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Pharmacological & Toxicological Interactions (with Alcohol): A Critical Study on Drug-Drug Interactions; (DDIs with Ethanol) & Its detection through Advance Forensic Practices. An Evolving Subspeciality of Forensic Pharmacovigilance & Polypharmacy

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Abstract: ***The purpose of this paper is to throw light on modern and advance methods for detection of DDIs in forensic practice. It shares insights on the interactions of drugs with alcohol and its adverse effects. This research is intended to bring in-depth study of few compounds & its effect on human body, symptoms, measures to counteract it & its methods of detection. This is developed through reviewing many different literatures of different sources and coagulated to form a paper of specialized drug interaction. In modern polypharmacy; which is a relatively new approach; where combination and integration of drugs are used from its vector positions and summation of its effects on the human body. This shall also aid in medical science but also gives a weapon to the criminal minded people in the society. Our idea is to spread awareness and bring some meaningful measures to fight these criminal tendencies by enumerating information on how such crimes are facilitated and how such crimes can be prevented. The main body of this report is divided into 3 major parts. The first part deals with all the information about interaction of drugs. The second part deals completely with alcohol and its pharmacology, as it is our object drug of research. The third part is further divided into 3 sub-parts; where we critically asses 2 cases of interaction of alcohol: (i) Marijuana-Nicotine; & (ii) LSD. At the end of our research, we shall conclude our findings to establish some critical evidences and modern procedures.***

Keywords: Drug-drug interaction, cannabis (THC) interaction with alcohol and nicotine, polypharmacy, forensically relevant interactions, pharmacological interactions.

1. Executive Summary

The foundation of this review is based on bringing light on various techniques of DDIs and its detection in modern era. DDIs have become very common in the field of polypharmacy as well as forensically in substance abuse. We have established deep understanding about commonly interacted substance abuse, its management, overdosing precautions, emergency measures & treatment. This helps in identifying victims with interactive metabolism through different coadministration of drugs and to aid in counteracting the same.

The first part of this paper stands as an educational survey on DDIs and the later on the substance abuse of EtOH or recreational alcohol. Through tables given in 2.2.2; one can develop counteractive pills; which can serve as an antidote on the effects of EtOH on the human body. The table given in 3.1.1 throws a light on dangerous DDIs occurring with EtOH and its symptoms as well as management procedures. This shall also help in developing anti-interactive pills to chemically neutralize effects on the victims of drug-drug interactions (with recreational alcohol). Alcohol is consumed with Cigarettes (Nicotine) & Cannabis (THC) in large scale. This creates undesirable effects on the body which can be counteracted through special antidotes prepared after understanding the effects from its toxicokinetic and toxicodynamic studies of the interaction. We have prepared this review paper to be a base on the preparation of antidotes for DDIS of EtOH / recreational alcohol. Our study remains a foundation for the clinical study as well as in vitro and in vivo examinations for the same in the future.

Finally, the last part of the paper consists of in-depth analysis of interaction of recreational alcohol (EtOH) with Cannabis (THC), Cigarette Smoking (Nicotine) & Lysergic Acid Diethylamide (LSD). The study revolves around the combined effect of these drugs and finding the right measure to treat the interaction by understanding its pharmacology & toxicology. Different trends are analyzed to generate conclusions and these trends shall point towards the right combination of drug required for antidoting the DDIs happening with its coadministration.

2. Introduction

2.1 Basic Terminologies of DDIs

Drug interaction is a change in the mechanism of action of a drug due to the contamination of another drug, substance, food or supplement. It may change its side effects, its action or its metabolism. Whenever the drug is administered with

another substance, both exposes itself with each other. This causes potential risk of internal metabolic reaction and can cause various undesirable effects. Usually, these undesirable effects are unwanted, hazardous, toxic and involuntary. [1]

There are a few categories in which interactions with drugs are classified into:

a) Drug-Food Interaction.
b) Drug-Disease Interaction.
c) Drug-Drug Interaction.
d) Drug-Chemical Interactions.

Here, we will be specifically talking about Drug-Drug Interaction (DDIs). DDIs are further categorized into few types according to its mechanism:

a) Behavioral Drug-Drug Interaction
b) Pharmaceutic Drug-Drug Interaction
c) Pharmacokinetic Drug-Drug Interaction
d) Pharmacodynamic Drug-Drug Interaction

Let us understand about the primary components of DDIs. Usually, the interaction occurs between two or more substances. The primary two substances involved in the DDIs are named:

- **Object Drug:** The drug whose activity is affected by the interaction.
- **Precipitant:** The agent which precipitates such interaction.

A drug interaction alters its result, in various processes of a drug's pharmacokinetic journey:

Table 1: Drug Interaction in pharmacokinetic journey

Absorption	Distribution	Metabolism	Excretion
Binds with another drug to reduce absorption. This happens due to chelation or complexing.	When a drug transporter protein is changed, induced or inhibited; the rate of absorption changes. This is due to modulation of these drug transporter protein.	Enzyme induction takes place and there is an increase in synthesis of an isoenzyme required for its metabolism	When the pH of urine is altered by the presence of another drug, there is an increase in excretion or retention of a drug.
By altering pH of one drug and affecting the rate of absorption of another. This happens due to change in gastrointestinal pH.	When the structure of binding protein is changed; there is a competition for binding sites on the serum protein itself. This competition between the drug results in displacement.	Enzyme inhibition takes place when there is inhibition of the isoenzyme required for metabolism.	Overall exposure of drug is altered when enterohepatic recirculation is affected by one drug's presence; leading to reduced recirculation of another drug. This change occurs due to enterohepatic shunt.
Causing change in the time of transit due to difference in motility in gastrointestinal tract.		When the first-pass metabolism is affected due to the changes in the portal circulation flow of one drug due to the presence of another drug. This produces changes in first pass metabolism.	There are changes in active renal tubular excretion due to competition for active transport system in renal tubules. This happens due to alteration in drug transporter proteins inside the kidney. This effects the elimination of the drugs.
When a drug transporter protein is changed, induced or inhibited; the rate of absorption changes. This is due to modulation of these drug transporter protein.		There are also some genetic factors which affect drug interactions. It occurs due to genetic polymorphism.	Changes in renal blood flow due to renal vasodilatory prostaglandin synthesis. This contributes to blood flow regulation in kidneys. Thus, renal excretion is altered.
There can also be malabsorption and have digestion impairment when certain drugs interact with certain drugs during its absorption process.			

Table 2: Pharmacodynamics VS Uptake

Pharmacodynamic	Uptake
Drugs with opposite pharmacological effects, when administered together give opposite results. These show antagonistic interactions.	When a drug occupies receptors on adrenergic neurons, it leads to differences in uptake, reuptake or receptor interactions. These changes neurotransmitter uptake of the drug.

DDIs can be classified in two categories, on the basis of its utility. Some are beneficial and some are hazardous. In Pharmacology, few DDIs are intentionally given in order to bring positive impact through cross-metabolism. However, few combinations are strictly avoided due to its toxicity. Hence, it is further classified into two classes:

a) **Beneficial Interaction:** When drugs show positive impact when consumed together. Some drugs are purposefully given together to counter the side effects or to generate additive effects into the patient.
b) **Adverse Interaction:** When drugs show negative impact when consumed together. Some drugs encounter destructive properties when administered together and the adverse effects are more prevalent than the positive ones.

There are interactions which can cause damage, potential harm and induce toxicity in the consumer. This can be utilized by people with malicious intention to commit crimes, robbery, rapes and other criminal activities. It is needful to closely regulate such interaction in our daily life. The extent to these interactions and its prevalence can tell us about how much

damage its combination can cause to an individual. The extent of this interaction is divided into 5 classes according to Stockley's Drug interactions:

Table 3: Stockley's Drug Classification

Class 1	Risk outweighs the benefit and should avoid.
Class 2	Allowed only in special conditions and emergencies.
Class 3	Minimize risk and consider alternatives. Monitor if both drugs are given.
Class 4	No special precautions needed and very negligible adverse effects.
Class 5	The drugs do not interact.

[3]

The overall effect of the drug interaction is equivalent to the sum of the pharmacological effects of individual agents. When we talk about pharmacodynamic interaction of the drug; it can be further categorized into two types:

a) **Synergistic Effect:** When its overall impact is greater than the additive effect.
b) **Antagonistic Effect:** When its overall impact is less than the additive effect.

We also categorize the interaction on drug by understanding where the drug is interacted. The site of interaction is also important in the study of drug interaction. It can either show its interaction at the receptor site of show its interaction in a non-specific manner. [4]

- Many drugs exert their effect by interacting with specific receptors located on cell membranes, cytoplasm or nucleus. The affinity for certain receptors can be agonist or antagonist. Thus, it will interact when administered concurrently. The competitive antagonism or competitive agonism can induce minimum or maximum effect.
- Agents that induce anesthesia interact in non-specific manner. There are several non-specific interactions that can lead to alterations in electrolytes, its concentration; changes in cardiovascular patterns, enzyme inhibition / agonism, hypokalemia, hyperkaliemia, hyponatremia, hypernatremia, hypomagnesaemia, hypermagnesemia, etc.

1.2 Detection of DDIs

Detection of DDIs is a tedious task for a forensic practitioner. When we talk about crimes, criminals prefer those substances which interact quickly in an acute manner. Interactions needed for criminal intention have its ideals set to - fast acting, long lasting & disappearing symptoms. Detection of these interactions can lead forensic experts to their way in reaching the victim or the perpetrator. There are various methods from which drug interactions can be detected:

1) **Statistical analysis from symptoms & responsive management systems:** There are various statistical methods used for understanding drug-drug interaction such as - additive model, multiplicity model, logistic regression method, the Ω shrinkage method, etc. [5, 6]
2) **Super Combo Drug Test (SupCD-T):** It is used in polypharmacy where we detect high-order drug interactions. It works through identification of optimal drug combinations. It increases statistical results to detect strongly correlated substances. However, it cannot differentiate single drug effect with its combination of effects. One needs multiple regression method to get more specified result.[7]
3) **Neural network-based method for drug-drug interaction (NDD):** These are a type of machine learning process which is called deep-learning. Here, interconnected nodes or neurons which resemble human brain are layered together. Some of its sub-types are:[8]
   a) **GADNN:** A graph attention-based deep neural network used for predicting DDIs by using 4 datasets. This method gives us an embedding vector for every drug based on its dataset & calculates the combination and contribution of each vector to find the probability of DDIs.[9]
   b) **NDD:** This is a method by which drug similarities are calculated and GIP for every drug pair is found. This is followed by selection of best available similarity and a matrix is formed to integrate it. The rows of the matrix denote each pair and two-layer feeding classification is performed.[10]
   c) **CNN-DD:** This isa semi-supervised algorithm where a convolutional neural network is used to predict DDIs. This method primarily performs selection from a combinational module and then a CNN-based prediction module follows. This module uses deep CNN model to get probabilities of the DDIs.[11]
   d) **MMCNN-DD**: This is another model that uses a multi-modal convolutional neural network (MCNN) and predicts the DDIs. This model also uses four sub-models for every feature of the drug and combines it to predict the DDIs.[12]
4) **Interaction Profile Fingerprints (IPFs):** In this method, different drugs are taken and its effects and interactions are converted into position vectors of interaction. A matrix is calculated and similarities are computed through unions. Furthermore, a new resultant matrix is formed by multiplicity & diagonal symmetry is used to get maximum value in the array. At the end, the result is evaluated by four independent tests and TC value is calculated. The resultant predicted effects are finally concluded.[13]
5) **Laboratory Testing of urine samples (IA) / (LC-MS):** There are various laboratory techniques used for determining DDIs. One such method is immunoassay (IA); where certain antibodies are allowed to interact with different compounds to detect selected drugs or metabolites based on threshold cutoff. It is an initial qualitative test to identify the presence of a certain drug. In modern techniques, we use liquid chromatography-tandem mass spectrometry (LC-MS/MS); where we separate sperate mixtures to identify molecules. It can also detect overdose & monitor substance abuse. It can also help in sold-phase extraction as well as a simple dilution sample extraction.[14]
6) **In Vitro & In Vivo experiments using PBPK model prediction:** A physiologically-based pharmacokinetic (PBPK) modelling is a pharmacological approach system where we integrate physiochemical and biological mechanism or interaction in predicting pharmacokinetic properties. In vivo systems are made on models of physiological tissues and organs including composition, volume, blood flows, etc. These descriptors are further integrated with compound-specific data and get

information of different drugs and its interaction. Similarly, in vitro systems are made to predict PK profile to develop accurate effects of drugs and its interaction.[15]

There are various different methods for detecting DDIs but we choose the process relevant to our analyte of interest (AOI) and our prevailing conditions and circumstances. Here, we are more concerned about forensic applications and specifically few important DDIs.

