Review on Risk of drug drug interaction with hepatotoxicity

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1.Abstract

The main aim of the article is to know the risky drug drug interaction with hepatotoxicity drug . to increase the ocurness regarding hepatotoxicity treatment while other drug taken

To improve understanding of drug interaction with hepatotoxicity agent to help for treatment. No of hepatotoxicity drug along with other drug shows dangerous interaction when two drug are used together their effect of each drug can be additive synergic or antagonist drug drug interaction it can be most common causes of medical error in developing countries, specially in elderly due to polytheraphy with a prevalence of 20-40%particular polytheraphy increase the complexity of the therapeutic management and there by the risk of clinical management and their by the risk of clinical important drug drug interaction which can be both induce development of adverse drug reaction or reduce clinical efficacy

Key word_ Liver, hepatotoxicity, drug interaction, risk, hypersensitivity reaction, mechanism, toxicity, disease

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2.Introduction

Medicine relations may have potentially life- hanging consequences in aged **grown-**ups, who may take several medicines at formerly for multiple conditions. Elderly cases are more susceptible to medicine relations than youngish cases because of age- related physiologic changes, an increased threat for complaint associated with aging, and the consequent increase in drug use. For the purpose of this review, medicine commerce was defined as a clinically meaningful revision in the effect of one medicine(object medicine) as a result of coadministration of another(precipitant medicine). Although some medicine in teractions may be used for remedial benefit, interaction may also increase the goods of a medicine, leading to toxin, or inhibit the goods of a medicine, leading to a lowered remedial benefit. A implicit medicine inter action was defined as an circumstance in which 2 medicines known to interact were coincidently specified, regard lower of whether adverse events passed. Medicine interac tions may astronomically be distributed as pharmacokinetic delivery of the object medicine to its point of action is altered by the precipitant) or pharmacodynamic(response of the object medicine is modified by the precipitant without changes in the pharmacokinetics of the object medicine).(1)medicines that inhibit or induce the cytochrome P450 CYP) isozymes are generally associated with pharmacokinetics relations.1 The part of medicine transporters is decreasingly appreciated as an important pharmacokinetics medicine- commerce medium.2 Pharmacodynamic relations may be prognosticated grounded on the pharmaco sense goods of a medicine, and the result may be cumulative or

3. Frequency of potential azole drug–drug interactions andconsequences of potential fluconazole

drug interactionsThe azoles are one of the three classes of systemic antifungal agents extensively used for treatment of suspected or proved fungal infections, and are effective. Still, they've numerous DDIs. A number of recent studies have addressed this issue. Still, utmost of these studies were conducted in either healthy levies, or in small groups of cases witnessing organ transplantations, suffering HIV infection or voiced in the ferocious care unit(ICU). In addition, utmost studies assessed changes in

pharmacokinetic parameters similar as drop in the serum attention of azole agents7 – 10 and increase(in utmost studies) or drop in serum attention of interacting medica tions.11 – 41 Although statistically significant changes were set up, the clinical significance of the DDIs was infrequently reported.31, 42,43 Multiple cases have also been reported of DDI- associated ADEs, ranging in inflexibility from mild gastrointestinal torture 44,45 to life- hanging QT extension.46 – 49 Little information is available regarding the frequency of DDIs with azole antifungal agents or the frequence and inflexibility of ADEs performing from these relations in routine outpatient care. To address these issues, we performed a retrospective cohort study with the pretensions of(1) sketching the use of specifics that have a known commerce with azole antifungals in a population of rehabilitated cases being treated for systemic fungal infection and(2) assessing the frequence of ADEs associated with fluconazole DDIs. (2)

For each of the following characteristics and out comes of dimension, counts with proportions, means with standard diversions and middles and interquartile ranges were determined as applicable age, coitus, insurance status, primary discharge DRG, DRG weight, underpinning conditions, individual medication for azole antifungals and azole- interacting medication and prevalence of implicit DDIs. When multiple implicit DDI incidents passed due to the same azole – medicine commerce during the same hospita lization, only one incident was counted.(3) All analyses were performed using the SAS statistical package SAS Institute,Inc., Cary, NC).59

