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Assessing Dots Therapy's Toxicity: A Comprehensive Analysis Of Side Effects Associated With Rifampicin, Isoniazid, Pyrazinamide, And Ethambutol

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Abstract: A key component in the treatment of tuberculosis (TB) is the Directly Observed Treatment, Short course (DOTS) method. But there are drawbacks to the regimen, which includes ethambutol, isoniazid, pyrazinamide, and rifampicin. In order to improve therapeutic efficacy and patient safety, this review seeks to assess the toxicity linked to each medication, highlighting the importance of careful monitoring and management.

Keywords: tuberculosis, dots therapy, rifampicin, ethambutol, isoniazid, pyrazinamide.

INTRODUCTION

Globally, tuberculosis continues to pose a serious threat to public health. The World Health Organization's DOTS approach has been essential in reducing tuberculosis cases through a standardised treatment plan. Despite its efficacy, complications and treatment interruptions may result from the side effects associated with the constituent medications, namely ethambutol, pyrazinamide, isoniazid, and rifampicin. Clinicians must comprehend the toxicity profiles of these drugs in order to maximise therapy and guarantee patient adherence.

Methodology

A thorough evaluation of the literature was carried out using the Cochrane Library, PubMed, and Google Scholar. "DOTS therapy toxic effects," "Rifampicin adverse effects," "Isoniazid toxicity," "Pyrazinamide side effects," and "Ethambutol toxicity" were among the search terms used. Relevance, calibre, and recentness were taken into consideration while choosing studies, with an emphasis on peer-reviewed literature and clinical trials.

An outline of DOTS treatment

The purpose of DOTS therapy is to eradicate Mycobacterium tuberculosis by means of a combination of drugs. The following is the standard regimen, which is given over a period of six to nine months: The bactericidal antibiotic

Rifampicin (RIF): An antiseptic that prevents the synthesis of RNA. –

Isoniazid (INH): A prodrug that interferes with the bacterial cell wall's ability to manufacture mycolic acid.

Ethambutol (EMB): Prevents the formation of cell walls.

Pyrazinamide (PZA): Breaks down the mycobacterial cell membrane.

DOTS THERAPY IN THE TREATMENT OF TUBERCULOSIS

There are different type of tuberculosis bacteria mainly Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium avium Mycobacterium africanium which generally causes Tuberculosis in a person. There is one more type of Mycobacterium species that causes Leprosy that is called as Mycobacterium leprae.

All this mycobacterium species of bacteria can cause a severe affect in the body affecting the bones, the central nervous system and majorly targeting the Pulmonary system since it is a Pulmonary diseases. If the bacteria enters the body and has colonize the brain its called **Tuberculosis meningitis** (the bacteria has infected the meninges layer of brain), if the bacteria invades the bone its called **Tuberculosis osteomyelitis**, if the bacteria invades the alveolar surface its called **Pulmonary tuberculosis.**

All the type of Tuberculosis as well as all the species of Tuberculosis can be treated by DOTS therapy which includes a drug combination called RIPE i.e **Rifampicin, Isoniazid, Pyrazinamide and Ethambutol.** The treatment period of the Tuberculosis may vary on basis of its severity, it might include Short term Treatment
(6month) and Long term treatment (12 month) and in case of Multiple Drug Resistance Tuberculosis (MDR) it Might go for a 24 month period treatment .

SHORT TERM TREATMENT PERIOD (6 MONTHS)

INITATION PHASE

It include four drug in combination for first **2 months**

Rifampicin

Dose – 600mg/OD

Isoniazid

Dose – 300mg/OD

Pyrazinamide

Dose – 1000mg for 40 to 55kg person

1500mg for 56 to 75 kg person

2000mg for 76 to 90kg person

Ethambutol

Dose – 800mg for 40 to 50kg person

1200mg for 56 to 75kg person

1600mg for 76 to 90kg person

CONTINUATION PHASE

This phase is followed by **4 months** of two drug therapy

Rifampicin

Dose – 600mg/OD

Isoniazid

Dose – 300 mg/OD

LONG TERM TREATMENT PERIOD (12 MONTHS)

INITATION PHASE

It include four drug for **2 months**

Rifampicin

Dose – 600mg/OD

Isoniazid

Dose – 300mg/OD

Pyrazinamide

Dose – 1000mg for 40 to 55kg person

1500mg for 56 to 75 kg person

2000mg for 76 to 90kg person

Ethambutol

Dose – 800mg for 40 to 50kg person

1200mg for 56 to 75kg person

1600mg for 76 to 90kg person

It also include Glucocorticoids for first 2 to 3 weeks.

