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REVIEW ARTICLE

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Clinically important and pharmacologically relevant drug interactions with alcohol

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ABSTRACT

Background: Alcohol is a psychoactive substance and this review is aimed to identify the pharmacokinetic and pharmacodynamic drug interactions of alcohol.
Methods: The databases such as Medline/PMC/PubMed, Google Scholar, Science Direct, Cochrane Library, Directory of open access journals, and reference lists were searched to identify related articles.
Results: Major pharmacokinetic drug interactions of alcohol are mediated by the drugs inhibiting aldehyde dehydrogenase (ALDH) enzyme and the pharmacodynamic drug interactions by the drugs potentiating central nervous system (CNS) depressant activities.
Conclusion: The drugs inhibiting ALDH, especially ALDH2 enzyme, can increase the risk of acetaldehyde associated adverse effects or disulfiram-like reactions such as facial flushing, nausea, and vomiting in alcoholics. The drugs, such as cephalosporins, metronidazole, sulphonamides, isoniazid, some antifungals, and sulfonylureas, may elevate the risk of disulfiram-like reactions while consuming alcohol concomitantly. Alcohol may potentiate the CNS depressant activity of drugs such as benzodiazepines, barbiturates, phenothiazines, opioid analgesics, and antihistamines. The risk of orthostatic hypotension might be elevated by the concomitant use of nitrates and alcohol and the risk of upper gastrointestinal bleeding is high among alcoholics taking nonsteroidal anti-inflammatory drugs. The prescribers and the pharmacists are required to be aware of medications interacting with alcohol to prevent adverse outcomes.

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Introduction

Alcohol is a psychoactive substance and its chronic use can lead to dependence. Alcohol use is associated with various health hazards including alcohol use disorders (AUD), infectious diseases, cardiovascular disease, cancer, diabetes, liver and pancreas disease, and others [1]. The incidence of AUD is higher among the public of developed countries due to cheaper price, easy availability, and promotion of alcohol [2]. AUD is a common psychiatric disorder and it is linked to increased number of episodes of depression, insomnia, severe anxiety, suicidal thoughts, and the abuse of other drugs [3]. Alcohol consumption was associated with 5.9% of all global deaths and 5.1% of global burden of disease and injury, in 2012 [4]. In 2015, it was estimated globally that 18.4% of adult population were heavy alcohol drinkers and 63.5 million were regarded as alcohol dependence cases [5].

Drug interaction is defined as the disruption of effects of one drug by the comedications or concurrently used supplements, tobacco smoke or alcohol. A drug interaction resulting in decreased therapeutic efficacy or increased rate of adverse effects is known as "Adverse drug interaction" [6]. It has been estimated that drug interactions accounted for 6%–30% of all side effects [7]. Concurrent use of multiple medications increases the risk of drug interactions [8]. The pharmacokinetic or pharmacodynamic profile of an object drug could be altered by the addition of precipitant drugs [9].

The prevalence of medication use is higher among people consuming alcohol. A study from

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Spain found that almost half of the participants of the study consume alcohol concomitantly with medications [10]. Concomitant use of medications and alcohol consumption can result in adverse drug interactions leading to enhanced risk of side effects. The administration of alcohol interacting drugs is common among the consumers of alcohol. The Pennsylvania Pharmaceutical Assistance Contract for the Elderly program has estimated that 19% of alcohol users had administered drugs having the potential of interaction with alcohol negatively [11]. Another study which surveyed alcohol users found that approximately 42% of current drinkers were using high-risk medications which could interact adversely with alcohol [12].

Methods

The literature review was done searching databases such as Medline/PMC/PubMed, Google Scholar, Science Direct, Cochrane Library, Directory of open access journals (DOAJ), and reference lists.

Results and Discussion

Alcohol can interact pharmacokinetically or pharmacodynamically with the concomitant prescription or over-the-counter medications.

