Ethanol toxicity

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3 Categories of Alcohols

1. Monohydroxy alcohols : They have only one hydroxyl (OH) group, e.g. ethanol, methanol, isopropanol, etc.

2. Dihydroxy alcohols : They possess two hydroxyl groups and are referred to as glycols, e.g. ethylene glycol, propylene glycol, etc.

3. Trihydroxy alcohols : They are not really alcohols, but only derivatives, e.g. propane derivative glycerol or glycerine.

Ethanol

Synonyms

Ethyl alcohol; Grain alcohol.

Physical Appearance

Clear liquid with a faint fruity odour, and sweetish burning taste.

It is both water soluble and lipid soluble

Sources

- Fermentation of sugar, cellulose, or starch
- Synthetic production from ethylene (method used in the production of beverage alcohol)
- Enzymatic hydrolysis of cellulose
- Obtained by the reaction of methanol with synthesis gas at 185°C and under pressure
- Anhydrous ethanol is manufactured by azeotropic distillation.
- Beverage ethanol is produced by fermentation of a sugar with yeast.

- The ethanol content of various alcoholic beverages is expressed by volume percent or by proof

- Apart from ethanol however, these beverages also contain several congeners to varying extent, e.g. low molecular weight alcohols such as methanol and butanol, as well as aldehydes, esters, phenols, tannins, and heavy metals (lead, cobalt, iron, etc.).

- Vodka is the purest form and contains no congeners. It is virtually odourless. White rum is also relatively pure.

Ethanol Content in Alcoholic Beverages

Beverage	*Ethanol Content (percentage by volume)*
Light Beer (Lager and Pilsener)	4 to 6
Heavy Beer (Ale and Stout)	6 to 8
Natural Wine (Cider)	2 to 3
Fortified Wine (Sherry and Port)	10 to 20
Whisky, Gin, and Brandy	40 to 45
Rum	40 to 50
Liqueurs (e.g. Cognac, Crème de menthe, Schnapps, etc.)	17 to 50

Uses

- Beverage—Popular alcoholic beverages include beer, wine, whisky, gin, brandy, rum, and vodka
- Solvent for after-shaves, colognes, mouthwashes, and perfumes.

Medicinal Uses

- Several antihistaminic, decongestant, multivitamin, and cough syrups contain varying percentage of alcohol
- Ethanol has been popular in the past as an antiseptic
- Ethanol sponging is an effective remedy for hyperthermia.

Uses

Medicinal Uses

- Injection of dehydrated alcohol (absolute alcohol) in close proximity of nerves or sympathetic ganglia is said to be effective for the relief of long lasting pain in conditions such as trigeminal neuralgia.
- Antidote for methanol and ethylene glycol
- Preservative
- Ethanol is used to extract nucleic acids from whole tissue or tissue culture in virtually all biotechnology processes.

Usual Fatal Dose

- One pint (approximately 550 ml) or quart (two pints or approximately 1100 ml) of a strong distilled spirit such as whisky taken in a short span of time can be lethal.

- The usual fatal dose corresponds to approximately 6 grams of ethanol/Kg body weight (adult); 3 gm/Kg (child).

- In terms of blood alcohol, a level in excess of 400 to 500 mg/100 ml is usually considered to be lethal.

Toxicokinetics

- Ethanol is toxic by oral, inhalation, subcutaneous, intravenous, intra-arterial, intraperitoneal, and dermal routes.
- Following oral administration, ethanol is rapidly absorbed from the stomach (20%) and small intestine (80%).
- Maximum or peak alcohol concentration in blood is reached in 30 to 90 minutes following the last drink.
- Vapourised ethanol can be rapidly absorbed by inhalation leading to intoxication