CONTINUATION PHASE

It include two drugs for **10 months**

Rifampicin

Dose – 600mg/OD

Isoniazid

Dose – 300mg/OD

WHAT ARE THE VARIOUS REASON FOR TOXICI EFFECT OF DOTS THERAPY IN THE BODY

1. POLYPHARMACY : It include use of four to five drug (isoniazid , rifampicin, ethambutol, pyrazinamide and sometimes streptomycin) although this drugs are required for treating Tuberculosis but it increases the burden on the body, especially the liver and kidney, which are responsible for metabolizing and excreting the drugs.

2. ADDITIVE TOXICITY: Each drug has its own potential toxic effect and its adverse reaction, so when five drug are used together their adverse effect and combine together and may cause more significant overall toxicity

3. PROLONGED EXPOSURE: Tb treatment last for 6 month to 12 month and for 2 years for MDR, the prolonged use of the drug may increase the cumulation of the drug in the body causing cumulative toxicity.

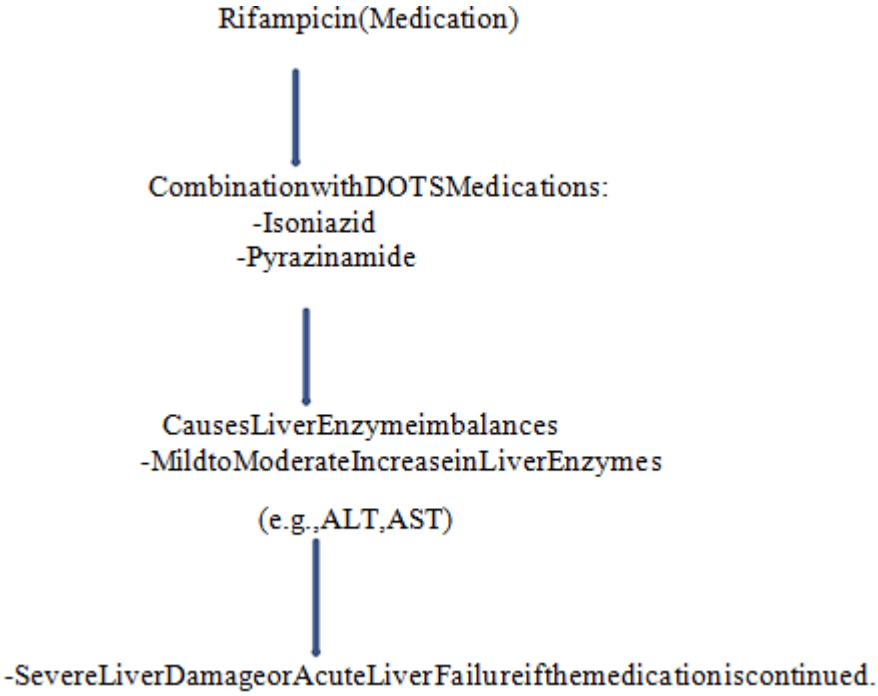
4. NUTRITIONAL STATUS : Many of the TB patient have poor nutritional status, which can affect the Drug ADME(Absorption, Distribution, Metabolism and Excretion) which can effect the organs involved in the process of ADME

5.GENETIC FACTOR: Drug are metabolize at different rates due on basis of each genetic variation, some people may metabolize the drug fast while some patient may metabolize it very slow which result in higher drug concentration in the body and may cause toxicity

VARIOUS TOXIC EFFECT OF THE DRUGS USED IN DOTS THERAPY

Rifampicin

1. Liver Toxicity: Rifampicin carries a significant risk of liver damage. When used with other drugs used in DOTS therapy, such as pyrazinamide and isoniazid, the results can vary from mild elevations in liver enzymes to more serious conditions, such as acute liver failure.