Pharmacokinetic drug interactions

The pharmacokinetic aspects of drugs like absorption, distribution, metabolism, and excretion could be modified by the alcohol consumption. Some of the orally ingested alcohol undergoes the first-pass metabolism by alcohol dehydrogenase (ADH) enzyme in the stomach. The blood alcohol levels are elevated by decreased first-pass metabolism of alcohol induced by the drugs like H2 receptor blockers (Cimetidine or ranitidine) or aspirin blocking stomach ADH activity [13] and the drugs including metoclopramide, cisapride, or erythromycin which accelerate gastric emptying [14].

Major portion of alcohol is metabolized in the liver mainly by ADH and CYP2E1 enzymes which can oxidize alcohol to form acetaldehyde which is oxidized further by aldehyde dehydrogenase (ALDH) enzyme [15]. The adverse effects of alcohol, such as flushing, nausea, vomiting, and others, are induced by acetaldehyde [16]. Hence, the drugs inhibiting ALDH, especially ALDH2 enzyme, can increase acetaldehyde associated adverse effects such as facial flushing, nausea, and vomiting [17].

Interactions increasing the risk of disulfiram-like reactions

Disulfiram is an inhibitor of ALDH enzyme, which is essential to convert acetaldehyde into acetate resulting in accumulation of acetaldehyde causing disulfiram-ethanol reaction characterized by tachycardia, flushing, nausea, and vomiting [18]. Disulfiram is useful to treat alcohol dependence by discouraging alcohol drinking [19].

The drugs inhibiting ALDH enzyme may elevate the risk of disulfiram-like reactions while consuming alcohol concomitantly (Table 1).

Antimicrobials

Antimicrobial drugs, such as cephalosporins, metronidazole, sulphonamides, isoniazid, and some antifungals, may elevate the risk of disulfiram-like reactions while consuming alcohol concomitantly.

Cephalosporins. Cephalosporins are β-lactam antibiotics and the cephalosporins such as cefotetan, cefoperazone, cefamandole, and moxalactam induce cephalosporin-induced disulfiram-like reaction (CIDLR) characterized by facial flushing, nausea or vomiting, angioedema, hypotension, shock, or death [20]. Cephalosporins may elevate the acetaldehyde concentrations by inhibiting ALDH enzyme [21]. Ceftriaxone also induced CIDLR reaction in a pediatric patient taking alcohol-containing medication [22]. Administration of cephalosporin should be avoided in alcoholics and the clinicians should advise the patients to avoid the consumption of alcohol or alcohol-containing medications while taking cephalosporin antibiotics [20].

Metronidazole. Metronidazole is an antibacterial and antiparasitic drug and the concomitant use of metronidazole and alcohol may result in a disulfiram-like reaction such as abdominal cramps, nausea, vomiting, headaches, and flushing or sudden death [23].

Sulphonamides. Cotrimoxazole is the combination of sulfamethoxazole and trimethoprim and is used to treat bacterial infections. The patients receiving cotrimoxazole may develop disulfiram-like reaction if they consume alcohol [24].

Antifungals. Griseofulvin is an antifungal drug and the administration of griseofulvin in an alcoholic patient may induce disulfiram-like reaction such as flushing, severe nausea, vomiting, diarrhea, and paresthesias in all extremities [25]. The patients consuming alcohol while taking ketoconazole may suffer a disulfiram-like reaction [26]. It is recommended to advise the patients to avoid

Table 1. Drug interactions of alcohol resulting in elevated risk of disulfiram-like reactions.

Interacting drugs	Mechanism of interaction	Comments
Cephalosporins	Inhibition of ALDH enzyme by Cephalosporins [21].	It is recommended to advice the patients to avoid alcohol consumption while taking Cephalosporins. Clinicians should advise the patients to avoid the consumption of alcohol or alcohol-containing medications while taking cephalosporin antibiotics [20].
Metronidazole	Inhibition of ALDH enzyme by Metronidazole [23].	It is recommended to advice the patients to avoid alcohol consumption while taking Metronidazole.
Sulphonamides	The patients receiving cotrimoxazole may develop disulfiram-like reaction, if they consume alcohol [24].	It is recommended to advice the patients to avoid alcohol consumption while taking Cotrimoxazole.
Antifungals	The patients consuming alcohol while taking Griseofulvin [25] or Ketoconazole [26] may suffer a disulfiram-like reaction.	It is recommended to advice the patients to avoid alcohol consumption while taking such antifungal therapy.
Isoniazid	The patients using Isoniazid may develop disulfiram-like reaction when they consume alcohol [27].	It is recommended to advice the patients to avoid alcohol consumption while taking such Isoniazid.
Sulfonylureas	Concomitant use of alcohol and longer acting, first generation sulfonylureas such as chlorpropamide and tolbutamide may result in disulfiram-like reaction [29].	It is recommended to advice the patients to avoid alcohol consumption while taking first generation sulfonylureas.

alcohol consumption while taking such antifungal therapy.

