Annals of Clinical Case Reports

Review Article
Published: 14 Nov, 2023

Drug Discovery, Drug Interaction, Drug Abuse, Alcohol Abuse: Compressive Review

*Saloni[1], Lokesh S[2], Vishal V[2], Deepanshu[2], Kaushal A[1] and Divy Mohan A[3]**

[1]University Institute of Engineering and Technology, Maharshi Dayanand University, India

[2]Department of Pharmaceutical Sciences, Maharshi Dayanand University, India

[3]Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, India

Abstract

This article gives a general summary of the steps involved in clinical trial stages, medication interactions, and alcohol generation. Target validation, lead compound selection, target identification, and lead optimisation are all steps in the time-consuming and expensive process of drug development. Finding the right target is essential for developing medications that can successfully cure a certain condition. The effectiveness and therapeutic actions of the target are verified by target validation. As a result of their activity against the target, lead compounds are chosen, but more optimisation is required to increase their efficacy and reduce adverse effects. Before moving on to clinical trials, preclinical investigations are then carried out to assess the drug's pharmacokinetics, pharmacodynamics, and toxicological effects. Clinical trials test a medicine on volunteers and are carried out in stages to evaluate its safety, effectiveness, and dose. While Phase 2 and Phase 3 studies evaluate efficacy and long-term effects, Phase 0 and Phase 1 trials concentrate on safety and dosage tolerance. Overall, this information highlights the intricate and thorough nature of drug discovery and development as well as the significance of rigorous preclinical and clinical research to confirm the safety and efficacy of novel medications.

Keywords: Alcohol abuse; Drug discovery; Drug interaction; Drug abuse; Pharmacokinetics; Pharmacodynamics; Toxicological effects

OPEN ACCESS

Correspondence:
Divy Mohan Arora, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India, Tel: 701506033

Received Date: *16 Oct 2023*
Accepted Date: *09 Nov 2023*
Published Date: *14 Nov 2023*

Citation:
Saloni, Lokesh S, Vishal V, Deepanshu, Kaushal A, Divy Mohan A. Drug Discovery, Drug Interaction, Drug Abuse, Alcohol Abuse: Compressive Review. Ann Clin Case Rep. 2023; 8: 2521.

ISSN: 2474-1655.

Introduction

Drugs have always been a part of our society where we rely on them for the treatment of various types of injuries and diseases [1]. Drug discovery involves finding new drugs that are therapeutically useful followed by a sophisticated process which includes various types of studies such as *in vitro* and *in vivo* studies [2]. The whole process of drug discovery and development can take more than 10 years of time interval with a cost of millions of dollars [3]. Earlier natural products like plants root shoot or even whole plants were used in treatment of any disease. These parts are able to give therapeutic effects but had a major drawback that the exact configuration of the drug compound was not known therefore, the observations were not adequate and the mechanism of action of drug compound was also not discovered [4]. With the advancement in technology, drug molecules or compounds are being derived from natural resources. The drug molecules are screened and tested and upon giving satisfactory results in drug discovery process it undergoes pre-clinical trials followed by various phases of clinical trials [5]. These studies are performed to ensure that the drug is capable to cure a specific disease and shows a negligible amount or no side effect at all [6]. Without proper authorization and satisfactory results no new drug is introduced in the commercial and marketed site [7]. Drug Interaction mainly associated with the reaction between two or more types of drug compounds but it is not limited to this; it can also occur between drug and food or supplement and even with beverages too [8]. There are various reasons for drug interaction; the administration of any drug during any medical illness can cause drug interaction [9]. For example, if a person suffering from hypertension administrated nasal decongestant it may cause severe reactions (Figure 1).

Drugs have potential to elevate the feeling of human being and disturb the hormonal balance of human body which results in numerous changes which are advantageous to human being and can also bring disaster to them [10]. The consumption of drugs can lead to momentual satisfaction which can easily make them liable. The term "liable" stand for repeated use of drug for pleasure and other social activities which can be due to peer pressure, socialism and personal deeds. It boosts the consumption demand of drug then the basic dose which directly target the human health [11].

Figure 1: Drug interaction between different components are medicinal condition of patients, food and drugs.

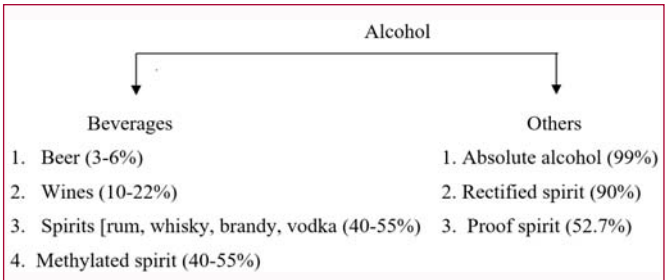

Figure 2: Types of alcohol present in the market.

Figure 3: Several steps involve in the drug discovery process.

Alcohol term refers to "Ethyl alcohol" or "Ethanol" in general, having formula C_2H_5OH. The production of alcohol includes fermentation of sugars with the help of Zymase enzyme of Yeast origin [12].

Sugar + Zymase (yeast) → Ethanol

Many types of alcoholic preparation are present in the market which is based on its proportion in those preparations as shown below [13] (Figure 2).

Alcohol comes from the category of psychoactive substance which has a high dependency property; alcohol has been widely used for centuries for its useful effects [14]. However, excessive use of alcohol is linked with the risk of inducing health related problems which mainly targets mental state as well as behavioral changes in the person [15]. Alcohol dependence is a major drawback of excessive alcohol consumption; also, several non-communicable diseases such as liver cirrhosis, cancer and cardiovascular diseases can develop in a healthy body with time [16].

Drug Discovery

Drug discovery is defined as a process in which new therapeutic medicines are discovered [17]. This process includes several steps such as (Figure 3),

1. Target Identification
2. Target Validation
3. Lead Compound
4. Lead Optimization

Target identification

In the drug discovery process the first and major step is to identify the origin of any disease for which a specific drug has to be discovered; the drug discovery revolves around the target identification [18]. Without any target no drug is able to show its therapeutic effects; that's why isolation of the target site is very crucial in the drug discovery process [17]. The target site can be a protein, gene or nucleic acid etc, based on its significant effects in any disorder. Target component can be identified based on its characterization at molecular level like its size, site efficacy, nature etc. [19]. The identification process of target relies on numerous techniques and approaches like data mining, expression profile of RNA proteins etc. target identification involves a deep understanding of the pathophysiology of disease through which the targeting of specific sites *via* drugs will become easier [20]. During the whole process of target selection, one thing that should put under consideration is that the target must have some specific properties such as rich availability of target, better efficacy towards disease than other sites and it has to be druggable [21].

Target validation

Validation process of target confirms the targets efficiency towards the disease. In development process of a drug these steps are most important because they signify the role of target in whole process [17]. It also tells us about the therapeutic activities of the target i.e., its behavior like it will be toxic, less effective or show greater efficiency etc. under normal as well as binded state with the drug molecule [17]. The target validation can be done with help of two approaches i.e., molecular approach and systems approach. Molecular approach signifies the target validation at molecular level such as cell, cell lining etc. whereas the system approach involves study of whole organism model for target validation [22].

Lead compound

Lead compounds are responsible for producing certain activities when bound with the target. The identification of lead compound is a process based on target activity from which we can categorize the compounds that have some or better therapeutic activity against target until then we are not able to identify the ideal lead component [23]. There are few examples where lead compound discovery was all sort of luck like the discovery of penicillin [24]. When a lead compound was found it doesn't give a testimony that it will not have any other effects rather than the desired activity [25]. Sometimes drugs have other activities on the human body rather than the actual activity. These effects are categorizes under side effects category which have to be reduced due to their dangerous effects on the body where structure modification is considered as the best option for this are plant [26]. From ancient times plants are always been the source for treatment

of disease. Generally, the active pharmaceutical ingredients in a plant are the lead components [27]. In this process a structure-based study is required to get a full scope of the lead activity against target which can be possible with the help of (Structural activity relationship) SAR. With SAR, most of the major issues of lead compound can be solved [28]. The selection of lead component not only depends on the structure and drug ability it also depends on some other factors like,

1. It's availability in nature/cost
2. *In vitro* as well as *in vivo* study to verify its approach
3. Toxicological studies of lead compound which can be done with the help of silico studies.

Due to the complex and composite procedure for selection of lead compounds only a few numbers of potential candidates are further promoted for the next stage [29].

Lead optimization

This process principle is to design a drug from lead compound which can be considered as a pre-clinical drug molecule [30]. The optimization process includes study of different synthesis methods as well as drug characteristics from which the maximum efficacy and efficient pathway will be selected [31]. The characterization of these lead compounds is based on numerous parameters like,

1. It's mechanism of binding,
2. Selection of target and
3. Efficacy etc.

The next step after lead optimization will be preclinical studies and to reach that it has to be qualified in various terms that is the lead compound should easily bind to the target and its configuration should be optimized i.e., better efficiency, less side effects [32]. Lead optimization is not limited to structure alteration but also depends on pharmacokinetic and pharmacodynamics effects of the compound [33]. With time, many researches were conducted and they came to the conclusion that the drug metabolism and kinetics also have some remarkable applications in screening of drug candidates [34]. They can evaluate drug molecules through *in vitro* studies which can specifically prognosticate the *in vivo* studies pharmacokinetics. Now, various new techniques like MALDI, mass spectroscopy are introduced which cause a revolutionary change in the process of lead optimization [35]. Lead optimization also includes changes in drug molecule characteristics. When a potential candidate is selected for the optimization the general characteristics of drug molecules such as size shape strength and also the pharmacological characteristics i.e., toxicity, bioavailability etc are optimized to such an extent that it should meet the acceptance criteria where they can show maximum activity [36]. Meanwhile, the mechanism of action of a drug molecule can be identified. The results of lead optimization are that it will provide a stable and efficient drug molecule who have maximum therapeutic effects and while undergoing this process a number of drug molecules are screened out with a ratio of about 5:5000 i.e., only about 5 drug molecules are able to reach pre-clinical studies from 5,000 drug molecules [37].

