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Drug Induced Liver Injury: A Comprehensive Review

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Abstract: Contributing predominantly to both acute and chronic disease affecting the liver, drug-induced liver injury leads to higher morbidity and mortality cases. This extensive review paper presents an in-depth analysis about knowledge state on DILI related to its pathophysiology, clinical presentations, diagnostics troubles and treatment strategies. The review of the literature shows that DILI is a complex condition, involving pharmacological, environmental, and genetic variables. The clinical appearance may vary widely from slight increases in liver enzymes to severe liver failure. The time interval between drug intake and the onset of symptoms also varies greatly. This review focuses on the strong need for early DILI diagnosis and treatment to avert liver failure and promote prognosis. We also take into account contemporary diagnostic modalities and treatment strategies, which may include imaging studies, liver biopsies, and biomarkers. This research, therefore, calls for basic scientists, pharmacologists, and clinicians to tackle DILI in a multidisciplinary approach. To enhance better understanding of this complex phenomenon and to encourage further study in this area, this paper attempts to present a comprehensive overview of DILI.

Index Terms – DILI, Hepatotoxicity, Drug induced liver injury, Risk Factors, Toxicity

I. INTRODUCTION

One frequent cause of liver damage is drug-induced liver toxicity. It mimics all types of acute and chronic liver illness and is responsible for almost half of cases of acute liver failure [1]. On eleven occasions, an estimated 1000 medications have been linked to liver illness [2]. Even though drug-induced liver damage usually goes away when therapy with the drug is stopped, this poses a significant diagnostic and treatment problem for doctors.The mechanisms underlying drug-induced liver disease, as well as the risk factors and clinical features linked to drug-induced hepatotoxicity, are summarised in this article.

II. PATHOGENESIS

One can classify drug-induced adverse hepatic events as either predictable (high incidence) or unpredictable (low incidence). Drugs like paracetamol that cause predictable liver damage typically do so in a matter of days and are typically caused by the parent drug or its metabolites directly causing liver damage [3]. There may be long (1 year) or intermediate (1–8 week) latency periods before unpredictable occurrences show up as overt or symptomatic disease. Isoniazid is an example of the latter, and phenytoin is an example of the former [4–5]. Immunomediated hypersensitivity reactions or idiosyncratic reactions account for the bulk of adverse drug-induced hepatocellular events, which are unpredictable. The pathophysiology of drug-induced liver injury typically includes the involvement of a toxic substance or metabolite that either directly affects the cell's biochemistry or triggers an immunological response. The clinical manifestation of hepatitis is caused by the resulting cell death in either scenario [2, 6]. Due in great part to the liver's role in chemical metabolism, the organ is vulnerable to drug-induced damage that is dependent on metabolism [7]. Drug

