REVIEW OF LITERATURE
Alcohol dependence (alcoholism) is a complex addictive disorder affecting millions of individuals worldwide and is a major cause of mortality and morbidity (Kessler et al., 1994; Leigh et al., 1999; Ezzati et al., 2006; Strat et al., 2008;). There are about an estimated 2 billion alcoholics worldwide and this number is on increase every year with added new drinkers including teenaged boys and girls (Liber, 2000). Reports reveal a large number of individuals suffer from nearly 60 alcohol attributable diseases and a number of other diseases with alcohol relatedness with an estimated 2 million deaths annually (Subramanian et al., 2005). Alcohol dependence and its disorders is an area of growing concern in India (Naga Venkatesha Murthy et al., 2007; Alcohol Atlas of India, 2008). Studies suggested that moderate (women who consume up to one standard drink per day and men who consume up to 2 drinks per day) drinking reduces the risk of coronary heart disease (CHD) (Stampfer et al., 2005) and beneficially modulates several other diseases such as duodenal ulcer, lithiasis, diabetes and rheumatoid arthritis. Moderate alcohol drinking often may lead to further indiscriminate excessive consumption causing health problems and social implications. Excessive alcohol consumption results in a broad spectrum of diseases such as ALD, CHD, gastro-intestinal and neurological disorders, etc. Alcoholism is perceived as a male problem till now, but there has been a clear indication of dramatic rise in number of female alcoholics, and the gap between alcoholism among women and men has narrowed in relation to both consumption and problems (Subramanian et al., 2005). A survey of police forces carried out by Channel 4 TV found that the number of women arrested for being drunk and behave disorderly rose by more than 50% in five years, from 3,847 in 2003/04 to 5,891 in 2007 (ias factsheet, 2008). Other reports also confirmed the increase in number of female alcoholics in India. An increased number of female alcoholics with disorders who turned up for treatment recently at National Institute of Mental Health and Neuro Science (NIMHANS), Bangalore is evident (Naga venkatesha murthy et al., 2007). Changed women's role in the modern world with economic freedom and loosening of inhibitions due to other factors may be the causes of increased alcohol use by women. It is well known that research on alcoholism involving humans and animals has been predominantly on males. Now the need for a better understanding of the
biological/biochemical mechanisms underlying sex differences in ethanol consumption is being increasingly recognized as evident from the recent studies (Cha et al., 2006). Several investigations have emphasized a need for extensive and intensive studies in this area (Ely et al., 2001; Hallman, et al., 2001).

Although the adverse effects of excessive alcohol intake are well known, caution should be exercised in recommending even moderate alcohol intake. Our results combined with those of other studies suggest that women who consume up to one drink per day have better cognitive function as well less cognitive impairment than non-drinkers. Moderate alcohol intake may be beneficial to cognitive function in women, but not necessarily in men (Yonker et al., 2005). Accumulated literature clearly revealed that females respond differently to alcohol indicating the existence of gender-based impact of alcohol. Hallman et al., (2001) and others have reported the differences in female alcoholics with males as well between female alcoholics with and without a history of additional substance misuse. Very limited information is available on females pertaining to alcoholism. Ely et al., (1999) have reported that the drinking levels in women approached those in men and the rates of drinking problem in women are likely to overtake those in men because of women’s greater physiological sensitivity to the effect of alcohol. Ladipo et al., (2003) have demonstrated that chronic alcohol consumption causes a reduction in myocardial function which is greater in females than in males, thus explaining at least in part, the difference in mean arterial pressure and heart rate with sex. There is a need for studies related to alcohol to understand the specific effects and mechanisms to facilitate therapeutic strategies such as de-addiction and alleviation of alcohol toxicity.