Pre-Clinical Studies

The next step after lead optimization is the preclinical study which has a significant importance in drug discovery because it provides a basic concept of drug metabolism and activity. This process involves

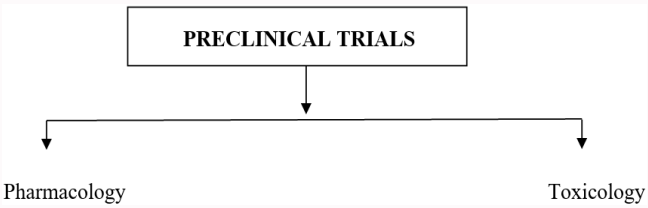

Figure 4: Categorized preclinical trials broadly into two ways.

study of drugs on animal species which can provide a comparative and evaluating data reports to conclude where the drug has potential to undergo clinical trials or not [38]. To perform preclinical trials the institute needs to get permission from respected authorities because the clinical trials have to be ethical as well as safe [39]. ICH proposed a general guideline for commencing of preclinical trials which includes some technical requirements which can ensure the basic acceptance criteria for development of a drug in the preclinical stage [40].

The preclinical trials are broadly categorized in two ways (Figure 4).

1. Pharmacology
2. Toxicology

Pharmacology

It is incorporates the pharmacokinetics and pharmacodynamics characteristics of drugs. It is required to eliminate all undesirable effects of the drug other than the therapeutic once or else it can actually cause damage to the humans who have administered the drug [41]. The pharmacokinetic characteristics involve a full scope study of ADME i.e., absorption, distribution, metabolism and excretion; to evaluate the drug in term of safety and efficacy in these parameters [42]. There are various factors which frequently alter the ADME parameters and these factors can be resolved with help of preclinical trials. Preclinical studies can actually provide a statistical report of factors affecting absorption rate i.e., route of administration, distribution rate i.e., dosage form and dissolution rate, metabolism rate and excretion rate i.e., half-life which directly affect the toxicological behavior of any drug [43].

Toxicological studies

It is *In vitro* and *in vivo* studies are helpful in determining the toxicological effects of drug molecules. *In vitro* studies comprise the evaluation based on proliferation of cells and its phenotype characteristics whereas; *in vivo* studies are more quantitative as well as quantitative [44]. There are some special cases where drugs are species specific in that condition selection of animal is solely based on drug molecule. The molecule which has better toxicological results will be prioritized than any other molecule [45].

The studies are helpful in collection pharmacological behavior and toxicological pattern of drug molecules with their mechanism of action which provide a gateway to the clinical trials.

Investigational New Drug Application (IND)

Investigational new drug is an application filed to get approval of authorities for developing a new drug molecule after preclinical trials. This application gives a data on which regulatory authorities evaluate the drug that it should undergo clinical trials or not [46].

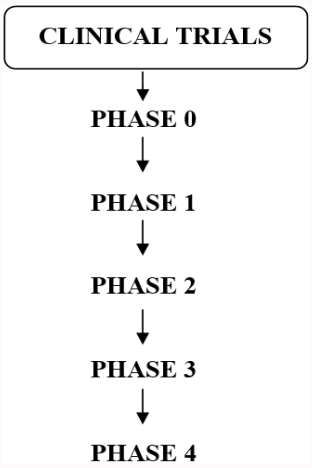

Figure 5: 5 phases of clinical trials.

Clinical Trials

Clinical trials are the last step of drug development. In this study volunteers are subjected to undergo treatment *via* newly developed drugs. Clinical trial's participants are required to follow specific guidelines and protocols during clinical trials [47]. The clinical studies are designed in such a way that each phase has a target to achieve and assessment protocol after completion of the target [48]. When the developer gets approval from authorities for IND application then he can actually conduct the clinical trials [49]. The protocols of clinical trials contain a brief note about what will be the objective and other details of clinical trials [50]. It includes -

- Selection procedure for volunteers
- Size of the group
- Study duration
- Administration route as well as dose
- Evaluation of parameters
- Data analysis

Clinical trials are composed of a total of 5 phases that is (Figure 5):

Phase 0

Phase 0 is the first-in-human trial entirely based on the regulatory guidelines. In this phase micro dozing studies are conducted i.e., micro dose of the original determined dose administered by volunteers. It's a small-scale study in which about 10 to 15 volunteers are involved. The purpose of this phase is to give a prior knowledge of drugs pharmacokinetic activities which can help to validate the drug molecule that it has some efficiency to target the target site or not [51].

Phase 1

Phase 1 as the name suggests this trial includes first administration of an actually determined dose of the drug to the participants. All the participants who are involved in phase 1 are healthy individuals because phase 1 commonly concentrates on the safety and doses of drugs which can be tolerated by the healthy human; phase 1 trial includes pharmacodynamics studies of the drugs. The phase 1 trial incorporates details about mechanism of action of drug molecule side effects related to the dose concentration and its efficacy; the compiled data of phase 1 helps in elucidating the phase 2 design. Almost 70% of drug molecules can clear the phase 1 trial and proceeds to the next phase [52].

Phase 2

The scope of this phase is much larger than the phase 1; it includes more than a few hundreds of participants. The phase 2 trial are related to the efficacy of the drugs and their side effects certainly the phase 2 data help to elucidate a therapeutic dose which can be used in large scale studies i.e., phase 3. The phase 2 studies compiled data help to elucidate new research methods and design for the next phase [53].

Phase 3

The phase 3 of clinical trials is the most sophisticated one out of all phases of clinical trials and also known as pivotal studies; as a large number of participants are involved in this phase i.e., a few hundreds to thousands [54]. Phase 3 studies are considered as confirmatory studies because the previous phase studies comprise study on a small number of volunteers for a short time interval whereas the phase 3 trial is more exploratory as it includes long term study on a group of people or a specific part of the population. Phase 3 trial data covers characteristic side effects which are not visible in phase 1 and phase 2 because of long-term study [55]. At the end of this phase the drug developer has all compiled data from drug development to drug effects (i.e., drug discovery, pre clinical and clinical trials) and if the drug is announced to be safe and efficient to use then the New Drug Application (NDA) can be filed to launch the drug in the market. Only a small number around 25% to 30% of drug molecules are able to clear the phase 3 and introduced to the market. The data has to be approved by the FDA or respective regulatory authorities to undergo phase 4 [56].

Phase 4

When the regulatory authorities approve a drug after completion of its phase 3 trial it will advance to the phase 4. This trial keeps the records of drugs after they enter in the drug market i.e., after their approval from regulatory authorities they are presented in the market for over-the-counter sale or prescribed sale [57]. Phase 4 includes monitoring of safety of drugs and any adverse drug reaction by drug present in the market [58]. Pharmacovigilance professionals and other supportive authorities helps in detection, risk assessment and maintain data which includes any other possible drug related problem. The drug molecules safety in cannot be measured in few months studies and to ensure that phase 4 evaluate a drug throughout its lifespan. During this interval if any risk occurs for a specific drug, the additional precautionary action will be taken by authorities as well as data for adverse drug reaction is also managed for additional evaluation of drugs [59].

Pharmacovigilance

Pharmacovigilance is the science related to the detection, assessment, understanding and prevention of the adverse effects of drugs or any other possible drug related problem. In this group of Pharmacovigilance professionals monitor the market and evaluate the drug based on its marketed incidence and provide a safe use data of drugs [60]. They also monitor the data related to clinical trials like participants personal data, their consent forms and the documents of institution that developed the drug and conducting its clinical trials. During clinical trials a standard template document containing clinical studies protocols was constructed, which comprise reports

concerning safety throughout whole study. These documents are reviewed and updated at regular intervals by pharmacovigilance professionals [61]. The pharmacovigilance approaches are not limited to phase 4, in phase 0 i.e., first-in-human trials they have an infrequent involvement. It can help to deduce a better understanding to the whole concepts of clinical trials and significance of these studies [62].

Effects of Drug Interaction

- Synergism- can increase drug action
- Antagonism- action of drug is decrease
- Adverse effect- sever or non-severe effects occur in body

Type of drug interaction

Drug-drug interactions: Drug-drug interaction generally occurs when two or more drugs administered together and it leads to changes in the overall effects of drugs; it can be either beneficial or toxic.

For example, when a sedative drug administered with antihistaminic drug it can induce excessive sleep and can lead to the death [63].

Drug-food/beverage interactions: Drug-food interaction is most common interaction out of all. In some special cases specific type of food is recommended because it can help to elevate the drug efficiency or *vice versa*.

For example, alcohol with sedatives may cause lower body dysfunctions and hallucinations [64].

Drug-medical condition interactions: This interaction is defined as the condition in which administration of any drug other than the prescribed drugs for medical illness affects the overall efficacy of prescribed drugs which results into either synergism or adverse effects [65].

For example, A person suffering from high blood pressure and taking a nasal decongestant with it may leads to high blood pressure problems.

Drug-nonprescription treatment: This is a reaction between a drug and a nonprescription treatment. These include over the counter medications, herbs, vitamins, or supplements.

Example, a diuretic and ibuprofen (Advil). The ibuprofen has anti diuretic effects cause salt retention and reduce the diuretic's effectiveness [66].

