ileal reabsorption which further alleviates the pruritic symptoms [38][39][41].

5.2 Pharmacokinetic of Rifampin

Absorption: Absorbed completely from the GI tract after oral administration. Food delay absorption.

Distribution: Distributed widely into body tissues and fluids, including ascitic, pleural, seminal, and cerebrospinal fluids, tears, and saliva; and into liver, prostate, lungs, and bone. Drug crosses the placental barrier and is 84% to 91% protein bound.

Metabolism: Metabolized extensively in the liver by deacetylation. It undergoes enterohepatic circulation.

Excretion: Undergoes enterohepatic circulation, and drug and metabolite are excreted primarily in bile; drug, but not metabolite, is reabsorbed. From 6% to30% of rifampin and metabolite appear unchanged in urine in 24 hours; about 60% is excreted in feces. Some drug appears in breast milk. Plasma half- life in adult is 1 ½ to 5hours, serum level rise in obstructive jaundice. Dosage adjustment isn't needed for patients with renal failure. Rifampin isn't removed by either haemodialysis or peritoneal dialysis [34].

5.3 Adverse Effect of Rifampin

Minor adverse effects

- Gastrointestinal reactions: Nausea, anorexia, and abdominal pain can occur in patients treated with rifampin. The incidence of gastrointestinal reactions varies.

However, the symptoms are rarely severe enough to warrant discontinuation of the drug. Gastrointestinal reactions can be treated as previously described for isoniazid.

- Orange-coloured tears, sweat, and urine: Patients should be alerted to the possibility that rifampin administration can cause discoloration of body fluids. Orange- coloured tears can stain contact lenses.
- Skin reaction: Pruritus, with or without erythema, occurs in 6% of patients receiving rifampin. This reaction is generally mild and, in most cases, does not warrant treatment discontinuation. It might be necessary to use topical or systemic medication (moisturizers, antihistamines, or even corticosteroids).
- Flu-like syndrome: Flu-like syndrome is rare and occurs in patients who use intermittent regimens that include rifampin.
- Fatigue, dizziness, headache, dyspnea, and ataxia can also occur in patients treated with rifampin.

Major adverse effects

- Exanthema: Exanthema can occur due to the use of rifampin or of another drug administered in combination with rifampin. If exanthema occurs, treatment should be discontinued, and the drugs should be subsequently reintroduced, one by one, in order to identify the causative drug. • Hepatotoxicity: Transitory and asymptomatic increases in the serum levels of bilirubin and hepatic enzymes occur in 5% of patients treated with rifampin. Those levels subsequently normalize, without the need to discontinue the treatment. However, cholestatic hepatitis occurs in 2.7% of the patient's receiving rifampin in combination with isoniazid and in up to 1.1% of those receiving rifampin in combination with antituberculosis drugs other than isoniazid.
- Immunological reactions: Thrombocytopenia, leukopenia, eosinophilia, haemolytic anaemia, agranulocytosis, vasculitis, acute interstitial nephritis, and septic shock can occur after rifampin administration. These reactions are rare and occur in less than 0.1% of the patients. However, these reactions are severe and call for a change in the therapeutic regimen [38]

5.4 Contraindication of Rifampin

Use during pregnancy: Rifampin is a category C drug. Rifampin has been used during pregnancy, and no teratogenic effects have been reported. As a precaution, neonates born to mothers who have been under treatment with isoniazid should be given vitamin K, in order to avoid postpartum haemorrhage.

Use during breastfeeding: Although rifampin is compatible with breastfeeding, the infant should be monitored for jaundice.

Use in patients with liver failure: Liver failure can impair rifampin clearance, increasing the serum levels of the drug. However, due to the important role that rifampin plays in tuberculosis treatment regimens, the drug is generally included, with the proviso that the patients be closely monitored through frequent clinical evaluations and laboratory tests (see also Drug-induced hepatitis).
Use in patients with kidney failure: Because rifampin is metabolized in the liver, the drug can be used at full doses in patients with kidney failure [38].

Interaction

Foods: Rifampin should be taken on an empty stomach. Foods decrease the absorption of the drug by as much as 26%, as well as increasing the time required for the drug to reach maximum concentration and decreasing that concentration by 15-36%.