Toxicokinetics

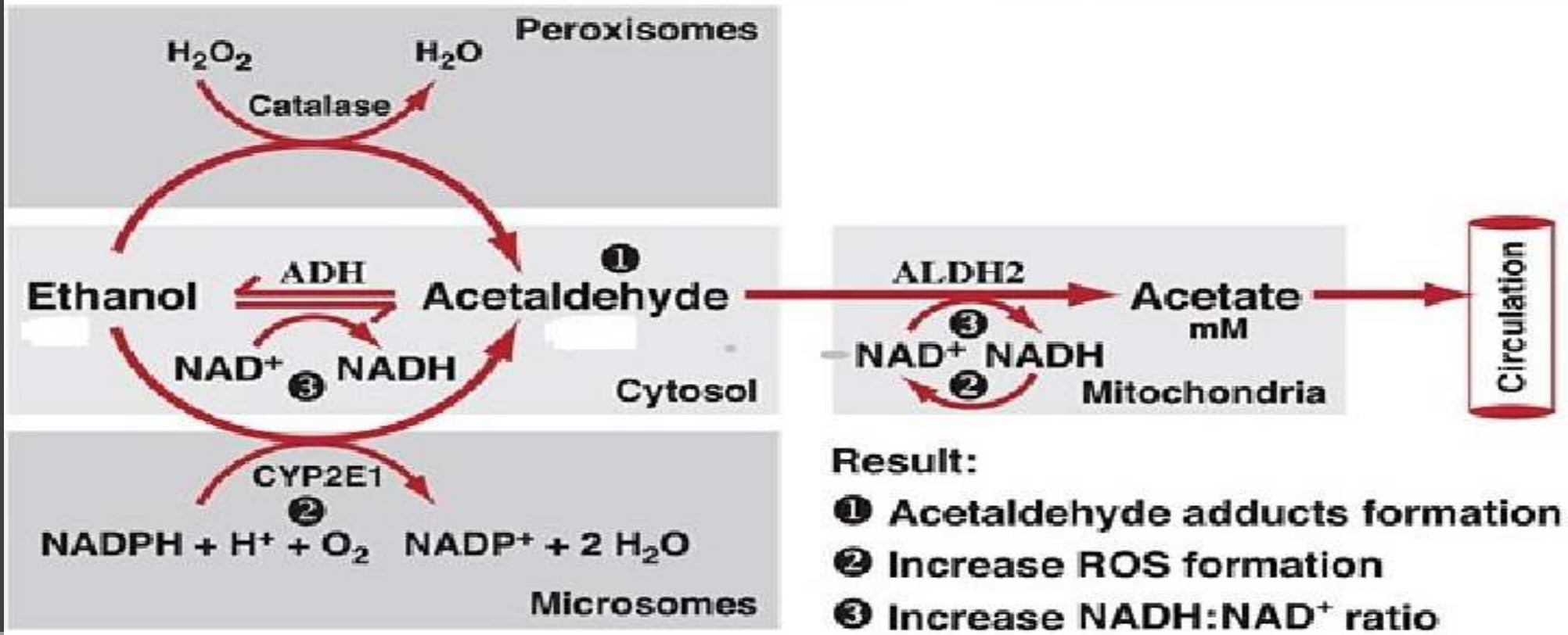
- Following an equivalent dose of ethanol, women achieve a higher blood alcohol level than do men as a result of decreased gastric alcohol dehydrogenase activity.

- Liver damage occurs after consumption of relatively smaller quantities of alcohol in women as compared to men.

Toxicokinetics
Metabolism and Mechanism

- Metabolism of alcohol is accomplished through 3 pathways in the liver
  1. **Alcohol dehydrogenase pathway (in the cell cytosol)**
  2. **Microsomal ethanol oxidising system (MEOS, located on the endoplasmic reticulum)**
  3. **Peroxidase-catalase system (in the hepatic peroxisomes**).

Pathways



Result:

❶ Acetaldehyde adducts formation

❷ Increase ROS formation

❸ Increase NADH:NAD^+ ratio

Toxicokinetics

1. **Alcohol dehydrogenase pathway (in the cell cytosol)**

The ratio of NAD to NADH (redox potential) is therefore dramatically altered which contributes to the development of metabolic abnormalities such as alcoholic ketoacidosis, impaired gluconeogenesis, and alterations in lipid metabolism.

2. **Microsomal ethanol oxidising system (MEOS)-**

After chronic ethanol consumption, microsomal ethanol-oxidizing system (MEOS) activity increases with an associated rise in microsomal cytochrome P-450 , especially CYP2E1

Half-lives of several drugs are shortened in chronic alcoholics because of accelerated metabolism, resulting in drug tolerance e.g. phenytoin, methadone, tolbutamide, isoniazid, warfarin, etc. There are also indications that chronic ethanol abuse may potentiate paracetamol hepatotoxicity.

Toxicokinetics

2. **Microsomal ethanol oxidising system (MEOS)-**

- **Conversion of hepatotoxic agents to toxic metabolites increases**

- **Significant release of free radicals which, in turn, diminishes reduced glutathione (GSH) and other defense systems against oxidative stress**

Toxicokinetics

3. **Peroxidase-catalase system:**

A tertiary pathway for the oxidation of ethanol is carried out by catalase, a peroxisomal enzyme that also catalyzes the removal of hydrogen peroxide (H_2O_2).

Although catalase has a much smaller role in alcohol oxidation than ADH or CYP2E1, it is important in cerebral function as inhibiting catalase has been found to decrease the rate of oxidation of ethanol to acetaldehyde by the brain

The ratio of NAD to NADH (redox potential) is therefore dramatically altered which contributes to the development of

Alcoholic ketoacidosis,

Impaired gluconeogenesis

Alterations in lipid metabolism.