Drug-alcohol: A very wide range of medications showed contradictory action when administered with alcohol. Administration of drugs with alcohol can delay its action and shows antagonism. It also increases the risk for side effects in psychoactive drugs, sedative and hypnotic [67].

Drug-disease: A drug can alter drug action which was taken during a particular disease; it can cause severe damages to the human body or even leads to severe allergic diseases.

For example, decongestants cause increase in the blood pressure and when administered by a person suffering from hypertension it can even leads to death [68].

Another example is metformin (a diabetes drug) and kidney disease. The consumption of metformin during any kidney disease is avoided because metformin accumulates in the kidneys of the infected person, which decreases the blood glucose levels in the body.

Drug-laboratory: Drugs can also manipulate laboratory tests. This may result in misleading test results. For example, tricyclic antidepressants interfere with skin prick tests for allergies [69].

Other factors in drug interactions

Genetics: The variation in gene make up in different gender can cause different drug action of an identical drug entity. As a result of their specific genetic code, drug metabolize extra quickly or extra slowly depending on the person. It can also affect the overall effects of drug which can even exceed the actual effectiveness [70].

Weight: A person weight plays a critical role in measuring the drug dosage; changement in weight of a person affects dosage and may increase or decrease the chances of drug interactions. If any of 5 kg to10 kg gain or loss in your weight, you must need a different prescription dosage of medications [71].

Age: Human bodies develop in many ways, some of which directly affect how our body reacts to drugs. The kidneys, liver, and circulation system slow down with age and are high in neonates. It results into low the metabolism and excretion of drugs from systemic circulation [72].

Sex (male or female): The different sexes have different anatomy and hormones play a major part in drug interactions.

For example, the prescribed dose of zolpidem (Ambien) for a female patient was lowered to half the amount prescribed to male. Drugs given in menstrual and in pregnancy are also changed as per requirements [73].

Lifestyle (diet and exercise): Certain diets show high drug interactions when combined with medication. For example, high fat intake shows reduction in the response of bronchodilators, used in asthma to treat symptoms [74].

Exercise: Exercise on daily basis can also alter the medications effects. For example, people who use insulin in treatment of diabetes can show hypoglycemia (low blood sugar) during exercise. In order to avoid these circumstances, they are suggested to change the time for food intake, exercise and administration of insulin to cure the hypoglycemia [75].

Dose: The term "dose" is the amount of medication prescribed to be taken or administered [76].

Dosage: The term "dosage" refers to an amount of medication given at specific periods of time. For example, once a day [77].

Route of administered: Route of drug administration also alters the rate and severity of drug interaction. As in cyanide poisoning hydroxocobalamin and sodium nitrite drugs are administered by I.V. route for better absorption, fast action and to stop poisoning [78].

Drugs also have an effect on the absorption method of different pills on their sequence of administration. Example - Antacids used in calcium tablets affect the absorption of the antifungal medication ketoconazole [79] (Table 1).

How the Drug Interactions Occur?

There are several mechanisms with the aid of which medicines have interaction with different medicines, meals, and different substances [80]. These interaction end result will be alteration in:

- The absorption of a drug into the body;
- Distribution of the drug within the body;

Table 1: Drug interaction categories and their descriptions.

Drug Interaction Categories	Descriptions
Contraindicated	Never use this combination of drugs because of the high risk for dangerous interaction
Serious	Potential for serious interaction; regular monitoring by your doctor required or alternate medication may be needed
Significant	Potential for significant interaction (monitoring by your doctor is likely required)
Minor	Interaction is unlikely, minor, or non-significant

- Alterations made to the drug during metabolism; and
- Removal of the drug from the body

Drug interactions can also arise when two drugs that have comparable (additive) effects or contrary (canceling) effects are administered together. For example, when drugs that could purpose sedation are taken simultaneously it will lead to conscious sedation [81].

The drug interactions between warfarin (Coumadin) and vitamin K-containing products, in which Warfarin acts by reducing the concentration of the active form of vitamin K in the body. Therefore, when vitamin K is taken, it reduces the effectiveness of warfarin [82].

Change in absorption

Maximum drugs are absorbed into the blood, after which they reach their target site of action. Maximum drug interactions are due to the altered absorption in the intestine [83]. There are various methods by which the absorption of drugs can be reduced

- An alteration in blood flow to the intestine;
- Change in drug metabolism (breakdown) by the intestine;
- Increased or decreased intestinal motility (movement);
- Alterations in stomach acidity, and
- A change in the bacteria that normally reside in the intestine.

Drug absorption also can also be affected if the drug's capacity to dissolve (solubility) is modified with the aid of any other drug or if a substance (for an instance, meals) binds to the drug and stops its absorption [84].

Change in drug metabolism and elimination

Most pills are eliminated *via* the kidney in both an unchanged form or metabolized by the liver. Consequently, the kidney and the liver are very essential sites of potential drug interactions. A few tablets are capable of reducing or increasing the metabolism of different pills with the aid of the liver or their removal by the kidney [85].

Metabolism of drugs is process in which the drug is dissociated into forms which are greater or less active or that are simpler for the body to eliminate through the kidneys. Maximum drug metabolism takes place inside the liver; however other organs such as intestine etc. also play a n important role [86]. The cytochrome P450 enzymes are a collection of enzymes inside the liver which are responsible for the metabolism of maximum drugs. Drugs and certain varieties of food might also affect the interest of these enzymes and therefore affect the concentration of medication which can be metabolized by those enzymes [87].

Drug allergies

Drug causing allergy is another type of drug interaction. It ranges from mild to life-threatening. Skin reactions, such as hives and rashes, anaphylaxis, a serious allergic reaction [88].

Penicillin is an antibiotic drug. Penicillin allergy is a reaction of your immune system to the penicillin. Penicillin allergies can be over-reported, which is a problem that can result in the use of less-appropriate and more-expensive antibiotic treatments. Therefore, an accurate diagnosis is needed when penicillin allergy is suspected to ensure the best treatment opted in the future. Similar drugs with similar chemical properties to penicillin also can result in allergic reactions [89].

Anaphylaxis

Anaphylaxis is a rare, life-threatening allergic reaction that causes the widespread dysfunction of body systems. It includes: Tightening of the airways and throat causing trouble breathing, Nausea, abdominal cramps, Vomiting, diarrhea, Dizziness, Weak or rapid pulse, Hypotension, seizures, Loss of consciousness, Delayed reactions resulting from penicillin allergy.

Rare symptoms of penicillin allergic reactions occur when overexposed to the drug for some time after you stop taking it [89]. It includes:

- Serum sickness- which may cause fever, joint pain, rash, swelling and nausea
- Drug-induced anemia- decreased count in red blood cells, which can cause fatigue, irregular heartbeats, shortness of breath, and other signs and symptoms.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which results in rash, high white blood cell counts, general swelling, swollen lymph nodes and recurrence of dormant hepatitis infection
- Stevens-Johnson syndrome or toxic epidermal necrolysis, which involves severe blistering and peeling of the skin
- Inflammation in the kidneys (nephritis), which can cause fever, blood in the urine, general swelling, confusion, and other signs and symptoms

Causes

Penicillin allergy occurs when our immune system becomes hypersensitive to the drug as a harmful substance, as if it were a viral or bacterial infection. Before the immune system can become sensitive to penicillin, you have to be exposed to the medication at least once [90]. If and when your immune system misidentifies Penicillin as a harmful substance, it develops an antibody to the drug which leads to immune system attack on the drug if further administrated. Chemicals released by this activity cause the signs and symptoms associated with an allergic reaction [91].

Previous exposure to penicillin may not be obvious while, small trace of it in the food supply is sufficient for a person's immune system to create an antibody to it [92].

Figure 6: Some drugs, like certain statins used to lower cholesterol, are metabolized by enzymes. As shown above, grapefruit juice can block the action of these enzymes, increasing the amount of drug in the body and may cause more side effects.

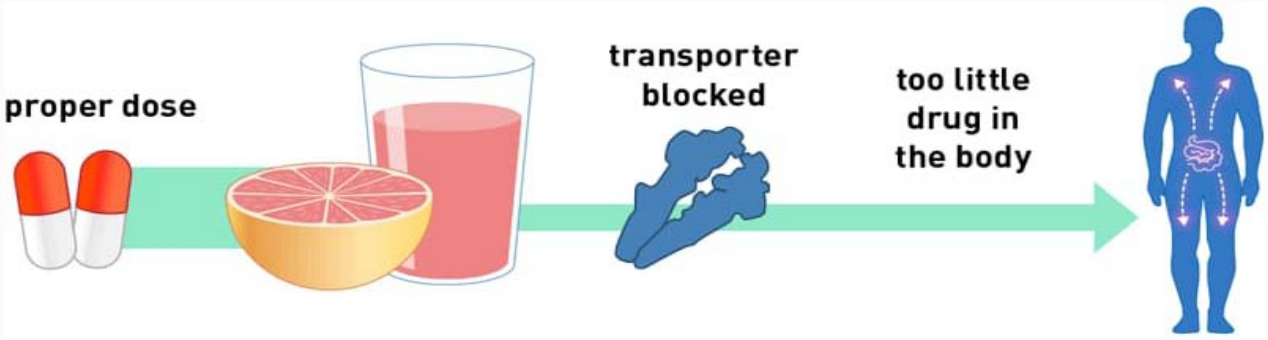

Figure 7: Some drugs which blocks the transporter.

Reaction to aspirin is common and it's common to have reaction to Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) too, including ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve) [93].

Aspirin allergy

An aspirin allergy, or a reaction to NSAIDs, can cause symptoms that range from mild to severe. Reactions occur within minutes to hours of taking the medication. They may include: Hives, Itchy skin, Runny nose, red eyes, swelling of the lips, tongue or face, Coughing, wheezing or shortness of breath [94].