Antacids :Antacids containing aluminium hydroxide delay the absorption of rifampin.

Drug-drug interactions: Anticoagulant, barbiturates, beta blockers, cardiac glycoside derivatives, chloramphenicol, cyclosporine, dapsone, disopyramide, estrogens, methadone, hormonal contraceptives, quinidine, tocainide, verapamil, decreases effectiveness of these drugs.

Hormonal contraceptives: rifampin inactivates such drug and may alter menstrual patterns. Advice hormonal contraceptive methods. Isoniazid: Increases hazard of isoniazid hepatotoxicity.

Para-aminosalicylate: may decrease oral absorption of rifampin, lowering serum levels. Administer drug 8 to 12 hour apart.

Drug- lifestyle: Alcohol use: may increase risk of hepatotoxicity. Discourage alcohol use [38].

6.ROLE OF PYRAZINAMIDE IN TREATMENT OF TUBERCULOSIS

Pyrazinamide is first line drug antituberculosis medication but is used only in combination with other antituberculosis medication such as isoniazid and rifampin. Pyrazinamide is associated with transient and asymptomatic elevation in serum aminotransferase levels and is a well-known cause of clinically apparent, acute liver injury that can be severe and even fatal.

Pyrazinamide is a synthetic pyrazinoic acid amide derivative with bactericidal property. Pyrazinamide is particularly active against slowly multiplying intracellular bacilli (unaffected by other drugs) by an unknown mechanism of action. Its bactericidal action is dependent upon the presence of bacterial pyrazinamide, which removes the amide group to produce active pyrazinoic acid. Pyrazinamide is an important component of multidrug therapy for tuberculosis [35]

6.1 Mechanism of Action of Pyrazinamide

Pyrazinamide is a prodrug that needs to be converted into its active form, pyrazinoic acid, by bacterial enzymes (nicotinamidase/ pyrazinamidase). The mechanism of action of pyrazinamide has yet to be fully understood. It is supposed that pyrazinamide enters the bacillus passively, is converted into pyrazinoic acid by pyrazinamidase, and reaches high concentrations in the bacterial cytoplasm due to an inefficient efflux system. The accumulation of pyrazinoic acid decreases the intracellular pH to levels that cause the inactivation of enzymes—such as fatty acid synthase I, which plays a fundamental role in synthesizing fatty acids—and, consequently, the impairment of mycolic acid biosynthesis. Resistance to pyrazinamide results from mutations in the pncA gene, which encodes the nicotinamidase/pyrazinamidase enzyme and prevents pyrazinamide from being converted into its active form [35][40][42].

6.2 Pharmacokinetic of Pyrazinamide

Absorption: Well, absorbed after oral administration, peak plasma time:1-2hour

Distribution: Distributed widely into body tissues and fluids, including lungs, liver, and CSF; 50% protein - bound. Not known if drug crosses the placental barrier.

Metabolism: Hydrolyzed in liver, some hydrolysis occurs in stomach.

Excretion: Excreted almost completely in urine by glomerular filtration. Not know if drug appear in breast milk. Elimination half life in adult is9 to10 hours; prolonged half-life in renal and hepatic [34][36][37].

6.3 Adverse Effect of Pyrazinamide

Minor adverse effects

- Gastrointestinal symptoms: Nausea, vomiting, and anorexia are common in patients treated with pyrazinamide.
- Hyperuricemia and arthralgia in non-gouty individuals: In non-gouty patients receiving pyrazinamide, hyperuricemia commonly leads to arthralgia. The mechanism is related to pyrazinoic acid, the principal metabolite of pyrazinamide, which inhibits the renal tubular secretion of uric acid. This rarely requires that pyrazinamide be discontinued or that the dose be adjusted. The hyperuricemia is typically asymptomatic, and the pain responds well to treatment with aspirin or nonsteroidal anti-inflammatory drugs.
- Exanthema and pruritus: Exanthema and pruritus are relatively common effects of pyrazinamide administration. In most cases, these improve with the administration of antihistamines.
- Dermatitis: Treatment with pyrazinamide can cause photosensitivity dermatitis.