3. Alcohol & DDIs

3.1 Alcohol as a toxicant

The primary component of alcohol is ethanol (EtOH). It is commonly consumed throughout the world orally. Different recreational drinks contain different composition of EtOH and have different tastes and flavours. Although there are positive impacts of alcohol on cardiovascular system when consumed in smaller acute doses, it is widely exploited. Alcohol; as a substance abuse is very common in multiple countries. Moreover, illicit manufacturing of EtOH can cause poisoning, Hooch tragedies and illegal smuggling of liquor. When certain substances mix with alcohol, it produces even more adverse effects and interactions which we shall see in detail. Let us first understand the mechanism of our object drug. [16]

Different drinks contain different concentration of EtOH and this is called its Alcohol by Volume (ABV):

Table 4: Alcohol By Volume Classification

Undistilled		Distilled	
Type	**ABV**	**Type**	**ABV**
Beer – Light	2-4%	Gin	35-55%
Beer – Hard	6-8%	Vodka	40%
Hard Cider	10-14-20%	Brandy	35-60%
Sake	16%	Whiskey	40-50%
Mead	10-14%	Rum	57.5-75.5%
		Tequila	40%
		Absinthe	40-90%
		Everclear	60-75-95%

[Alcohol By Volume; Beer, Wine, Liquor; Kristina Ackerman; July 5, 2022]

When EtOH is ingested, it enters the bloodstream and moves to your organs. In a healthy person, blood circulation takes place in **90 seconds**. Thus, effects are seen after 15-45 minutes of its exposure to the body. The liver metabolizes a drink in one hour, however; it is yet dependent on various factors such as age, gender, weight, health, idiosyncrasy etc. Although, the blood alcohol concentration (BAC) is reduced by **0.015 /hr** or at a mean rate of: **015 g / 100mL / hr.** It is detected in various parts of the body:

- Blood: **Up to 6 hours**
- Breath: **12-24 hours**
- Saliva: **12-24 hours**
- Urine: **12-24 hours**
- Hairs: **90 days**

The effects can vary from person to person; talking about males with little tolerance; who have just started drinking; they might see the symptoms when **BAC reaches 0.05%.** A woman of 68 kgs will acquire a BAC of 0.10% in one hour if she drinks 4 drinks. However, few general impairments are seen at different BAC levels:

- 05% - Detectible
- 07% - Impaired driving and spontaneous sensations
- 10% - intoxicated
- 20% - reduced consciousness
- 30% - unconsciousness
- 40% - fatal dosage

[16]

3.2 Pharmacology of EtOH

Once, EtOH is ingested into the system, the absorption takes place through the process of passive diffusion via gastrointestinal mucosa. **20%** of the EtOH is absorbed through the lining of stomach and about **80%** is absorbed from the small intestine. The process is regulated by **pyloric sphincter** and the movement of the fluid in the GI tract. Since it is absorbed through the GI tract and its mucosa; it goes through the **first pass metabolism in the liver.** Subsequently it reaches to its systemic concentration. Approximately 20% of orally consumed EtOH goes through first pass metabolism. Further studies have found that the enzyme **Alcohol Dehydrogenase** (ADH) is mainly responsible for its metabolism. Once absorption is finished; remaining alcohol is distributed in blood, brain and skeletal system. Its distribution mainly depends on **Total Body Water** (TBW) as it is a **hydrophilic small size molecule**. It also depends on *body weight, gender and age*. The volume of distribution of ethanol is ***0.6 L/kg in women and 0.7 L/kg in men***.

3.2.1 Pharmacokinetic Study of EtOH

Stage I: Ingestion – Alcohol is usually ingested through oral route. Weather it may be for recreational use or for medicinal purposes. Hence, it goes through the process of first pass metabolism via GI tract.

Stage II: Absorption – There are various factors that affect the absorption of EtOH. Gastric Emptying is one of the most prevailing factors. Gastric ADH is also an important factor that metabolizes EtOH before its metabolism into the circulation. However, slower the gastric emptying, slower will be the metabolic activity in the liver. This is because of the saturation kinetics of ADH and only a small fraction gets metabolized. Hence, presence of food increases the time taken by EtOH to reach its maximum BAC. Another reason being the presence of Soda and sweetener along with the alcohol. Sodas show faster absorption of alcohol and presence of sucrose reduces the absorption of EtOH.

The pyloric muscle controls the emptying of stomach; which being close affects the absorption of EtOH. The rate of absorption again increases when the stomach content reaches duodenum and jejunum and villi / microvilli in small intestine.

Another factor which affects absorption is when the person suffers from low or restricted blood flow to liver. This will induce slower metabolism and faster BAC is achieved. Smoking nicotine and tobacco also decreases the rate of absorption because it delays gastric emptying and maximum BAC is not achieved faster. However, **the drugs that activate**

pyloric sphincter increases the rate of gastric emptying and so does the absorption occur faster.

Stage III: Distribution – Transport of the EtOH happens with body fluids and tissues in accordance of the presence of water. Rate of equilibrium will depend on the ratio of blood flow to tissues. Furthermore, EtOH does not bind with any proteins of plasma or other biomolecules and easily crosses the blood-brain barrier. This is why it causes brain impairment as its primary symptom. Once, liver metabolizes it; it reaches hepatic vein to the heart and it is pumped to the entire systemic circulation. Subsequently it reaches the lungs. Those organs which have higher rate of blood flow acquire more EtOH in faster manner. This includes brain, kidney, liver, heart, etc. On the other hand, bulky skeletal muscles take much longer time to attain EtOH.

Talking about fluids, the bio fluids contain higher amount of EtOH like saliva, urine, sweat, etc. in comparison to the blood, serum and plasma. This is because EtOH distributes itself in water compartments. People with more fatty tissues take longer time to distribute EtOH than those with lesser fatty tissues.

Stage IV: Metabolism – EtOH produces more energy than other psychotropic drugs. This is the main reason of active state of person in the first stage of alcohol ingestion. It produces around 7.1Kcal /gm which is greater than carbs and proteins. Inside the liver, it breaks down in numerous steps:

a) Primarily through ADH when it oxidizes EtOH to acetaldehyde CH3CHO which is also a toxic compound. This ADH is present in cytosol fraction of hepatocytes. This is more toxic than the parent drug.
b) In the next step; aldehyde dehydrogenase (ALDH) further oxidizes acetaldehyde into acetate CH3COO-R rapidly. This is found in mitochondria. This is also a toxic compound but its toxicity is much lesser than the previous one.
c) The next step is catalase; where alcohol is oxidized in peroxisomes in organelles of the cells. This happens because the products formed leaves the liver and enters Krebs cycle to convert itself into carbon dioxide and water.

A secondary pathway also removes alcohol at very high concentration which is of Cytochrome P450 2E1 (CYP2E1). This is located in south endoplasmic reticulum in microsomal fraction. This contains large family of proteins called cytochrome P450) mono-oxygenase. These take part in degradation and metabolism of many drugs and xenobiotics. This plays important role in oxidation reaction:

$CH_3CH_2OH + H^+ + O_2 \rightarrow CYP2E1 \rightarrow CH_2CHO + NADP^+ + 2H_2O$

Table 5: Dual types of Metabolisms

Oxidative Metabolism	Non-Oxidative Metabolism
1. Alcohol to Acetaldehyde	Type 1: Ethyl Glucuronide (EtG) and Ethyl Sulfate (EtS)
2. Acetaldehyde to Acetic Acid	Type II: Fatty Acid Ethyl Esters (FAEE)
3. Acetic Acid to Carbon Dioxide & Water	Type III: Phosphatidylcholine

In the first-pass metabolism, an ample amount of dose is disposed before it reaches its systemic circulation. In case of EtOH; this happens due to enzymes of liver and gut. There is yet another non-oxidative metabolism through which EtOH metabolizes. There is a very small amount of EtOH that undergoes conjugation reaction to produce ethyl glucuronide (EtG) and ethyl sulphate (EtS). This EtG curve is risen slower and reaches peak concentration in 1-2 hour later than BAC peak of EtOH. EtG is 1000 times lower than EtOH in blood.

Another non-oxidative metabolite includes various fatty acid ethyl esters (FAEE). These are the family of neutral lipids and are a product of esterification of fatty acids with EtOH. This causes EtOH induced damage in organs where it accumulates. It is synthesized in hepatoma cell line in tissue culture. It metabolizes EtOH to ethyl esters. Free fatty acids are released by intracellular hydrolysis of fatty acids and incorporate into cellular cholesterol esters. Thus, it changes cholesterol mechanism in humans. Increase in EtOH concentration shows increase in formation of fatty acid ethyl esters and so does triglycerides or cholesterol formation. The reaction rate curve shows a linear structure but there is an initial lag which suggests that there is a consistent sigmoid between 2 substrates.

Another non-oxidative metabolism takes place through phosphatidylcholine. It forms Phosphatidylethanol (PEtOH). These are group of phospholipids which are formed through enzymatic reactions in cell membranes. It is measured in blood & erythrocytes. Phospholipase D (PLD) forms phosphatidic acid (PA) from hydrolysis of phosphatidylcholine (PC). However, when EtOH is present, PLD promotes another transphosphatidylation reaction and forms PEtOH. This PEtOH is a group of molecules that contains carboxylic acid and glycerophospholipids analogues.

Stage V: Elimination – The main route of EtOH excretion is from urine, sweat, breath and fluid excretion. Less than 10% of the dosage is ingested and large amount is excreted. Most of the alcohol is eliminated through oxidative metabolism and around 10% is removed from lungs, kidneys and skin. [17, 18, 19]

3.2.2 Pharmacodynamics of EtOH

Persistent Exposure & Effects – The bioavailability of the fraction (F) of the dose is expressed in percentage of systemic circulation reached from its unchanged form. EtOH is categorized as a CNS depressant and it can manifest various effects as relief from anxiety, ataxia, general anesthesia and disinhibition. Chronic EtOH exposure causes functional as well as structural change in the brain. EtOH works on gamma-aminobutyric acid (GABA) receptors, glutamate, serotonin, dopamine and other opioids. It works as an agonist for GABA and antagonist for n-methyl-d-aspartate (NMDA) receptors.

Another effect which EtOH shows is dopamine release from nucleus with very less potent effect. It shows reinforcing effect of EtOH through dopaminergic and opioid peptidergic systems. Although, when the exposure is chronic, is shows upregulation of NMDA and downregulation of GABA.

Both acute and chronic use can cause hypotension & impair motor functions, cognitive dullness and similar effects of depressants. Chronic users have liver cirrhosis and effects of extreme malnutrition is also seen. Although, pharmacodynamic effects are more seen in systemic circulation.

EtOH causes injury to cells by dehydration and precipitation of cytoplasm / protoplasm. However, this also provides anti0fungal as well as anti-bacterial action. When injected near nerve tissues it causes neurolysis (nerve degradation). It binds directly to acetylcholine serotonin for glutamate and such interactions induce sedative effects by mediating GABA receptors and glycine receptors; although it also acts as anti-infective agent. Summing up activities of EtOH in the table given below:

Table 6: EtOH Pharmacodynamics

Enzyme / Protein	Role Of EtOH on the enzyme / protein	Role of enzyme / protein on the body.
Gamma-aminobutyric acid receptor subunit alpha-1	**AGONIST**	It is a hetero-pentameric ligand-gated chloride channel and is a major inhibitor neurotransmitter in brain. In activation, it allows selective flow of chloride anions to go down their electrochemical gradient. This chloride influx reduces neuron ability to generate new action potential and reduces nerve transmission. It preserves the structural information but changes functional activity towards orbitofrontal cortex.[PubMed:23909897, PubMed:25489750, PubMed:29950725, PubMed:30602789, PubMed:23909897, PubMed:29950725, PubMed:30602789, PubMed:23909897, PubMed:25489750] [20, 21, 22, 23]
Glutamate receptor ionotropic, NMDA 3A	**ANTAGONIST**	This function as hetero-tetrameric, ligand-gated cation channel with low calcium permeability with low voltage-dependent block by Mg2+. This participates during the development of neural circuits, synaptic refinement and restricts spine maturation / growth. Its subunits are activated by glycinergic receptor-complexes and D-serine. It functions by activating, deactivating and desensitizing kinetics, pH and Ca2+ permeability to allosteric modulators – this affects signaling and limits the maturation of inactive synapses [PubMed:38598639]. [24, 25, 26, 27]
Glycine receptor subunit alpha-1	**AGONIST**	These are ligand-gated chloride channels and it is triggered by extracellular glycine, taurine and beta-alanine. It displays faster desensitization and down regulates neuronal excitability as well as generates inhibitory post-synaptic currents. Its activity is potentiated by EtOH and induce sedative effects. [28, 29, 30]
Glycine receptor subunit alpha-2	**AGONIST**	These are also ligand-gated channels and it is triggered by taurine and beta-alanine. It plays important role in synaptic plasticity and neuronal excitability. It also contributes to post-synaptic currents [PubMed:15302677, PubMed:16144831, PubMed:2155780, PubMed:23895467, PubMed:25445488, PubMed:26370147, PubMed:34473954, PubMed:15302677, PubMed:25445488.]. [31]
Voltage-dependent L-type calcium channel subunit beta-1	**INHIBITOR**	This is a regulatory subunit of L-type calcium channel which regulates the channels containing CACNA1A as pore-forming subunit by increasing the presence of channel complex at the cell membrane [PubMed:1309651, PubMed:15615847, PubMed:8107964, PubMed:15615847, PubMed:1309651]. [32, 33]
Voltage-dependent L-type calcium channel subunit alpha-1C	**INHIBITOR**	This subunit gives rise to L-type calcium currents and it mediates the influx of calcium ions into the cytoplasm by triggering the release of sarcoplasm. It plays role in excitation-contraction coupling in heart and normal rhythming of the heart. It is also required for normal contraction of smooth muscle cells in blood vessels and intestines. It also plays important role in maintaining blood pressure regulation through arterial smooth muscle cells. It belongs to high-voltage activated HVA group & binds with alpha-actinin [PubMed:12181424, PubMed:15454078, PubMed:15863612, PubMed:16299511, PubMed:17224476, PubMed:20953164, PubMed:23677916, PubMed:24728418, PubMed:26253506, PubMed:27218670, PubMed:29078335, PubMed:29742403, PubMed:30023270, PubMed:30172029, PubMed:34163037, PubMed:8099908, PubMed:15454078, PubMed:15863612, PubMed:17224476, PubMed:24728418, PubMed:26253506, PubMed:28119464]. [34]
Voltage-dependent L-type calcium channel subunit alpha-1S	**INHIBITOR**	This gives rise to L-type calcium currents in skeletal muscles. It plays role in excitation & contraction coupling in muscles of skeletal system through RYR1. This triggers Ca2+ release from sarcoplasmic reticulum for muscle contraction. It has calmodulin binding function. [35]
Acetylcholinesterase	**ACTIVATOR**	This hydrolyzes acetylcholine rapidly which is a neurotransmitter and it is releases into the synaptic cleft to terminate the signal transduction at the neuromuscular junction. This is an acetylcholine binding protein and is plays role in neuronal apoptosis. [36]
All-trans-retinol dehydrogenase [NAD(+)] ADH7	**SUBSTRATE**	This protein catalyzes the NAD-dependent oxidation of all-trans-retinol, alcohol and omega-hydroxy fatty acids and their derivatives. This catalyzes in the oxidative direction with higher efficiency and participates in retinoid metabolism, fatty acid omega-oxidation and elimination of cytotoxic aldehydes from lipid peroxidation [PubMed:15369820, PubMed:16787387, PubMed:9600267, PubMed:15369820, PubMed:16787387, PubMed:15369820, PubMed:16787387, PubMed:9600267]. [37]
Voltage-dependent L-type calcium channel subunit alpha-1D	**INHIBITOR**	This is voltage-sensitive calcium channel (VSCC) mediator which involves calcium ions entry to excitable cells for variety of calcium-dependent processes like muscle contraction, neurotransmitter release, gene expression, hormone release, cell motility, cell death or cell division. The isoform of 1D gives rise to L-type calcium currents and are blocked by dihydropyridines (DHP) and benzothiazepines and phenylalkylamines. [38]
Cytochrome P450 1A1	**INHIBITOR**	This protein is involved in the metabolism of various endogenous substances like fatty acids, steroid hormones, vitamins, etc. This uses molecular oxygen by inserting oxygen

		into the substrate and reducing it into water molecule. It has 2 electrons given by NADPH via cytochrome P450 reductase. It converts arachidonic acid towards epoxyeicosatrienoic acid (EET); which is used as lipid mediators in vascular system. It also plays a major role in catalyzing all-trans retinoic acid in extrahepatic tissues [PubMed:10681376, PubMed:11555828, PubMed:12865317, PubMed:14559847, PubMed:15041462, PubMed:15805301, PubMed:18577768, PubMed:19965576, PubMed:20972997, PubMed:10681376, PubMed:11555828, PubMed:12865317, PubMed:14559847, PubMed:15041462, PubMed:15805301, PubMed:18577768, PubMed:19965576, PubMed:20972997, PubMed:20972997, PubMed:10681376]. [39]
Cytochrome P450 1A2	**SUBSTRATE**	This protein is of a similar class that of the above protein but it specifically metabolizes cholesterol towards 25-hydroxycholestrol and regulates cellular cholesterol homeostasis. It also acts as a major enzyme for all-trans retinoic acid biosynthesis in the liver. Catalyzes the N-hydroxylation of heterocyclic amines & O-deethylation of phenacetin. It also metabolizes caffeine via N3-demethylation. It functions as a aromatase activity [PubMed:14725854, PubMed:10681376, PubMed:21576599, PubMed:11555828, PubMed:12865317, PubMed:10681376, PubMed:11555828, PubMed:12865317, PubMed:19965576, PubMed:9435160]. [40]
Cytochrome P450 2B6	**INHIBITOR**	This participates in the metabolism of endocannabinoids and steroids and uses molecular oxygen to reduce the substrate to form a water molecule via CYP450 reductase. It also hydroxylates steroid hormones including testosterone at C-16 and estrogen at C-2. This plays vital role in oxidative metabolism of lipids and drugs and functions in anadamide 11,12 epoxidase activity [PubMed:11695850, PubMed:22909231, PubMed:12865317, PubMed:21289075, PubMed:12865317, PubMed:21289075]. [41]
Cytochrome P450 2C9	**INHIBITOR**	This catalyzes the epoxidation of double bonds of polyunsaturated fatty acids (PUFA) along with metabolizing cholesterol towards 25-hydroxychoelstrol which regulates cholesterol homeostasis. It shows low catalytic activity for formation of catechol estrogens. It also metabolizes plant monoterpenes like limonene to produce carveol and perillyl alcohol. It mainly functions by (R)-limonene 6-monooxygenase activity [PubMed:11950794, PubMed:25994031, PubMed:9435160, PubMed:9866708, PubMed:21576599, PubMed:12865317, PubMed:15766564, PubMed:19965576, PubMed:7574697, PubMed:9866708]. [42, 43]
Cytochrome P450 2C19	**INHIBITOR**	This hydroxylates PUFA specifically at the omega-1 position. It also metabolizes plant monoterpenes and a number of therapeutic agents like anticonvulsants, S-mephenytoin, omeprazole, imipramine, etc. It hydroxylates fenbendazole at 4' position [PubMed:18577768, PubMed:19965576, PubMed:20972997, PubMed:18577768, PubMed:23959307]. [44]
Cytochrome P450 2E1	**INDUCER, SUBSTRATE**	This is involved in the mechanism of fatty acids at specifically omega-1 position displaying the highest catalytic activity for saturated fatty acids. It is involved in the metabolism of xenobiotics [PubMed:10553002, PubMed:18577768, PubMed:10553002, PubMed:18577768]. [45, 46, 47, 48, 49, 50, 51]
Cytochrome P450 3A4	**INDUCER, INHIBITOR, SUBSTRATE**	This plays a major role in metabolism of androgens, particularly in oxidative deactivation of testosterone by metabolizing testosterone into biologically less active 2beta- and 6beta-hydroxy-testosterone. It also contributes in formation of oxysterol and cholesterol degradation along with bile-acid biosynthesis. This also helps in metabolism of retinoids and catalyzes sulfoxidation of anthelminitics albendazole and fenbendazole. It is also involved in vitamin D catabolism and calcium homeostasis along with inactivation of hormone calcitriol [PubMed:29461981, PubMed:11695850, PubMed:10759686, PubMed:10681376, PubMed:21576599]. [51, 52, 53, 54, 55, 56, 57]
Cytochrome P450 4A11	**INDUCER**	This metabolizes the oxidation of terminal carbon through omega oxidation of saturated and unsaturated fatty acids. It acts as a major omega-hydroxylase for lauric acid in liver and plays a role in signaling molecule as vasoconstrictive as well as natriuretic with overall effect on arterial blood pressure. It also degrades very long chain fatty acids initiating shortening of chain and some little activity towards prostaglandins A1 and E1. It functions with alkane 1-monooxygenase activity [PubMed:7679927, PubMed:18065749, PubMed:18182499, PubMed:7679927, PubMed:10620324, PubMed:10660572, PubMed:15611369, PubMed:15611369, PubMed:1739747, PubMed:7679927, PubMed:8914854, PubMed:10553002, PubMed:10660572]. [58]
ADH A1	**SUBSTRATE**	This oxidizes primary as well as secondary alcohols and EtOH is a very poor substrate. Its function lies in NAD+ activity [PubMed:2738060, PubMed:2738060]. [59, 60, 61, 62]
ADH 1C	**SUBSTRATE**	This plays a major role in ethanol catabolism and high activity for ethanol oxidation. Its specific function lies in NAD+ activity. [63, 64, 65, 66]
ADH Class-3	**SUBSTRATE**	This catalyzes long chain oxidation of primary alcohols and also of glutathione; along with oxidation of long chain omega-hydroxy fatty acids to produce intermediate aldehydes and finally dicarboxylic acid. It also clears cellular formaldehyde, being a cytotoxic and carcinogenic metabolite. It also catalyzes the NADH-dependent reduction of S-nitro-glutathione for regulating protein S-nitrosylation [PubMed:33355142, PubMed:16081420, PubMed:8460164]. [67]
All-trans-retinol dehydrogenase [NAD(+)] ADH1B	**SUBSTRATE**	This catalyzes NAD-dependent oxidation of all-trans retinol and its derivatives along with its participation in metabolism of retinol. It functions along with alcohol dehydrogenase NAD+ activity [PubMed:15369820, PubMed:16787387]. [68, 69, 70, 71]
ADH 6	**SUBSTRATE**	This catalyzes the NAD-dependent oxidation of primary alcohols to the corresponding ketones. [72]
Aldo-keto reductase family 1 member A1	**SUBSTRATE**	This catalyzes wide variety of NADPH-dependent reduction of carbonyl compounds to their corresponding alcohols. It shows enzymatic activity towards endogenous metabolites like aromatic and aliphatic aldehydes, ketones, monosaccharides and bile acids. It also

		prefers negatively charged substrate like glucuronate and succinic semialdehyde. It is a detoxifying enzyme for hyperglycemic conditions as well as for lipid-derived aldehydes like acrolein. However, it performs activation of procarcinogens like polycyclic aromatic hydrocarbons, anthracyclines doxorubicin and daunorubicin. It is an inhibitor of protein S-nitrosylation through degradation of S-nitroso-coenzyme A helping in renal tubules metabolism. However, it displays no activity towards retinol [PubMed:10510318, PubMed:30538128, PubMed:10510318, PubMed:30538128, PubMed:11306097, PubMed:18276838, PubMed:30538128, PubMed:31649033]. [73]

When we talk about alcohol, it is majorly a **cytochrome P450 2E1 Inducer**. Hence, it interacts synergistically with similar inducers and antagonistically with cytochrome P450 inhibitors. CYP is one of the most important group of enzymes that participate in metabolism of toxins & drugs. It is found in ***liver, intestinal wall, lungs & kidneys***. It is also found in endoplasmic reticulum as well as mitochondria of liver cells.

EtOH shows its symptomatic effect with:

Table 7: Synergistic and Antagonistic Effect Of EtOH

Synergistic Effect	Antagonistic Effect
Carbamazepine	Sodium Valproate
Rifampicin	Isoniazid
Phenytoin	Cimetidine
Griseofulvin	Ketoconazole
Phenobarbitone	Fluconazole
Sulphonyl-urea's	Chloramphenicol
	Erythromycin
	Sulfonamides
	Ciprofloxacin
	Omeprazole
	Metronidazole

[74]

Hence, when EtOH is consumed with synergistic compounds mentioned above, the effect of alcohol is pronounced or multiplied with the combining or interacting substance. On the other hand, when alcohol is consumed with antagonistic compounds mentioned above; the effect of alcohol is reduced and minimized due to counter-interaction of such drugs. We shall study such interactions and its effects, symptoms and management in the next sub-topic.

4. Interactions With EtOH

4.1 Polypharmacy of EtOH

DDIs also produce specific as well as systemic effect on the body depending on its site, administration & combination. Acute EtOH intoxication occurs in CNS with 20-30 mg/dl in the blood with increased reaction time, diminished fine motor skills and impulsivity at its peak. This impairs judgement. With more levels like 30-100 /dl; it causes excitation and euphoria. Slightly more intoxication till 100-150 /dl causes mental clouding, disorganization and impaired memorization. With 150-200 mg /dl causes ataxia, with slightly higher causes stupor around 200-300 mg/dl and finally with 300-400 mg/dl becomes a fatal dose. When interaction of other drugs takes place with EtOH; these effects either become pronounced, diminished or complicated. With synergistic agents, these effects get more pronounced and with antagonistic agents; the effects are seen to be reduced. However, with antagonistic agents the precipitant drug effects are seen more pronounced.

Drugs like paracetamol, aspirin, opioids, benzodiazepines, etc. need to be avoided along with EtOH. These causes serious toxicity with polypharmacy trends in the negative side. With chronic EtOH as well as interaction various symptoms like dementia, shrinkage of brain, polyneuritis, pellagra, tremors, seizures, defects of cognitive function, Korsakoff's psychosis, megaloblastic anemia and Wernicke's encephalopathy occurs; alongside of cardiovascular issues like tachycardia, arrhythmias, cardiomyopathy and hemorrhagic stroke.