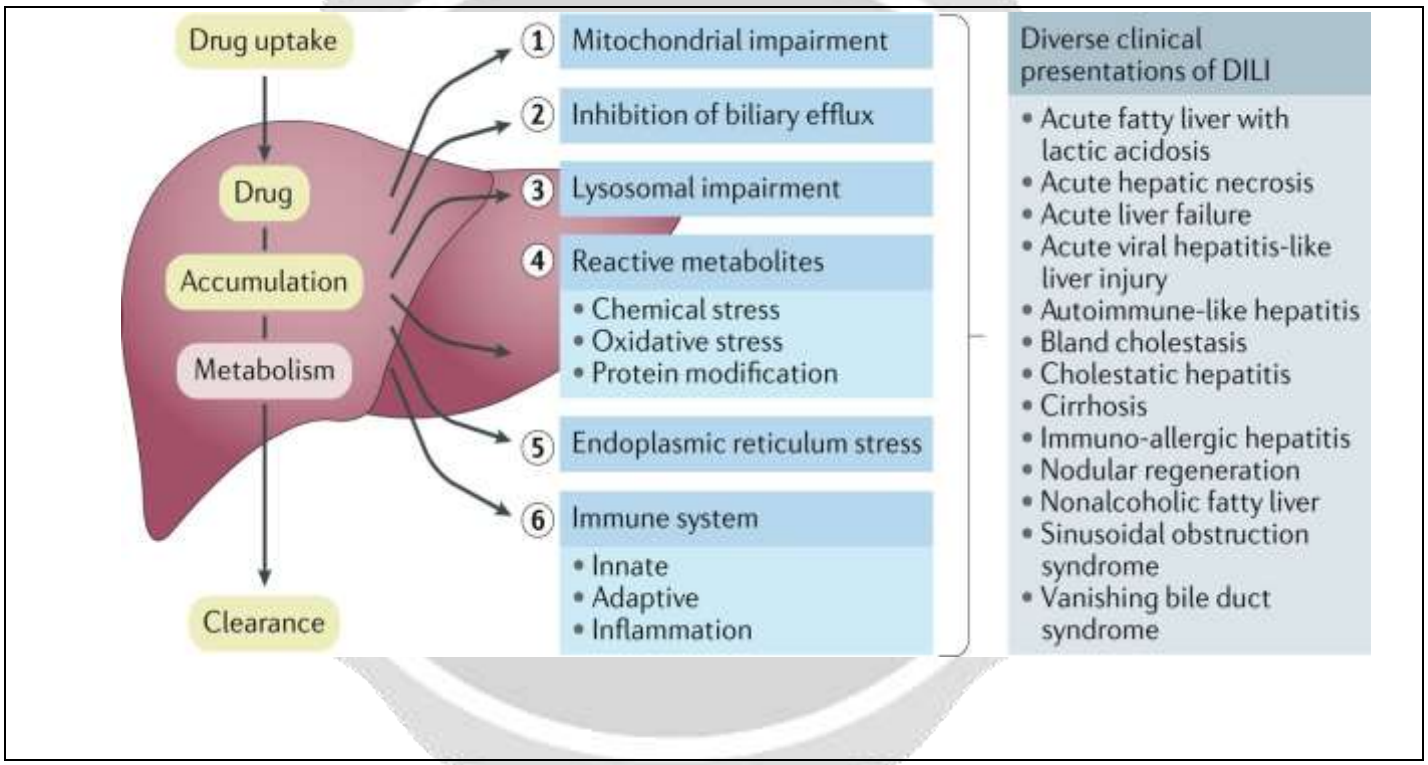

Fig. drug induced liver injury with hepatotoxicity

4. Drug interaction with itraconazole, fluconazole and tarbinafine and their managemant

Understanding the medium of medicine interac tions may help the prescriber to avoid them. Medicine relations are considered clinically significant if the remedial effectiveness of one of the interacting medicines is dropped or if an adverse response mani fests itself.8 The more important adverse medicine-medicine relations do with medicines that have a serious tox icity and low remedial indicator.3 In similar cases fairly small changes in the medicine position may have important adverse consequences. Medicine relations may be either pharmacokinetic or pharmacodynam ic.3 In a pharmacokinetic medicine-medicine commerce, a medicine may alter the immersion, distribution, metabolism, or elimination of another drug.9 As a consequence, there may be an increase or drop in the attention of medicine at the point of action. (4)Because individualities may vary in the rate of disposition of a given medicine, the

extent of a medicine commerce that alters pharmacokinetic parameters are not always predictable.3 still, the consequences can be relatively significant.