If you are suffering from asthma, nasal polyps, chronic sinusitis or chronic hives (urticaria), you're more likely to have a reaction to aspirin or NSAIDs. When a reaction occurs, it can worsen symptoms of these conditions [95].

Some types of drugs that grapefruit juice can cause problems (interact) with

Some statin drugs to lower cholesterol, such as Zocor (simvastatin) and Lipitor (atorvastatin) [96].

Some drugs that treat high blood pressure, such as Procardia and Adalat CC (both nifedipine). Some organ-transplant rejection drugs, such as Neoral and Sandimmune capsules or oral solution (both cyclosporine) [97].

Some anti-anxiety drugs, such as BuSpar (buspirone); Some corticosteroids that treat Crohn's disease or ulcerative colitis, such as Entocort EC and Uceris tablet (both budesonide) [98].

Some drugs that treat abnormal heart rhythms, such as Pacerone and Cordarone tablet (both amiodarone); Some antihistamines, such as Allegra (fexofenadine) [99].

Grapefruit juice does not affect all the drugs in the categories above. The severity of the interaction can be different depending on the person, the drug, and the amount of grapefruit juice you drink [100]. Talk to your health care provider or pharmacist, and read any information provided with your prescription or non-prescription (OTC) drug to find out:

How grapefruit juice affects some drugs. When drugs are swallowed, they may be metabolized by enzymes and absorbed using transporters in cells found in the small intestine. Grapefruit juice can cause problems with these enzymes and transporters, causing too much or too little drug in the body [101] (Figure 6, 7).

Other drugs, like fexofenadine, are moved by transporters into the body's cells.

ACE Inhibitors

Food intake decreases the bioavailability of captopril by 42% to 56%. This interaction has limited clinical relevance though because the haemodynamic and humoral effects of captopril are not significantly affected by food. Food intake also decreases the bioavailability of perindopril by 35% which is associated with a clinically significant decrease in ACE inhibition [102].

Antihypertensive

Researches on the effect of food on the bioavailability of hydralazine are conflicting yet one study showed a 104% to 145% increase in bioavailability when hydralazine was taken with a meal (reduced first-pass metabolism) [102].

Diuretics

The bioavailability of furosemide (frusemide) is reduced by 16% to 45% when taken with food. In one study, it was associated with a reduction in diuretic response, whereas diuresis in another study was almost unaffected [103].

Drug Affecting Cardiovascular System

Cardiac Glycosides and Antiarrhythmics ingestion with regular meal does not affect the bioavailability of digoxin but ingestion of a high amount of dietary fiber present in fiber preparations reduces the bioavailability of digoxin by 16% to 32%. Due to the narrow therapeutic index of digoxin, a high-fiber diet (such as that used as an intervention for patients with hypercholesterolaemia) may result in treatment failure requiring dosage adjustment [104].

Agents Affecting the Alimentary

Administration of the synthetic prostaglandin analogue misoprostol with food reduces its rate of absorption as well as the height of its initial peak plasma concentration by 63% without affecting its bioavailability because the systemic adverse effects associated with misoprostol are related to high peak drug concentrations, taking the drug with food decreases the incidence of adverse effects, while maintaining the desired drug effects [105].

The bioavailability of the antiemetic ondansetron is increased by 14% when administered after a meal, which is probably not clinically significant. Taking the oral antidiabetic agent troglitazone with or shortly after a meal increases its bioavailability by 59%, which may be reflected in an improved insulin action-enhancing effect [106].

Agents Affecting the Blood and Blood Forming Organs

Intake of a regular meal does not affect the bioavailability of warfarin. The pharmacodynamic effect of warfarin may be directly antagonized by the ingestion of foodstuffs rich in vitamin K such as cabbage, broccoli, liver and certain dietary supplements.

A single excessive intake of vitamin K-rich food has no clinically significant impact on the anticoagulant effect of warfarin; however, a continuous daily ingestion of high amounts of vitamin K-rich food for one week may lead to warfarin resistance requiring dosage adjustments. Despite being low in vitamin K, avocado intake has been reported to cause warfarin antagonism, although the exact mechanism is obscure [107]. Since phenprocoumon is pharmacodynamically similar to warfarin, it is assumed to have similar interactions with vitamin K-rich food.

Drug Tolerance

Decrease in response to any drug refers to Drug tolerance, tolerance may develop by repeatedly use of drug. The drug tolerance often leads to disturbance in physiological balance of body due to consumption of drugs [108].

Drug Abuse

Drug abuse is psychological condition, where a consumer used to take medicine (psychoactive substances, alcohol or illegal drugs) repeatedly for producing pleasurable effect on the brain [109]. Ligands which are capable of altering the psychological conditions such as mood, behaviour, feelings, they are liable to repetitive use to derive euphoria, withdrawal from reality [110]. The discontinuation in the consumption of desired drug disturbs the body and cause characteristic withdrawal symptoms known as abstinence syndrome. Numerous drug leads to the drug abuse when administered without proper consult to the doctor i.e., Opioids, depressants, stimulant drugs and barbiturates [111].

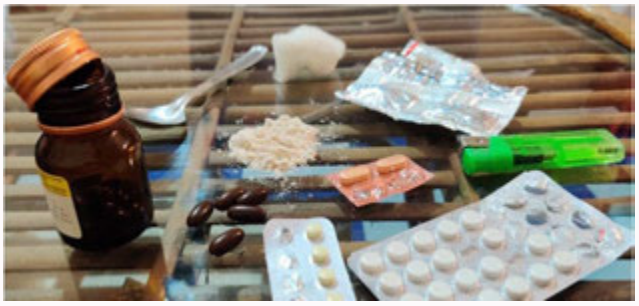

Figure 8: Integrated treatment conduct simultaneously cause addiction.

Drug abuse also includes the self-medication which results in consumption of higher amount of drug than the prescribed or approved amount of drug [112]. Drug abuse is of two types:

Continuous use

The regular consumption of drug by the person who doesn't want to discontinue the regularity of these drug consumption. E.g., opioids and sedatives etc.

Occasional use

The conjunction of drug depends on needs administrator. It can be consumed high enough to danger the life of the consumer or it can be a standard dose enough to give pleasure sensation or any other unspecific enhancement required by the administrator. E.g., cocaine, psychedelics, cannabis and alcohol consumption.

Drug Addiction

Drug addiction is condition in which individual is habitual to taking drugs without any reason. Individuals become addicted to drug by using them repeatedly without consultation [112]. Also, the edits often procure some amount of drug with themselves. The addicts which are introduced to some specific NGOs and other social helpers have withdrawal symptoms and often have relapses which can leads to dangerous effects on the body. Those individuals often feel as though they can't work properly without their drug of choice. So that it can affect CNS which leads to many issues related their overall health, professional goals and personal relationship. And over time if it left untreated, they will be progressive serious side effect and may be fatal [113] (Figure 8).

Drug addiction is progressive brain disease that requires an integrated treatment of the mind, body and spirit. Without treatment, brain changes can be long-lasting and the disease can be fatal [114].

Warning symptoms of drug addiction

- Loss of control
- Continued problems despite negative consequences
- Drop in attendance and performance at work or institution
- Acting out in particular relationship. Particularly if someone is trying to address their substance problems
- Going out of one's way to hide the quantity of drugs taken

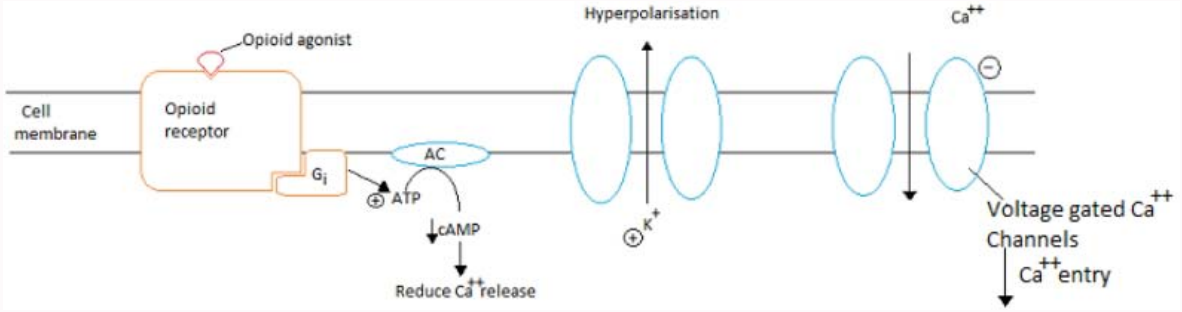

Figure 9: Mechanism action of opioid in cell.

- Demanding to use more and more of the drug in order to produce the same effect

Effects of drug addiction in body

Continuous use of drugs or drug addiction may affect every organ of our body, these effects may be fatal, they include:

- CNS problems- Seizures, stroke, anxiety, hallucination
- Cardiovascular disease- Arrhythmia, myocardial infarction
- Respiratory problems- Lung cancer, emphysema, and breathing problems
- GIT problems- Abdominal pain, vomiting, constipation, diarrhea
- Contraction of HIV, hepatitis, and other illnesses
- Kidney and liver damage
- Changes in appetite, body temperature, and sleeping patterns, stroke
- Pancreatitis
- Malnutrition
- Insomnia and sleep disorders

Drug Withdrawal Reactions

Neither all important drugs nor medication drugs leads to drug dependency it often depends on the person who's administrating the drug. However, the interruption in a therapy because of administration of other drugs destined to lead to intensified as well as targeted state which will be worst than the current state [115] e.g.