**Hormonal milieu is responsible for differential physiological responses in females**

Women and men are genetically very similar, except that different hormones enter the brain at different times and different tempos, encouraging some brain cells to sprout more than others at time periods critical to brain development. Males and females are undifferentiated until the sixth week of gestation, when testes develop in males and begin to produce androgens. Follicle stimulating hormone (FSH) is found in the pituitary glands of both the sexes by fetal week-10 and its concentration increases dramatically, but only in females, between weeks 12 and 20. FSH is thought to play a key role in fetal ovarian development, but the influence of ovarian secretions on the brain during fetal life is not
nearly as well understood as that of testosterone (Fingen et al., 1988). In humans maximum central nervous systems (CNS) sensitivity to the organizational effects of gonadal steroids is presumed to occur between gestational weeks 14 and 16 when peak concentrations of testosterone are found in fetal serum (Rubinow and Schmidt, 1996). From then until puberty, the brains hormonal environment is again very similar in females and males. Females reach sexual maturity earlier than males. Although the extent of difference varies with genes, geography and nutritional factors, it appears to be a fact in all mammals and for good measure in birds as well (Caswell and Weeks, 1986) during sexual maturity hormone levels of women fluctuate cyclically over a much larger range than those of men at female menopause ovarian secretion shuts down. In men the testes continue to produce testosterone which is partly converted to estradiol in the brain but at an increasingly slower rate. In very old age, the women brain hormonal environment is once again similar in the two sexes. These male/female contrasts are thought to play in the expression of many neuropsychiatric illnesses (Seeman, 1997). Several workers failed to demonstrate alcohol-induced increases in aggression in women and it was found that when offered a choice of aggressive and non-aggressive response irrespective of alcohol dose (Hoaken and Pihl, 2002). On the contrary a recent study (Dougherty et al., 1996) found that alcohol produces significant increase in women’s aggression, on a point subtraction laboratory measure of aggression.

Alcohol and its metabolism

Ethanol is the chief constituent in several alcoholic beverages and is responsible for characteristic effects of alcohol. Beer, wine and liquor have different alcohol levels. Most beers have up to 5 per-cent alcohol, although some beers exceed 6 per-cent. Wine contains 8 to 14 per-cent alcohol, and hard liquor (whisky, brandy, rum, zin etc) is typically 35 to 45 per-cent alcohol. Beer but hard liquor is labeled by “proof” which is twice the alcohol percentage (an 80 proof whiskey is 40 percent alcohol). Consumed alcohol requires no digestion prior to absorption, and absorption begins immediately in the mouth and esophagus where small quantities enter the blood stream. Although alcohol absorption continues in the stomach, the small intestine efficiently absorbs most of the alcohol a
person consumes (Ramakrishnan, 1983). Unlike other anesthetics, alcohol is consumed in relatively large quantities for longer periods (Lieber, 1991). Blood alcohol levels reach maximum concentration in few minutes after ingestion of alcoholic beverage like whisky or beer, about a level of 20 mM ethanol in blood is indicative of intoxication (Hoek and Taraschi, 1988). When equal amounts of alcohol is consumed by man and woman, blood alcohol concentration in woman rapidly rises to the maximum when compared to men in general (Hoeksema, 2004). Carbonation hastens absorption, whereas food delays it. Alcohol from blood is cleared rapidly as little is lost through lungs by diffusion and its further passage to all other tissues through capillary network with which it comes in contact till it reaches equilibrium between blood and tissues except adipose tissue (Narayana Reddy, 1994). About 80% of alcohol absorbed is oxidized in the liver and remaining 10% is excreted in breath, urine, sweat, saliva, milk, tears, and faeces (Narayana Reddy, 1994; Ramakrishnan, 1983; Lieber, 1991). However, in the digestive tract, mainly in the stomach alcohol diffuses into gut cells and travel via portal vein directly to the liver where most alcohol metabolism takes place. On the other hand, alcohol is subjected to renal clearance (Seitz and Oneta, 1998). The body works extra hard to get rid of and quickly metabolizes and it removes it from blood.

The liver selectively metabolizes alcohol and there exists alternative pathways to handle excess consumption (Swift and Davidson, 1998). Mitochondrial alcohol dehydrogenase, a zinc containing enzyme converts alcohol to acetaldehyde, and aldehyde dehydrogenase quickly and effectively converts acetaldehyde to acetate. When large amounts of alcohol prevail, the microsomal ethanol-oxidising system (MEOS) operates at a faster speed to process alcohol quickly and converts it to acetaldehyde. Hence, this route is an overflow pathway (Insel et al., 2004). The peroxisomes contain the enzyme catalase which is capable of peroxidation of ethanol to acetaldehyde and water in presence of hydrogen peroxide. The hydrogen peroxide is generated in smooth endoplasmic reticulum by NADPH oxidase utilizing hydrogen equivalent and molecular O₂ for the formation of NADP⁺.
NADPH + H⁺ + O₂ → NADP⁺ + H₂O₂

\[ \text{C₂H₅OH + H₂O₂} \rightarrow \text{CH₃CHO + 2H₂O} \]