metabolites can be either free radicals or electrotrophic compounds that undergo or promote a range of chemical processes, including lipid peroxidation, covalent binding to proteins, lipids, or nucleic acids, or the depletion of reduced glutathione (figure 1). The cytoskeleton, microtubules, mitochondria, the endoplasmic reticulum, and the nucleus are all directly impacted by each of these. By activating and inhibiting transcription factors, signalling kinases, and gene-expression patterns, they may also have an indirect effect on cells or ganelles. Cell death from the resulting intracellular stress is brought on by either swel The primary cause of liver injury is hepatocyte death, however other potential targets include bile duct epithelium [12] and sinusoidal endothelial cells [11]. Cytokine-induced hepatotoxicity can also result from sensitisation to cytokines specific to the liver [6, 9]. An immunological response and immune-mediated damage could result from the reactive metabolite's covalent binding to or modification of liver proteins, including cytochrome P450 enzymes [13, 14]. To differentiate this immune-mediated drug-induced hepatitis from non-immune-mediated drug-induced hepatitis, it is typically characterised by eosinophilia, fever, or other allergic reactions [15]. It's unclear how the immune-mediated pharmacological reaction is induced, although it might have something to do with haptens [16].ling and lysis (necrosis) or cell shrinking and nuclear disassembly (apoptosis) [6, 8–10]. The primary cause of liver injury is hepatocyte death, however other potential targets include bile duct epithelium [12] and sinusoidal endothelial cells [11]. Cytokine-induced hepatotoxicity can also result from sensitisation to cytokines specific to the liver [6, 9]. An immunological response and immune-mediated damage could result from the reactive metabolite's covalent binding to or modification of liver proteins, including cytochrome P450 enzymes [13, 14]. To differentiate this immune-mediated drug-induced hepatitis from non-immune-mediated drug-induced hepatitis, it is typically characterised by eosinophilia, fe ver, or other allergic reactions [15]. It's unclear how the immune-mediated pharmacological reaction is induced, although it might have something to do with haptens [16]. Generally speaking, low-molecular-weight organic compounds and medications do not cause immunogenic reactions; however, this can change if they attach to a macromolecule, like a protein. A cytochrome P450-produced drug metabolite that possesses hapten properties would covalently attach to a liver protein and change that protein [17]. When the immune system interprets this changed protein as alien, it can attack normal hepatocellular components, leading to an autoimmune reaction. But this theory doesn't account for a lot of the immune-mediated drug-induced hepatitis. Drugs like halothane, for example, frequently undergo covalent binding (haptenation), which infrequently results in immune-mediated damage [18]. n addition to altering a protein, a reactive metabolite could also need to damage or stress liver cells in order to trigger an immune response [19]. Some medications only or mostly cause cholestasis. A number of them, including chlorpromazine [21] and sulindac [20], are linked to hypersensitivity-type reactions. Little is known about the precise immunological targets of these unpleasant reactions of the hypersensitivity type. Nonetheless, they are probably connected to the bile duct because portal inflammation and biliary damage are the most common histological findings. Ductal damage may come from hazardous metabolites travelling through canalicular excretion reacting with macromolecules in the duct cells or going through further metabolism there [15]. Therefore, an unfavourable immune response to the liver and/or bile duct that causes a disease with clinical signs that are hepatic, cholestatic, or a combination of these, the mechanisms of which are unclear, is known as drug-induced immune-mediated damage.

III. CLINICAL AND PATHOLOGICAL SYMPTOMS OF DRUG-INDUCED LIVER DISEASES

The clinical and pathological manifestations of liver diseases caused by drugs A characteristic signature, consisting of a latency time and a clinical and pathological pattern, is typically present in individual medicines that cause liver disease (table 1). Most adverse responses resemble the symptoms of acute hepatitis, cholestasis, or mixed presentations, as was previously mentioned.Figure 2 provides the recognised definitions for these reactions. Some medications, like augmentin, display multiple distinct characteristic reactions; others do not. Short (hours to days), intermediate (1–8 weeks), or long (1–12 months) latency periods are also possible. In certain situations (such as with erythromycins or augmentin), Withdrawing the drug may result in a delayed effect. Up to three or four weeks following the end of an antibiotic course, this could happen. Although the exact mechanism is unknown, the effect might be brought on by the drug's long-term retention in the body along with the delayed onset of an immune response. After stopping the causing medication, cholestatic reactions often last longer; this is likely because cholangiocytes replenish and repair more slowly than hepatocytes. A self-propagating immunological response can also endure, though this is probably extremely uncommon. The gene-expression profile is a recently developed component of the signature reaction. The mechanism of unpredictable reactions will be better understood if toxicogenomics is used to find a characteristic pattern of gene expression for hepatotoxins [22]. When overt liver damage does not occur in a small study population, the combination of toxicogenomics and proteomics may also offer the technology to identify individuals at risk and anticipate hazardous potential.

IV. RISK FACTORS

A complicated interaction between the drug's chemical characteristics, environmental factors (such as the use of alcohol or other medications concurrently), age, sex, underlying disorders (such as HIV or diabetes), and genetic factors contributes to the chance of developing hepatotoxicity [23, 24] (figure 3). Concomitant drug usage and diseases are the risk variables that have been studied the most. Recent data indicates that people infected with HIV, hepatitis B, and hepatitis C have higher rates of drug-induced liver damage, which may be related to cytokine imbalance in these individuals. Genes that affect cell injury and repair as well as those that regulate drug handling (metabolism, detoxification, and transport) are examples of genetic influences. Furthermore, several of the genes encoding drug-metabolizing enzymes and drug transporters have functionally significant genetic polymorphisms [25]. However, a drug-metabolizing enzyme's functional involvement in drug metabolism determines whether a genetic variation of that enzyme has therapeutic significance. There has also been evidence of familial vulnerability to the toxic effects of metabolites, suggesting that these may be inherited deficiencies in the defence against particular drug-related diseases [26].