1) When irregular dose of beta blockers for angina pectoris adminstred, it will lead to the increased precipitation of myocardial infarction that worsen the case.

2) Sudden interruption in antiepileptic drugs administration can lead to intensified seizures with increased frequency.

Classification of Drugs

There are a large variety of such drugs, in which people get addicted to after repeated use. Four major groups of these drugs and their effects are as follows

1. Sedative and Tranquillizers- Barbiturates and benzodiazepines depress CNS activity; give feeling of calmness, relaxation and drowsiness.

2. Opiate Narcotic- Opium, morphine suppresses brain activity, Heroin relaxed pain.

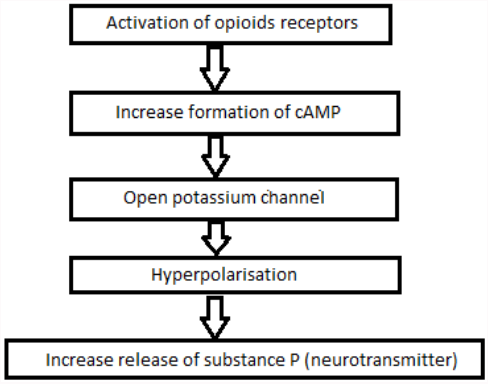

Figure 10: Mechanism action of opioid in cell.

3. Stimulants- MDMA, Amphetamines, Ya ba make person more wakeful, Cocaine active, cause excitement.

4. Hallucinogens LSQ, Mescalin, psilocybin alters thoughts, feeling and Ganja, charas, hashish perception.

Mechanism of action of opioid narcotics (Figure 9, 10).

Effect of Drug and Alcohol Combination

Simultaneously using drugs and alcohol may produce dangerous effect and can lead to death. When Barbiturates and alcohol consumes together, both doubles the effect of each other. A mixture of cocaine and heroin called speed ball, gives spontaneous kick of cocaine and prolonged pleasure of heroin [116].

Combined effects

1. Synergistically Alcohol & Barbiturates markedly increased depressant effect.

2. Combined effect of Alcohol & valium dramatically increased sedative.

3. Alcohol + Marijuana or Hashish decreased coordination increased reaction time impair judgement.

4. Alcohol + Aspirin increased changes of damage to gastric mucosa.

5. Alcohol + Antihistamines marked drowsiness

Management and treatment

There are several therapies for management of drug addiction, even for a severe cases treatment are exist which helps, often, there are

combination of these therapies;

Detoxification: Patient should have resists to taking drugs, allowing them to leave the body. You may need healthcare supervision to detox safely [117].

Medication-assisted therapies: During detox, medicine can help control craving and relieve withdrawal symptoms [118].

Behavioral therapies: Cognitive behavioral therapy or other psychotherapy (talk therapy) can help deal with addiction's cause. Therapy also helps build self-esteem and teaches healthy coping mechanisms. Cognitive behavior approaches include socializing the addicts with preventing him from relapses and introducing to other factors involved in their growth such as, providing a brief conceptual understanding to the addicts about the drug i.e., it's history and results of its intake and skill training meeting with the Motto to enhance the perceptional view through discussion and by receiving views of other post addicts of same drugs Dulhan the risk factors and vulnerable state of addicts [119].

Medication:

Barbiturates & benzodiazepine: There is no specific drug for barbiturate abuse, if patient's condition is serious, he should hospitalize and urine alkalization using $NaHCO_3$ is best option for reducing absorption of drug [120]. There is a drug named Flumazenil, a specific benzodiazepine antagonist. It is used for treatment of benzodiazepine and Z drug toxicity.

Alcohol: There are several three drugs- Disulfiram, Naltrexone and Acomprosate, which are FDA-approved for treatment of alcohol abuse [121].

Opioids: Methadone, Buprenorphine and Naltrexone are FDA approved drugs for the treatment of opiate addiction [122].

Tobacco: There are several products exist in market like Nicotine patch, gum, spray and lozenge. And doctor prescribes Bupropion or varenicline [123].

- Flumazenil is a selective GABAA receptor antagonist, used in treatment of BZD & Z-drugs toxicity. it is administered *via* IV, optic insertion or intranasally

- Disulfiram is one of the FDA approved drug for treatment of alcohol dependence. It is second line drug (Naltrexone and acomprosate are first line drug). Disulfiram is safe and efficient for both, in short term and long-term treatment.

- Naltrexone is a drug of choice for maintenance therapy in opioid poisoning. It is used for both alcohol and opioid deaddiction, by reducing craving and feeling euphoria associated with drug addiction. It is long acting and used orally or by injection in muscle.

- Acomprosate is first line treatment for alcohol deaddiction. It appears to work for maintenance of abstinence from alcohol. It also reduces craving for alcohol.

- Methadone is used for deaddiction of opioid as maintenance therapy. It is very long acting and orally effective drug. Excellent oral bioavailability & it is rapidly absorbed form GIT and detect in plasma within 30 min after oral administration.

- Buprenorphine is FDA approved medicine used for treatment of opioid deaddiction. It is an opioid partial agonist; it produces effects such as euphoria or respiratory depression at low to moderate doses. It can be used sublingually (under the tongue), in buccal cavity and by injection (IV or Sc).

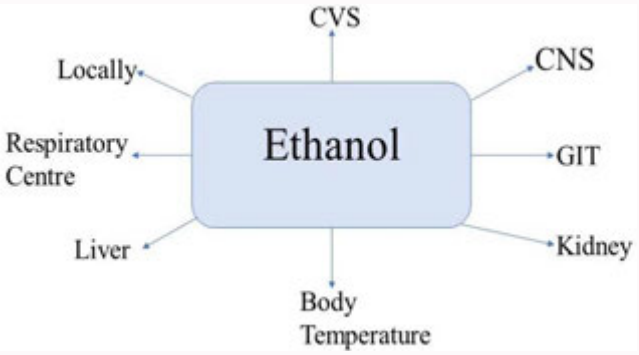

Figure 11: Alcohol effects on various body parts.

- Bupropion is FDA approved for used in combination with a stop smoking program. Bupropion is an antidepressant drug, works by inhibiting dopamine reuptake and nor adrenaline reuptake, it has a CNS stimulant action. But this medicine is also used for smoking cessation.

Pharmacological Effects of Alcohol

Alcohol affects various body parts which includes (Figure 11),

Cardio vascular system

- At low dose- Skin flushed through cutaneous and gastric vasodilation.

- At moderate dose- Induce Tachycardia i.e., Increased blood pressure and sympathetic stimulation

- At high dose- leads to vasomotor centre depression as well as decrease in blood pressure.

Central Nervous System (CNS)

Alcohol acts as neuronal depressant,

- At low dose (30 mg/dl-60 mg/dl)- induce euphoria and apparent excitation.

- At moderate dose (50 mg/dl-100 mg/dl)- mood and feelings

- At high dose (100 mg/dl-150 mg/dl)- mental clouding and disorganization of thoughts

- At overdose (150 mg/dl-300 mg/dl)- sloppy behavior, Ataxia, and paralyze the medullary centers which may lead to the death.

These are some side effects of alcohol at different dose on CNS.

Gastro intestinal tract

- At low dose- acts as a strong gastric secretion's stimulator.

- At high dose- inhibits gastric secretions causing vomiting, gastritis and mucosal congestion.

Kidney

- Anti-diuretic hormone secretion is inhibited by alcohol which results in diuresis.

Liver

- Small to moderate doses lead to liver damage. A long-term

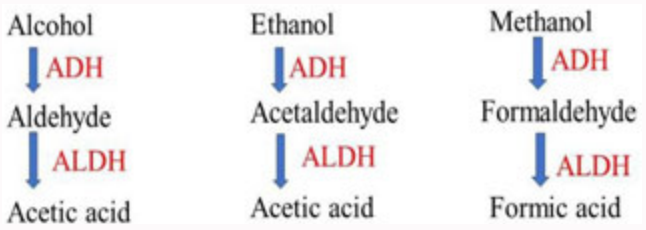

Figure 12: Metabolism of alcohol, ethanol, and methanol in cell.

Table 2: Body organ and effect of alcohol-disulfiram action.

Body organ	Effect of alcohol-disulfiram action
Skin	Sweating, warmth, flushing
Lungs	Hyperventilation, dyspnea
Eyes	Blurred vision
GIT	Nausea, vomiting
Brain	Vertigo, anxiety, confusion, syncope
Oral cavity	Thirst, acetaldehyde breath odor
Heart	Palpitation, chest pain, Tachycardia, Hypotension

administration of high dose cause development of fatty liver which leads to Cirrhosis.

- Chronic alcoholism cell necrosis results in fibrosis.

Respiratory centers

- Alcohol has direct depressant action on the respiratory centre.

Interactions

1. Alcohol consumption with antihistamines, anxiolytics, antidepressants, opioids, sedatives and hypnotics has a synergistic action in depression of CNS.

2. CYP (CYP2E1) enzyme is induced in case of chronic alcoholism.

3. Insulin and sulfonylurea also produce synergistic action with alcohol, their hypoglycemic effect is enhanced.

4. Gastric bleeding may occur when Aspirin and other NSAIDs are consumed with alcohol.

Toxicity of alcohol

Alcohol is categorized in CNS (Central Nervous System) depressant. The consumption of immense amount of alcohol may lead to respiratory depression, coma, death and certain other disorders. The symptoms of ethanol toxicity are not limited to the above defined system but it can also cause impairment to liver and many other organs [124]. Alcohol withdrawal manifests as a continuum, ranging from tremor to seizures, hallucinations, and life- threatening autonomic instability in severe withdrawal (delirium tremens) [125]. From a study it was observed in the United States (US), about half of adult population is contemporary drinkers, 20 are former drinkers, and 30 to 35 are lifetime abstainers. The consumption of alcohol is not limited to the adults but preteens and teenagers are also involved in this. For utmost drinkers, the frequency and amount of alcohol consumption doesn't impair physical or mental health or the capability to safely carry out daily necessities. However, acute alcohol intoxification is a significant factor in injuries; particularly include injuries related to interpersonal violence, suicide and motor vehicle crashes [126]. Chronic alcohol abuse interferes with one's capability to socialize and work. Although it is estimated through various studies that about 13.9% of adults meet the criteria for alcohol dependency [127].