Acetaldehyde is then oxidized to acetate by a mitochondrial enzyme aldehyde dehydrogenase which is also NAD⁺ linked. Acetate formed from ethanol is activated to acetyl CoA. The acetyl CoA formed is ultimately oxidized via citric acid cycle for the energy yield. Alcohol has high energy content yielding 7.1 kcal/g on oxidation. Much of the acetate formed from ethanol escapes from the liver and enters into blood. Virtually, every other cell with mitochondria can oxidize it to CO₂ by the TCA cycle (Elkeles and Tavil, 1983). Acetaldehyde, the intermediate in the formation of acetate from ethanol, can also escape from the liver. Acetaldehyde forms covalent bonds with functional groups of biologically important compounds. Formation of acetaldehyde adducts with proteins in tissues and blood of animals and humans drinking alcohol has been demonstrated. Such adducts may provide a marker for past drinking activity of an individual (Swift and Davidson, 1998). Recent studies have suggested that acetaldehyde directly participates in the pathogenesis of alcoholism (Ramakrishnan, 1983; Elkeles and Tavil, 1983; Niemela, 2007). Chronic administration of acetaldehyde during 3 weeks induced metabolic tolerance to ethanol (USDA, 1997).

**Alcohol-induced biochemical adaptive changes in biomembranes**

Alcohol is consumed in large quantities over prolonged periods and blood alcohol levels reach maximum concentration in a few minutes after ingestion; 20 mM ethanol is considered to be indicative of intoxication (Hoek and Tarashi, 1988). Chronic excessive alcohol consumption involves biophysical and biochemical changes in the membranes, and the organism tends to develop a set of adaptive responses to the continued presence of ethanol, presumably, aimed to counteract undesirable effects of this exposure. Such physiological adaptive responses and changes have been demonstrated and confirmed in synaptosomal, mitochondrial, erythrocyte membranes and also in many other membrane preparations (Chin and Goldstein, 1977; Ellingsan et al., 1988; Waring et al., 1992). The adaptive response is detected in membrane preparations isolated from rats that have been fed ethanol over a prolonged period (3-4 weeks) and had blood alcohol levels around 50
mM. Ethanol concentrations of 50-150 mM, which cause significant membrane dis ordering in control preparations, have little or no effect in membrane preparations from ethanol fed animals. This adaptive response is referred to as membrane tolerance (Ponnappa, et al., 1982; Hoek and Taraschi, 1988; Waring et al., 1982; Ponnappa and Rubin, 2000).

A Mn\(^{2+}\)-dependent peroxidase is induced in *Neurospora crassa* by ethanol stress (Ramasamma, 1994). Another example for such adaptive response is that chronic ingestion is followed by proliferation of smooth endoplasmic reticulum associated with a proportional increase in cytochrome P-450, cytochrome P-450 reductase and other components of the mixed MEOS. MEOS activity shows a significant increase as evidenced by the rate of acetaldehyde production and an increase in NADPH consumption (Seitz and Oneta, 1988).

By virtue of its lipid solubility, ethanol can enter the polar core of the biomembranes thereby increasing their fluidity. It acts like many anesthetics including anesthesia. The pharmacological effects of ethanol are related to its ability to perturb bilayer (Houslay and Stanley, 1984). There is now considerable evidence that microsomal, mitochondrial and synaptosomal plasma membranes from brain and erythrocyte taken from ethanol-treated animals are resistant to fluidizing effect of ethanol. This is achieved by increasing cholesterol:phospholipid ratio (Houslay and Stanley, 1984; Chin et al., 1978; Jain et al., 1988). The intoxicating effect of ethanol on the nervous system can be attributed to its modification of membrane fluidity and alterations of membrane receptors and ion channels. Under pathological conditions, alterations in chemical composition, properties and functions of membranes serve as indices to assess the damage and aetiology of the manifestations (Devlin, 1997). Alcohol induced disordering action on membrane under the influence of cholesterol was reported by Johnson et al., (1992). The precise mechanism of action of alcohol on central nervous system is yet to be understood fully (Houslay and Stanley, 1984; People et al., 1996). However, several significant changes in the chemical composition, properties, and functions of membranes are reported in various models (Chin and Goldstein, 1977; Kaur et al., 1994). Ethanol did indeed fluidize various
membranes. Ethanol-induced disordering effects in many membranes have been reported in several studies (Chin and Goldstein, 1977; Chin et al., 1978; Taraschi et al., 1986). Several morphological, structural and functional changes in membranes of various subcellular organelles have been reported (Waring et al., 1982; Devaud et al., 2006).

**Alcohol vs. nitric oxide**

Nitric oxide (NO) is a signaling molecule that had been shown to be involved in diverse cellular functions and is known to mediate various physiological as well pathological processes (Azizi et al., 2005). Current literature reveals that the metabolic status of NO and functional status between oxidation and anti-oxidation systems in animal/human body are in close relationship with health (Zhou et al., 2000). If the metabolism of NO is abnormal and the dynamic balance between oxidation and anti-oxidation is disturbed, there will be an increase in free radical concentration. Consequently, free radical chain reactions will aggravate the damage in the animal/human body (Hiramoto et al., 2003). Several studies clearly demonstrated the role of NO in alcohol-induced events (Venkatraman et al., 2003; Yuan et al., 2006). There is paucity of information concerning the role of NO-induced differential response in relation to gender in chronic alcoholism.