Pathogenesis

- Genetic factors (ADH2 ,ALDH2)
- Toxic metabolites of ALDH (adducts)
- Free radicals and oxidative stress (ROS)
- Role of immune system
- Hypermetabolic state of hepatocyte
- Cytokines (TNF ,TGF)
- Malnutrition

Acetaldehyde generated from alcohol catabolism inducing lipid peroxidation and acetaldehyde-protein adduct formation.

Induction of cytochrome P-450 generating reactive oxygen species (ROS) and augmenting catabolism of other drugs to form potentially toxic metabolites.

Impaired metabolism of methionine resulting in reduced glutathione levels that are normally protective for oxidative injury.

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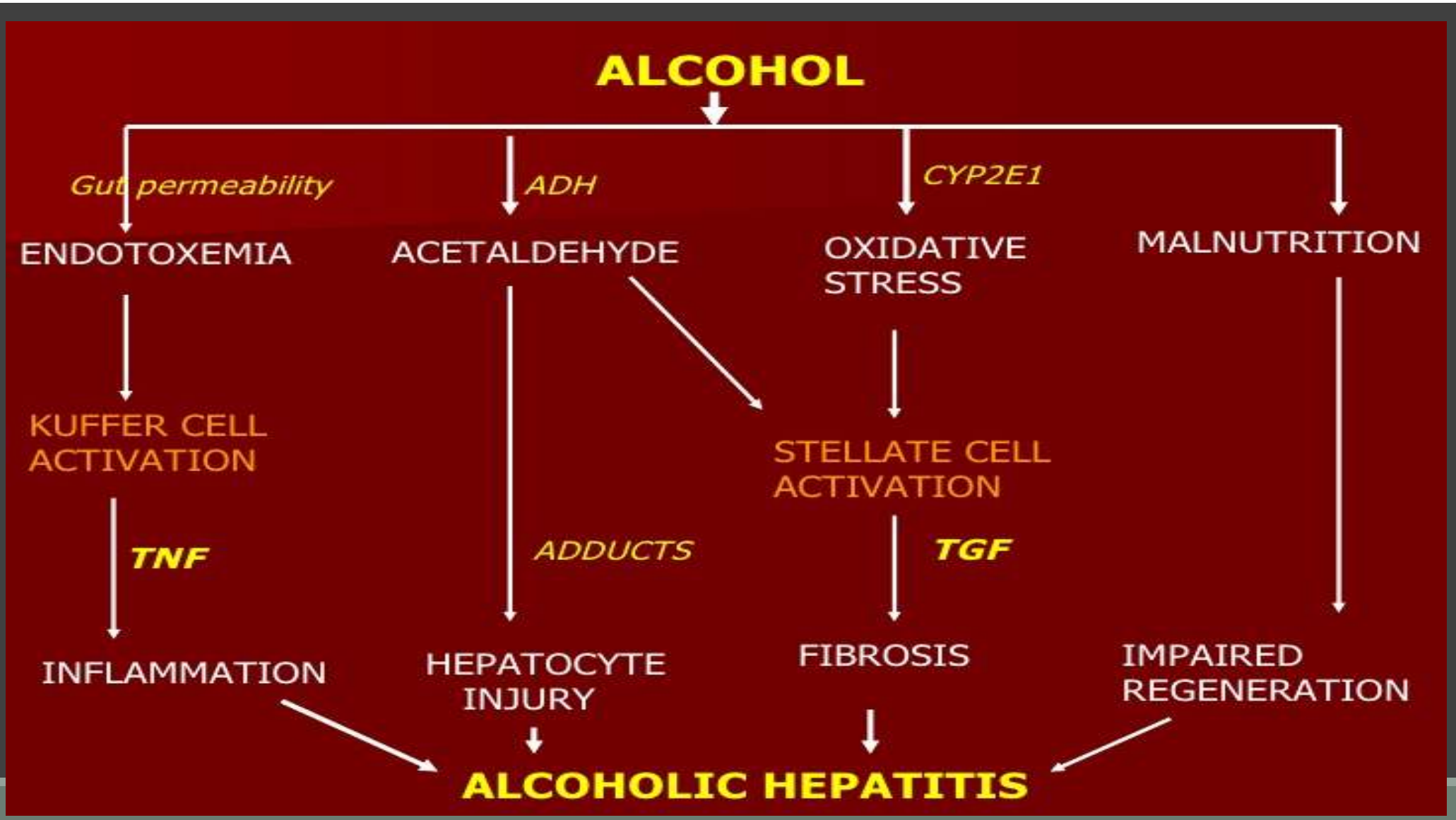
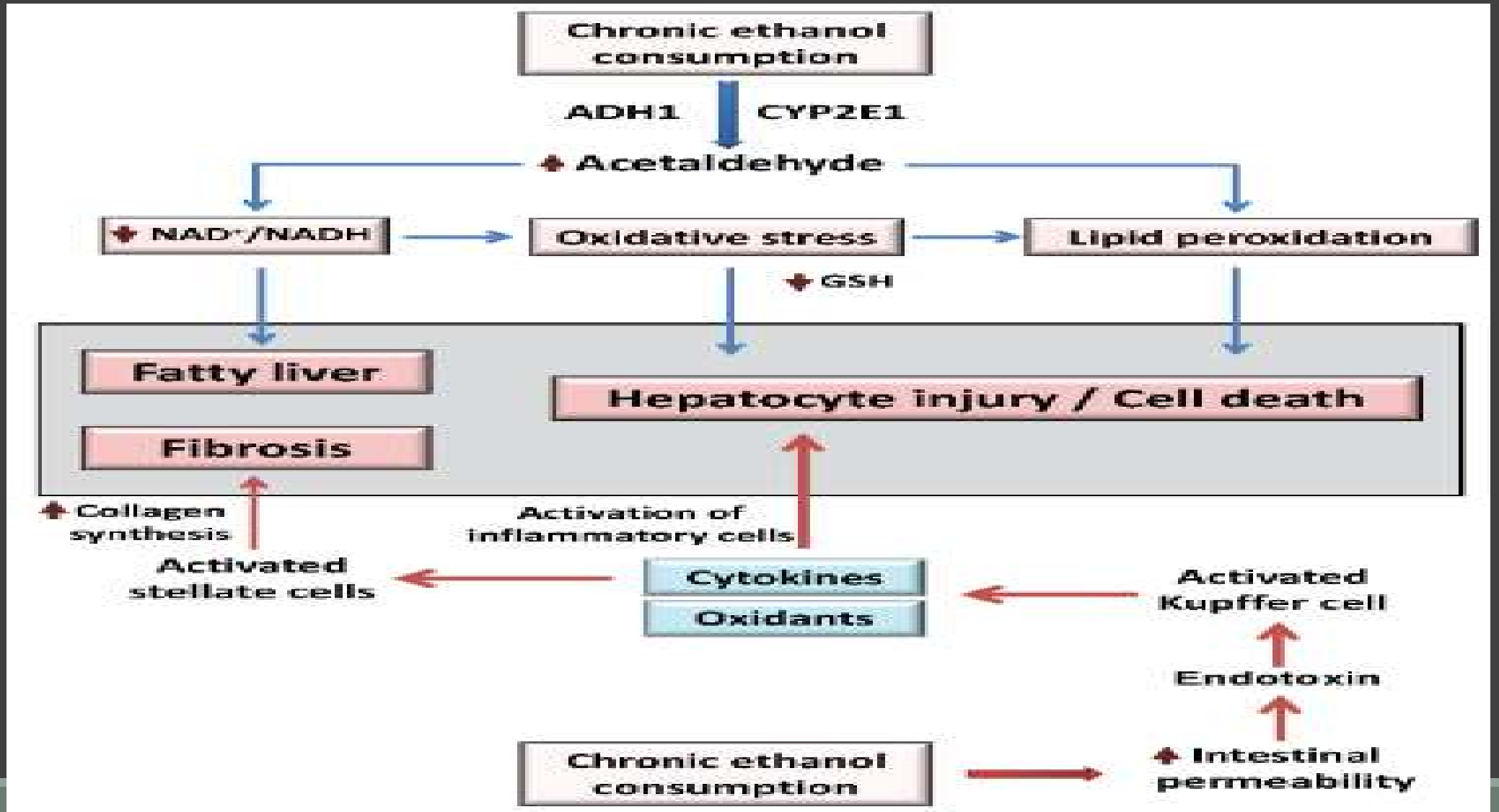
Alcohol becoming a caloric food source, resulting in malnutrition and vitamin deficiency.

Alcohol-mediated release of bacterial endotoxin from the gastrointestinal tract causing increasing inflammatory responses

- Ethanol acts by enhancing gamaaminobutyric acid (GABA)-nergic function through interaction with GABA A receptors and associated chloride ion channels.