V. MECHANISMS OF DRUG INJURY

In most human and animal situations, drugs can cause liver injury in a predictable dose-dependent manner (intrinsic DILI) or in an unpredictable, non-dose-dependent manner (idiosyncratic DILI).

Intrinsic Drug-Induced Liver Injury

In the US, paracetamol poisoning accounts for around half of all ALF cases and is the most frequent cause of severe intrinsic DILI. Since nonintentional overdoses resulting from various patient beliefs account for approximately half of paracetamol toxicity deaths, most of these deaths are avoidable. [27,28] Furthermore, as long as N-acetyl-cysteine is given within 8 hours of intake, it is a very potent antidote that can lessen the harmful effects of an acute overdose. [29-32] In the middle of the 1970s, it was found that hepatocytes' metabolism of paracetamol produces the reactive metabolite N-acetyl-p-benzoquinone. intracellular glutathione, which reduces and detoxifies the imine [NAP QI]. Overdosing on this metabolite overwhelms glutathione's reducing ability, causing NAPQI to covalently modify many intracellular structures, which results in zone 3, centrilobular hepatocyte necrosis. [34-35] In 1977, N-acetyl cysteine was introduced as a specialised treatment for acetaminophen-induced hepatotoxicity due to its constant and well-defined character. By aiding in the regeneration of glutathione, N-acetyl-cysteine detoxifies accumulated acetaminophen metabolites. Specific guidelines for the safe use of this extremely popular drug have been made easier by the dose-related way that acetaminophen damages the liver. Twenty billion nonprescription paracetamol pills are sold in the US each year, and the medical system spends $87 million on addressing overdose consequences. [31-36] In order to reduce the frequency of unintentional overdoses, the US Food and Drug Administration (FDA; Silver Spring, Maryland) issued recommendations in 2009 that identified combination drugs as a common source of unintentional paracetamol overdose. In order to encourage manufacturers to lower the dosage of acetaminophen to 325 mg each dose and to emphasise the possibility of severe hepatotoxicity, the FDA also recommended lowering the maximum daily dose from 4000 mg to 3250 mg. [36]

Idiosyncratic Drug-Induced Liver Injury

In contrast to idiosyncratic DILI, which is defined by hepatotoxicity that happens in a very small percentage of people who are exposed to a drug at the same dose for the same amount of time, intrinsic drug damage has a rather predictable trajectory. Antimicrobials (amoxicillin-clavulanate, nitrofurantoin, sul famethoxazole-trimethoprim, ciprofloxacin, and isoniazid) are the most common causative agents that cause DILI in the United States.[37,38] Idiosyncratic drug responses are also a result of newer medications used to treat autoimmune diseases (like tumour necrosis factor a [TNF-a] inhibitors) and cancer (like tyrosine kinase inhibitors). Since most occurrences of idiosyncratic DILI are minor, self-limited injuries that fully reverse once the offending chemical is found and removed, it is difficult to estimate the incidence of this condition. Nonetheless, 13% to 16% of potentially fatal acute/fulminant liver failure episodes in the US are caused by idiosyncratic DILI. [27, 28] Furthermore, the FDA frequently removes medications from the market due to idiosyncratic DILI.[38], [39] Hypersensitivity (also known as immunologic) and metabolic mechanisms of injury are the two main categories into which idiosyncratic DILI may be separated. Fever, rash, granulomas, and eosinophilia in the peripheral blood or tissue biopsy sample are the hallmarks of hypersensitivity-type reactions, which account for 23% to 37% of all idiosyncratic DILIs.[40-41] Since there is no evidence of hypersensitivity in the remaining cases, they are assumed to be metabolic in nature. By distributing the 2000 or fewer instances of symptomatic DILI between small and major hospital settings across the United States,

the number of cases at any one institution is kept to a minimum. It is also impossible for a single institution to compile a number of cases that are comparable because these cases represent hundreds of distinct chemical components. Therefore, case reports, which included a limited number of patients and were gathered at one or a few institutions, were the original source of early knowledge about DILI. The rarity of idiosyncratic medication reactions limits the effect of case reports, despite the fact that they have been an essential source for DILI. To obtain a more thorough understanding of DILI, large national registries have been established to centralise and standardise the study. [42] Funded by the National Institutes of Health (Bethesda, Maryland), the Drug-Induced Liver Injury Network (DILIN) in the United States started recruiting patients for prospective analyses in 2004. To far, the network has gathered over 600 cases at 12 collaborating US institutions. Having a network tailored to the United States is crucial because drug use varies greatly depending on regional medical practices as well as national drug approval and restrictions. The different distribution of offending agents among nations has been verified by formal assessments between national registries.[43]