The development of alcohol-induced liver toxicity is influenced by many mechanisms including changes in metabolism, inflammation and fibrogenesis (Savolainen et al., 1995). In addition to hypoxia, oxidative and nitrosative stress have been suggested as key factors capable of both initiating and sustaining the mechanisms of pathogenesis leading to alcohol liver disease (ALD) (Bailey and Cunnighan, 1999; Wheeler, 2000). Further, mitochondrial damage plays a significant role in this process. Cytochrome C oxidase contains an oxygen binding site i.e., the principal target for the interaction of NO in regulating several aspects of mitochondrial function including formation of reactive oxygen species (ROS) (Brown, 1995; Ramachandran et al., 2002). NO production, although generally considered beneficial, can become deleterious on reaction with superoxide, resulting in the formation of peroxynitrite (Reiter et al., 2000). This occurs in
response to chronic ethanol exposure formation of peroxynitrial radical leading to many adverse consequences (Venkatraman et al., 2003).

Now it is well known that NO regulates virtually every critical cellular function and also mediates cellular damage in a wide range of conditions. NO itself is potentially toxic. Moreover, its oxidation products are more toxic. NO often interacts with superoxide thereby forming peroxynitrite. Further studies also revealed the formation of many reactive nitrogen species. Although peroxynitrite is a strong oxidant it reacts at a relatively slow rate with most biological molecules (Niziolek et al., 2003). Peroxynitrite is able to cross cell membranes through anion channels and reacts slowly and selectively through the cell making the biological and pathological implications. Peroxynitrite favors collective reactions with key moieties in proteins such as thiols, iron-sulphur centers and zinc fingers. Further, it interacts with lipids and nucleic acids (Mantena et al., 2007). As a result, many nitrated products are formed leading to cytotoxicity in broad actions such as inflammation, cardiovascular disease, neurodegeneration diabetes and other pathologies (Denicola and Radi, 2005). According to a working hypothesis proposed by Iimuro et al., (1997) higher plasma endotoxin levels lead to more extensive kupffer cell activation in females than in males. As a consequence, increase in free radical-producing inflammatory cells in the liver occur. This could explain why females develop alcohol-induced liver injury more rapidly and to a greater extent than males (Iimuro et al., 1997).

Now it is well known that NO is produced from the terminal guanidine nitrogen of L-Arginine by the actionin of the enzyme nitric oxide synthase (NOS) numerous cell types and many isoforms of NO have been recognized among which three types (nNOS, cNOS, and iNOS) are well studied. NO production is increased in response to chronic alcohol via induction of inducible NOS (Radi et al., 2002). This has important raminifications for toxicity because NO and its metabolite peroxynitrite (ONOO\(^-\)) have been implicated as key mediators of mitochondrial dysfunction (Beckman and Crow, 1993; Radi et al., 2002). NO diffuses into mitochondria and reacts with O\(^2-\) to produce ONOO\(^-\), a reactive metabolite responsible for inactivation of mitochondrial proteins via posttranslational modifications.
Figure 1 The multifaceted biological effects of NO

- Antioxidant
- Inhibits leukocyte adhesion
- Protects against TNF toxicity

**Protective**
- Vascular tone
- Cellular adhesion
- Vascular permeability
- Neurotransmission
- Bronchodilation
- Inhibits platelet adhesion
- Immune surveillance system
- Renal function

**Regulatory**
- Inhibits enzyme function
- Induces DNA damage
- Induces lipid peroxidation
- Increased susceptibility to radiation
- Depletes antioxidant system
- Toxic metals
- Alkylating agents

**Deleterious**
(Radi et al., 2002). NO produced from different cell types is capable of diffusion to great distances at physiological oxygen tensions in tissue. As such produced NO would be capable of distant endocrine vasodilatation resulting in loss of local metabolic and flow regulated vasi-control (Pacher et al., 2007). Several studies revealed that NO interacts with various important biomolecules resulting in the formation of nitrated lipids (Kalyanaraman, 2004), nitrated proteins (Luchsinger et al., 2003), nitrosamines (Zheng and Hogg, 2005), iron nitrosyls (Whitfield et al., 2001), etc. Further, NO appears to be involved in DNA damage regulation of metabolism and also in several membrane-dependent processes (Shiva et al., 2005; Ghafourifar and Cadens, 2007). Though the involvement of NO in alcohol-induced events is well documented, its precise role, mechanism and effects are yet to be understood fully. NO is known to influence the composition, physico-chemical properties as well as functions of blood, liver, heart, nerve system and brain, and also other tissues to a large extent. Several studies indicated a novel role of NO in the pathogenesis of alcohol hepatotoxicity (Pacher et al., 2005; 2007).