- Studies demonstrate that in the acute form of ethanol use, NMDA receptor function is inhibited, while chronic ethanol use results in up-regulation of NMDA receptors


ALCOHOL
Gut permeability
ADH
CYP2E1
ENDOTOXEMIA
ACETALDEHYDE
OXIDATIVE STRESS
MALNUTRITION
KUFFER CELL ACTIVATION
STELLATE CELL ACTIVATION
TNF
ADDUCTS
TGF
INFLAMMATION
HEPATOCYTE INJURY
FIBROSIS
IMPAIRED REGENERATION
ALCOHOLIC HEPATITIS


Chronic ethanol consumption
ADH1
CYP2E1
Acetaldehyde
NAD+/NADH
Oxidative stress
Lipid peroxidation
GSH
Fatty liver
Hepatocyte injury / Cell death
Fibrosis
Collagen synthesis
Activation of inflammatory cells
Activated stellate cells
Cytokines
Oxidants
Activated Kupffer cell
Endotoxin
Chronic ethanol consumption
Intestinal permeability

- In adults, the average rate of ethanol metabolism is 100 to 125 mg/kg/hr in occasional drinkers, and upto 175 mg/kg/hr in habitual drinkers.
- The blood alcohol level generally falls at a rate of 15 to 20 mg/100 ml/hr.
- This may be higher (upto 30 mg/100 ml/hr) in chronic alcoholics.

Toxicokinetics-Excretion

- More than 90% of ethanol ingested is metabolised in the body, and only 5 to 10% is excreted unchanged by the kidneys, lungs, and sweat

- Excretion of ethanol by the lungs obeys ***Henry's Law*** : *the ratio between the concentration of ethanol in the alveolar air and the blood is constant.*

- This alveolar air/blood constant (1 : 2100) forms the basis for reliably estimating blood alcohol concentration by breath analysis.

Diagnosis

- Bedside test—Place 1 ml of unknown solution plus 1 ml of acetic acid and 1 drop of H_2SO_4 in a test tube and heat gently for 1 minute. A characteristic, strong fruity odour (due to ethyl acetate) is positive for ethanol.

- Blood alcohol level—The blood alcohol concentration (BAC) estimated by immunoassay or gas chromatography
- Determine serum electrolytes, glucose, ethanol. Hypoglycaemia, hypokalaemia, and metabolic acidosis (lactic or ketoacidosis) may occur.
- BUN, creatinine, liver transaminases, and CPK may be useful in identifying secondary effects, such as hepatotoxicity (chronic ethanol use), respiratory depression, or rhabdomyolysis (if seizures are present).
- Osmolality: Serum or plasma osmolality allows estimation of blood ethanol level. A blood ethanol concentration of 150 mg% (32.5 mmol/L) increases osmolality by 21.6 milliosmoles/kg water. The following equation is said to give good correlation with blood ethanol concentration: BAL (g/L) = osmolal gap/27
- Qualitative determination of urinary ethanol is commonly included in a toxicology screen. However, urinary ethanol levels may be falsely elevated in patients with diabetes.

Acute Alcohol Poisoning (Intoxication, Inebriation)

Blood Alcohol Concentration (mg/100 ml)	*Stage of Intoxication*	*Clinical Features*
0 – 50	Sobriety	Near normal behaviour
50 – 100	Euphoria	Feeling of well being, sociability, talkativeness, increased self confidence, decreased inhibitions,fine movements affected
100 – 150	Excitement	Emotional instability, impairment of memory and comprehension, increased reaction time, mild ataxia
150 – 200	Confusion	Disorientation, confusion, vertigo, diplopia, ataxia, slurred speech, staggering gait
200 – 300	Stupor	General inertia, diminished response to stimuli, inability to stand or walk, vomiting
300 – 500	Coma	Unconsciousness, abolished reflexes, subnormal temperature, incontinence of urine and faeces, respiratory compromise
> 500	Death	Death due to respiratory failure

Acute poisoning treatment

Airway protection and ventilatory support.

Activated charcoal is not useful

Stomach wash.

Thiamine 100 mg IV

Intravenous fluids.

Dextrose

Recommended when bedside glucose level is less than 60 mg/100ml

Adult—25 grams (50 ml of 50% dextrose solution) intravenously; may repeat as needed

Paediatric—0.5 to 1 gram dextrose per kg as 25% dextrose solution or 10% dextrose solution (2 to 4 ml/kg).

Glucose administration should be preceded by 100 mg of thiamine IV or IM if chronic alcoholism or malnutrition is suspected to prevent Wernicke's encephalopathy

Some drugs have been tried to hasten the elimination of ethanol or reverse its intoxicating effects, including- naloxone, physostigmine, and caffeine but are not truly effective

Recently, flumazenil (3 mg IV) has been shown to be effective (in experimental studies) in reversing the respiratory depression associated with ethanol ingestion.

Haemodialysis can eliminate ethanol 3 to 4 times more rapidly than liver metabolism.

Useful in patients

- with excessive blood levels,
- impaired hepatic function
- whose condition deteriorates in spite of maximal supportive measures

Withdrawal syndromes

Seizures

Onset : 7 to 48 hours.