Alcohol alone can elevate HDL, tPA (tissue plasminogen activator), inhibit platelet activation & cause pancreatitis. However, with numerous other agents; effects can have drastic change. Let us understand a few in upcoming section. [75]

4.1.1 Class 1 DDIs with EtOH

There are about 500-600 drugs that react with alcohol. Among those, 540 are well known. Among those 540; 38 showed major drug interaction with potential dangers, 491 showed moderate interactions and 11 showed mild interaction with alcohol. We have discussed the potential class 1 major DDIs in the table below:

Table 8: Class 1 DDIs with EtOH

Drug	Interaction	Symptoms	Management
Acetaminophen [76]	Acetaminophen-induced hepatotoxicity, with fatal hepatitis and frank hepatic failure. The proposed mechanism is induction of hepatic microsomal enzymes during chronic alcohol use, which may result in accelerated metabolism of acetaminophen and increased production of potentially hepatotoxic metabolites.	Stomach bleeding, abdominal pain, abdominal swelling & liver damage. It can also cause skin reactions & headaches.	Alternative analgesic/antipyretic therapy may be appropriate. However, if acetaminophen is used, these patients should be cautioned not to exceed the recommended dosage (maximum 4 g/day in adults and children 12 years of age or older)
Amobarbital [77]	Tolerance of these agents may occur with chronic use. The mechanism is through inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically.	It results in additive CNS effects, including impaired coordination, sedation, and death.	A medical detox is important.

Acitretin [78]	It leads to the formation of etretinate, which has a much longer half-life than acitretin. The longer elimination of etretinate relative to acitretin increases the duration of teratogenic potential for female patients. Etretinate remains in plasma and fat for 52 months after acitretin was discontinued.	Fetal abnormalities have been seen with the administration of acitretin, etretinate, and similar retinoids.	A 2-month stopping therapy must be prepared and executed.
Benznidazole [79]	It results in a disulfiram-like reaction. The presumed mechanism is inhibition of aldehyde dehydrogenase (ADH) by metronidazole in a manner similar to disulfiram. Alongside the ingestion of alcohol, inhibition of ADH results in increased concentrations of acetaldehyde & accumulation that produces an unpleasant physiologic response called 'disulfiram reaction'. *One study found neither elevations in blood acetaldehyde nor objective or subjective signs of a disulfiram-like reaction to ethanol in six subjects treated with metronidazole (200 mg three times a day for 5 days) compared to six subjects who received placebo.*	Flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, vomiting, sweating, thirst, chest pain, palpitation, dyspnoea, hyperventilation, tachycardia, hypotension, syncope, weakness, vertigo, blurred vision, and confusion. Severe reactions may result in respiratory depression, cardiovascular collapse, arrhythmia, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.	Consumption of EtOH and products containing propylene glycol is specifically contraindicated during and for at least 3 days after completion of metronidazole and benznidazole therapy.
Butabarbital [80]	Tolerance of these agents may occur with chronic use. The mechanism results due to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically.	This results in additive CNS effects, including impaired coordination, sedation, and death.	The sedative effect can be harmful and also cause vomiting, nausea, dizziness & coordination problems. It is important to detox both these substances and GI Tract needs to be stabilized.
Buprenorphine [81]	The mechanism of interaction probably involves some degree of additive pharmacologic effects. Preclinical studies also suggest that benzodiazepines can alter the usual ceiling effect on buprenorphine-induced respiratory depression and render the respiratory effects of buprenorphine appear similar to those of full opioid agonists.	This may increase the risk of buprenorphine overdose, severe respiratory depression, coma, and death. The coadministration may also increase the risk of hypotension. Abrupt withdrawal may lead to withdrawal symptoms. Severe cases of benzodiazepine withdrawal, results in numbness and tingling of extremities, hypersensitivity to light and noise, hallucinations, and epileptic seizures.	If coadministration is necessary, the dosage and duration of each drug should be limited to the minimum required to achieve desired clinical effect. One should be monitored closely for signs and symptoms of respiratory depression and sedation, and advised to avoid driving or operating hazardous machinery until they know how these medications affect them. Due to potential risk of overdose and death, dependence on sedative-hypnotics is considered a relative contraindication for office-based buprenorphine treatment of opioid addiction.
Butalbital [82]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically.	Concurrent acute use of barbiturates and ethanol may result in additive CNS effects, including impaired coordination, sedation, and death.	This gives a risk for overdosing and one needs to seek emergency medications. Emphasize on effects of muscle relaxation and muscular coordination; ASAP.
Cycloserine [83]	Coadministration with alcohol may potentiate the central nervous system adverse effects of Cycloserine and its prodrug, terizidone.	These effects may include dizziness, drowsiness, depression, anxiety, psychoses, memory impairment, confusion, and convulsions.	This can cause seizures and convulsions. A heavy and long-term plan for vitamin B6 needs to be administered to recover from the damage.
Disulfiram [84]	The mechanism is probably related to inhibition of aldehyde dehydrogenase, the enzyme responsible for the oxidation of acetaldehyde to acetyl CoA. This also results in accumulation of acetaldehyde.	Consumption of ethanol with disulfiram may cause flushing, nausea, blurred vision, dyspnoea, tachypnoea, tachycardia, and hypotension; also, death.	This can cause flushing, nausea and other symptoms which can become unbearable. Alcohol detox is thus required.
Droperidol [85]	The use of Droperidol has been associated with QT interval prolongation, torsade de pointes	It can produce hypokalaemia and/or hypomagnesemia,	The dosage of Droperidol should be individualized and titrated to the desired

	and other serious arrhythmias. The mechanism of action includes antagonism of dopamine receptors & interference with GABA-, norepinephrine- & serotonin-mediated activity in CNS. The sedative effects are multiplied.	drugs known to increase the QT interval with certain other drugs or alcohol abuse may increase the risk of prolonged QT syndrome. In addition, central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased.	effect. Routine vital sign and ECG monitoring is recommended.
Eluxadoline [86]	This may be related to the sphincter of Oddi spasm. It is metabolized by CYP450 & a slow formation of glucuronide takes place. is a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist that acts locally in the enteric nervous system, possibly decreasing adverse effects on the central nervous system.	This increases the risk of acute pancreatitis and symptoms like persistent nausea, vomiting, abdominal tenderness, and upper abdominal pain, especially that which is made worse after eating or radiates to the back or shoulders.	Immediate treatment for pancreatitis and inflammation must be administered.
Ethionamide [87]	This enhances the central nervous system exciting effect of protionamide. Use of EtOH with another thiocarbamide derivative ethionamide, precipitates a psychotic reaction. Alcohol tolerance is reduced during protionamide treatment. It is mainly metabolized in liver by Mycobacterium tuberculosis and binds with NAD+ to inhibit InhA by disruption of mycolic acid.	This can cause mental or mood changes along with liver disease. Methemoglobinemia can be seen with increased salivation, metallic taste of mouth and abdominal pain with loss of appetite and sores in the mouth.	This may cause liver problems and mood swings. Hence, it is important to administer psychological medications for mood relief and liver tonics. Immediate alcohol stoppage is required.
Flibanserin [88]	One experiences orthostatic hypotension when standing from a sitting position. Systolic and diastolic blood pressure reductions is also seen. Somnolence was also seen. It is a norepinephrine-dopamine inhibitor and has important function on sexual activities. It is metabolized by CYP3A4 & CYP2C19.	This potentiates the risk of severe hypotension, syncope, and central nervous system depression. Systolic blood pressure reductions ranged from 28 to 54 mmHg and diastolic blood pressure reductions ranged from 24 to 46 mmHg is seen.	One requires therapeutic intervention with ammonia salts or placements in supine / Trendelenburg position. One should minimize the risk of hypotension, syncope, accidental injury, and central nervous system depression.
Fomepizole [89]	This reduces the rate of elimination EtOH by 40%. The mechanism is via alcohol dehydrogenase inhibition. By a similar mechanism, EtOH will decrease the rate of elimination of fomepizole since it is a competitor of ADH.		Since it is an inhibitor of ADH and causes toxicity through metabolites getting into blood stream; it is important to go for haemodialysis.
Hydrocodone [90]	Alcohol may potentiate the central nervous system (CNS) depressant effects of opioid analgesics including hydrocodone. Consumption of EtOH while taking sustained-release formulations of hydrocodone causes rapid release of the drug, resulting in high systemic levels of hydrocodone that may be potentially lethal. Alcohol apparently can disrupt the release mechanism of some sustained-release formulations. The rate of absorption of hydrocodone from an extended-release formulation was found to be affected by coadministration with EtOH increases in hydrocodone peak plasma concentration and a decrease in the time to peak concentration. Alcohol also increased the extent of absorption by an average of 1.2-fold.	Concomitant use may result in additive CNS depression and impairment of judgment, thinking, and psychomotor skills. In more severe cases, hypotension, respiratory depression, profound sedation, coma or death.	This shall cause vomiting, drowsiness and fainting. Hence, it is important to administer CNS stimulants and add drugs to control the side effects of interaction on nervous system.
Hydromorphone [91]	Alcohol may potentiate the central nervous system (CNS) depressant effects of opioid analgesics including hydromorphone.	This results in additive CNS depression and impairment of judgment, thinking, and psychomotor skills. In more severe cases, hypotension,	It increases the risk of overdose as it is a semi-synthetic opioid. It is important to detox any of the drug since it causes nerve damage.

	Consumption of EtOH while taking sustained-release formulations of hydromorphone causes rapid release of the drug, resulting in high systemic levels of hydromorphone. Thai is potentially lethal even in opioid-tolerant patients. Alcohol appears to disrupt the extended-release mechanism, causing 'dose-dumping' into the bloodstream. The effect of alcohol was more pronounced in a fasted state.	respiratory depression, profound sedation, coma, or even death may occur.	
Ketamine [92]	In addition, opioid analgesics, barbiturates, and benzodiazepines may prolong the time to complete recovery from anaesthesia. It is a non-competitive derivative antagonist of NMDA receptors and glutamate is the full agonist for it. It produces functional dissociative anaesthesia. It becomes dangerous when this psychedelic substance mixes with depressant.	This results in profound sedation, respiratory depression, coma, and death.	Close monitoring of neurologic status and respiratory parameters, including respiratory rate and pulse oximetry, is recommended. Dosage adjustments should be considered according to the patient's clinical situation.
Leflunomide [93]	This induces hepatotoxicity & potentiates the risk of liver injury associated with leflunomide. The risk is thought to extend to teriflunomide, its principal active metabolite, because recommended dosages of both result in a similar range of plasma concentrations of teriflunomide. Liver enzyme elevations were generally mild and resolved while continuing treatment. Marked elevations occurred infrequently and reversed with dose reduction or discontinuation of treatment.	Elevated liver transaminases, hepatitis, jaundice/cholestasis, hepatic failure, and acute hepatic necrosis have been seen. They experience potential signs and symptoms of hepatotoxicity such as fever, rash, itching, anorexia, nausea, vomiting, fatigue, malaise, right upper quadrant pain, dark urine, pale stools, and jaundice.	Liver enzymes and bilirubin should be measured prior to initiation of leflunomide / teriflunomide therapy and at least monthly for the first six months of treatment and every 6 to 8 weeks thereafter. Those with preexisting liver disease or elevated baseline liver enzymes are at higher risks. Those who develop elevated serum ALT greater than three times ULN should discontinue and be given washout procedures with cholestyramine or activated charcoal to accelerate elimination of leflunomide's active metabolite from plasma.
Levomethadyl Acetate (LAAM) [94]	The central nervous system and respiratory depressant effects of levo-methadyl acetate may be potentiated by concomitant use of other agents with CNS depressant effects. LAAM is metabolized by a process called N-demethylation through CYP450 & CYP3A4. The first and second metabolites are more potent than the drug.	This risks in developing respiratory depression, hypotension, profound sedation, syncope, coma, and even death should be considered.	One should be advised to avoid driving, operating machinery, or engaging in potentially hazardous activities requiring mental alertness and motor coordination until they know how the medications affect them
Lemborexant [95]	This increases the plasma concentrations and potentiates pharmacologic effects of the CNS-active agent, Lemborexant. It increases the peak plasma concentration (Cmax) and systemic exposure (AUC) of lemborexant by 35% and 70%. It is metabolized primarily by CYP3A4 and secondarily by CYP3A5 through oxidation of dymethylpyrimidine followed by oxidation / glucuronidation.	Use in combination may result in additive CNS depression and/or impairment of judgment, thinking, and psychomotor skills.	This shall affect your motor coordination and alertness. Hence, one can detox alcohol and advise CNS stimulant. Liver tonics may also be required.
Lomitapide [96]	It induces hepatotoxicity & potentiates the risk of liver injury. Hepatic steatosis associated with lomitapide may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. However, hepatic fat accumulation is reversible. It can cause elevations in serum transaminases and hepatic steatosis. One has elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3 times the upper limit of normal (ULN). It also increases hepatic fat, with or without concomitant increases in transaminases.	It shows fever, rash, itching, anorexia, nausea, vomiting, fatigue, malaise, right upper quadrant pain, dark urine, pale stools, and jaundice.	One should have serum ALT, AST, alkaline phosphatase, and total bilirubin measured prior. The dosing adjusted or interrupted as necessary. Since alcohol may increase levels of hepatic fat and induce or exacerbate liver injury, one taking lomitapide not consume more than one alcoholic drink per day.
Mephobarbital [97]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes	It results in additive CNS effects, including impaired coordination, sedation, and death.	This can cause overdosing, headache and addiction in many individuals. However, management differs from individual to individual.