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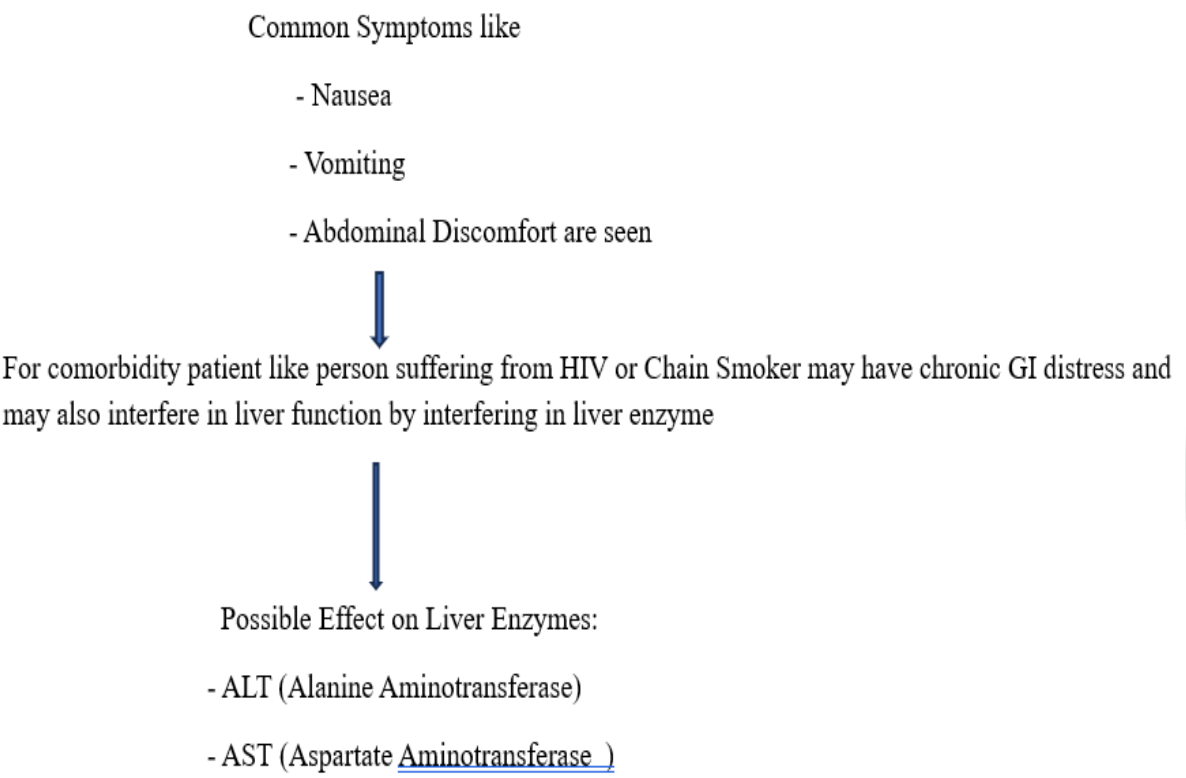
2. Gastrointestinal Problems: Nausea, vomiting, and abdominal discomfort are typical adverse effects. Patients who are HIV positive and smokers are more likely to experience chronic gastrointestinal distress, and these symptoms frequently appear early in the course of treatment.



3.Allergic and Skin Reactions: Rifampicin commonly results in allergic reactions, such as rashes on the skin and pruritus, or itching. Pruritus affects a large proportion of individuals and can last for up to two weeks, especially in those who are HIV positive

Allergic and Skin Reactions

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Skin Rashes

Itching (Pruritus)

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- Itching May Last Up to Two (Increased Risk in HIV-positive Individuals)

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Potential Impact on Liver Enzymes:

- ALT (Alanine Aminotransferase)

- AST (Aspartate Aminotransferase)

4.Neurological Effects: Rifampicin could also affect the central nervous system, which could lead to symptoms like headaches, dizziness, and, in extreme cases, seizures or disorientation. Peripheral neuropathy's defining feature, numbness, is also observed, particularly in individuals with comorbidity cases

Neurological Effects

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Common Symptoms:

- Headaches

- Dizziness

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Less Common Symptoms:

- Seizures

- Disorientation

↓

Further results in

Numbness (Peripheral Neuropathy)