Features: Clonic-tonic movements, with or without loss of consciousness.

Alcoholic ketoacidosis

Onset : 24 to 72 hours

Delirium tremens

Onset : 3 to 5 days

Wernicke-Korsakoff syndrome

This is very rare as a withdrawal phenomenon

The Clinical Institutes Withdrawal Assessment-Alcohol Revised (CIWA-Ar) scale can be used to measure its severity.

The scale includes 10 common signs and symptoms of alcohol withdrawal

Scores of 0-9 indicate absent to minimal withdrawal, scores of 10-19 indicate mild to moderate withdrawal (marked autonomic arousal) and scores of 20 or more indicate severe withdrawal

Chronic poisoning treatment

General supportive care

Treated in a quiet room with low lighting and minimal stimulation

Immediate intravenous access for administration of drugs and fluids

Adequate sedation should be provided to calm the patient as early as possible and physical restraints may be used as required in order to prevent injuries due to agitation

Fluid and electrolyte imbalances must be promptly corrected.

Adequate nutrition must be ensured with care to prevent aspiration in over-sedated patients

Vitamin B supplementation helps to prevent Wernicke's encephalopathy (WE).

Chronic poisoning treatment

Detoxification

Detoxification is the process of weaning a person from a psychoactive substance in a safe and effective manner by gradually tapering the dependence producing substance or by substituting it with a cross-tolerant pharmacological agent and tapering it

For DT, seizures,

Chlordiazepoxide (a benzodiazepine) was far better in preventing seizures and DT in patients with alcohol withdrawal compared to chlorpromazine, hydroxyzine, thiamine or placebo

chlordiazepoxide has a slight advantage over the other benzodiazepines or anticonvulsants

Anticonvulsants have not been proven to be better than benzodiazepines and considered in mild withdrawal states due to their advantages of lower sedation and lower chances of dependence or abuse potential

Dose of benzodiazepine required per day is calculated according to the average daily alcohol intake

An estimate of the amount of alcohol consumption is given by the following formula:

Alcohol (in g) = Volume of liquor (ml) × 0.008 × (%) ethanol content in the liquor (w/v)

Fixed dose regimen

Loading dose regimen

Symptom-triggered treatment (STT)

Symptom-monitored loading dose (SML)

Rapid loading with close monitoring

Ref:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085800/

	Diazepam	Chlordiazepoxide	Lorazepam	Oxazepam
Equivalent doses (to 10 g alcohol)	5 mg	25 mg	1 mg	15 mg
Onset of action	Rapid	Intermediate	Intermediate	Slow
Half-life	Long	Long	Short	Short
Active metabolites	Yes	Yes	No	No
Hepatic metabolism	Yes	Yes	No	No
Routes of administration	Oral/intravenous	Oral	Oral/sublingual/intravenous/intramuscular	Oral

Chronic poisoning treatment

Withdrawal syndromes-

Alcoholic hallucinosis—Administration of phenothiazines (e.g. chlorpromazine 100 mg, 8th hourly).

The patient may be given low doses of antipsychotics like chlorpromazine 100-200 mg/day or risperidone 1-3 mg/day to control severe agitation due to hallucinations.

The hallucinations last about a week in most cases, but may last up to 1 month in some patients after which the antipsychotic can be stopped.

Alcoholic ketoacidosis-

Correction of volume depletion

infusion of solutions of normal saline with dextrose

Thiamine (50 to 100 mg) to prevent development of Wernicke-Korsakoff syndrome

Delirium tremens

Treatment: » Well lit, reassuring environment.

» For agitation—diazepam 10 mg IV initially, and then 5 mg every 5 minutes until full control, followed by 5 to 10 mg orally 3 times daily.

» Thiamine in the usual dose.

» Correction of fluid and electrolyte imbalance.

Wernicke-Korsakoff syndrome

Characterised by drowsiness, disorientation, amnesia, ataxia, peripheral neuropathy, horizontal nystagmus, and external ocular palsies

When recovery from Wernicke's encephalopathy is incomplete, a chronic amnesic syndrome develops called Korsakoff's psychosis

Administration of thiamine 50 to 100 mg IV daily, infused slowly in 500 ml of fluid for 5 to 7 days, and fluid replacement.

The following drugs have also been tried with varying degrees of success for withdrawal

Carbamazepine—It has been shown to be effective in treating alcohol withdrawal, including delirium tremens.

Chlormethiazole—It is one of the most popular drugs used for alcohol withdrawal abroad, and is administered in a rapidly reducing dosage over 6 to 7 days. However it is itself associated with a strong abuse potential.