	chronically. This occurs by N-demethylation forming phenobarbital.		
Metronidazole [98]	This results in a disulfiram-like reaction. The mechanism is inhibition of aldehyde dehydrogenase (ALDH) by metronidazole in a manner similar to disulfiram. Further it results in increased concentrations of acetaldehyde, the accumulation of which can produce an unpleasant physiologic response referred to as the 'disulfiram reaction'.	Flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, vomiting, sweating, thirst, chest pain, palpitation, dyspnoea, hyperventilation, tachycardia, hypotension, syncope, weakness, vertigo, blurred vision, and confusion. Further it shows respiratory depression, cardiovascular collapse, arrhythmia, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.	This causes acetaldehyde accumulation in the body. Hence, one needs to address the same.
Metformin [99]	Alcohol potentiates the effect of metformin on lactate metabolism, this increases the risk of lactic acidosis. It causes hypoglycaemia or hyperglycaemia in patients with diabetes. The mechanism involves inhibition of both gluconeogenesis & counter-regulatory response to hypoglycaemia.	Small interaction can lower blood sugar; specially when taken empty stomach. Chronic interaction causes impaired glucose tolerance and hyperglycaemia. One experiences malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress (usually after stabilization of metformin therapy, when GI symptoms are uncommon). With greater interaction; there may be hypothermia, hypotension, and resistant bradyarrhythmia.	Diabetes patients should avoid consuming alcohol if their blood glucose is not well controlled, or if they have hypertriglyceridemia, neuropathy, or pancreatitis. Alcohol should not be consumed on an empty stomach / after exercise, as it may increase the risk of hypoglycaemia. Metformin should be withdrawn promptly if lactic acidosis is suspected. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels should be diagnosed.
Mipomersen [100]	This induces hepatotoxicity & potentiates the risk of liver injury. Mipomersen can cause elevations in serum transaminases and hepatic steatosis. Mipomersen increases hepatic fat, with or without concomitant increases in transaminases. In clinical trials of patients with heterozygous familial hypercholesterolemia and hyperlipidaemia, the median absolute increase in hepatic fat was ~ 10%. It is metabolized initially by endonucleases then exonucleases & binds to mRNA to code apoB-100 and leads to double stranded RNA. This is further degraded by RNase H & stops the translation of mRNA to form subsequent protein.	They experience fever, rash, itching, anorexia, nausea, vomiting, fatigue, malaise, right upper quadrant pain, dark urine, pale stools, and jaundice. Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury.	One should have serum ALT, AST, alkaline phosphatase, and total bilirubin measured & the dosing should be adjusted or interrupted as necessary.
Methohexital [101]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically. There are hepatic mechanisms that break methohexital to non-active metabolites and then they are rapidly excreted. It goes through side-chain oxidation with biotransformation in terminal activity through demethylation and oxidation.	This results in additive CNS effects, including impaired coordination, sedation, and death.	Since this can cause swelling, jaundice and severe liver injury; it is advised to detox any of these immediately. Both these have sedative effects; thus, it is not advised to use it simultaneously. Try mild stimulants to recover.
Morphine [102]	Alcohol may potentiate the CNS-depressant effects of opioid analgesics including morphine & diamorphine. may occur. Consumption of EtOH with taking sustained-release formulations of morphine causes rapid	This gives additive CNS depression and impairment of judgment, thinking, and psychomotor skills.	This can cause brain to block the pain signals and it is required to give drugs to stabilize the brain.

	release of the drug, resulting in high systemic levels of morphine. This would be lethal. EtOH disrupts the release mechanism of some sustained-release formulations. 'Dose-dumping' into the bloodstream is conceivable. Morphine is metabolized by liver enzyme UGT2B7 and UGT1A1 and UGT1A8 where primarily it is broken into morphine-3-glucuronide and morphine-6-glucuronide. It is then excreted by bile and urine.	In severe cases, hypotension, respiratory depression, profound sedation, coma, or death	
Nifurtimox [103]	Use of EtOH with nitrofurans results in a disulfiram-like reaction. The mechanism is inhibition of aldehyde dehydrogenase (ALDH) by nitrofurans in a manner similar to disulfiram. Ingestion of EtOH, inhibition of ALDH results in increased concentrations of acetaldehyde & the accumulation produces an unpleasant physiologic response referred to as the 'disulfiram reaction'. It is metabolized by various oxidation and reduction reactions; primarily by Nitroeductase. It produces 2 major inactive metabolites: M-4 and M-6, which are cysteine conjugate of nifurtimox and hydrolytic cleavage respectively.	Symptoms include flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, vomiting, sweating, thirst, chest pain, palpitation, dyspnoea, hyperventilation, tachycardia, hypotension, syncope, weakness, vertigo, blurred vision, and confusion. Severe interaction results in respiratory depression, cardiovascular collapse, arrhythmia, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.	This can increase the side effects of the drug; however it is specific from person to person.
Phenobarbital [104]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically. It is metabolized in liver through enzymes CYP2C9 and CYP2C19 & CYP2E1; through hydroxylation & glucuronidation, giving many isoenzymes.	This results in additive CNS effects, including impaired coordination, sedation, and death.	Since both act as sedatives together, it causes dizziness and chances of overdose. Benzodiazepines are considered the first line of treatment for the withdrawal symptoms. One also needs to control seizures as it is reported in many cases.
Pentobarbital [105]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically. It is metabolized by inactive metabolite hydroxy-pentobarbital via oxidation.	This shows additive CNS effects, like: impaired coordination, sedation, and death.	This shall cause cardiac arrest and hence, it shall never be administered together. One needs to seek emergency attention for the same.
Primidone [106]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically. It is metabolized by phenobarbital (PB) and phenylethylmalonamide (PEMA). This is done through anticonvulsant activity.	This shows additive CNS effects, including impaired coordination, sedation, and death.	This can increase the side effects of primidone and the drug's efficacy. Causing dizziness, drowsiness and other symptoms. CNS stimulants should be advised as these shall cause severe depression together.
Pexidartinib [107]	Concomitant use of other potentially hepatotoxic agents may potentiate the risk of liver injury. Since it is a tyrosine kinase inhibitor, it targets CSF1R, KIT proto-oncogene receptor tyrosine kinase& FMS-like tyrosine kinase 3 (FLT3) for internal tandem duplication mutation.	Serious cases of hepatotoxicity, some fatal, have been seen. We can see potential signs of hepatotoxicity such as fever, rash, itching, anorexia, nausea, vomiting, fatigue, malaise, right upper quadrant pain, dark urine, pale stools, and jaundice.	One should have liver function tests, including AST, ALT, total bilirubin, direct bilirubin, ALP, and gamma-glutamyl transferase (GGT). They may require a dosage reduction, to be withheld, or permanently discontinued based on the severity of the hepatotoxicity. Recurrence of increased serum transaminases, bilirubin, or ALP may occur. Liver function tests should be performed weekly for the first month after rechallenge.
Propoxyphene [108]	This shows additive CNS- and/or respiratory-depressant effects with propoxyphene. Misuse of propoxyphene, either alone or in	60% increased risk of hip fracture in the elderly, and the risk was further	One should be monitored for potentially excessive or prolonged CNS and respiratory depression and other CNS

	combination with EtOH has been a major cause of drug-related deaths, particularly in patients with a history of emotional disturbances, suicidal ideation, or alcohol and drug abuse. This goes first pass metabolism through hepatic as well as intestinal enzymes: CYP3A4 mediated by N-demethylation to norpropoxyphene. Other pathways include ring hydroxylation and glucuronide formation. It binds to opioids receptors to decrease the perception of pain.	increased by concomitant use of psychotropic agents; presumably due to additive psychomotor impairment.	adverse effects. Avoid activities requiring mental alertness until they know how these agents affect them.
Secobarbital [109]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically. This binds to GABA-receptor sites to enhance GABA activity and depresses reticular activity system. It increases the activity of Azelastine and hypotensive activities of Alisartan medoxomil.	This can give additive CNS effects, including impaired coordination, sedation, and death.	This shall synergistically act as sedative and CNS depressant. The effect of depressant shall get pronounced and nerve signalling is affected. Hence, treatment for insomnia, sedation and CNS regulation is important.
Sodium Oxybate [110]	The central nervous system and respiratory depressant effects of Sodium Oxybate, which is the sodium salt of gamma hydroxybutyrate (GHB), may be potentiated by concomitant use of sedative-hypnotic agents. The mechanism is not completely understood but involves cytosolic enzyme, GHB-dehydrogenase & mitochondrial transhydrogenase.	One can see serious adverse reactions like: respiratory depression, hypotension, profound sedation, syncope, coma, and death.	This interaction shall cause respiratory depression, low blood pressure and fainting. Hence, it is important to seek immediate medical attention and vitals should be checked frequently. Treatment depends from patient to patient.
Teriflunomide [111]	This induces hepatotoxicity & potentiates the risk of liver injury associated with leflunomide. The risk is thought to extend to teriflunomide, its principal active metabolite. Liver enzyme elevations were generally mild (2 times the upper limit of normal or less). Marked elevations (greater than 3-fold ULN) occurred infrequently and reversed with dose reduction or discontinuation. The estimated duration of exposure before onset of severe liver injury differed from 9 days to 6 years.	Elevated liver transaminases, hepatitis, jaundice/cholestasis, hepatic failure, and acute hepatic necrosis have been reported. One sees signs of hepatotoxicity like - fever, rash, itching, anorexia, nausea, vomiting, fatigue, malaise, right upper quadrant pain, dark urine, pale stools, and jaundice.	One who develops elevated serum ALT greater than three times ULN should discontinue and be given washout procedures with cholestyramine or activated charcoal to accelerate elimination of leflunomide's active metabolite from plasma, which otherwise may take up to two years. Monitoring should be conducted at least weekly until the ALT value is normal.
Thiopental [112]	Tolerance of these agents may occur with chronic use. The mechanism is related to inhibition of microsomal enzymes acutely and induction of hepatic microsomal enzymes chronically. It is metabolized in the liver and redistributed to peripheral compartment. It shows ring desulfuration and generates active metabolite pentobarbital which would be 3-10% of its concentration.	Concurrent acute use of Thiopental and EtOH results in additive CNS effects, including impaired coordination, sedation, and death.	This shall increase the sedative effects and the patient might fall into severe CNS depression. Synergistic effect shall be seen and drowsiness shall be seen instantly. Treatment depends from contraindications.

4.1.2 Class 2 DDIs with EtOH

There are also certain drugs that fall under class 2 for interacting with EtOH. We would not be discussing these in detail but these drugs also need to be avoided when alcohol is consumed. Although, these will show lesser adverse reaction and effects than those mentioned in the class 1 category. There are around 491 drugs that moderately show DDIs with EtOH:

Table: 9.1: Class 2 DDIs with EtOH

Acarbose	Baclofen	Cabergoline	Daclizumab	Efavirenz	Felbamate
Acebutolol	Bedaquiline	Calaspargase pegol	Dantrolene	Empagliflozin	Felodipine
Acetohexamide	Belladonna	Canagliflozin	Dapagliflozin	Enalapril	Fenfluramine
Acetylcarbromal	Benazepril	Candesartan	Daridorexant	Enalaprilat	Fenoldopam
Acrivastine	Bendroflumethiazide	Cannabidiol	Deserpidine	Entacapone	Fenoprofen
Albiglutide	Benzphetamine	Cannabis	Desipramine	Epirubicin	Fentanyl
Alfentanil	Benzthiazide	Captopril	Desvenlafaxine	Eplerenone	Fexinidazole
Alfuzosin	Benztropine	Carbamazepine	Deutetrabenazine	Eprosartan	Fidanacogene
Allopurinol	Bepridil	Carbetapentane	Dexbrompheniramine	Ertugliflozin	elaparvovec
Alogliptin	Betaxolol	Carbinoxamine	Dexchlorpheniramine	Escitalopram	Flavoxate
Alprazolam	Bexagliflozin	Cariprazine	Dexfenfluramine	Esketamine	Fluoxetine