**Women and alcohol**

Reports clearly revealed that alcohol consumption by women has increased worldwide to a large extent. Besides, studies demonstrated that men and women respond differently to alcohol. Blood alcohol rises faster in women. So, women become more intoxicated than men with an equivalent dose of alcohol (NIAAA, 1992; Alcohol Alert, 2008). Accordingly, moderate drinking is usually defined as “two standard drinks for men and one for women” (Lucas et al., 2005)

Roman (1986) reported that a greater physiological deterioration among women as compared with men who have similar drinking histories. Fetal alcohol syndrome (FAS) is a major problem associated with women drinking behavior. The dosage and duration of alcohol ingestion probably determines the point in time at which the liver converts from an adaptive response to an injurious response. Nevertheless, even relatively acute administration of alcohol can result in structural damage to sub cellular organelles. Experimentally, in animals and man, ultra structural changes have been noted in mitochondria and in smooth and rough endoplasmic reticulum. In case of the SER, these have been identified as hypertrophy of the machinery concerned with ethanol metabolism.
Both alcohol and acetaldehyde have been shown to be capable of inhibiting oxidative phosphorylation. Whatever the mechanism, the result is impaired mitochondrial function in general, and reduced ability to regenerate NAD in particular, and in turn, a reactive failure to metabolize acetaldehyde (Tavil and Cooksley, 1983). Women metabolize alcohol more slowly than men. Several factors are responsible for alcohol’s greater effect on women.

1. **Body size and composition:** Alcohol has a smaller volume of distribution in women because adipose tissue into which it diffuses slowly because of the poor blood supply forms greater proportion of body mass in women (33%) than in men (21%). Man on an average tends to have more body water for distribution of alcohol whereas women generally have smaller volumes of distribution for water soluble drugs such as ethanol which may account for higher blood alcohol concentrations (BAC) of women at comparable quantities (Hardy *et al.*, 1999). There is paucity of information regarding the precise gender-based requirements of water.

2. **Differential enzyme activities and metabolism:** Women metabolize less ethanol than men because of lower levels or less activity of gastric ADH. The size of liver in females was reported to be smaller in comparison to males. Differences in metabolism and elimination are important considerations (Roman, 1986; Baraona *et al.*, 2001). Alcohol pharmacokinetics during menstrual cycle leading to slightly faster elimination of alcohol during luteal phases and women’s drinking which appear to be hazardous and remain unverified. In general, women tend to drink more slowly than men (Baraona *et al.*, 2001). There is very little information on to what extent women and men take food with alcohol (NIAAA, 2001). Concurrent use of other substances may alter the effects of alcohol. There is huge gap in our knowledge on this matter. All these things are to be taken into consideration when comparing the effects of alcohol on women and men. There is also a need for in depth research on behavioral factors affecting how alcohol is consumed. Further gender differences in alcohol absorption, metabolism and elimination are to be
How Alcohol Affects Your Body

**Brain**
Drinking alcohol leads to a loss of coordination, poor judgment, slowed reflexes, distorted vision, loss of memory, and even blackouts.

**Heart**
Drinking alcohol could cause your blood pressure to rise, increase your heart rate, cause your heart to beat abnormally, and can increase the size of your heart.

**Liver**
Drinking alcohol could cause diseases such as cirrhosis (sir-o-sis). It also can cause hepatitis (inflamed liver) or even liver cancer, which weakens the liver's ability to clot and keep our blood free from poisons and bacteria.

**Stomach**
You're putting empty calories into your body, which could cause weight gain. If you drink too much, you may vomit because alcohol is toxic. Drinking alcohol can also cause stomach ulcers and cancer.

**Reproductive System**
Heavy drinking can cause painful periods, heavy flow, discomfort before your period (PMS), and irregular periods (not getting your period when you're supposed to). Drinking also raises the risk of getting sexually assaulted and having unsafe sex.
investigated. Too little is known about how these processes are linked to levels of sex hormones.