Clonidine and gamma-hydroxybutyric acid have also shown promising results in the treatment of withdrawal symptoms. The former is given at a dose of 60 to 180 mcg/hr IV, and the latter 50 mg/ kg, orally.

Tiapride, an atypical neuroleptic agent which is a selective dopamine D2-receptor antagonist. But it should be given only as an adjunct while seizures, hallucinosis, etc., are being taken care of by other drugs

It is effective in ameliorating psychologic distress associated with alcohol abstinence

For delirium, the recommended dose is 400 to 1200 mg/day 6th hourly, while the maintenance dose subsequently to help abstain from alcohol should not exceed 300 mg/day

Aversion therapy

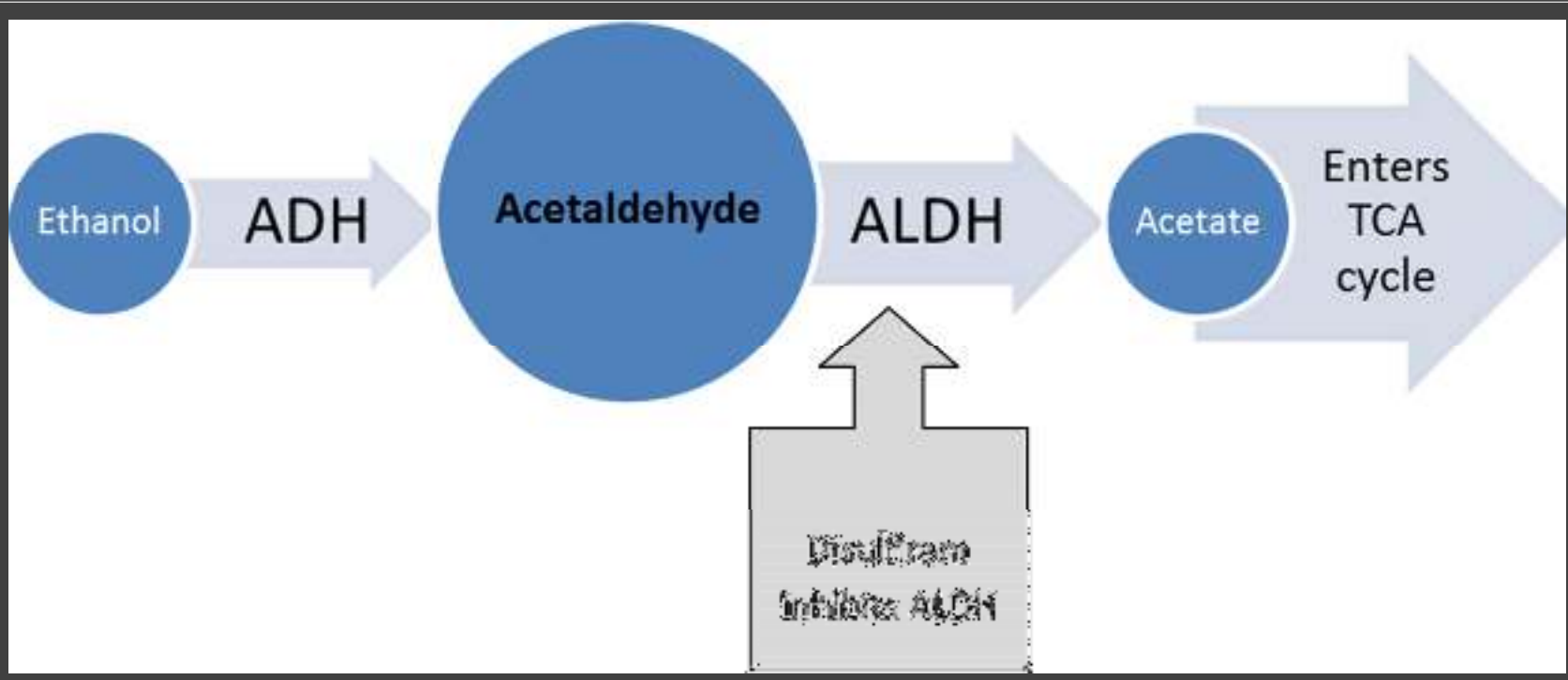
Main aim in the treatment of alcoholism is to gradually wean away the patient from the clutches of ethanol, once the acute manifestations of withdrawal have been taken care of

Called de-addiction or detoxification

One of the more successful detoxification ways is to administer a drug called disulfiram

Disulfiram

It is a disulfide molecule (tetraethylthiuram) which interferes with the oxidative metabolism of ethanol at the acetaldehyde stage, as a result of which acetaldehyde accumulates producing unpleasant symptoms*


Ethanol
ADH
Acetaldehyde
ALDH
Acetate
Enters TCA cycle

Principles of disulfiram therapy

Patient is off alcohol for a minimum period of 12 hours before starting therapy.