Amiloride	Biperiden	Carisoprodol	Dexmedetomidine	Eslicarbazepine	Fluphenazine
Amitriptyline	Bisoprolol	Carteolol	Dextroamphetamine	Esmolol	Flurazepam
Amlodipine	Black cohosh	Carvedilol	Dextromethorphan	Estazolam	Flurbiprofen
Amoxapine	Brentuximab	Cefamandole	Dezocine	Eszopiclone	Fluvastatin
Amphetamine	Brexanolone	Cefmetazole	Diazepam	Ethacrynic acid	Fluvoxamine
Amyl nitrite	Brexpiprazole	Cefoperazone	Diazoxide	Ethchlorvynol	Fosinopril
Anisindione	Brimonidine ophthalmic	Cefotetan	Diclofenac	Ethosuximide	Fosphenytoin
Apomorphine	Brimonidine topical	Cenobamate	Dicumarol	Ethotoin	Furazolidone
Apraclonidine ophthalmic	Brivaracetam	Cerivastatin	Dicyclomine	Etodolac	Furosemide
Aprocitentan	Bromocriptine	Cetirizine	Diethylpropion	Etomidate	
Aripiprazole	Brompheniramine	Chlophedianol	Difelikefalin	Exenatide	
Asenapine	Bumetanide	Chloral hydrate	Diltiazem	Ezogabine	
Ashwaganda	Bupropion	Chlorcyclizine	Dimenhydrinate		
Asparaginase erwinia chrysanthemi	Buspirone	Chlordiazepoxide	Diphenhydramine		
Asparaginase escherichia coli	Butorphanol	Chlormezanone	Diroximel fumarate		
Aspirin		Chlorothiazide	Divalproex sodium		
Atenolol		Chlorphenesin	Doxazosin		
Atorvastatin		Chlorpheniramine	Doxepin		
Atropine		Chlorpromazine	Doxepin topical		
Avanafil		Chlorpropamide	Doxylamine		
Azatadine		Chlorthalidone	Dronabinol		
Azelastine nasal		Chlorzoxazone	Dulaglutide		
Azilsartan medoxomil		Citalopram	Duloxetine		
		Clemastine			
		Clevidipine			
		Clidinium			
		Clobazam			
		Clofarabine			
		Clomipramine			
		Clonazepam			
		Clonidine			
		Clorazepate			
		Clozapine			
		Codeine			
		Cyclizine			
		Cyclobenzaprine			
		Cyproheptadine			

Table 9.2: Class 2 DDIs with EtOH

Gabapentin	Halazepam	Ibuprofen	Kava	Labetalol	Magnesium salicylate
Gabapentin enacarbil	Haloperidol	Idelalisib	Ketoconazole	Lacosamide	Maprotiline
Ganaxolone	Heroin	Ifosfamide	Ketoprofen	Lamotrigine	Mazindol
Glimepiride	House dust mite allergen extract	Iloperidone	Ketorolac	Levamisole	Meclizine
Glipizide	Hydralazine	Imipramine		Levamlodipine	Meclofenamate
Glyburide	Hydrochlorothiazide	Indapamide		Levetiracetam	Mefenamic acid
Glycopyrrolate	Hydroflumethiazide	Indomethacin		Levocetirizine	Melatonin
Guanabenz	Hydroxyzine	Insulin		Levodopa	Meloxicam
Guanadrel	Hyoscyamine	Insulin aspart		Levoketoconazole	Mepenzolate
Guanethidine		Insulin aspart protamine		Levomilnacipran	Meperidine
Guanfacine		Insulin degludec		Levorphanol	Mephenytoin
		Insulin detemir		Linagliptin	Meprobamate
		Insulin glargine		Liraglutide	Mesoridazine
		Insulin glulisine		Lisdexamfetamine	Metaxalone
		Insulin inhalation, rapid acting		Lisinopril	Methadone
		Insulin isophane		Lithium	Methamphetamine
		Insulin lispro		Lixisenatide	Methdilazine
		Insulin lispro protamine		Lofexidine	Methocarbamol
		Insulin regular		Loperamide	Methotrexate
		Insulin zinc		Lorazepam	Methotrimeprazine
		Insulin zinc extended		Losartan	Methoxyflurane
		Interferon beta-1a		Lovastatin	Methscopolamine
		Interferon beta-1b		Loxapine	Methsuximide
		Irbesartan		Lumateperone	Methyclothiazide
		Isocarboxazid		Lurasidone	Methyldopa
		Isoniazid			Methylphenidate
		Isosorbide dinitrate			Metoclopramide
					Metolazone
					Metoprolol
					Metronidazole topical
					Metyrosine

		Isosorbide mononitrate Isotretinoin Isradipine Ivermectin			Mibefradil Midazolam Miglitol Milnacipran Minoxidil Mirtazapine Mitotane Mixed grass pollens allergen extract Moexipril Molindone Morphine liposomal

Table: 9.3: Class 2 DDIs with EtOH

Nabilone Nabumetone Nadolol Nalbuphine Naltrexone Naproxen Nateglinide Nebivolol Nefazodone Niacin Nicardipine Nifedipine Nimodipine Nisoldipine Nitroglycerin Nitroprusside Nortriptyline	Olanzapine Oliceridine Olmesartan Olopatadine nasal Opicapone Opium Orphenadrine Oxaprozin Oxazepam Oxcarbazepine Oxybutynin Oxycodone Oxymorphone	Paliperidone Papaverine Paraldehyde Paramethadione Paroxetine Pegaspargase Peginterferon beta-1a Penbutolol Pentazocine Perampanel Pergolide Perindopril Perphenazine Phenacemide Phendimetrazine Phenelzine Phenindamine Phenoxybenzamine Phensuximide Phentermine Phentolamine Phenylpropanolamine Phenytoin Pimozide Pindolol Pioglitazone Piroxicam Pitavastatin Polythiazide Posaconazole Pramipexole Pramlintide Pravastatin Prazosin Pregabalin Procarbazine Prochlorperazine Procyclidine Promazine Promethazine Propantheline Propiomazine Propofol Propranolol Protriptyline Pyrilamine	Quazepam Quinapril Ragweed pollen allergen extract Ramelteon Ramipril Rasagiline Rauwolfia serpentina Red yeast rice Remdesivir Remifentanil Remimazolam Repaglinide Reserpine Rifampin Risperidone Ropinirole Rosiglitazone Rosuvastatin Rotigotine Rufinamide	Safinamide Salsalate Saxagliptin Scopolamine Selegiline Semaglutide Sertraline Sibutramine Sildenafil Silodosin Simvastatin Sitagliptin Sotagliflozin Sotalol Sparsentan Spironolactone St. John's wort Stiripentol Sufentanil Sulfamethoxazole Sulindac Suvorexant	Tadalafil Tamsulosin Tapentadol Tasimelteon Telmisartan Temazepam Terazosin Tetrabenazine Thalidomide Thiethylperazine Thioguanine Thioridazine Thiothixene Tiagabine Timolol Timothy grass pollen allergen extract Tinidazole Tirzepatide Tizanidine Tolazamide Tolbutamide Tolcapone Tolmetin Tolterodine Topiramate Torsemide Trabectedin Tramadol Trandolapril Tranylcypromine Trazodone Triamterene Triazolam Trichlormethiazide Trifluoperazine Triflupromazine Trihexyphenidyl Trimeprazine Trimethadione Trimethaphan camsylate Trimethobenzamide Trimipramine Tripelennamine Triprolidine Troglitazone Trospium

Table 9.4: Class 2 DDIs with EtOH

Valbenazine Valerian Valoctocogene roxaparvovec Valproic acid	Valsartan Vardenafil Varenicline Venlafaxine	Verapamil Verteporfin Vigabatrin	Vilazodone Vortioxetine Warfarin Zaleplon	Ziconotide Ziprasidone Zolmitriptan	Zolpidem Zonisamide Zuranolone

[113]

Aim & Objective *(Critical Study with CBD, THC, Nicotine & LSD)*

The objective behind this study is to identify the interaction of EtOH with different drugs for its positive and negative impacts. To perform detailed analysis on detecting interactions for forensic purposes. Various detection methods are to be studied in order to achieve a clear picture about identification, understanding and developing symptomatic as well as effective techniques to negate crimes associated with it. We shall study few combinations in detail to gain insights on its detection, management & counter-measures for the same. We shall devise and understand methods of analysis, detection and treatment for such scenarios; in emergency as well as long-term support / care.

We would try to generate better ideas and fast deliverance of justice as well as faster relief to the victim in any of the medico-legal cases regarding alcohol and its interaction. In this paper, we have chosen to study DDIs of alcohol with marijuana (THC) & (CBD) as well as tobacco / nicotine in a comparative manner. This shall give us a clear distinct idea about these two interactions. Another study is based on a synthetic drug called Lysergic Acid Diethylamide (LSD) and its combined effect with EtOH. Towards the end, we shall list many such drugs which is a top-pick for criminals to conduct malicious activities like loot, rape, robbery, etc.

5. Marijuana (Cannabis) VS Nicotine (Cigarette Smoking) with EtOH

5.1 Toxicology of Cannabis

Marijuana's primary components consist of **THC** and **CBD**. THC is the chief psychoactive ingredient in the Marijuana plant whereas CBD is not psychoactive. Both have similar structure with **21 C-atoms, 30 H-atoms & 2 O-atoms**. THC is the main compound that causes high sensations; whereas CBD does not produce it. CBD is available in oils, vaporize oils, capsules, etc. On the other hand, THC is an active psychotic substance which causes euphoria, hallucinations, pain relief, etc. The effect of THC depends from person to person. CBD on the other hand helps in solving issues related to epilepsy, anxiety & depression.

Laboratory tests related to the confirmation of THC lies through various different methods. The most common is:

a) ***Duquenois–Levine reagent:*** This was developed by Pierre Duquénois. One needs to add Duquenois–Levine reagent to dried petroleum ether extract & add hydrochloric acid & chloroform. This is a colour test which turns it purple. It consists of **ethanol, acetaldehyde & vanillin**.
b) ***Azo dyes Fast B Blue:*** Azo dyes are also used to test through TLC. This is a superior test from that of Duquenois–Levine test.
c) ***Beam's Test:*** There is also a specific CBD test - Beam's test where test sample is mixed with 5% potassium hydroxide & 95% ethanol. After 10 minutes; CBD manifest bluish pink / violet colour.
d) ***Hair / Saliva / Serums:*** There are also hair tests which are used to detect cannabis. It can be around 90 days from the use of the substance & 1.5 inches grown hair. It measures marijuana parent metabolite inside the hair shaft and eliminates external combination. Cannabis is also predicted from a simple saliva test and its inactive metabolite. Delta 9 THC is the parent compound and its detection can lead up to 72 hours.
e) In blood, Marijuana is detected from 12-24 hours up to 7 days. On the other hand, THC-COOH is found in urine. Moreover, neurological testing contains more alpha waves than delta and slight inactivation of motor control sites.

5.1.2 Cannabis & EtOH

When these substances are interacted with EtOH, the combined effect alters brain wiring abruptly. Brain connectivity is altered. This is found using magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI). This is because dynamic functional network connectivity (dFNC) is tested by the same. These techniques are used for testing combine effects and DDIs of **EtOH and Cannabis / EtOH and Nicotine**.

Dynamic functional network connectivity (dFNC) presumes that - the whole brain connectivity sequentially iterates through a finite set of connectivity patterns. These are termed as **dFNC States**. These states present some differences - according to the subjects & at an instantaneous moment in time. [114]

5.2 Toxicology of Nicotine

Nicotine releases catecholamines and increases heart rate along with cardiac contractility. It also constricts cutaneous and coronary blood vessels. This is followed by increase in blood pressure. It is a sympathomimetic drug and reduces sensitivity to insulin. It also contributes to endothelial dysfunction. This shall lead to coronary artery disease. Nicotine is not a direct carcinogen but can be a tumour promoter. It inhibits apoptosis in animals and results in impaired killing of cancer cells. However, it leads to greater tumour invasion and metastasis.

It acts on nAChRs to mimic or replace the effect of nicotine. It is a stimulatory alkaloid that binds to stereospecific nAChRs on autonomic ganglia, adrenal medulla and neuromuscular junctions of the brain. It gives reward effect in limbic system and stimulant effect at locus ceruleus. Intravenous administration can release acetylcholine, norepinephrine, dopamine, serotonin and vasopressin along with beta-endorphin and ACTH.

Themetabolism follows a multiple pathway; it transforms into N-methylnicotinium to nicotine imine and cotinine. This cotinine transforms to cotinine glucuronide, nicotine-1-N-ocide, nornicotine, 3-hydroxycotinine and cotinine N-oxide. This also has some sub-products like nornicotine, nicotine glucuronide, norcotinine, nicotine-1-N-oxide, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, (S)- Nicotine delta-1, 5'-iminium ion & 2-hydroxynicotine. [115]

5.2.2 Nicotine & EtOH

It is an agonist for nAChRs; which are ionic receptors composed of 5 homomeric or heteromeric subunits. Nicotine binds with these receptors on dopaminergic neurons in the coritoc-limbic pathways. This causes the channels to open and allow conductance of cations: sodium, calcium, potassium, etc. This further leads to depolarization to activate

voltage-gated calcium channels. This will allow more calcium to reach the axon terminal. Such calcium stimulates the vesicle trafficking towards the plasma membrane and releases dopamine into the synapse. This dopamine binds to the receptors and it is responsible for euphoric, relaxing and addictive properties. It also binds with chromaffin cells in adrenal medulla and opens the ion channels that influxes sodium. This again causes depolarization of the cell and activates the voltage-gated channels. This releases epinephrine from intracellular vesicles into blood stream causing vasoconstriction, increased blood pressure, heart rate and blood sugar.