Isoniazid. Isoniazid is an antitubercular drug and the patients using isoniazid may develop disulfiram-like reaction including palpitations, skin flushing, headache, nausea, and vomiting when they consume alcohol [27].

Sulfonylureas. Sulfonylureas might be used as second-line antidiabetic drugs to treat patients with type 2 diabetes [28]. Concomitant use of alcohol and longer acting, first-generation sulfonylureas such as chlorpropamide and tolbutamide may result in disulfiram-like reaction [29].

Interactions increasing the risk of hepatotoxicity

The patients consuming alcohol chronically may develop hepatotoxicity due to the administration of paracetamol (Table 2).

Paracetamol. Paracetamol or acetaminophen is an antipyretic drug that helps to reduce the elevated body temperature. The risk of hepatotoxicity might be elevated due to the administration of paracetamol in patients consuming alcohol regularly [30]. The capacity for the synthesis of glutathione that is essential to detoxify *N*-acetyl-*p*-benzoquinone imine (NAPQI), the toxic metabolite of paracetamol, might be decreased in chronic alcoholics [31].

Abrupt cessation of alcohol consumption may increase the risk of paracetamol-induced liver damage as the chronic alcoholics may be vulnerable to unopposed CYP2E1-mediated metabolism of paracetamol [31]. The alcoholics should be advised to not to exceed the maximum daily dose (4 g) of paracetamol to avoid hepatotoxicity.

Pharmacodynamic drug interactions

Alcohol suppresses the central nervous system (CNS) by increasing the function of Gamma-aminobutyric acid receptors resulting in hyperpolarization of cells through the influx of chloride ions [32]. Hence, alcohol may potentiate the CNS depressant activity of drugs such as benzodiazepines, barbiturates, phenothiazines, opioid analgesics, and antihistamines.

Interactions increasing the risk of CNS depression

The drugs inducing CNS depression may enhance further risk of CNS depression while consuming alcohol concomitantly (Table 3).

Benzodiazepines. Benzodiazepines include drugs like alprazolam, diazepam, lorazepam,

Table 2. Drug interactions of alcohol resulting in elevated risk of hepatotoxicity.

Interacting drugs	Mechanism of interaction	Comments
Paracetamol	The capacity for the synthesis of glutathione that is essential to detoxify NAPQI, the toxic metabolite of paracetamol, might be decreased in chronic alcoholics [31].	The Alcoholics should be advised to not to exceed the maximum daily dose (4 g) of paracetamol to avoid hepatotoxicity.

Table 3. Drug interactions of alcohol resulting in elevated risk of CNS depression.

Interacting drugs	Mechanism of interaction	Comments
Benzodiazepines	Concomitant use of Benzodiazepines and Alcohol result in excessive impairment of motor skills, sedation and decreased driving skills due to their additive CNS depressant activities [34].	The patients taking Benzodiazepines could be advised to avoid consuming alcohol to prevent complications.
Barbiturates	The risk of sedation is enhanced in patients taking barbiturates and consuming alcohol together [11].	The patients need to be educated regarding the complications associated with the combination of barbiturates and alcohol.
Phenothiazines	The use of Phenothiazines in alcoholics may enhance the risk of respiratory depression through additive CNS depressant activities [38].	The patients taking Phenothiazines could be advised to avoid consuming alcohol to prevent complications.
Opioid analgesics	Concomitant administration of opioid analgesics and alcohol may result in elevated risk of respiratory depression due to additive CNS depressant effects [41].	The patients taking Opioid analgesics could be advised to avoid consuming alcohol to prevent complications.
Antihistamines	The risk of sedation and dizziness might be enhanced in patients taking first generation antihistamines and Alcohol together, due to additive CNS effects [43].	The patients need to be educated regarding the complications associated with the combination of First generation antihistamines and alcohol.

midazolam, and many others. They are prescribed to treat anxiety, insomnia, muscle spasm, and seizures [33].