Major adverse effects

- Severe exanthema and pruritus: If severe exanthema and pruritus occur, pyrazinamide should be discontinued.
- Rhabdomyolysis with myoglobinuria and kidney failure: Rhabdomyolysis with myoglobinuria and kidney failure is a rare complication of pyrazinamide treatment and requires that the drug be discontinued.
- Acute arthritis in gouty individuals: In patients receiving pyrazinamide, acute arthritis is rare, except in those with a history of gout. The symptoms improve with the use of moisturizers and allopurinol, as well as with dietary changes.
- Hepatotoxicity: Pyrazinamide is the most hepatotoxic of the drugs cited in the present study. Therefore, it is essential that the doses of the drug be adjusted to the weight of the patient. Liver impairment is rare if the drug is administered at a maximum dose of 35 mg • kg−1 • day−1. The new guidelines for the treatment of Tuberculosis in Brazil recommend a dose of 1,600 mg for patients who weigh more than 50 kg, which is likely to reduce the hepatic adverse effects of the

drug. In patients with pyrazinamide-induced hepatitis, the drug should be temporarily discontinued or even replaced [38][42].

6.4 Contraindication Of Pyrazinamide

Use during pregnancy: Pyrazinamide is a category C drug. The WHO considers it safe to use pyrazinamide during pregnancy. In Brazil, pyrazinamide has been used for more than two decades as part of regimen I (RHZ), and no risks have been reported.

Use during breastfeeding: Although pyrazinamide is considered compatible with breastfeeding, the infant should be monitored for jaundice.

Use in patients with liver failure: Pyrazinamide is a hepatotoxic drug, the effect of which is more evident in individuals with liver disease. These patients should be closely monitored and should undergo clinical examination and laboratory tests more frequently than is necessary for patients without liver disease.

Use in patients with kidney failure: The metabolites of pyrazinamide are eliminated by the kidney and can accumulate in patients with kidney failure, which requires that the dose of the drug be decreased. The risk of developing pyrazinamide-induced hyperuricemia also increases in patients with kidney failure. The daily dose should be reduced to half when creatinine clearance is lower than 10 mL/min. Patients with creatinine clearance lower than 30 mL/min or those on haemodialysis should be given pyrazinamide at a dose of 25-35 mg/kg, three times a week.

Interactions

Foods: Foods have very little impact on the absorption of pyrazinamide. The drug can be taken at mealtime.

Antacids: Antacids do not interfere with the absorption of pyrazinamide.

Other drugs: Probenecid, rifampin, isoniazid, and ethionamide can potentiate the toxic effects of pyrazinamide. The combination of pyrazinamide and zidovudine can reduce the effect of pyrazinamide. Pyrazinamide antagonizes the effects of probenecid and decreases the serum concentration of cyclosporine. Pyrazinamide can increase the serum concentrations of uric acid, and it might be necessary to adjust the doses of allopurinol and colchicine in patients under gout treatment [38][42].

CONCLUSION

Early diagnosis and effective treatment are the key elements to control tuberculosis. Understanding of epidemiology of tuberculosis is essential for its effective control. This review tried to summarize the epidemiology aspect of tuberculosis in global.

Despite the availability of several chemotherapeutic medications, tuberculosis remains a top infectious illness worldwide, owing to a shortage of novel drugs, notably for MDR and XDR infections, as well as those who are HIV/AIDS co-infected. As a result, new anti-TB medications with fewer side effects and greater therapeutic qualities are urgently needed to combat MDR and XDR-TB strains while also shortening treatment duration.

We must accept the "poor" side effects of hepatotoxicity, even though INH has many "positive" elements, such as its efficacy in eliminating TB throughout populations. Changing the INH regimen, which is already effective in treating tuberculosis, could be a faster solution to novel medication efficacy trials. There appears to be a preponderance of research that suggests that lowering or increasing the dosage, along with careful monitoring based on the patient's metabolic genetic profile, could lessen these hepatotoxic consequences.

Treatment for TB might have unfavourable side effects. Referral centres and trained experts with knowledge of the therapeutic options available are often responsible for the handling of more severe circumstances (which are, thankfully, infrequent). Professionals can adjust their approach to each unique instance based on accurate diagnoses and understanding of the pharmacological properties of the medications involved.

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