VI. DILI CAUSING AGENTS

The Amoxicillin-Clavulanate that has been tried and tested.The most common cause of DILI in a number of series from various nations is amoxicillin-clavulanate.[42, 44, 45, 47] Worldwide, amoxicillin is used extensively to treat a wide range of infections. This semisynthetic b-lactam is frequently used in conjunction with clavulanic acid to prevent bacterial b-lactamases from breaking down amoxicillin and making it useless. Compared to amoxicillin alone (0.3 per 10,000 prescriptions), the incidence of DILI is significantly higher when amoxicillin and clavulanic acid are used together (1.7 per 10,000 prescriptions). [47,49] Similarly, recurrence occurs more frequently after rechallenge with amoxicillin-clavulanic acid than after rechallenge with amoxicillin alone.[50] Amoxicillin-clavulanate-induced liver damage is unique; the risk rises with age, the number of prescriptions taken, and the length of treatment. For older individuals who have several medicines, the risk rises by 5.2 per 10,000 prescriptions.[45,48,49] Men are marginally more vulnerable. Double-null heterozygosity for glutathione S-transferase (GSTT1/GSTM1) and the presence of the HLA class II antigens DRB1*15 and DQB1*06 are genetic variables that raise the risk of amoxicillin-clavulanate poisoning. [51,52] The latter finding implies that this enzyme plays a role in drug detoxification since its absence prolongs exposure to the drug's intermediate metabolites.[53] Liver disease symptoms include fever, jaundice, pale stools, dark urine, pruritus, nausea, and stomach discomfort. These symptoms often appear six weeks after treatment starts. or a condition caused by a virus.[54,45,50] Many individuals exhibit hypersensitivity symptoms, including skin rashes and eosinophilia; Stevens-Johnson syndrome may also develop.[42,49] A cholestatic, hepatocellular, or mixed hepatocellular cholestatic pattern of damage can be seen in laboratory tests.[42,45] Elderly patients who have received lengthier treatment regimens seem to experience cholestatic and mixed patterns of harm, while younger patients who have received shorter treatment durations are more likely to experience hepatitic damage.[54]. Histologic patterns can also change with time, leading to a cholestatic profile from an initial hepatitic or mixed pattern of injury.[54,55] Acute cholestasis may be seen in very early biopsies, although cholestatic hepatitis is the most common histological manifestation of amoxicillin-clavulanate liver injury (Figure 8, A and B). [55] There have been several documented occurrences of significant bile duct damage. These demonstrate widespread inflammatory cell infiltration of the biliary epithelium, which is associated by cytoplasmic vacuolization, nuclear irregularity, and biliary epithelium eosinophilia. Serum alkaline phosphatase levels may be correlated with the extent of bile duct damage, but histologic cholestasis and the length of jaundice are typically uncorrelated.[56,57] There have been isolated reports of granulomatous hepatitis and bile duct loss following amoxicillin-clavulanate exposure.[50,55,58] The majority of patients recover from amoxicillin-clavulanate-induced DILI in 4–6 months. [45,50,57] Rare patients may get abrupt liver failure and mortality or ductopenia.[58,59]; in one series, 2.9% of patients had serious consequences.

Fluoroquinolones.—Due to their broad antibacterial coverage and efficacy, fluoroquinolones are the most often used antibiotics, frequently empirically. [59,60] According to the DILIN study, they are also the most frequent cause of idiosyncratic drug harm.[44] The different fluoroquinolones exhibit comparable clinical presentations and patterns of damage, which is consistent with a "class effect." Fluoroquinolone-induced liver damage has a brief latency period of two to nine days and a sudden onset that starts while the patient is still receiving the antibiotic. Eosino philia, fever, and rash are typical immunoallergic symptoms.[61-65] There is a wide range of damage patterns, including cholestasis, mixed patterns, and hepatocellular patterns. The usage of corticosteroids is beneficial for patients with noticeable signs of hypersensitivity. The majority of individuals with hepatotoxicity linked to fluoroquinolones recover, but the

duration of their disease may be extended. Even though it is uncommon, both acute and chronic liver failure and mortality can happen. However, the incidence of acute liver failure caused by amoxicillin-clavulanate is higher (10 cases per 10 million prescriptions) than that caused by levofloxacin, moxifloxacin, and gatifloxacin (2.1, 6.6, and 6.1 cases per 10 million prescriptions, respectively).86% The short latency period, frequent occurrence of eosinophilia and skin rash, and increased damage upon reexposure seem to indicate that fluoroquinolone hepatotoxicity is a hypersensitivity reaction.87.88 Individuals who are sensitive to one fluoroquinolone will exhibit heightened sensitivity to other fluoroquinolones.[69]