3. Hormonal milieu: In addition to biological (anatomical and physiological) differences, biochemical aspects are influenced by hormones. Studies related to alcoholism reveal that androgens and estrogens influence the effects of alcohol. Female rats release more corticosterone than males in response to alcohol and suggested that those corticosteroids may play a role in the rate of alcohol metabolism (Rivier, 1993). Almelda et al., (1998) reported the existence of gender differences in alcohol preference and consumption mediated through dihydrotestosterone (DHT) in rats. Further, sex differentiation of brain and sex steroid milieu might account for the typical male and female patterns of alcohol preference and ingestion (Almelda, 1998). Other studies revealed that gene expression changes that are controlled by sex hormones are responsible for greater susceptibility of female gender leading to ethanol induced liver injury (Almelda, et al., 1998). Green et al., (2004) have concluded that health may be benefited on moderate drinking more in women than men. Recent studies clearly revealed the existence of the role of nitric oxide in gender differences (Cederbaum et al., 1987; Spitzer, 2002; Ronis et al., 2004; Tirapelli et al., 2007).

Horton et al (2002) revealed that nutritional state can significantly impart differential postprandial metabolism in men and women with respect to triglyceride uptake which was attributed to sex steroid environments in men vs women. Reversal of sex differences in lipid metabolism in gonodacterized rats were observed by Coleman et al., (1957) The effects of gonadectomized much more pronounced in the male than in female animal. Such differences certainly lead to differential response to alcohol by females.

Estrogens are neuroprotective with respect to neurological degeneration growth and susceptibility to toxins. The cyclic fluctuations of estrogens and progesterone enhance response to stress, which confers susceptibility to depression and anxiety (Colantoni, 2000). Earlier studies showed that alcoholic liver disease
readily develops in women than in men and its progression may also be quicker (Cederbaum, 1987; Ewald and Frost, 1988; Thurman et al., 1999; Enomoto et al., 2000; Groffon et al., 2000; Nanji et al., 2002; and). Certain ovarian steroids such as allopregalone, pregalone and progesterone have effect on the brain and brain functions. Further they interfere in the interaction between GABA_\alpha_ receptor and alcohol. In general allopregalone is a positive modulator of GABA_\alpha_ receptor with sedative, anxiolytic and anticonvulsant effects in both humans and animals (Seeman, 1997).

4. Differences in physiology of organs: It is well known that there exists certain differences in structure of brain, the ratio of white matter to gray matter and volume of brain and composition related to brain differences in sex organs, differences in vasculature of different organs such as intestine may also contribute to the gender differences in alcohol sensitivity and differences in blood alcohol levels (BAL) (Pfefferbaum, 2001). Different cognitive processes are altered by chronic ethanol exposure in male and female rats and the neurobiological mechanisms responsible for these differences remain to be determined.

Owing to emerging evidences on the impact of female gender on alcohol, few researchers have undertaken studies using women and female animal models for research and the design of the experiments, selection of models and doses of alcohol administered were at scientist's discretion and reporting ambiguous results. Further, several researchers have repeatedly emphasized a need of studies on females pertaining to alcoholism (Saunders and Williams, 1981; Moscato et al., 1997; Jang et al., 1997; Almeda et al., 1998; Spitzer 1999; Ronis et al., 2004; Rahav et al., 2006). A number of differences exist between the sexes in rates of illness and course of illness with Alzheimer's disease, schizophrenia, alcoholism and mood and anxiety disorders (Seeman, 1997; Hommer et al., 2001). An increasing number of women are financially independent and tend to adopt male drinking habits. Hence, the incidence of alcoholism is increasing among women (Subramanian et al., 2005; Walter, 2005; Naga Venkatesh murthy et al., 2007).
Figure 3 Multiple pathological effects of alcohol toxicity affecting several body organs

THE PERILS OF EXCESSIVE DRINKING

Brain
Damage to the frontal lobes of the brain, including the cerebellum and cerebral cortex.

Depression
Heavy alcohol consumption gradually destroys the brain cells and can result in depression, memory loss and intellectual deterioration.

Liver Disease
Excessive long-term consumption of alcohol may lead to fatty liver, alcoholic hepatitis, cirrhosis and liver cancer.

Digestive Disorders
Heavy drinkers may suffer from digestive tract diseases, such as gastritis, pancreatitis and cancer of the upper digestive tract.

Nerve Damage
Malnutrition disturbs nerve functioning, causing symptoms such as cramps and numbness.

Muscle Disease
Heavy drinking damages the red and white muscle fibers.

Mouth & Throat Cancer
High levels of alcohol intake increase the risk of cancers of the mouth, tongue and throat.

Heart Disease
Heavy drinkers are more susceptible to high blood pressure and coronary heart disease. They are more likely to suffer from heart failure or stroke.