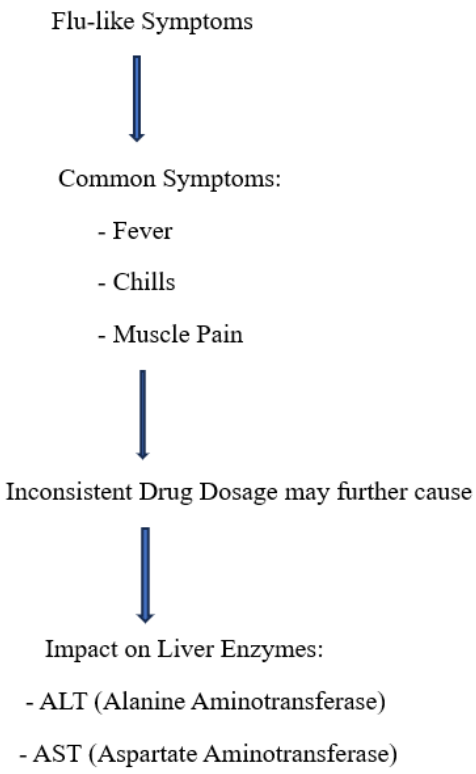
↓

Greater risk of Individuals with Conditions Like HIV

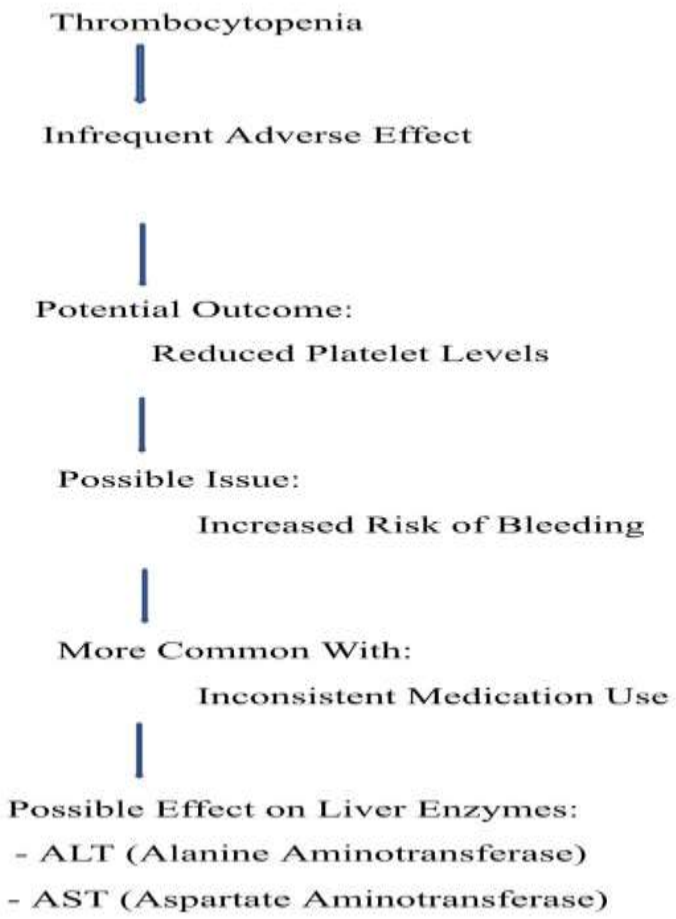
Possible Effect on Liver Enzymes:

- ALT (Alanine Aminotransferase)

5.Flu-like Syndrome: This less frequent side effect, which typically occurs after irregular drug dosage, consists of chills, fever, and aches in the muscles.

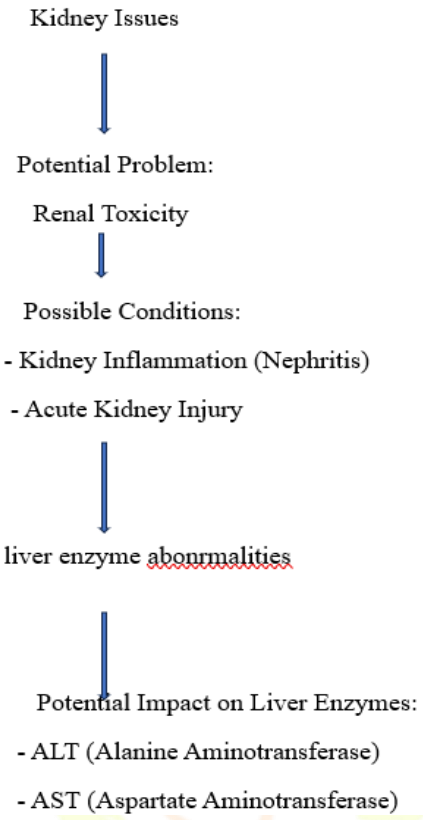


6. Thrombocytopenia: If rifampicin is taken infrequently, it may occasionally cause a decrease in platelet counts, which could lead to bleeding problems.