Since alcohol and nicotine both are stimulants, they will cause synergistic effect on the brain for short duration of time and a dopaminergic boost. This shall show a downward curve after sometime and may lead to addictive behaviour. **The main change is the cross tolerance of these two drugs. When combined together, the cross-tolerance of these two drugs increases rapidly and causes dependence easily.** [116]

5.3 DDIs Involving Cannabis, Nicotine, EtOH

These substances of abuse are modifiers of the dopamine-reward systems which affects the Nucleus Accumbens (NAc) and ventral tegmental area (VTA). However, this happens through different molecular mechanisms in cannabis, nicotine and EtOH. There is also a difference in contrast in the brain while using all these 3 substances individually as well as interactively.

Table 10: DDIs with EtOH, Cannabis and Nicotine

EtOH	Cannabis	Nicotine
Trend 1: Decreased connectivity mainly in areas of sensorial and motor control, as a result of the dFNC outcome and the alcohol use disorder.	**Trend 2:** Produces alterations of functional connectivity which include the orbitofrontal cortex, default mode network, and insula.	**Trend 3:** Increases connectivity between dorsal striatum and sensorimotor areas.
Trend 4: Produces dysfunctions in connectivity between the NAc and cortical areas, even the ones with increased activation during stimuli & response demanding tasks. This gives changes in the functional connectivity of cognitive, motor, and coordination.	**Trend 5:** Produces increased level of brain acetylcholine; but only on large doses. It does not have any major effect on nAChR.	**Trend 6:** Binds to nicotinic acetylcholine receptors (nAChR) & changes dopaminergic signalling in the areas of the reward pathways like - VTA and NAc.
Trend 7: The connectivity between the motor and a high visual processing area was reduced.	**Trend 8:** Induces a stronger increment of connectivity through the brain, in selected dFNC states, than decrements. A series of axonal impairment in the hippocampus (fornix), splenium, commissural fibres. and morphological changes in the amygdala, prefrontal cortex & cerebellum.	**Trend 9:** The effect of nicotine in functional connectivity is more prominent in areas like the insula.
Trend 10: Functional connectivity was reduced due to inhibition of GABA receptors.	**Trend 11:** Functional connectivity was increased in middle frontal gyrus, precentral gyrus, superior frontal gyrus, posterior cingulate cortex & cerebellum.	**Trend 12:** This increases functional connectivity in motor, attention, and memory brain areas.

The use nicotine and marijuana together enhance nAChR (Nicotinic acetylcholine receptors) availability in the prefrontal cortex and the thalamus greater than the singular substance use. This also increases connectivity disruptions in frontoparietal regions as well as posterior cortical. Thus, we have seen complex interaction of these 3 substances which largely depends on individual factors.

Table 11: Different Trends on different interactions

EtOH & Cannabis	EtOH & Nicotine	EtOH & Cannabis & Nicotine
Trend 1 is Lower.	Trend 1 is Higher.	Trend 1 is lower.
They do not show cognitive enhancement features of EtOH and show mild disorientation.	They are sensitive to the cognitive enhancement effects of nicotine.	The cognitive effects vary from time to time and form upside down curve with every dose.
Trend 2 was prominent & surface area and volume of orbitofrontal cortex was increased.	Trend 2 was seen in some cases and not seen in some cases. Largely dependent on individual characters.	Trend 2 was seen in chronic users only.
Trend 3 was not seen.	Trend 3 was seen additively pronounced.	Trend 3 was seen opposite.
Trend 4 was altered. Connectivity was increased rather than any dysfunction.	Trend 4 was seen.	Trend 4 was pronounced and more dysfunctions and imbalances were seen.
Trend 5 was seen partially on selective sites.	Trend5 was not seen.	Trend 5 was suppressed; Trend 4 & 6 were actively seen.
Trend 6 was not seen.	Trend 6 was seen.	Trend 6 was increased. More addictive behaviour was seen.
Trend 7 was not seen.	Trend 7 was reduced. (Nicotine reduces connectivity of the ECN and the DMN).	Trend 7 was seen.
Trend 8 was seen.	Trend 8 was not seen.	Trend 8 was not seen.
Trend 9 was seen.	Trend 9 was increased.	Trend 9 was seen occasionally.
Trend 10 was not seen.	Trend 10 was increased by some amount.	Trend 10 was seen partially.
Trend 11 was seen	Trend 11 was absent.	Trend 11 was seen

Trend 12 was absent.	Trend 12 was absent.	Trend 12 was absent.
Alcohol effect was diminished; Cannabis effect was increased. Complimentary Effects were seen on DDIs.	**Alcohol effect and nicotine effect was additive. Synergic effects were seen on DDIs.**	**Alcohol, Nicotine and Cannabis Effects were seen on peak during its administration. Nicotine effects faded the fastest. Alcohol & Cannabis effects persisted one after another (depending on their turn of exposure).**

However, we can use IPFs and NNDs to find accurate results for these drug interactions or conduct clinical trials for confirmatory analysis for the same. Our data suggests that these interactions can cause differential results when combined and when singularly in use.

To combat EtOH & cannabis interaction; a selective neurostimulator can be used for emergency situation. For fighting the withdrawal symptoms due to chronic use; a psychedelic substance therapy can be performed. Acetylcholine and guanine can be used specifically to manage other symptoms along with a digestive aid.

To combat EtOH & Nicotine interaction; specific muscle relaxant and sedative can be used; along with enzymes that can bring back the balance between serotonergic as well as dopaminergic pathways for chronic abusers. Glutamatergic transmission can be increased to combat the damage done by the DDI and induce positive reinforcement.

To combat EtOH, Nicotine & Cannabis DDIs; specific combination can be devised; to give relief to acute toxic effects and for long-term therapeutic use for combating withdrawal as well as correction of chronic damage / disharmony in brain chemicals.

6. Lysergic Acid Diethylamide (LSD) with EtOH

6.1 Toxicology of LSD (Lysergic Acid Diethylamide)

LSD was synthesized in 1938 and it is a psychoactive substance. It was used as an experimental drug for psychosis; since it had neurotransmitter altering properties which can be used for psychotherapeutic procedures. These therapies were named psycholytic and psychedelic therapy. From mid 1960s, it became illegal. Nearly 10,000 papers were written on scientific research over this substance. Its natural occurrence comes from parasitic rye fungus called Claviceps Purpurea. Albert Hoffman synthesized it derivative and accidentally discovered its psychological properties. Towards the end of 1960s, it was used for recreational and spiritual practices leading to the psychedelic movement. The protest was declined & the use of LSD was banned. **Despite of its successful and safe use as a psychotherapeutic adjunct and experimental tool** *[McGlothlin WH, Arnold DO. LSD revisited: A ten-year follow-up of medical LSD use. Arch Gen Psychiatry 1971; 24:35–49.], [Cohen S. Lysergic acid diethylamide: Side effects and complications. J Nerv Ment Dis 1960; 130:30–40.] [Malleson N. Acute adverse reactions to LSD in clinical and experimental use in the United Kingdom. Br J Psychiatry 1971; 118:229–230.]* **no legal clinical research has been done for the same**. Although there is no physical damage using LSD; some complications were found psychiatrically. However, these complications have declined through 1960-70s. Its composition is $C_{20}H_{25}ON_3$ with an indole system consisting a tetracyclic ring.

LSD significantly alters the state of consciousness due to its stimulation effect as euphoria with hypnagogic experiences and dreams. Few traumatic experiences called “Bad Trips” have also been experienced with mood swings. Psychomotor functions may get temporarily impaired but learning processes are unaffected. Memory was affected especially visual memory. [117]

There are various detection methods to detect LSD:

a) Ehrlich Test: Add few drops of sample with Ehrlich reagent. It is used to detect indoles, pyrroles & nitrogen compounds. The reagent consists of p-dimethylaminobenzaldehyde (DAMB) in 95% EtOH & hydrochloric acid as catalyst. A positive test shows blue to purple colour change.
b) Radioimmunoassay: This technique is also used to test for LSD. It measures specific antigen in the sample using radioactive techniques. For 300 mcg dosage; trends for 1.5-5.5 are seen.
c) LLE & HPLC: Liquid-Liquid Chromatography as well as High Performance Liquid Chromatography is also used to detect LSD from samples. The sample extraction of LSD takes place in a matrix of Methanol easily. It can be tested from blood, urine and hairs.
d) For quantitative analysis: One needs to extract the sample through 1% tartaric acid & chloroform X3; further basify the aqueous layer and extract again using chloroform. Recombine the extracts and centrifuge. Evaporate under nitrogen and reconstitute the solvent.

6.2 LSD & EtOH

LSD has high affinity towards serotonin (5-HT) receptors & with dopaminergic D1-5 receptors. The main mechanism is through 5-HT_{2A} receptors in cortical and subcortical regions. LSD is metabolized by CYP450 – CYP1A2, CYP3A4, CYP2C9, CYP2C19 & CYP2D6; primarily from 1A2 & 3A4.

When 2 drug interact with the same receptor, they compete for binding leading to pharmacological alterations. This is due to inhibition of CYP450 and this can also alter the circulating metabolites and influence the effect of drug. There is also an interaction with P-glycoprotein (P-gp) that is a membrane transporter to facilitate various drugs and its presence in livers, GI tract and kidneys; as well as the blood-brain barrier.

It acts on G-protein coupled receptor for serotonin and causes ligand binding through a conformation change in signaling via guanine nucleotide-binding proteins to modulate downstream effectors. It releases diacylglycerol (DAG) & inositol 1,4,5-triphosphate (IP3) by activating phospholipase C-beta. This promotes the release of Ca2+ ions from intracellular stores. *[PubMed:1330647, PubMed:18703043, PubMed:19057895, PubMed:21645528, PubMed:22300836,*

PubMed:35084960, PubMed:38552625, PubMed:28129538, PubMed:35084960, PubMed:18703043, PubMed:28129538, PubMed:35084960] It plays a role in regulation of behavior in response to anxiogenic situations by contraction of intestinal smooth muscles & arterial vasoconstriction.

It also mediates inhibitory neurotransmission via alpha proteins through signaling inhibition in adenylate cyclase activity and activates phosphatidylinositol calcium 2nd messenger system to regulate Ca2+ ion release. Beta-Arrestin family also mediates receptor desensitization and re-sensitization processes and regulates serotonin release as well as dopamine release. This regulates the level of dopamine in brain. [118]

6.3 DDIs Involving LSD & EtOH

DDIs involving the coadministration of EtOH and LSD have effects on the serotonergic as well as dopaminergic receptor systems. Hallucinations increase and there is more disorder than its therapeutic advantages. Few trends are listed below and those are further analyzed in the later table:

Table 12.1: Trends of EtOH & LSD

EtOH	LSD
Trend 1: Decreased connectivity mainly in areas of sensorial and motor control, as a result of the dFNC outcome and the alcohol use disorder.	**Trend 2:** LSD significantly increased connectivity between almost all RSN pairs. It altered perception of sound and time.
Trend 3: Produces dysfunctions in connectivity between the NAc and cortical areas, even the ones with increased activation during stimuli & response demanding tasks. This gives changes in the functional connectivity of cognitive, motor, and coordination.	**Trend 4:** LSD increased the strength towards sub-cortical as well as thalamic nuclei through inter-cluster connectivity. It reduced connectivity between thalamic and stratum. Overall, functional connectivity was increased.
Trend 5: The connectivity between the motor and a high visual processing area was reduced.	**Trend 6:** the connectivity between Striatum and Thalamus was reduced.
Trend 7: It is psychologically addictive due to the effect of dopaminergic pathways involved in it.	**Trend 8:** It is physically addictive but psychologically non-addictive. Withdrawal symptoms are seen on chronic use only.
Trend 9: Dopaminergic receptors are primary and serotonergic receptors are secondary.	**Trend 10:** Serotonergic receptors are primary and dopaminergic receptors are secondary.
Trend 11: It inhibits GABA receptors and inhibits connectivity in the brain.	**Trend 12:** It does not affect the GABA receptors.
Trend 13: Acetylcholine release is potentiated by nicotinic acetylcholine receptors.	**Trend 14:** Acetylcholine release is inhibited.

Table 12.2: Trends of EtOH & LSD

EtOH & LSD
Trend 1 & Trend 2 were seen simultaneously without any additive effect.
Trend 3 & Trend 4 were contradictory and LSD suppressed the effects of Trend 3.
Trend 5 & Trend 6 showed additive effects.
Trend 7 & Trend 8 were simultaneously killed by each other. Except chronic abuse withdrawal of each drug was managed by the other one.
Trent 9 & Trend 10 were contradictory and LSD managed to suppress the trend of EtOH (*except chronic abuse*).
Trend 11 was seen partially & Trend 12 was not seen.
Trent 13 & Trend 14 were contradictory and LSD suppressed the trend of EtOH.
The DDIs showed that it blocks or decreases the response to psychedelics but likely potentiates the 5-HT receptors for serotonin.
LSD significantly reduced the effects of EtOH; along with its withdrawal symptoms, without diminishing any effects of LSD. The DDI caused no synergistic effect but showed antagonistic effects over EtOH's mechanism.

To combat EtOH & LSD interaction, one should use GABA receptor modulators as required. The extent of EtOH & LSD intake allows us to measure the correct combinations for management of DDIs. Some neuro-stimulants can also be used to correct the impaired motor functions. Choline supplements can help chronic users. Special combinations need to be devised with few antioxidants to regain the functioning of the brain with minimum withdrawals. In order to study DDIs more precisely, one can study NNDs and IPFs to structure combat medications and treatments. One can also use clinical trials to establish practical utility for the same.