A. Itraconazole

Anticonvulsants(eg, phenytoin, phenobarbital carbamazepine).43, 46- 48 Coadministration with itraconazole may be associated with reduced serum attention of the triazole. Phenytoin may enhance the first- pass metabolism and hepatic metabolism of the triazole by CYP 3A The pharmacologic goods of hydantoins(phenytoin, etho toin, and mephenytoin) may be increased as a result of inhibition of hydantoin metabolism.43 Antihistamines(astemizole, terfenadine).49- 55 Concurrent administration of astemizole and itra conazole is contraindicated because elevated con centrations of astemizole and its top metabo lite, desmethylastemizole, may affect.49, 50 also, coadministration with terfenadine results in increased tube situations of the antihistamine(5). Both of these antihistamines are contraindicated with itra conazole because of an increased threat of torsades de pointes ventriculartachycardia.51- 53 Antimycobacterial agents(rifampin, isoni azid, rifabutin).56- 58 Coadministration with itra conazole may be associated with dropped serum itraconazole attention because the metabolism of the triazole is convinced. In addition, itraconazole may increase serum rifabutin situations

B.Fluconazole

Antidepressants, tricyclic(eg, amitriptyline, nortriptyline).129, 130 Three case reports with flu conazole appeared to significantly raise serum situations of amitriptyline. Fluconazole may intrude with amitriptyline demethylation by the CYP 2C9 isoform. Antihistamines(eg, terfenadine, astemi zole).131- 134 Coadministration of fluconazole at mul tiple boluses of 400 mg or advanced with terfenadine is contraindicated. Coadministration of fluconazole at boluses lower than 400 mg/ day should be precisely covered. Use of fluconazole in cases concur rently taking astemizole may affect in elevated situations of the ultimate. (6)In the absence of definitive information, care should be taken when administering astemizole with fluconazole. Cases should be precisely covered

Oral antifungals	Contraindications and cautions
Terbinafine	• Hypersensitivity to terbinafine • Lactation • Severe hepatic or renal disease
Itraconazole	• Hypersensitivity to itraconazole • Pregnancy or lactation • Congestive heart failure

Fig._contraindicated drug with itraconazole and possible alternarnative

C.TERBINAFINE

In discrepancy to ketoconazole, itraconazole, and flu conazole, terbinafine is an allylamine that demon strates a weak substrate commerce with cytochrome P Terbinafine acts as a substrate for a frac tion of cytochrome P- 450 by which it's fleetly metabolzed . No significant response has been observed between terbinafine and terfenadine, 203 midazo getaway, 204 triazolam, 152 nifedipine, 205 digoxin, 206 testos terone, 207,208 glyburide, 209 and antipyrine.210, 211 Terbinafine doesn't inhibit CYP 3A4. The allylamine may beget a weak induction of some CYP isoforms with a drop in the tube attention of

some coadministered medicines(substrates of CYP 3A4) by 10 to30.211 exemplifications are terfenadine acid metabo lite203 and cyclosporin.212

Drug interactions affecting clozapine levels

Clozapine is an atypical antipsychotic primarily indicated for the operation of treatment resistant schizophrenia and reduction in the threat of intermittent suicidal geste