Metabolism

Alcohol is metabolized in liver through oxidation where different enzymes responsible for oxidation of ethanol [128]. The enzymes involved in the process of oxidation of ethanol are:

a) Aldehyde Dehydrogenase (ALDH),

b) Alcohol Dehydrogenase (ADH),

c) Cytochrome P450 (CYP2E1) and

d) Catalase

Primarily enzyme ADH (Alcohol Dehydrogenase) metabolizes substrate i.e., Ethanol to Acetaldehyde (C_2H_4O) and further enzyme ALDH (Aldehyde Dehydrogenase) helps in conversion of Acetaldehyde (C_2H_4O) into acetic acid ($C_2H_4O_2$) and Acetyl-CoA (substrate for Citric Acid Cycle). It produces cellular energy and eliminates water and carbon dioxide.

Whereas ADH metabolizes methanol to form Formaldehyde and further into formic acid, which is poisonous when present in large volume. The minimum toxic concentration of methanol is approximately 500 mg/L and it needs urgent medical care [129]. Formic acid start accumulating in the body and it leads to somnolence, unsteadiness and ultimately these symptoms will escalate into headache, vomiting, abdominal pain and vertigo. Other than that, it leads to inflammation in eye (conjunctivitis), insomnia and visual failure whereas formaldehyde causes age-related damages to the neurons [130] (Figure 12).

Tolerance

Tolerance is a chronic effect which develops with time, whereas analogous quantities are related to lower in toxification. Tolerance is originated by modification changes in CNS cells induced by metabolic enzymes. The high blood alcohol content signifies the tolerance level [131]. However, ethanol tolerance is incomplete but after consuming a significant amount of ethanol it will display a considerable in toxification and impairment [132]. Alcohol tolerance also initiates tolerance to some other drugs such as CNS depressants (like barbiturates, benzodiazepines, nonbarbiturate sedatives). Alcohol tolerance always comes with physical dependency which has dangerous withdrawal effects [133]. The excessive alcohol consumption generally causes liver diseases such as adipose liver, alcoholic hepatitis, cirrhosis. The severity of the liver disease can vary due different factors like duration, frequency of alcohol consumption etc. [134].

Dependence

Alcohol dependence is a chronic condition of a person that generally has a history of excessive drinking. Dependence and alcohol abuse are two different terminologies but categories under alcoholism [135].

Alcohol dependence is divided into psychological dependence and physiological dependence where a psychological dependent subject believes they need alcohol and physiological dependent subject's body becomes chemically dependent on alcohol [136].

Disulfiram is used only in psychological dependent persons

whereas it's contraindicated in physiological dependent persons. Because if a physiological dependent person does not get alcohol, it causes withdrawal symptoms and it can lead to the death of the subject [137].

Management of dependence

Management of alcohol is managed through psychological, social and medical arbitration. Alcohol deaddiction includes these of two phases:

Detoxification: Detoxification improves the various signs and symptoms associated with the withdrawal of alcohol like Tachycardia, anxiety, confusion, convulsion, collapse etc.

Rehabilitation: Rehabilitation helps the patients to encounter the problems associated with the use of alcohol in future. Rehabilitation has showed repetitively successful results in the management of alcohol dependence with high degree of acquiescence in individuals.

Currently, Disulfiram, Naltrexone and Acomprosate are approved drugs used in the treatment of dependence of alcohol. However, still there is no sign from randomized controlled clinical trials of disulfiram improves abstinence rates over long term intake. Aversive remedy with disulfiram combinational therapy used in certain cases but it needs supervision through a medical specialist. Both naltrexone and acomprosate ameliorate outgrowth in rehabilitation of alcohol dependent cases, but seem to act on different aspects of drinking pathology. Naltrexone decreases the relapse related to heavy drinking by attenuating the satisfying effects of alcohol [138].

Disulfiram

Disulfiram is the drug which is approved by the Federal Drug Administration (FDA) for treatment of alcohol dependency. Disulfiram is a safe and effective medicine for those patients who are interested in terminating the alcohol consumption for short term as well as long-term. They undergo medication therapy under the supervision of a physician [139].

Mechanism of action of disulfiram

Disulfiram is a prodrug that converts to an active metabolite, diethyldithiocarbamate, in the stomach. After that it reaches to the blood in blood vessels which initiate changes diethyldithiocarbamate and it became diethyldithiocarbamic acid which is later degenerated to diethylamine and carbon disulfide [140]. Disulfiram irreversibly inhibits aldehyde dehydrogenase by resisting Nicotinamide Adenine Dinucleotide (NAD) at the cystiene residue in the active site of the enzyme. Aldehyde dehydrogenase is a hepatic enzyme which is responsible for the oxidative catabolism pathway for alcohol metabolism. It converts aldehyde to acetate [141].

Disulfiram alcohol reaction

At therapeutic dose of disulfiram, alcohol consumption results in increased serum acetaldehyde level due to disulfiram inhibiting its metabolism. Increased level of serum acetaldehyde causes palpitation, diaphoresis, vertigo, facial flushing, nausea, hypotension and tachycardia. Therefore, Disulfiram isn't an anti-craving medicine and doesn't modulate the neurobiological mechanism of addiction [142] (Table 2).

Other uses of disulfiram

1. Disulfiram is also used in the management of Cocaine dependence because it inhibits Dopamine Beta Hydroxylase (DBH) enzyme which converts dopamine to nor-adrenaline, it results into accumulation of dopamine and it leads to increased euphoric effect.

2. Used in treating drug resistant fungal infection especially for Candida as primary or secondary adjuvant.

3. Used in malignancy because it helps in inhibiting ABC transporter protein this is responsible for resistance.

4. It is also found that Disulfiram metabolite induces P53, facilitating apoptosis and cell death of malign

5. ANT cells, its role as anti-cancer agent are still under research.

Some drugs showing Disulfiram like reaction

- Cephalosporin (cefotetan, celoperazole)
- Griseofulvin
- Metronidazole
- Procarbazine, Physicians advises patients not to use these drugs along with alcohol.

References

1. Khantzian EJ. The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. Harv Rev Psychiatry. 1997;4(5):231-44.
2. Sliwoski G, Kothiwale S, Meiler J, Lowe Jr EW. Computational methods in drug discovery. Pharmacol Rev. 2014;66(1):334-95.
3. Dickson M, Gagnon JP. Key factors in the rising cost of new drug discovery and development. Nat Rev Drug Discov. 2004;3(5):417-29.
4. Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, et al. Plants and human health in the twenty-first century. Trends Biotechnol. 2002;20(12):522-31.
5. Chen J, Luo X, Qiu H, Mackey V, Sun L, Ouyang X. Drug discovery and drug marketing with the critical roles of modern administration. Am J Transl Res. 2018;10(12):4302.
6. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. Neurology. 1996;47(2):425-32.
7. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharm Sin B. 2015;5(5):442-53.
8. Koziolek M, Alcaro S, Augustijns PA, Basit AW, Grimm M, Hens B, et al. The mechanisms of pharmacokinetic food-drug interactions-A perspective from the UNGAP group. Eur J Pharm Sci. 2019;134:31-59.
9. Abubakar AR, Chedi BAZ, Mohammed KG, Haque M. Drug interaction and its implication in clinical practice and personalized medicine. National J Phy Pharmacy Pharmacol. 2015;5(5):343-9.
10. Broom DM, Johnson KG, Broom DM. Stress and animal welfare. London: Chapman & hall, 1993.
11. Furedi F. Culture of fear revisited. A&C Black. 2006.
12. Kunick J. Biomass-Based Fuels Through Biochemical Routes. Biomass-to-Bioethanol. 2015.
13. Berardi A, Perinelli DR, Merchant HA, Bisharat L, Basheti IA, Bonacucina G, et al. Hand sanitisers amid CoViD-19: A critical review of alcohol-based products on the market and formulation approaches to respond to increasing demand. Int J Pharm. 2020;584:119431.
14. Room R. Stigma, social inequality and alcohol and drug use. Drug Alcohol Rev. 2005;24(2):143-55.