7. Outcome & Prospects

By studying various DDIs and its pharmacology and toxicology; one can help resolve the collective effects of these interactions. There can be acute interactions causing emergency challenges in resolving it and can also have chronic withdrawal effects on the other hand. The treatment for both is different. Acute toxicity can be resolved through immediate measures and counteracting dosage of certain receptor binders. On the other hand, long term treatment can be planned through inhibiting or activating mechanism of the affected sites in neural networks.

a) The study with interaction helps us to reduce the adverse effects of these interactions and allow specific treatment in bringing the individual back to its normal state of consciousness. Let's say EtOH and Cannabis interaction has occurred and cannabis has suppressed the effects of EtOH inhibiting G-Proteins in the body. This can be resolved by treating for the same. G-Proteins are of different classes: Class A, Class B, Class C, Class D, Class E & Class F. Among these, Class A, B, C & F sustain in the human body. Class A can be activated through adding Vitamin A and agonizing Rhodopsin;

Class B contains secretin which helps stabilize the pH of duodenum and can be regulated through either histamine release of maintaining the pH of the stomach via antacids and alkaline water. Class C contains glutamate receptors which can be activated through L-Glutathione & Class F contains Frizzled receptors which can regain its activity through influx of Vitamin D intake. The effect is adhesin inhibition is actually useful for our body and there is no need to fix it. Thus, maintaining these while the administration of cannabis (THC) shall reduce the effects of THC without down streaming the effects of CBD. A combination of these drugs shall combat the interactive effects of EtOH and Cannabis or Cannabis alone.

Prospects: Utilizing this, we can devise a formula that can aid in bringing back the state of consciousness of an individual affected with cannabis toxicity or the interaction of THC & EtOH. We just need **Retinol, L-Glutathione, Antacids, Vitamin D3, Magnesium, Zinc & Alkaline water** for treating THC effects on the body; if taken in precise order and under medical guidance. Certain conditions may also need a few extra supplements like choline additives, cognitive enhancers, etc. for chronic long term users to stabilize properly.

b) In the same manner, nicotine and EtOH interaction can also be studied to find a treatment for acute as well as chronic users. Nicotine acts on nicotinic acetylcholine receptors in hypothalamus and mediates hunger, food intake and energy expense. It enhances cognitive function. However, when taken with EtOH or consumed chronically, it enhances cognition and then reduces it dramatically. The spike of cognitive enhancement, followed by cognitive decline. It also suppresses appetite. However, withdrawal is not there; the symptoms of withdrawal develop over time. This is because of nicotine's ability to induce dopamine firing and its adverse effects. This can be treated by adjusting the Gerd-reflux. Thus, an over-the-counter medicine for gastrointestinal reflux diseases can be given to adjust the digestive system. **Rabeprazole & ondansetron can also be used if the individual has vomiting. In absence of vomiting, Rabeprazole with Domperidone can be useful**. Further, nicotine either closes or opens the ion channels by changing receptor function of nAChRs. It binds and opens the ion channels to depolarize the membrane. This causes desensitization. The re-polarization can happen through cholinergic anti-inflammatory response, mechanism of electrolytes (specifically **sodium & potassium**), enhancing sensory cognitive functions. This can be achieved through **choline supplements; electrolyte influx**. A treatment of antagonist and agonist simultaneously in morning and night shall help regain the functioning of the nAChRs within 25 days (also depending on the idiosyncrasy). This shall help the individual to regain the balance without suffering much with withdrawals and dopamine surges. The treatment should contain **ample probiotics and less fat** diet in order to balance the system faster. Certain supplements can help reduce other problems like – **magnesium, caffeine, fish oil, proteins, tyrosine, sunlight exposure and melatonin / vitamin D** treatment. For chronic users, exercise and **silymarin** can be additionally useful. **Vitamin Bs and C; with Biotin** should also be added in order to combat kidney disorders. Especially **Pantothenic Acid (***If not diabetic* & creatinine is normal**) & Folic Acid** shall help. For acute toxicity, ACT (Activated Charcoal) treatment should be done prior. For chronic users, B12 treatment should follow after the body has regained its order.

However, when we talk about simultaneous coadministration of cannabis, EtOH and Nicotine, the body shall respond individually. If the body responds to effects of THC more pronounce than nicotine effects, it shall show different symptoms and effects. If the body responds to EtOH more pronounce than THC effects, it shall show different symptoms. Hence, individual analysis is necessary when all the 3 toxins are co-administered.

c) When LSD is taken along with EtOH; we need to work on serotonin reuptake inhibition primarily. Anti-depressants need to be prescribed in order to reduce unwanted functional connectivity in the brain. Since, EtOH causes cognition boost and decline subsequently; the apparent co-administration with LSD will boost functional connectivity in few regions of the brain. At the time of decline; the graph will be peculiarly slower and acetylcholine receptors will be inhibited. Thus, we first treat the primary affecting receptors 5-HT, i.e. serotonin using anti-depressants. We can also use tricyclic anti-depressants if norepinephrine is also released in significant amount. This shall lower down anxiety and depressive effects of the brain. The specific action takes place of 5-HT2A receptors. The target medications for those receptors include:

1) **Trazodone (suitable for acute and chronic users)**
2) **Nefazodone (suitable for acute and chronic users)**
3) **Amitriptyline (to treat anxiety attacks post use)**
4) **Cyproheptadine (if GI tract is affected and liver damage is a possibility)**
5) **Quetiapine (for those affected psychotically)**
6) **Cyproheptadine**
7) **Methysergide (in case of migraine, headache and hangover symptoms)**
8) **Mirtazapine (For chronic users fighting insomnia & withdrawal)**
9) **Volinanserin (for sleep maintenance – yet in investigation trials)**
10) Ziprasidone (to manage agitation and panic attacks for withdrawal symptoms)
11) Olanzapine (to treat chronic users)
12) **Clozapine (for chronic users with high idiosyncrasy)**
13) Promazine (For acute users)
14) **Chlorpromazine (if vomiting and Gerd disorders are seen with nausea and irritation)**
15) Thioridazine (for chronic user affected psychologically)
16) **Propiomazine (if insomnia is observed)**
17) Minaprine (for users that are on the verge of being on the chronic side)
18) **Mesoridazine (THE BEST MEDICATION FOR INTERATION WITH EtOH)**
19) **Aripiprazole (for chronic users fighting with withdrawal symptoms physically & psychologically)**

20) Paliperidone (If only psychological events are observed)
21) **Clomipramine (When no physical but mental changes are seen; suitable for long term treatment)**
22) Sertinidole (to treat cases of hallucinations)
23) Mianserin (to treat anxiety attacks post use)
24) Iloperidone (to treat disorders of personality)
25) Asenapine (to treat psychological disorders)
26) Deramciclane (for individual with psychotic and anxiety issues)
27) Asenapine (For acute treatment)
28) **Molindone (For those facing personality changes)**
29) Loxapine (suitable for those with mild issues)
30) **Doxepin (those with insomnia, anxiety and mild disorientation)**
31) **Desipramine / Nortriptyline (acute and chronic users at initial stages)**
32) Fluspirilene (if psychosis is observed simultaneously)
33) Thiothixene (for managing psychological issues)
34) Lurasidone (For not- habitual users in their chronic withdrawal times)
35) **Amperozide (THE SECOND-BEST MEDICATION AS IT ALSO LOWERS DOPAMINERGIC ACTIVITY)**
36) **Brexpiprazole (those observing agitation and dementia with chronic use or acute toxicity)**
37) Cariprazine (for those observing episodes of psychosis)
38) ***Dosulepin* (*if other medication is not giving desired results*)**
39) ***Etoperidone (if parkinsons and motor controls are impaired)***
40) Blonanserin (for acute short-term treatment)
41) **Zotepine (for initial treatment and those affected first few times)**
42) Risperidone (for chronic users)
43) **Cyclobenzaprine (if muscular rigidity or spasms are seen)**
44) Pipotiazine (if there is no agitation and psychotic hallucinations)
45) **Metergoline (THIS IS ANOTHER BEST DRUG SINCE IT INHIBITS LACTIN PRODUCTION)**
46) Haloperidol (if dementia and agitation is seen simultaneously)

One cannot just give dopamine inhibitors as it will suppress other activities. Hence, it is important to fight LSD symptoms prior to EtOH symptoms in case of interaction observed. However, amny of the EtOH effects will automatically be suppressed by the LSD itself; since it is an antagonist for EtOH metabolism in the body. Hence, in case of its interaction; our primary treatment plan for emergency as well as long-term should be treating **the imbalance of serotonin, cortisol, prolactin, oxytocin and epinephrine** RESPECTIVELY.

8. Forensic Significance & Admissibility

Drug interactions have become very common these days because of the availability of different street drugs and recreational alcohol. Drugs, when combined with recreational alcohol, produce undesired effects. These effects may show synergistic effects of alcohol or multiplicative effects of the precipitant drug. Every-thing depends on the combination of objective and precipitant drugs. These interactions are tricky. Few are challenging to solve and it's important to bring the subject back to the normal state of consciousness.

There are 2 major things for which interactions need to be addressed forensically and medico-legally. The first one is to bring back subjects in their normal state of brain rhythm; get the state of awareness and mental stability back. In acute poisoning, it's important to address the problem quicker with newly devised solutions, antidotes and counteracting drugs. These cases of emergency are sometimes life threatening or sometimes the question of bringing the subjects into the state of awareness for getting clues and evidence. In drug encounters it is important to bring the subjects back into the state of mental clarity with combating pills. These pills need to be specifically made from special combinations of drug which act as an antagonist to the reactions caused by a specific drug interaction.

Secondly, talking about long-term withdrawal from the drug interaction; it is important in making the patient, victim or the individual free from the after-effects of the DDIs. Certain DDIs create long-term addiction and physiological as well as psychological errors. These need to be addressed with a long-term treatment plan. Hence, certain combinations are needed to nullify and reverse the potential damage caused by the interaction.

Thirdly, it is also needed to keep a check on malpractice of multi-speciality hospitals as they carry out patient retention through such DDIs. Patients are given drugs; whose interaction shall treat one disorder and create another one. Through this, the patient remains circling in the hospital with different doctors and gets manipulated. Such malpractices should stop as it is a physical as well as psychological abuse of a patient. The patient becomes a victim to a doctor's malpractice. Hence, forensic scientists must address this problem with a forensic interaction kit; that shall be useful for catching such DDIs and institutions. With such research, DDI Kits may be devised for the same.

Fourthly, it is also important to carry such DDIs-Detection kits which shall help traffic police to catch people intoxicated and driving under influence of multiple drugs. This shall also help police to find, verify and test criminals found in alleged regions. Similarly, quantification of unknown drugs shall also be performed through this and other combat pills should also be introduced for public as well as police safety.

9. Conclusion

Hence, we can treat DDIs of different compounds with different combination of drugs and allow it to stabilize the body to regain its normal functioning. This includes fixing the tripod of life, the neural network in the brain, the blood circulation and hormonal balance. This can be achieved by simply aiding the body with a combination of drugs and supplements to counteract the effects of the interaction taken inside it.

For Cannabis alone or with EtOH; a simultaneous administration of Retinol, with an antacid with alkaline water and subsequent treatment with Magnesium, Vitamin D3 and

Zinc Sulfate shall allow the G-proteins & the receptor sites to simultaneously align back to its normal state. Further, adding L-Glutathione and electrolytes shall repair the deficiency caused due to rapid influx of nutrients and impaired metabolism. This treatment with conditional tendency shall aid in reducing the harmful effects of THC without altering the effects of CBD on the body. For chronic users; Ginseng, L-arginine, L-lysine and certain extra micronutrients are required. This is because the quick metabolism due to cannabis use drains the micronutrients in your body.

For nicotine and DDIs involving nicotine as EtOH; one is advised to follow a treatment starting by regulating gastrointestinal reflux & aligning the cognitive functioning. This can be done through Rabeprazole along with ondansetron or domperidone (as required). Cognitive function shall be aligned with long term treatment of agonist and antagonist simultaneously at different time of the day. Along with this, choline supplements and electrolytic balance must be maintained – specially of sodium and potassium. With some diet regulation and influx of magnesium, vitamin D, B, C and liver tonics; the person shall regulate the interactive effects of EtOH and nicotine. For acute effects; ACT treatment is advised prior to the main treatment plan & for chronic effects; B12 treatment is advised post to the main treatment.

For LSD & EtOH interactions we need to suppress only few effects of LSD; since the rest shall be negated by the co-administration of EtOH itself. These includes targeting 5-HT receptors, cortisol, prolactin, epinephrine & oxytocin. Mesoridazine, Amperozide & Metergoline are our primary treatment plan for those affected with the DDIs and further complications shall need other medications along with it mentioned in point 7. Observing ABCs of the body and liver, endocrine system; we can further find relevant combination for individual use.

Thus, for every DDIs; we can devise counteracting combat medications for fighting acute effects as well as chronic effects after long-term use. This can help in regaining the state of consciousness in emergency situations and also for fighting withdrawals symptoms physically as well as psychologically.

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