In schizophrenia or schizoaffective complaint(Lehman etal. 2010). Still, a subset of cases fail to respond or have only a partial response to clozapine, leading clinicians to search for implicit addition strategies to ameliorate issues. (7)Psychotropic specifics used in combination with clozapine include antidepressants, antipsychotics and mood stabilisers(Calabrese & Gajwani, 2000; Fuchs, ; Chan & Sweeting, 2007). Non-psychotropic specifics are also added for operation of associated medical conditions. Smoking and smoking conclusion have also been reported to affect clozapine situations leveThe clozapinenorcloza pine rate has practical significance; for illustration, a rate of,0.5 suggests either poor adherence within the last 24 hours or that differences in cure schedule might be salutary; and a rate 3 suggests that either immersion of clozapine from the last cure may not have been completed at the time the sample was attained, or that clozapine metabolism is impregnated either because of the cure specified or because of inhibition of clozapine metabolism by a coadministered medicine Yusufi etal. 2007). Besides specifics, other demographic variables can also affect clozapine situations including gender, race, age, smoking geste

And weight. The gender- associated differences can be a function of hormonal balance, body composition, and/ or exertion of certain enzymes(Rowland & Tozer, 1995).(8) The age related differences can be a function of medicine immersion, distribution, detention in gastric evacuating, and/ or changes in renal and/ or hepatic elimina tion(Haring etal. 1989). Changes in body water spaces, muscle mass, organ blood inflow, and organ function are related to body weight and can prompt volume of distribution and concurrence(Rowland & Tozer, 1995)

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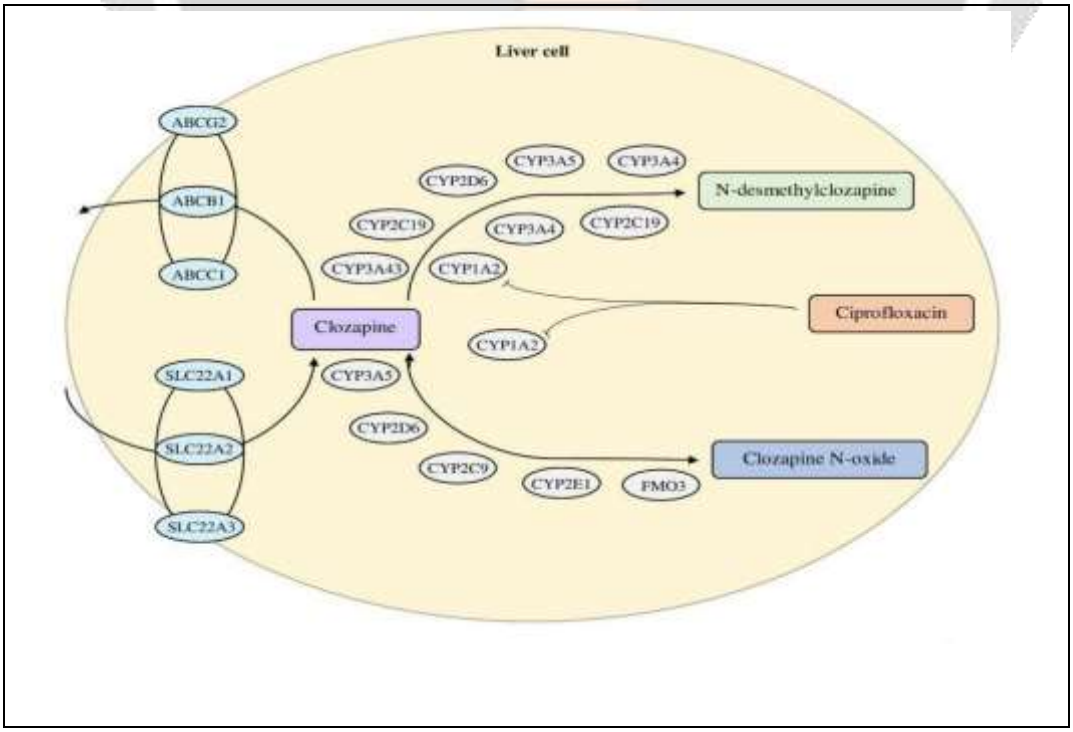