Sexual Problems
Alcohol leads to Erectile Dysfunction (ED) in men and infertility in women.
Researchers suggest that alcohol affects brain structure differentially in men and women. As there exists differences in the functioning of brain's two hemispheres, normally differential asymmetries leading to perceptual abilities are evident. Hommer et al., (1996) showed that alcoholic women have smaller gray and white matter volumes and greater Cerebrospinal fluid volumes than healthy non-alcoholic women and that the brain volume differences between alcoholic and non-alcoholic women particularly in gray matter are considerably larger than those found between alcoholic and non-alcoholic men. Further, it was concluded that women are more vulnerable to many of the medical consequences of alcohol use than men (Hommer et al., 2001). Padmini and Sundari (2007) observed damage to membrane lipids and oxidation of membrane protein thiols affecting adversely the membrane fluidity and flexibility leading to decreased resistance to haemolysis of erythrocytes in women who consume alcohol.

Studies also revealed that women develop hepatic and cardiac complication of alcoholism earlier in the course of disease than men do. According to animal studies female rats also develop severe alcohol induced liver injury than male rats(Thurman et al., 1999; Griffon et al., 2000; Nanji et al., 2002). Gubala and Zuba (2003) showed gender differences in the pharmacokinetics of ethanol in saliva and blood after oral ingestion. It is well established that gender directly influences the cardiovascular system. Zheng et al., (2004) observed changes in the small intestine vasculature which represent a potential mechanism for the circulatory gender difference between male and females and androgens play an inhibitory role on small intestinal endothelial function. Thurman et al., (1999) put forth forwarded mechanisms of alcohol induced hepatotoxicity that involves activation of kupffer cell by endotoxin in rats leading to alcoholic liver injury in which females are more sensitive to these changes. Coelantoni et al., (2003) observed difference in cytokine responses that contribute to the enhanced sensitivity of female liver to ethanol induced injury. Colantoni (2003), Enomoto et al., (2000) demonstrated that activated kupffer cells are involved in alcohol induced fat accumulation in rat liver by releasing prostaglandin E2. Galuccii et al., (2004), observed that differential expression of liver interleukin-6 receptor α in female rats is responsible for alcohol liver disease (ALD). Nanji et al., (2002) showed that increased endotoxmia and lipid peroxidation in female rats stimulating NFkB
activation and chemokine production (TNF-α, COX2 upregulation) are responsible for enhancement of liver injury in females. Mann et al., (2005) demonstrated higher vulnerability to alcoholic damage among women and also gender selective effects of chronic ethanol in women leading to adaptation at molecular level.

Studies of Cha et al., (2006), indicated that sex-dependent and cycle-dependent differences in ethanol sensitivity are manifested at both the behavioral and neurophysiological levels and may have important implications for our understanding of the neurobehavioral effects of ethanol. Susan Nolon-Hoeksema (2004) reported that women appear to suffer more negative consequences in a number of domains than men from drinking a given amount of alcohol. Studies of Jung et al., (1999) revealed that neuroprotective effects of estrogen treatment against alcoholic damage in men and women. Female susceptibility to the toxic effects of alcohol has been observed in hepatic, cerebral, cardiac and muscular alternations. Similarly females were found to be more sensitive to the toxic effects of alcohol on peripheral nerve fibers and alcoholic neuropathy unrelated to malnutrition. Alcoholic damage related to all the above mentioned disorders were described in several reviews. Spitzer (1999) found gender differences in NO production by alveolar macrophages in ethanol intoxicated rats. On the contrary Ronis et al., (2004) ruled out the greater susceptibility to ethanol induced hepatotoxicity in females than in male rats. Hallman et al., (2001) reported that female alcoholics with and without multiple substance misuse show differences in various biochemical parameters when compared to males. Further such co-morbidity seems to be more frequent among females than among male alcoholics (Moscato et al., 1997; Breitenfeld et al., 1998; Van et al., 1998). Crippens (1999) reported the gender differences in blood ethanol level but not in brain. Female rats differ significantly from males in their mesolimbic dopamine activity as related to ethanol drinking (Myers et al., 1998) opined a major drawback in most experimental studies of ethanol preferring strains of rats is the minimal usage of female gender. Sumida et al., (2004) reported that chronic alcohol consumption results in gender dependent differences in whole body glucose production and regulation.
Alcohol vs Neuroendocrine system and Brain