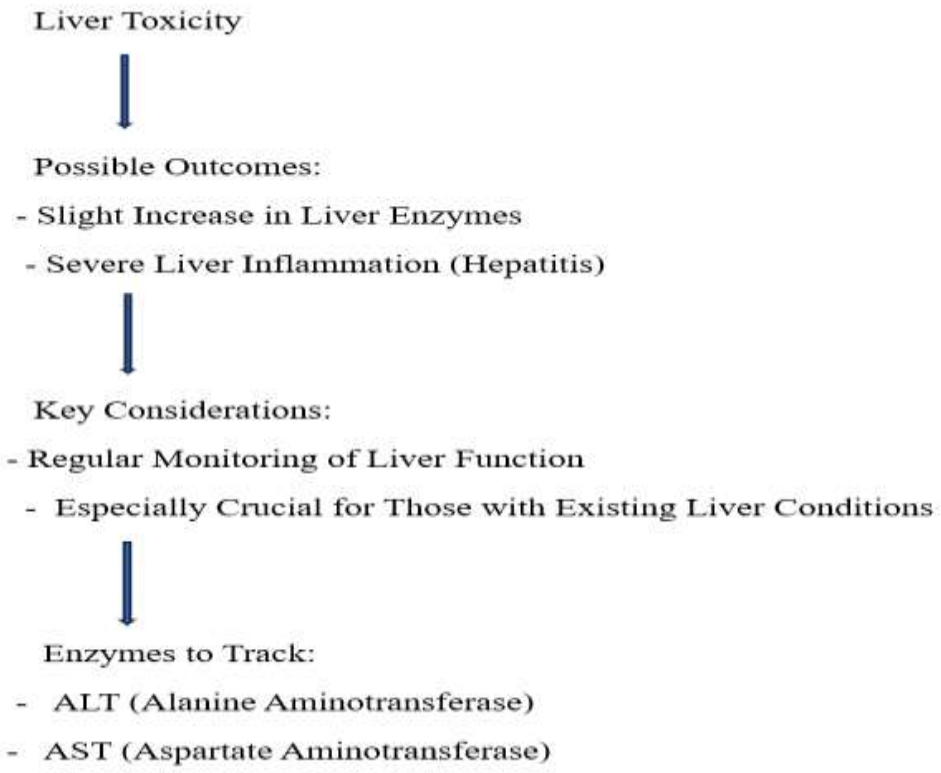
7. Kidney Issues: Rifampicin may result in renal toxicity, which may give rise to acute kidney injury or

nephritis, both of which are often linked to hypersensitivity reactions.

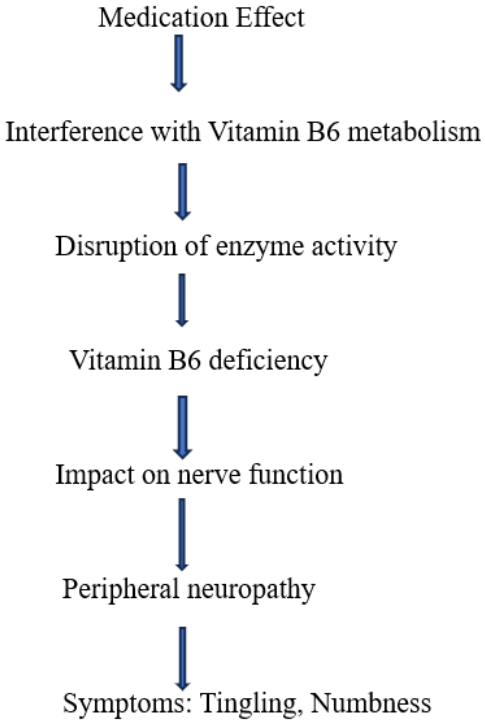


Isoniazid

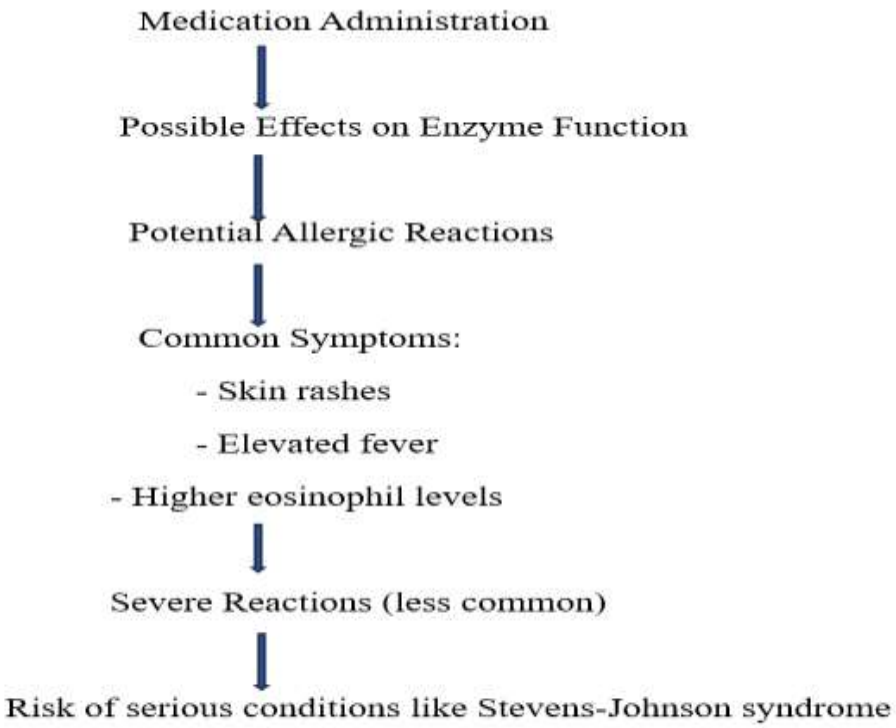
1. Liver Damage: Isoniazid may cause damage to the liver, ranging from a slight elevation in enzyme levels to a severe case of hepatitis. Regular liver function testing is essential, particularly for those with pre-existing liver conditions.