Fig. physiologicle mechanism and drug drug interaction of hepatotoxicity

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Like with all drugs, the majority of unfavorable hepatic reactions necessitate the drug's metabolism to hazardous reactive metabolites and free radicals. The severe clinical state known as acute or fulminant liver failure (FLF) is defined by a rapid loss of hepatocytes (80–90%), the emergence of hepatic encephalopathy/coagulopathy, and a diminished ability to metabolize medications and enzymes [79, 80]. ADR or herb-induced hepatotoxicity predominates in North America and Europe, but hepatotropic or hepatitis viruses are among the most frequent causes of abrupt liver failure in underdeveloped countries [81, 82]. Direct overwhelming toxicity, non-lethal sensitization to eventual lethal immunological responses, and haptenisation, leading to an immuno-allergic reaction are a few potential cellular or molecular pathways. (9). In addition to acting directly on hepatic molecules, some natural pyrrolizidine alkaloids of Senecio, Heliotropium, and Crotalaria species, etc. also alkylate DNA, resulting in chromosomal damage, cross-linking, mutations, and apoptotic cell death [83]. For example, pyrrolizidine alkaloids, certain flavonoids, alkylating compounds, crystalline glycosides, pulegone, safrole, sennosides, potassium atractylate, gummiferin, and nordihydroguaiaretic acid are known phytochemicals or active components in herbal preparations that cause hepatotoxicity. Notably, pyrrolizidine toxicity, which causes hepatic veno-occlusive disease, is known to be hazardous to liver endothelial cells. [83-86]. Additionally, wall germander (Teucrium chamaedrys) and chapparal (Larrea tridenta) have been linked to hepatic zonal necrosis [83-87]. Pennyroyal (Mentha pulgeium) causes hepatic necrosis and microvesicular steatosis, whereas Teucrium polium is known to cause hepatitis and fibrosis [83, 86, 87]. In addition, the Distaff thistle (Atractylis gummifera) also results in renal failure and panlobular hepatic necrosis [84–87]. Hepatotoxicity from Indian ayurvedic medicine has been observed far less frequently than from TCM. In a case report, a woman who used several ayurvedic treatments for vitiligo was found to have acute hepatitis; babchi (Psoralea corylifolia) was thought to be the culprit [88]. It has been reported that the ayurvedic drug brahmi, also known as Asiatic pennywort (Centella asiatica), is linked to granulomatous leprosy.[91].

5. Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations

Mechanism of action

Isoniazid is a prodrug that must be activated by the M. tuberculosis catalase-peroxidase enzyme KatG. Upon activation, isoniazid creates organic and oxygen-derived free radicals that damage bacterial DNA and ultimately cause the bacillus to die. (10)These free radicals include superoxide, hydrogen peroxide, and peroxynitrite. KatG mutations, which reduce the action of isoniazid and stop the prodrug from being transformed into its active metabolite, are the most frequent type of isoniazid resistance mechanism.(15,17

Metabolization and excretion

Isoniazid is metabolized in the liver through acetylation by N- acetyltransferase, which produces acetylisoniazid and isonicotinic acid. The acetylation rate is a inheritable characteristic and thus varies from case to case. Certain cases present the rapid-fire acetylator phenotype, whereas others present the slow acetylator phenotype.(11) There's contestation as to whether the ultimate are more likely to develop instantiations of hepatotoxicity than are the former, there being no differences between these phenotypes in terms of antimicrobial exertion. Isoniazid is excreted by the order(70- 96), generating, for the utmost part, inactive metabolites. In cases with the rapid-fire acetylator phenotype, 7 of the isoniazid excreted in urine can appear as free isoniazid, whereas 37 can appear as conjugated isoniazid in cases with the slow acetylator phenotype. (12)A small proportion is excreted in feces. The half- life of isoniazid is roughly 1 h(range0.5-1.6 h) in cases with the rapid-fire acetylator phenotype and 2- 5 h in those with the slow acetylator phenotype; in cases with liver complaint or order failure, the half- life of isoniazid can be indeed longer.(16,18)

6.Drug interactions affecting clozapine levels

A. Antidepressants

There is one case report for fluoxetine (Sandson et al. 2007), where a fivefold rise in clozapine levels was observed. Ferslew et al. (13)(1998) reported a case of fatal drug interaction with fluoxetine resulting in death from conpulmonary edema, visceral vascular congestion, paralytic ileus, gastroenteritis and eosinophilia.