DIAGNOSIS

The diagnosis of DILI cannot be made using any particular or diagnostic clinical presentation, laboratory test, or histologic pattern. As the pattern and severity of harm varies depending on the drug and the patient, so do the signs and symptoms of DILI. Similar to this, DILI can exhibit a wide range of histologic patterns based on the host and the drug. Assigning causality to a medicine is consequently a painstaking process that necessitates, on the one hand, closely tying drug administration to disease start and, on the other, ruling out competing causes of liver diseases. The late 1980s The Council for International Organisations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) was established as a result of meetings organised by the Council for International Organisations of Medical Sciences (Geneva, Switzerland) and the Pharmaco Vigilance Division of Roussel Uclaf (Paris, France). The CIOMS/RUCAM was the first attempt to establish standardised definitions of liver injury and establish point-based criteria suggestive of DILI, where higher scores corresponded to a higher probability of DILI. [70-71] The scores are then converted into suspect categories: excluded (scoring ¼ 0), probable (score 6–8), possible (score 3–5), unlikely (score 1–2), and definite or highly probable (score. 8). The CIOMS/RUCAM scale, now popularly known as the CIOMS scale, has undergone extensive evaluation over time and shown excellent interobserver agreement and the capacity to accurately identify DILI. [72,73] The CIOMS scale hasn't been easily incorporated into the majority of clinical practices, nevertheless, and practitioners find it to be burdensome. Though they haven't been as thoroughly examined, other evaluation techniques like the Maria and Victorino (MV) clinical scale and the Naranjo Adverse Drug Reactions Probability Scale (NADRPS) have been created in the hopes of developing a more straightforward way to identify causality for DILI. Despite the MV clinical scale's high interobserver reliability, there isn't much agreement with the other scales. The COIMS scale was found to be significantly more indicative of the existence of real DILI, despite the very low agreement between the CIOMS and MV scales when compared head-to-head. [73] Similar findings were seen when the CIOMS and NADRPS scales were compared. The NADRPS's poor negative predictive value (29%) and low sensitivity (54%) significantly reduce its capacity to accurately identify DILI. [72] The most popular and dependable scale for establishing causation in DILI is still the CIOMS.

DILIN's Expert Consult System for Diagnosing DILI

A structured expert opinion method was developed by the US DILIN to evaluate causation in DILI. [74] A comprehensive clinical history, serial laboratory tests, history of prior liver illness, alcohol consumption, serology for viral and autoimmune hepatitis, and serum levels of ceruloplasmin, a-1 antitrypsin, ferritin, and iron were all included in a 65-page case report form that was generated from the patient charts. A comprehensive case summary (clinical narrative) and a condensed case report form (summary case report form) were prepared from this in-depth report and submitted for evaluation. Three hepatologists with expertise in DILI made up the review group. After evaluating the case separately, each hepatologist gave a causation score on a 5-point scale: certain, highly likely, plausible, possible, and unlikely. Every reviewer evaluated the case using the RUCAM scale as well. sprocedure to determine a drug's causality. While the DILIN expert consult system had higher interobserver agreement than the RUCAM scale, there was little linkage between the two adjudication techniques and significant interobserver variation within both systems.

Epidemiology

Given the variety of cultures, customs, healthcare systems, and the absence of standardised reporting procedures and criteria, it is challenging to ascertain the actual prevalence of DILI globally. Trends in the incidence of DILI over time have not been explicitly examined in any study. Despite the fact that two ongoing prospective investigations in the USA and Spain have not shown any significant variations in the prevalence of DILI over time, these studies are not population-based and, as a result, do not allow for the analysis of changes in incidence over time. Nonetheless, the percentage of patients in follow-up studies whose DILI was brought on by dietary and herbal supplements has been rising [77,78].