15. Adler N, Matthews K. Health psychology: Why do some people get sick and some stay well? Annu Rev Psychol. 1994;45:229-59.
16. Parry CD, Patra J, Rehm J. Alcohol consumption and non-communicable diseases: Epidemiology and policy implications. Addiction. 2011;106(10):1718-24.
17. Hughes JP, Rees, Kalindjian SB, Philpott K. Principles of early drug discovery. British J Pharmacol. 2011;162(6):1239-49.
18. Silverman RB, Holladay MW. The organic chemistry of drug design and drug action. Academic Press. 2014.
19. Xu L, Anchordoquy T. Drug delivery trends in clinical trials and translational medicine: Challenges and opportunities in the delivery of nucleic acid-based therapeutics. J Pharm Sci. 2011;100(1):38-52.
20. Katsila T, Spyroulias GA, Patrinos GP, Matsoukas MT. Computational approaches in target identification and drug discovery. Comput Struct Biotechnol J. 2016;14:177-84.
21. Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: Confronting the challenges of antibacterial discovery. Nat Rev Drug Discov. 2007;6(1):29-40.
22. Oberdörster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K, et al. Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy. Part Fibre Toxicol. 2005;2:8.
23. Wheeler GN, Brändli AW. Simple vertebrate models for chemical genetics and drug discovery screens: lessons from zebrafish and Xenopus. Dev Dyn. 2009;238(6):1287-1308.
24. Bérdy J. Bioactive microbial metabolites. J Antibiot (Tokyo). 2005;58(1):1-26.
25. Berliner L, Conte JR. The effects of disclosure and intervention on sexually abused children. Child Abuse Negl. 1995;19(3):371-84.
26. Tapia EM, Intille SS, Larson K. Activity recognition in the home using simple and ubiquitous sensors. International Conference on Pervasive Computing. 2004;158-75.
27. Jamshidi-Kia F, Lorigooini Z, Amini-Khoei H. Medicinal plants: Past history and future perspective. J Herbmed Pharmacol. 2017;7(1):1-7.
28. Macías FA, Marín D, Oliveros-Bastidas A, Castellano D, Simonet AM, Molinillo JMG. Structure-Activity Relationships (SAR) studies of benzoxazinones, their degradation products and analogues. Phytotoxicity on standard target species (STS). J Agric Food Chem. 2005;53(3):538-48.
29. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000;44(1):235-49.
30. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011;162(6):1239-49.
31. Kapetanovic IM. Computer-Aided Drug Discovery and Development (CADDD): In silico-chemico-biological approach. Chem Biol Interact. 2008;171(2):165-76.
32. Mignani S, Rodrigues J, Tomas H, Jalal R, Singh PP, Majoral JP, et al. Present drug-likeness filters in medicinal chemistry during the hit and lead optimization process: How far can they be simplified? Drug Discov Today. 2018;23(3):605-15.
33. Copeland RA, Pompliano DL, Meek TD. Meek. Drug-target residence time and its implications for lead optimization. Nat Rev Drug Discov. 2006;5(9):730-9.
34. Lin JH, Lu AY. Role of pharmacokinetics and metabolism in drug discovery and development. Pharmacol Rev. 1997;49(4):403-49.
35. Cohen J, Vincent JL, Adhikari NKJ, Machado FR, Angus DC, Calandra T, et al. Sepsis: A roadmap for future research. Lancet Infect Dis. 2015;15(5):581-614.
36. Venkatesh S, Lipper RA. Lipper. Role of the development scientist in compound lead selection and optimization. J Pharm Sci. 2000;89(2):145-54.
37. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011;162(6):1239-49.
38. Eddershaw PJ, Beresford AP, Bayliss MK. Beresford, and Martin K. Bayliss. ADME/PK as part of a rational approach to drug discovery. Drug Discov Today. 2000;5(9):409-14.
39. Yarborough M. Do we really know how many clinical trials are conducted ethically? Why research ethics committee review practices need to be strengthened and initial steps we could take to strengthen them. J Med Ethics. 2021;47(8):572-9.
40. Kern P. Medical treatment of echinococcosis under the guidance of Good Clinical Practice (GCP/ICH). Parasitol Int. 2006;55:S273-82.
41. Mager DE. Target-mediated drug disposition and dynamics. Biochem Pharmacol. 2006;72(1):1-10.
42. Zolnik BS, Sadrieh N. Regulatory perspective on the importance of ADME assessment of nanoscale material containing drugs. Adv Drug Deliv Rev. 2009;61(6):422-7.
43. Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol. 2013;14:1.
44. Astashkina A, Mann B, Grainger DW. A critical evaluation of *in vitro* cell culture models for high-throughput drug screening and toxicity. Pharmacol Ther. 2012;134(1):82-106.
45. Khan K, Kar S, Sanderson H, Roy K, Leszczynski J. Ecotoxicological modeling, ranking and prioritization of pharmaceuticals using QSTR and i-QSTTR approaches: Application of 2D and fragment-based descriptors. Mol Informatics. 2019;38(8-9):1800078.
46. Dimasi JA. Risks in new drug development: Approval success rates for investigational drugs. Clin Pharmacol Ther. 2001;69(5):297-307.
47. Vats V, Kaushik N, Sharma L, Aror K, Verma PK. A review on traditional systems of medicine. J Pharm Res Rep. 2022;3(4):1-6.
48. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-91.
49. Fox JL. Antimicrobial peptides stage a comeback: Better understanding of the mechanisms of action, modification and synthesis of antimicrobial peptides is reigniting commercial development. Nat Biotechnol. 2013;31(5):379-83.
50. Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: A narrative review. Postgrad Med. 2011;123(5):194-204.
51. Kim H, Porcher T, Raychowdhury S, Shah A, Slayton T, Zhang S. Scientific Commercialization: From Bench to Bedside. 2012.
52. Friedman LM, Fuberg CD, DeMets DL, Reboussin DM, Granger CB. Fundamentals of clinical trials. Springer. 2015.
53. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet. 2018;391(10128):1357-66.
54. Llovet JM, Bisceglie AMD, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-711.
55. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. Lancet. 2002;360(9327):103-8.

56. Hirai Y, Kinoshita H, Kusama M, Yasuda K, Sugiyama Y, Ono S. Delays in new drug applications in Japan and industrial R&D strategies. Clin Pharmacol Ther. 2010;87(2):212-8.

57. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. Lancet. 2007;370(9605):2103-11.

58. Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: What is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol. 2007;47(9):1074-86.

59. Elisabetta P, Raschi E, Piccinni C, Ponti FD. Data mining techniques in pharmacovigilance: Analysis of the publicly accessible FDA Adverse Event Reporting System (AERS). Data mining applications in engineering and medicine. Intech Open. 2012.

60. Härmark L, Grootheest ACV. Pharmacovigilance: Methods, recent developments and future perspectives. Eur J Clin Pharmacol. 2008;64(8):743-52.

61. Biswas P. Pharmacovigilance in Asia. J Pharmacol Pharmacother. 2013;4(Suppl 1):S7-S19.

62. Muller PY, Brennan FR. Safety assessment and dose selection for first-in-human clinical trials with immunomodulatory monoclonal antibodies. Clin Pharmacol Ther. 2009;85(3):247-58.

63. Wiśniowska B, Tylutki Z, Wyszogrodzka G, Polak S. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect-comprehensive overview of clinical trials. BMC Pharmacol Toxicol. 2016;17:1-15.

64. Chan LN. Drug-nutrient interactions. JPEN J Parenter Enteral Nutr. 2013;37(4):450-9.

65. Bushra R, Aslam N, Khan AY. Food-drug interactions. Oman Med J. 2011;26(2):77.

66. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015:11:1061-75.

67. Heilig M, Egli M. Pharmacological treatment of alcohol dependence: Target symptoms and target mechanisms. Pharmacol Ther. 2006;111(3):855-76.

68. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282-319.

69. Cox L, Williams B, Sicherer S, Oppenheimer J, Sher L, Hamilton R, et al. Pearls and pitfalls of allergy diagnostic testing: Report from the American college of allergy, asthma and immunology/American academy of allergy, asthma and immunology specific IgE test task force. Ann Allergy Asthma Immunol. 2008;101(6):580-92.

70. Ingelman-Sundberg M. Pharmacogenetics: An opportunity for a safer and more efficient pharmacotherapy. J Intern Med. 2001;250(3):186-200.

71. Alomar MJ. Factors affecting the development of adverse drug reactions. Saudi Pharm J. 2014;22(2):83-94.

72. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, and therapy in infants and children. New Eng J Med. 2003;349(12):1157-67.

73. Vishal V, Kunal, Dhiman A, Vashist E, Kumar R, Dhiman S, et al. Exploration of Heterocyclic compounds in cancer therapeutics. Ann Romanian Soc Cell Biol. 2020;24(2):574-605.

74. Arteaga-Badillo DA, Portillo-Reyes J, Vargas-Mendoza N, Morales-González JA, Izquierdo-Vega JA, Sánchez-Gutiérrez M, et al. Asthma: New integrative treatment strategies for the next decades. Medicina (Kaunas). 2020;56(9):438.

75. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: Joint position statement. Diabetes care. 2010;33(12):e147-67.

76. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med. 1990;150(9):1881-4.

77. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: Terminology and definitions. Value Health. 2008;11(1):44-7.

78. Bebarta VS, Brittain M, Chan A, Garrett N, Yoon D, Burney T, et al. Sodium nitrite and sodium thiosulfate are effective against acute cyanide poisoning when administered by intramuscular injection. Ann Emerg Med. 2017;69(6):718-25.e4.

79. Chin TW, Loeb M, Fong IW. Effects of an acidic beverage (Coca-Cola) on absorption of ketoconazole. Antimicrob Agents Chemother. 1995;39(8):1671-5.

80. Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, Pinto MDS. Bioavailability of bioactive food compounds: A challenging journey to bioefficacy. Br J Clin Pharmacol. 2013;75(3):588-602.

81. Pamu S, Sing T, Ravi S, Ranganayakulu SV. Evaluations of drug-drug interactions in hypertensive patients in secondary care hospital. J Pharm Biol Sci. 2017;12(02):45-50.

82. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy. Chest. 2012;141(2):e44S-e88S.

83. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: A review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet. 2005;44:467-94.

84. Vishal, Arora D, Kumar V, Singla C, Dhiman A. Medicinal plants with immunomodulatory potential against corona virus. In: Manmohan G, editor. COVID-19 and lockdown in the world. Maharashtra: Eureka Publications. 2020;117-30.