Administer disulfiram only by the oral route.

Warn the patient explicitly that while he is on disulfiram, alcohol must not be consumed even in small quantity since it can provoke a severe (and sometimes fatal) reaction

Disulfiram is 250 mg/day which may have to be taken for an indefinite period of time.

Adverse effects-halitosis (rotten egg odour due to sulfide metabolites), pruritis, headache, drowsiness, impotence, peripheral neuropathies, depression, mania, psychosis, and hepatotoxicity.

The patient must be closely monitored and dosage reduced if necessary.

Other than disulfiram, there are numerous other substances which evoke a similar reaction with ethanol

Table 14.4: Disulfiram-Ethanol Reaction

GIT	*CNS*	*CVS*	*Skin*	*RS*
Abdominal pain	Blurred vision	Syncope	Sweating	Tachypnoea
Nausea	Confusion	Hypotension	Flushing	
Vomiting	Vertigo	Tachycardia	Sensation of heat	
	Headache	Dysrhythmias	Pruritis	
	Weakness	Chest pain		
		Myocardial infarction		

Table 14.5: Substances Producing Disulfiram-like Reaction With Ethanol

Pharmaceuticals		*Chemicals*	*Miscellaneous*
Antimicrobials	Other Drugs	Calcium cyanamide	Activated charcoal
Cephalosporins	Chlorpropamide	Carbon di sulfide	Mushrooms
Chloramphenicol	Glipizide	Hydrogen sulfide	*(Coprinus*
Furazolidone	MAO Inhibitors	Tetra ethyl lead	*Clitocybe)*
Griseofulvin	Tolbutamide	Tri & Tetra chloro ethylene	
Metronidazole			
Nitrofurantoin			

Supportive psychotherapy

Psychotherapy, it is group therapy which is effective in the long, term management of abstinence

Self-support organisations such as Alcoholics Anonymous (AA) play an important role. The AA which had its origins in the USA in 1935 now has more than 53,000 groups spread worldwide including India.

Meetings are generally held once a week and are informal affairs conducted in a friendly atmosphere.

Generally two or three speakers share their experiences during each session relating to their addiction and recovery.

Summary of recommendations

General measures (for all patients in alcohol withdrawal period)		A quiet room with low lighting and minimal stimulation Intravenous access, fluid and electrolyte maintenance Adequate nutrition, prevent aspiration Adequate sedation, physical restraints (minimum period of time)	
Thiamine supplementation (for all patients with chronic alcohol use)		Prevention of Wernicke's encephalopathy - 250 mg intramuscularly daily for 3-5 days Suspected case of Wernicke's encephalopathy - 250 mg intramuscularly twice daily for 3-5 days, continue for up to 2 weeks in those who show improvement	
Specific treatment protocols depending on severity of withdrawal state	Minor withdrawals (CIWA-Ar<10)	No acute medical illness, no past history of severe withdrawals, seizures, or DT	Supportive care alone, observe for 36 h, STT if symptoms emerge anytime. FD if out-patient treatment and minor withdrawals present
	Minor withdrawals (CIWA-Ar<10)	Current acute medical illness, or past history of seizures, DT	SML with 20 mg diazepam - 60 mg and observe in-patient, or FD if out-patient treatment
	Moderate withdrawals (CIWA-Ar 10-19)	No acute medical illness, no past history of severe withdrawals, seizures, or DT	In-patient care with SML, or FD (if personnel not trained or not adequate or patient wants outpatient treatment)
	Moderate withdrawals (CIWA-Ar 10-19)	Current acute medical illness, or past history of seizures, or DT	In-patient care is preferable. Treat with SML. Out-patient care with FD if in-patient care is not possible
	Severe withdrawals, without seizures or DT (CIWA-Ar>19)	With or without past history of seizures or DT	In-patient treatment with SML. If in-patient care is not possible, observe in emergency services. SML or FD (as feasible) until CIWA-Ar<10 for a period of 6 h
	Seizures	In-patient management is a must. Lorazepam 2 mg intravenous/intramuscular stat followed by SML	
	DT	In-patient management is a must. Rapid loading with close monitoring to achieve light somnolence, followed by SML or SML alone	
	Hallucinosis	In-patient management and treatment due to risk of DT. Fixed dose benzodiazepines over SML. In case of persistent hallucinations, low doses of antipsychotics may be prescribed for a period of one to 2 weeks until symptoms remit	

DT – Delirium tremens; CIWA-Ar – Clinical institutes withdrawal assessment- alcohol revised; STT – Symptom-triggered treatment; FD – Fixed dose regimen; SML – Symptom-monitored loading