Asia: Over a two-year period, 17 referral university hospitals in South Korea participated in the region's only prospective countrywide research of DILI. According to this study, the most frequent causes of hospitalisation due to DILI were traditional and herbal medications, which were linked to over 72% of cases, with an extrapolated incidence of 12 cases per 100,000 people annually [80]. The projected yearly incidence

in China, according to a retrospective study, is [84].80 instances per 100,000 people in the general population, which is significantly higher than the rates in western nations. [81] The health care systems of technologically advanced Asian nations, such South Korea and Singapore, frequently use traditional medical films.[82] In Japan, the incidence and percentage of DILI brought on by traditional medicines is rising [83], despite the fact that herbal and traditional medicines are less incorporated into the healthcare system. The percentage of DILI brought on by dietary supplements and traditional medicines varies greatly among Asian nations, ranging from 15% in Japan22 to about 27% in China23 and 71% in Singapore [85]. The prevalence of DILI brought on by traditional medications is rising in China and India, respectively [86,87]. Given that 22.7% of people with tuberculosis worldwide reside in India28 and that three of the four first-line anti-tuberculosis medications (isoniazid, rifampicin, and pyrazinamide) have the potential to be hepatotoxic, it is not surprising that DILI brought on by anti-tuberculosis medications is a major cause of ALF in India.[90]

USA - In 2014, 20 people who presented with suspected DILI to gastroenterologists in Delaware were found to have idiosyncratic DILI, resulting in an annual incidence of 2.7 cases per 100,000 adults [91]. This study examined the incidence of DILI in the USA. DILI was linked to the use of prescription drugs in 8 people (57%), antibiotics in 36%, and herbal and nutritional supplements in 6 people (43%), among the 14 people who were further characterised. In Kaiser Permanente, an integrated health care system in northern California, the population-representative prevalence of drug-induced ALF was examined in another study [92]. Idiosyncratic DILI was the cause of 1.02 (95% CI 0.6–1.6) cases of ALF per 1,000,000 person-years, despite acetaminophen accounting for 56% of drug-induced ALF cases in this study. ALF was more frequently caused by dietary supplements and herbal remedies. Other areas Hepatologists from 10 different nations came together to form the US DILI Network's (DILIN) transnational prospective Latin American arm in 2011. The Spanish DILI Registry's established procedure and adjudication standards are also followed by this project. Of the 330 patients with well-phenotyped DILI in this network, amoxicillin-clavulanate was the most frequent cause, with hepatocellular injury accounting for 60% of cases. These results are consistent with those of other prospective DILI registry studies.

DILI phenotypes specific to drugs

Numerous distinct medications seem to have various effects on the phenotypic or clinical pattern of harm following DILI. The following factors are significant in this clinical variation: R-value (the ratio of ALT in ULN/AlkPhos in ULN), de Ritis ratio (the ratio of AST/ALT), latency (the number of days from the start of the drug to the presentation of abnormal liver tests), dechallenge (the number of days from the peak of abnormal liver tests to a value less than 50% of peak), extrahepatic manifestations like rash, autoantibody detection, gender, and others. Several noteworthy clinical aspects can be found by reviewing recent case series that assessed particular clinical variables, such as gender, latency, dechallange, biochemical profile (R-value), de Ritis ratio, and others.

Distribution of genders in DILI

Despite the paucity of evidence, it seems that some medications may be more prone to produce DILI in one gender than the other (Figure 1a).[93-112] Beta interferon is one of the most notable gender-specific clinical phenotypes; in a group of patients with DILI induced by this substance, 90% of the patients were female, and it was unclear if beta interferon actually caused DILI in the two cases that were recorded in men.[113] It should be mentioned that some of these evaluations probably contain inherent bias because, for instance, it is improbable that women use anabolic steroids at a higher rate than men. On the other hand, women may be more prone than males to use weight loss supplements like OxyelitePro®.

Particular Examples of phenotypes unique to a medicine

It is evident from the data at hand that various medicines have distinct phenotypes (Table 2). For instance, INH has a longer latency than medications like amoxacillin/clavulanic acid and mostly produces a pure hepatocellular pattern. On the other hand, methylprednisolone appears within the first few months of exposure, while beta-interferon and nitrofurantoin primarily appear after 12 weeks of exposure and appear to be specific to females. The extraordinary clinical phenomenon known as "bland cholestasis," which is brought on by anabolic steroids, is characterised by a high bilirubin level that is usually much out of proportion to the elevated aminotransferases.[113]

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