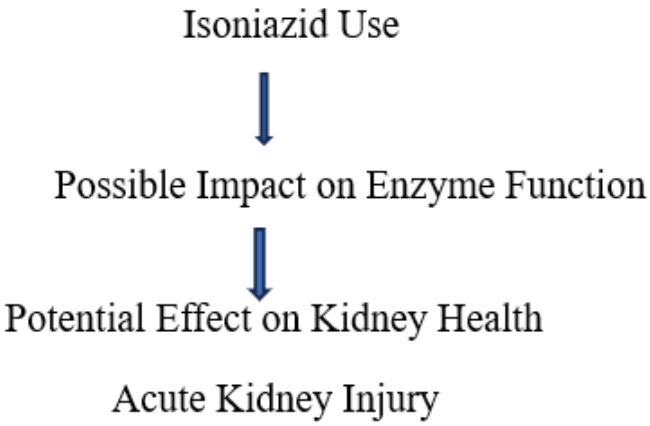
2.Damage to Nerves: The medicine may cause peripheral neuropathy by compromising the metabolism of vitamin B6, which is essential for the health of nerves. Possible symptoms include tingling and numbness. Avoiding this side effect might be possible with vitamin B6 supplements.



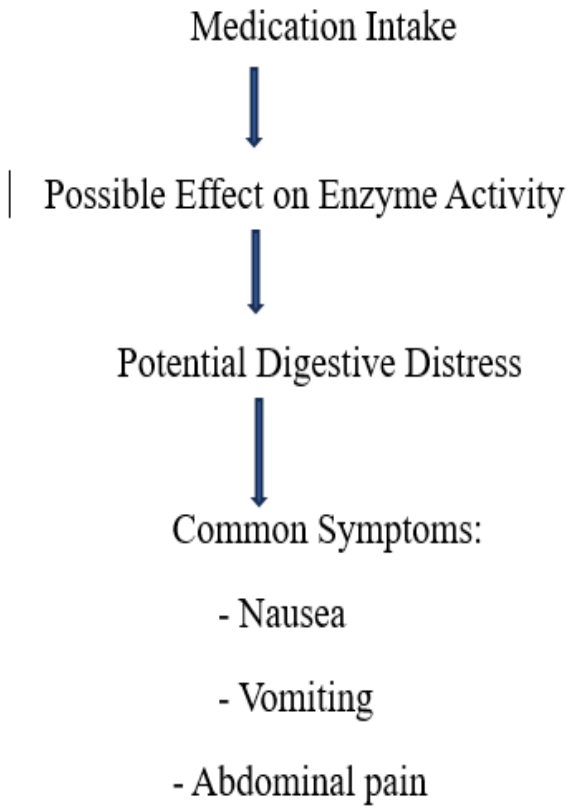
3.Allergic Reactions: Some patients may experience allergic reactions, such as rashes, fever, and elevated eosinophil counts. Severe reactions are rare, but they can lead to life-threatening conditions such as StevensJohnson syndrome.



5. Effects on the kidneys: Isoniazid may negatively impact kidney function, especially in people who are taking high dosages or who already have renal problems.