B. Anticonvulsants

The result was discontinuation of carbamazepine double increase in clozapine concentration (Raitasuo et al. 1993). A case of neuroleptic malignant tumor syndrome was reported by Müller et al. (1998), who concluded that clozapine and carbamazepine is not considered safe for risk neutropenia and decreased seizure threshold. Later, a doubling of clozapine serum levels reported discontinuation of valproic acid Conca et al. (2000).(14) Centorrino et al. (1994) reported a mild increase in serum clozapine level (about 6%) with valproic acid 11 patients In contrast, Longo and Salzman (1995) reported a 15% increase in blood clozapine level. in seven patients after addition of valproine acidic Coexistence of two mechanisms interaction (CYP 1A2 enzyme inhibition and repelling protein binding) causing the opposite changes in total concentration of clozapine explain the opposite results (Finlay and Warner,1994). This supports clinical importance therapeutic monitoring of serum clozapine. reports Two case reports suggested a worsening of the situation psychosis after adding phenytoin to reduce in plasma clozapine concentrations (Miller, 1981).

C antipsychotics

Because another antipsychotic is often added scaling strategy is important to consider the safety of these combinations. (15)Clozapine only interactions with antipsychotics occurred with aripiprazole and risperid one one report of an interaction with risperidone clozapine. The result was the addition of aripiprazole in reducing the concentration of clozapine (Avari et al. 2011) and was accompanied by severe deterioration of illusions and hallucinations in one case report (Avari et al. 2011). The remaining five cases (Abu-Tair et al. 2006) reported improvement negative symptoms after the combination clozapine and no change in clozapine levels was noticed. The mechanism of this interaction not well understood