Alcoholism affects endocrine functioning and disrupts normal growth and endocrine development through its effects on hypothalamus, pituitary gland and various targets organs such as ovaries and testis. Moreover, bone density and growth are affected. Devaud et al., (2006) have shown significant differences between the sexes in behavioral responses and neuroadaptation to chronic alcohol consumption and withdrawal. Accumulated evidences suggested that treatment of alcoholism, including withdrawal, should be tailored to the patient’s gender and hormonal status (Devaud et al., 2006). Sex differences in brain and endocrine mediated stress processes in alcoholics are evident while flight or fight response is seen in males, women often evince tend or befriend behaviors (Taylor et al., 2001; Troisi, 2001) which is rather than responding aggressively to a challenge, women are more likely to nurture in others in stressful situation. Further, women exhibit a greater release of stress hormone cortisol in response to stress compared with men suggesting there is a greater physiological response in females compared with males (Born et al., 1995; Van Cautes et al., 1996; Stroud et al., 2002). Another major physiological parameter affected by alcohol is the hypothalamus-pituitary-gonadal (HPG) axis, which regulates the synthesis of gonadal steroids in both males and females (Lee et al., 2001). The hypothalamus produces gonadotropin-releasing hormone (GnRH), which travels to the pituitary, where it stimulates the release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH) into the blood stream (Femandez-Solari et al., 2004). LH and FSH control testosterone synthesis and secretion as well as sperm development in the testes of male animals and follicular rupture and ovulation in females (Selvage and Rivier 2003). In males, GnRH is secreted in pulsatile, noncircadian manner. In females, the hormone is secreted in a cyclical manner throughout the menstrual or estrus cycle in response to changing levels of estradiol and progesterone secreted from the ovaries (Devaud et al., 2006). Alcohol detrimental effects on developing brain as well as adult brains is the most serious concern. It is now well established that even uncomplicated alcoholics who have no specific neurological or hepatic problem show signs of brain damage and cognitive system (Nixon, 1994., Hommer et al., 1996). Recent studies using neuroimaging technology, magnetic resonance spectroscopy, positron emission topography
contributed significantly for understanding such changes. Further DNA micro-arrays and proteomics might also provide clues to this important problem (Berman et al., 1997 and Pfefferbaum et al., 2001).

Though the entire endocrine system is affected by alcohol consumption in males and females hypothalamic pituitary-gonadal and--adrenal axis are regarded as the main sites of actions of alcohol. Sarkola et al., (2001) suggested that liver should be included as a major site in acute endocrinological effects of alcohol on steroid hormones in women as the catabolism of steroid hormones is mediated by alcohol induced changes in the redox state in liver. Alcoholism has been shown to decrease testosterone in healthy man and an elevated Estradiol with a decrease in estrone levels in women during alcohol intake have been found.

Studies of Baer et al., (2001) and other studies reveal that moderate alcohol consumption decreases cardiovascular disease risk in post menopausal women by improving lipid profiles. Coldwell et al., (2005) have shown that alcohol use may affect male and female brains differently and also demonstrated that adolescent female may be somewhat more vulnerable to adverse alcohol effects with continued drinking, these adolescent may at an increased risk for behavioral deficits.

Augustynska et al., (2007) have explained that the menstrual cycle disturbances in alcoholic women are most prominent around the middle part of the cycle and age influences the pattern of hormonal changes Gill, (2000) has reported increased level of plasma Estradiol associated with alcohol intake in pre menopausal women.

The oxidokinetic data obtained by Onyesom and Emmanuel (2004) suggested that Nigerian women may be more susceptible to alcohol effect than Nigerian men and oral fructose seems promising in the treatment of Nigerian alcoholics. Aytacoglu et al., (2005) reported that high dose acute alcohol administration aggravates systemic and local oxidative stress leading to acute lung injury, ranging from mild pulmonary dysfunction to severe lung injury. It should be borne in mind that rapid onset of the acute respiratory distress syndrome (ARDS) may also be due to increased oxidative stress following alcohol abuse especially when ischemia of the extremities and traumatic accidents are concomitantly present. Therefore, precaution against ARDS may prevent morbidity and mortality in alcohol-induced lung damage in at-risk patients.
Reports reveal that chronic alcohol abuse results in morphological, metabolic and functional brain damage which may to some extent be reversible with early effects upon abstinence. Walter (2005) stated that gender represents an influencing factor and impacts on tolerance of a substance, on abuse patterns, dependence and disorders as well therapeutic programs. In general more men than women are alcohol dependent or have alcohol problems, but women are at greater risk for adverse effects and alcohol related diseases. Death rates among female alcoholics are 50-100% higher than those of men. Almost every third injury event in females and in almost every other event in males is alcohol-related, showing that alcohol plays an important part in fatal injuries in females even though it is mostly a male problem (Harmeet et al., 2006)


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