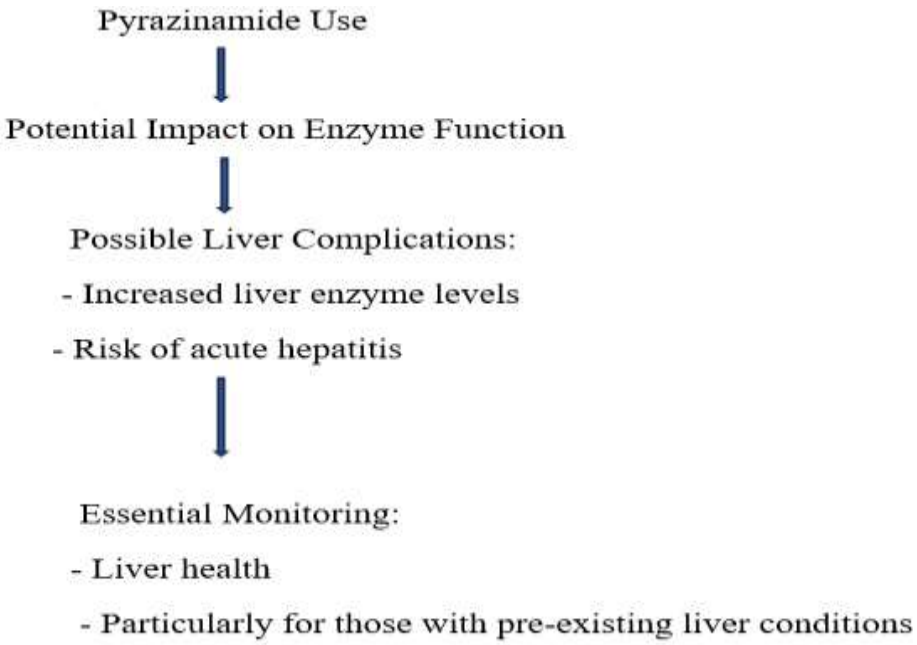


5.Digestive Problems: People may experience gastrointestinal problems, such as nausea, vomiting, and abdominal pain. These symptoms might nonetheless be irritating even if they are usually not severe.

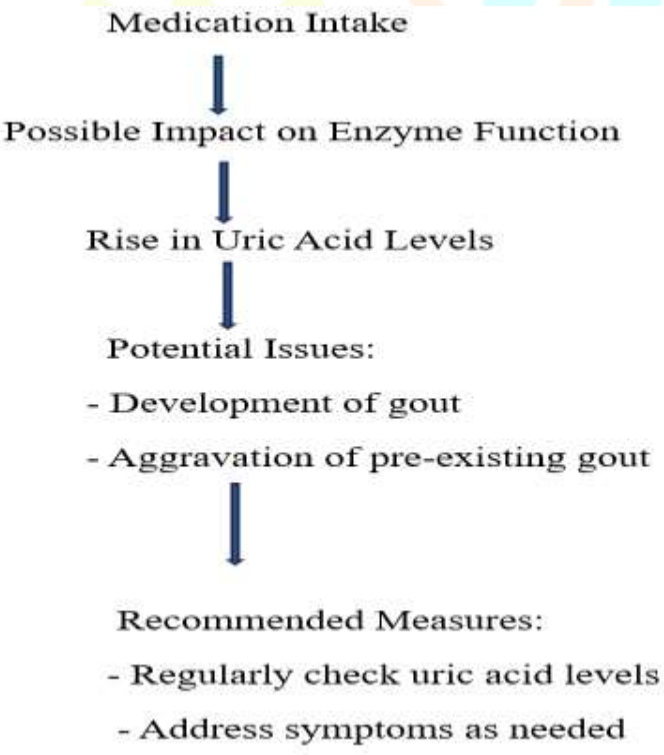


Pyrazinamide

1. Liver Damage: Pyrazinamide can result in a range of liver problems, including acute hepatitis and mild increases in liver enzyme levels. Monitoring liver function is essential, particularly in those with preexisting liver conditions.



2.Elevated Uric Acid: The drug may cause an increase in uric acid, which could cause gout or make preexisting gout worse. It is advised to treat symptoms and regularly check uric acid levels.



3.Digestive Issues: People may have symptoms such as nausea, vomiting, and abdominal pain that are associated with digestion. To control these symptoms, a dosage adjustment or supportive care are frequently employed.

Medication Intake

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Nausea

Vomiting

Abdominal Discomfort

4. Skin Reactions: Skin allergies can cause rashes and other skin reactions. Though rare, severe responses do occasionally occur.

Skin Reactions:

- Rashes

↓

Allergic Responses

- Severe Reactions (rare)

5. Discomfort in the Muscles and Joints: Pyrazinamide may occasionally result in discomfort in the muscles and joints. To manage these side effects, pain management and dose adjustments are often necessary.

Pyrazinamide

↓

Causes Muscle and joint pain

6.Kidney Function: Kidney function may be impacted, especially in those who already have renal issues. Kidney health needs to be examined for these individuals.