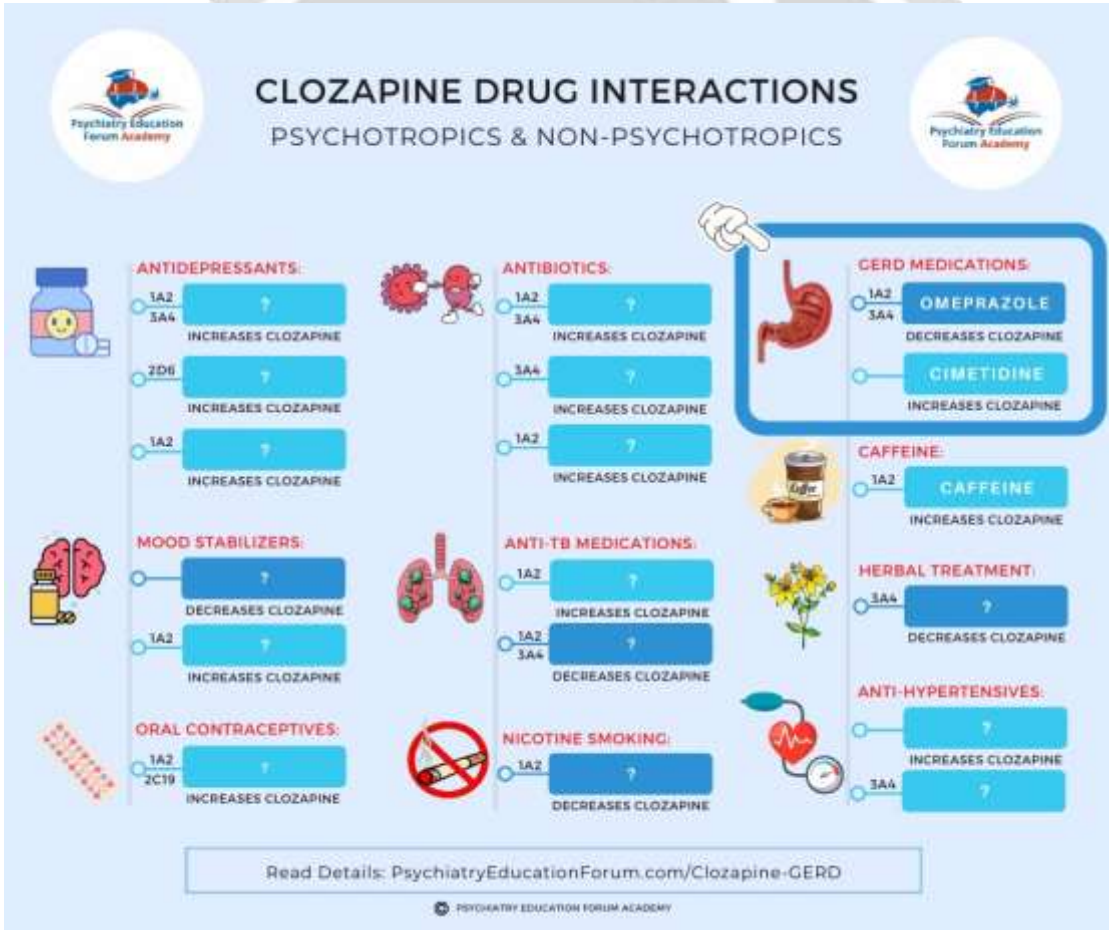

Fig. factor affeting clozapine level

7.Old and New Antirheumatic Drugs and the Risk of Hepatotoxicity

ANFLAMMATORY NONSTEROIDAL DRUG

Acute idiosyncratic liver injury caused by NSAIDs is a common occurrence, with hospitalization rates ranging from 3-23 per 100,000 patients annually.10,16 Diclofenac, nimesulide, and sulindac have been linked to an increased risk of hepatotoxicity despite the fact that it is challenging to pinpoint which NSAID carries this risk. The likelihood of suffering a liver injury is higher in females who are concurrently taking other potentially hepatotoxic medications.(16)
Hepatotoxicity from diclofenac is an illustration of an idiosyncratic medication reaction.18 A hospital referral happens in 6.3 per 100,000 users, 15% of patients who routinely take the medication for a long time see transaminase elevation, 5% exhibit a 3-fold rise, and 85% of patients start experiencing liver damage within 6 months of commencing diclofenac.13 Hepatocellular injury is connected liver damage