85. Patsalos PN, Fröscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia. 2002;43(4):365-85.

86. Buxton ILO, Benet LZ. Pharmacokinetics: the dynamics of drug absorption, distribution, metabolism, and elimination. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 1996;3(1996):e27.

87. Vats V, Batra J, Dhiman A. Information communication technology: Opportunity and challenges in pharmacy during COVID-19 (No. 4166). EasyChair. 2020.

88. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Con sensus on drug allergy. Allergy. 2014;69(4):420-37.

89. Alwakeel, Reem. Penicillin allergy along with ulternative drugs for penicillin.

90. Pichler WJ, Beeler A, Keller M, Lerch M, Posadas S, Schmid D, et al. Pharmacological interaction of drugs with immune receptors: the pi concept. Allergol Int. 2006;55(1):17-25.

91. Uetrecht J. Immune-mediated adverse drug reactions. Chem Res Toxicol. 2009;22(1):24-34.

92. Dayan AD. Allergy to antimicrobial residues in food: Assessment of the risk to man. Vet Microbiol. 1993;35(3-4):213-26.

93. Durrance SA. Older adults and NSAIDs: Avoiding adverse reactions. Geriatr Nurs. 2003;24(6):348-52.

94. Simon RA. NSAIDs (including aspirin): Allergic and Pseudoallergic reactions. UpToDate. Waltham, MA: UpToDate Inc (2009).

95. Stevenson DD. Diagnosis, prevention, and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. J Allergy Clin Immunol. 1984;74(4 Pt 2):617-22.

96. Chisholm MA, Tackett KL, Kendrick BD, DiPiro JT. Assistance programs available for medications commonly used in transplant patients. Clin Transplant. 2000;14(4 Pt 1):269-81.

97. Danese S, Siegel CA, Peyrin-Biroulet L. Review article: Integrating budesonide-MMX into treatment algorithms for mild-to-moderate ulcerative colitis. Aliment Pharmacol Ther. 2014;39(10):1095-103.

98. Swapna G, Pravallika B, Poojitha J. A review on drug-drug interaction studies on amiodarone and levofloxacin. Res J Pharm Pharmacodyn. 2019;11(4):147-52.

99. Mouly S, Lloret-Linares C, Sellier PO, Sene D, Bergmann JF. Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort? Pharmacol Res. 2017;118:82-92.

100. Németh K, Plumb GW, Berrin JG, Juge N, Jacob R, Naim HY, et al. Deglycosylation by small intestinal epithelial cell β-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. Eur J Nutr. 2003;42(1):29-42.

101. Raia Jr JJ, Barone JA, Byerly WG, Lacy CR. Angiotensin-converting enzyme inhibitors: A comparative review. DICP. 1990;24(5):506-25.

102. Bouayad L, Padmanabhan B, Chari K. Can recommender systems reduce healthcare costs? The role of time pressure and cost transparency in prescription choice. MIS Quarterly. 2020;44(4).

103. Schmidt LE, Dalhoff K. Food-drug interactions. Drugs. 2002;62(10):1481-502.

104. Cicero AFG, Ferroni A, Ertek S. Tolerability and safety of commonly used dietary supplements and nutraceuticals with lipid-lowering effects. Expert Opin Drug Saf. 2012;11(5):753-66.

105. Gurnany E. Gastro retentive drug delivery system-A review. J Pharm Res. 2011;4(6):1899-908.

106. Litou C, Effinger A, Kostewicz ES, Box KJ, Fotaki N, Dressman JB. Effects of medicines used to treat gastrointestinal diseases on the pharmacokinetics of coadministered drugs: A PEARRL review. J Pharm Pharmacol. 2019;71(4):643-73.

107. Vashisht E, Singh G, Vats V, Dhiman A, Singla C. An update on epidemiology of depression: A major concern. Ann Romanian Soc Cell Biol. 2020;24(2):616-24.

108. Chaturvedi S, Singla C, Vats V, Dhiman A. Applications of phytopharmaceuticals in targeting metabolic disorders. In drug delivery systems for metabolic disorders. Academic Press. 2022;425-32.

109. World Health Organization. Neuroscience of psychoactive substance use and dependence. 2004.

110. O'Brien CP. Drug addiction and drug abuse. Goodman and Gilman's the pharmacological basis of therapeutics. 2006;11:607-27.

111. Wong S, Ordean A, Kahan M. Substance use in pregnancy. J Obstet Gynaecol Can. 2011;33(4):367-84.

112. Tomas A, Kusturica MP, Tomić Z, Horvat O, Koprivica DD, Bukumirić D, et al. Self-medication with antibiotics in Serbian households: A case for action? Int J Clin Pharm. 2017;39(3):507-13.

113. Padgett DK, Gulcur L, Tsemberis S. Housing first services for people who are homeless with co-occurring serious mental illness and substance abuse. Res Social Work Pract. 2006;16(1):74-83.

114. Shapiro F. Eye Movement Desensitization and Reprocessing (EMDR): Basic principles, protocols, and procedures. Guilford Press. 2001.

115. Julien RM. A primer of drug action: A concise nontechnical guide to the actions, uses, and side effects of psychoactive drugs, revised and updated. Holt Paperbacks, 2013.

116. Bourgois PI. In search of respect: Selling crack in El Barrio. No. 10. Cambridge University Press. 2003.

117. Roche AM, Watt K, Fischer J. General practitioners' views of home detoxification. Drug Alcohol Rev. 2001;20(4):395-406.

118. Maheshwari K, Vishal, Dhiman A, Singla C, Sharma A. Gestational diabetes: Management and treatment. In: Manmohan G, editor. Role of women in nation building Maharashtra: Eureka Publications. 2021;204-12

119. Vishal K, Singla C, Sharma A, Dhiman A. An update of phytochemical and therapeutic properties of Ipomea carnea. J Phar Phytochem. 2021;10(1):1-6.

120. Erickson TB, Thompson TM, Lu JJ. The approach to the patient with an unknown overdose. Emerg Med Clin North Am. 2007;25(2):249-81; Abstract vii.

121. Witkiewitz K, Saville K, Hamreus K. Acamprosate for treatment of alcohol dependence: Mechanisms, efficacy, and clinical utility. Ther Clin Risk Manag. 2012;8:45-53.

122. Alderks CE. Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003-2015 (update). The CBHSQ report. 2017.

123. Arora KV, Verma PK. A review on pharmaceutical suspension and its advancement. Ann Clin Case Rep. 2022;7:2321.

124. Mihic SJ, Harris RA. Hypnotics and sedatives. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. McGraw Hill Medical, New York. 2011:457-80.

125. Romach MK, Sellers EM. Management of the alcohol withdrawal syndrome. Annual Rev Med. 1991;42(1):323-40.

126. Arora K, Vats V, Kaushik N, Sindhawani D, Saini V, Arora DM, et al. A systematic review on traumatic brain injury pathophysiology and role of herbal medicines in its management. Curr Neuropharmacol. 2023;21(12):2487-504.

127. Dimeff LA, Baer JS, Kivlahan DR, Marlatt GA. Brief alcohol screening and intervention for college students (BASICS): A harm reduction approach. Guilford Press. 1999.

128. Lindros KO. Alcoholic liver disease: Pathobiological aspects. J Hepatol. 1995;23 Suppl 1:7-15.

129. Liesivuori J, Savolainen H. Methanol and formic acid toxicity: Biochemical mechanisms. Pharmacol Toxicol. 1991;69(3):157-63.

130. Hunter BT. The sweetener trap and how to avoid it: The power and politics of sweeteners and their impact on your health. ReadHowYouWant.com. 2010.

131. Tabakoff B, Cornell N, Hoffman PL. Alcohol tolerance. Ann Emerg Med. 1986;15(9):1005-12.

132. Rhodes JS, Best K, Belknap JK, Finn DA, Crabbe JC. Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. Physiol Behav. 2005;84(1):53-63.

133. Nicholson KL, Balster RL. GHB: A new and novel drug of abuse. Drug Alcohol Depend. 2001;63(1):1-22.

134. Vats V, Bala M, Dhiman A, Kumar R, Dhiman S, Singla C. Novel drug delivery system: Resealed Erythrocytes. Turk J Comp Math Edu. 2020;11(2):706-19.

135. Rehm J, Gmel Sr GE, Gmel G, Hasan OSM, Imtiaz S, Popova S, et al. The relationship between different dimensions of alcohol use and the burden of disease-an update. Addiction. 2017;112(6):968-1001.

136. Blume SB. Chemical dependency in women: Important issues. Am J Drug Alcohol Abuse. 1990;16(3-4):297-307.

137. Shorter D, Hsieh J, Kosten TR. Pharmacologic management of comorbid post-traumatic stress disorder and addictions. Am J Addict. 2015;24(8):705-12.

138. Addolorato G, Mirijello A, Leggio L, Ferrulli A, Landolfi R. Management of alcohol dependence in patients with liver disease. CNS Drugs. 2013;27(4):287-99.

139. Vats V, Kunal, Bala M, Dhiman A, Dhiman S, Singla C. Prediction of anti-viral activity of Ipomoea carnea. Ann Romanian Soc Cell Biol. 2020;24(2):538-44.

140. Basso J, Mendes M, Fortuna A, Vitorino R, Sousa J, Pais A, et al. Nanotechnological approaches in cancer: The role of celecoxib and disulfiram. Drug Rep Cancer Ther. 2020;353-93.

141. Singh S, Brocker C, Koppaka V, Chen Y, Jackson BC, Matsumoto A, et al. Aldehyde dehydrogenases in cellular responses to oxidative/electrophilic stress. Free Radic Biol Med. 2013;56:89-101.

142. Linden CH, Rocky Mountain poison center. Clinical Toxicology Fellowship School of Medicine University of Colorado.