Concomitant use of benzodiazepines and alcohol result in excessive impairment of motor skills, sedation, and decreased driving skills due to their additive CNS depressant activities [34]. The patients taking benzodiazepines be advised to avoid consuming alcohol to prevent complications.

Barbiturates. Barbiturates are therapeutically used as sedatives or hypnotics, antiepileptic agents, and intravenous anesthetics. Nowadays, barbiturates are not used widely due to their adverse effects like sedation, addiction, and exacerbation of seizures upon withdrawal. However, the barbiturate like phenobarbital is still in use as an anticonvulsant drug [35].

The risk of sedation is enhanced in patients taking barbiturates and consuming alcohol together [11]. The patients need to be educated regarding the complications associated with the combination of barbiturates and alcohol.

Phenothiazines. Phenothiazines are synthetic antipsychotic drugs, which include chlorpromazine, promethazine, prochlorperazine, thioridazine, and others [36]. Phenothiazines are used mainly as neuroleptic, antihistaminic, and antiemetic agents [37].

The use of phenothiazines in alcoholics may enhance the risk of respiratory depression through additive CNS depressant activities [38].

Opioid analgesics. Opioid analgesics are narcotic pain relievers and they are indicated in the treatment of moderate to severe pain [39]. Opioid analgesics include morphine, hydromorphone, fentanyl, meperidine, oxycodone, and others [40]. Concomitant administration of opioid analgesics and alcohol may result in elevated risk of respiratory depression due to additive CNS depressant effects [41].

Antihistamines. Antihistamines are classified as first-generation antihistamines, which include chlorpheniramine, brompheniramine, diphenhydramine, triprolidine, hydroxyzine, and clemastine and second-generation antihistamines including loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, and ebastine. First-generation antihistamines are capable of producing CNS effects due to their ability to penetrate blood–brain barrier as they are highly lipophilic [42]. The risk of sedation and dizziness might be enhanced in patients taking first-generation antihistamines and alcohol together, due to additive CNS effects [43].

Other pharmacodynamic interactions

Nitrates

Nitrates including nitroglycerin and isosorbide are indicated for the treatment of angina pectoris and hypertension. The risk of orthostatic hypotension might be elevated by the concomitant use of nitrates and alcohol [44].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are therapeutically used as pain relievers and anti-inflammatory agents to treat osteoarthritis, rheumatoid arthritis, and other conditions [45]. The risk of upper gastrointestinal bleeding (UGIB) is elevated with the alcohol consumption [46] and the use of NSAIDs such as aspirin and ibuprofen found also be associated with UGIB [47]. The risk of UGIB is high among alcoholics taking NSAIDs and the heavy drinkers should be advised to avoid using NSAIDs while consuming alcohol [48].

Conclusion

Alcohol consumption is common among the global population and certain drugs appeared to interact with alcohol pharmacokinetically and pharmacodynamically. The drugs inhibiting ALDH, especially ALDH2 enzyme, can increase the risk of acetaldehyde associated adverse effects or disulfiram-like reactions such as facial flushing, nausea, and vomiting in alcoholics. The drugs such as cephalosporins, metronidazole, sulphonamides, isoniazid, some antifungals, and sulfonylureas may elevate the risk of disulfiram-like reactions while consuming alcohol concomitantly. The patients consuming alcohol chronically may develop hepatotoxicity due to the administration of paracetamol.

Alcohol may potentiate the CNS depressant activity of drugs such as benzodiazepines, barbiturates, phenothiazines, opioid analgesics, and antihistamines. The risk of orthostatic hypotension might be elevated by the concomitant use of nitrates and alcohol and the risk of UGIB is high among alcoholics taking NSAIDs.

The prescribers and the pharmacists are required to be aware of medications interacting with alcohol to prevent adverse outcomes.

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Conflicts of interest

The author declared that he has no conflicts of interest.

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