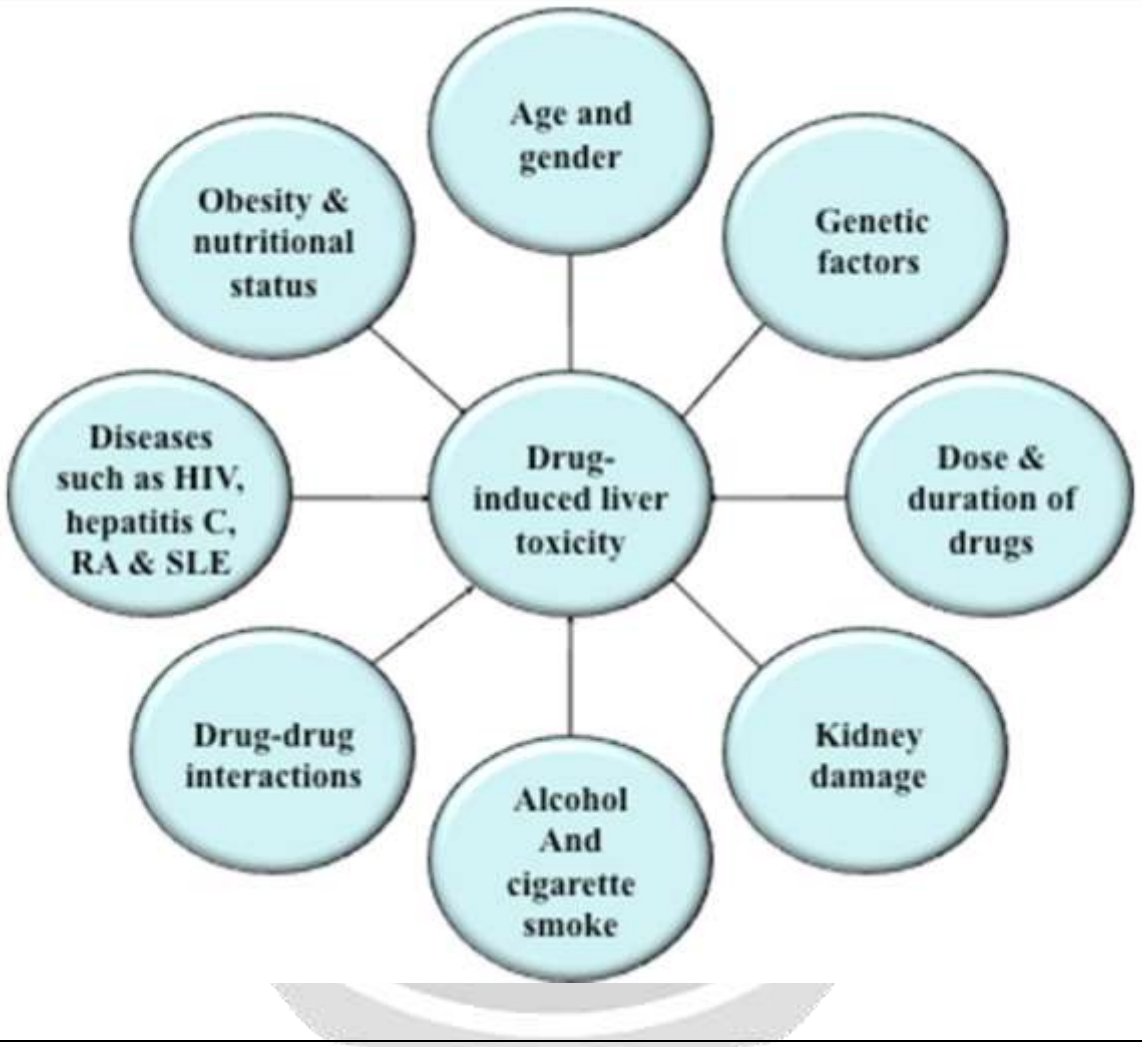

Fig. drug induced hepatotoxicity

A Clinician's Guide to Drug-Drug Interactions With Direct-Acting Antiviral Agents for the Treatment of Hepatitis C Viral Infection:

General Drug-Drug Interaction MechanismsClinically significant drug-drug interactions often happen during the drug's pharmacokinetic profile's metabolism or absorption phases. Absorption interactions typically take place by either directly binding the index agent or by changing the internal pH.Drug metabolism-related interactions are also frequent. Many medications are oxidized by the cytochrome P450 (CYP450) enzyme system, in particular the 3A4 (CYP3A4) isozyme. By administering inhibitors, inducers, and/or substrates of this enzyme system, medication concentrations may fluctuate in a way that is clinically significant.1 Other enzymes that metabolize medicines function according to similar induction and inhibition principles(17)

Active transport proteins P-glycoprotein (P-gp) and breast cancer resistance protein interactions may also influence medication bioavailability by either enhancing excretion or reducing cellular absorption.(18)The liver and digestive system contain both P-gp and CYP450 enzymes.4 Prior to

systemic absorption, oral medicines are potentially eliminated by intestinal CYP450 and P-gp, a process known as "first pass metabolism." When intestinal CYP450 and P-gp are inhibited, a second drug may be more readily available for systemic absorption.
These metabolic pathways are used to break down the DAAs used to treat HCV, making them vulnerable to drug-drug interactions. Figure 1 displays the typical.

Drug Interactions That Are Clinically ImportantAgents of Human Immunodeficiency VirusAnti-protease agents. Protease inhibitors generally reduce the activity of the CYP3A isozyme. (19)However, protease inhibitors for HIV and HCV differ in terms of their ability to suppress the respective viruses. Both simeprevir and ritonavir are CYP3A inhibitors, although ritonavir has a substantially stronger inhibitory effect. When administered simultaneously, simeprevir and ritonavir cause a six-fold increase in simeprevir exposure.5Additionally, the combined inhibition of the two drugs may have a considerable impact on the concurrent administration of other drugs. It is not advised to use the two medicines simultaneously due to this higher concentration.5 Alterations in simeprevir plasma concentrations can also be brought on by atazanavir, fosamprenavir, lopinavir, indinavir, nelfinavir, saquinavir, tipranavir, and ritonavir.

Conclusion

The aim of this study was to evaluate the incident and type of clinical risk of dru drug interaction in patients with hepatotoxicity.

The study highlighted that patients with hepatotoxicity are particularly vulnerable to drug-drug interaction when they take the other treatment along with hepatotoxicity treatment

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