Pyrazinamide

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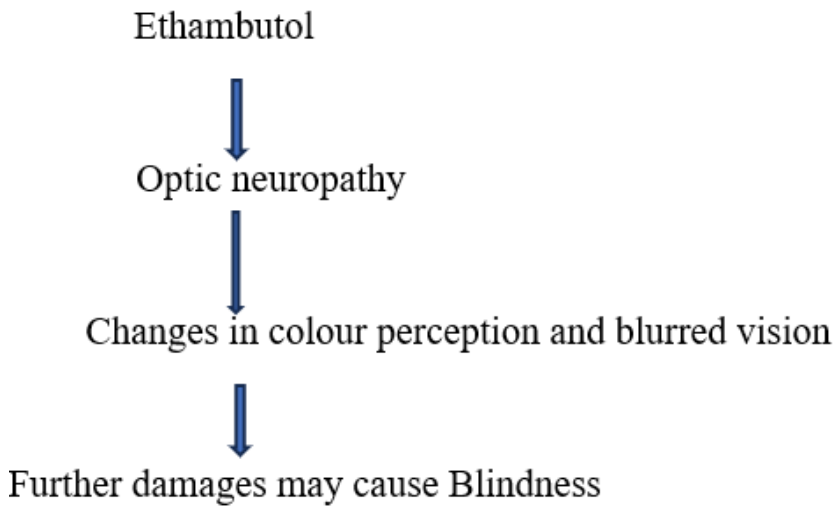
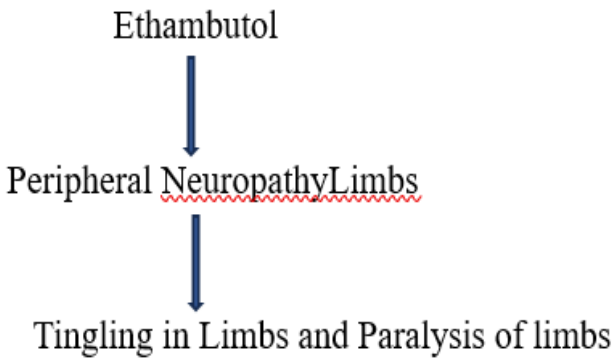
Affect kidney function

Ethambutol

1. Visual Issues: Ethambutol may result in optic neuropathy, which may lead to issues like poor eyesight and altered colour perception. Regular ocular examinations are recommended because severe cases may lead to blindness.

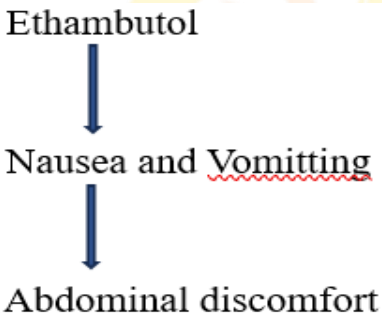


2.Damage to Nerves: Peripheral neuropathy might occur, owing to which limbs may become paralysed, tingling, or numb. It might not happen frequently, but for certain individuals, it could be extremely unsettling.

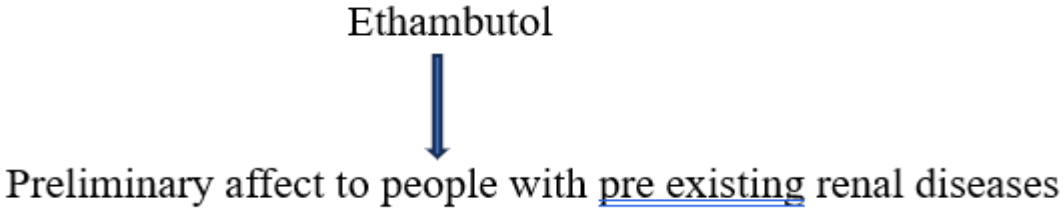


3.Allergic Reactions: As a result of allergies, patients may have joint discomfort, fever, or skin rashes. Although they are rare, severe reactions do happen.

4.Digestive Issues: This medicine may cause nausea, vomiting, and abdominal pain. Usually, supportive care or dose adjustments are enough to keep them under control.

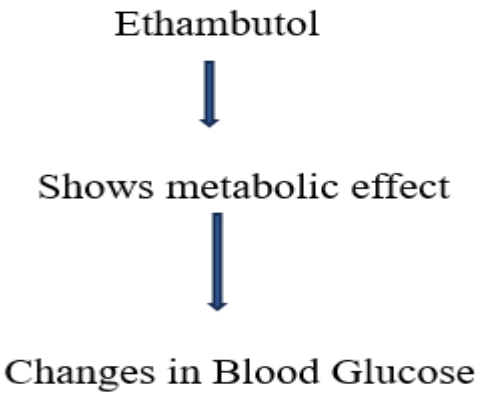


6. Kidney Function: Ethambutol may affect kidney function, particularly in individuals with pre-existing renal impairment. In these circumstances, it is imperative to monitor renal health.



7. Impact on Metabolism: Ethambutol can occasionally result in metabolic issues, such as changes in blood sugar levels. Monitoring and controlling these changes may become imperative.

8.



CONCLUSION :DOTS therapy, which successfully uses a combination of medications to manage the disease, continues to be a pillar in the fight against tuberculosis. But careful monitoring is necessary to minimise side effects due to the toxicity of the main drugs, including pyrazinamide, ethambutol, isoniazid, and rifampicin. Treatment length and intensity, especially for multidrug-resistant tuberculosis patients, increase the risk of additive toxicity, polypharmacy, and protracted drug exposure. Improving treatment outcomes and lowering complications require addressing these issues through individualised treatment regimens and frequent patient reviews. In order to optimise DOTS therapy for safer and more effective management of the disease, continued research and clinical monitoring are crucial since tuberculosis remains a worldwide health concern.

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