Alcohol abuse today

At present, alcohol plays a key role in issues of drug abuse. National and international epidemiological studies show the following emerging problems:

- Lowering of the age of first use of alcohol
- Increasing number of females who abuse alcohol
The drinking of alcohol is one of the most pressing problems in Western countries.
Alcohol problems are due to several factors:
• availability of alcoholic beverages
• social acceptance
• traditional use of alcohol in the culture
• genetics
• environmental factors

ITALY

(23 February, 2001: Italian law about alcohol problems)
Statistical data, years 2006-2007:

- Total alcohol consumed
- Percentages of young people and women who drink

At present, the mean annual consumption per person is 7.5 liters, which exceeds the OMS recommended limits of 6 liters per year for people above 15 years old and 0 liters for those fifteen and younger

From: Relation of Minister of Health to Parliament 10/12/2008
Italy 2007
ISTAT data, 17 April 2008.

68.2% of the sample - almost 49,000 individuals ages 11 and up - used alcohol at least one time in the previous 12 months.

19.9% of the 11-15 year olds in the sample declared use of alcohol at least once per year.

Comparison of data from 1998 and 2007 shows an increase of young women who drink:
- from 53.7% to 60.9% in the ages 18-19ys
- from 58.4% to 63.2% in the ages 20-24ys

At-risk behaviours

1. Daily alcohol use exceeding 3 units per day for men and 2 units per day for women
2. Alcohol use outside of meals
3. Binge drinking

Ages 11-17 years:
- 23.3% of males and 14.2% of females declared at least one at risk behaviour in the last year.
At-risk behaviours and ages

Mean of the whole population = 18.9%

Age differences:
18-34ys: 21.8%.
35-64 ys: 15.3%
Over 65 ys: 27.6%

(Age itself seems to be a factor in at-risk drinking)

Alcohol-drinking outside of meals

Ages 14-17 ys: Weekly use of alcohol outside of meals increased from 12.6% (1998) to 20.5% (2007) = +62.7%

Gender differences:
Girls: from 9.7% to 17.9% (+84.5%)
Boys: from 15.2% to 22.7% (+49.3%)

“Narrowing the gap” = the tendency toward the reduction of gender differences in alcohol use
**Woman and alcohol in Italy**

*today 67% of women drink alcohol instead of 43% in the 1980’s.*

*35-45 age range includes the most women who abuse alcohol. “Binge drinking” behavior is common both with friends and also ALONE.

*Education attained and women who drink:
  • Primary school: 43%
  • Higher Degree: 73.7%

(The gender gap in alcohol use is narrowing at the high school level)

---

**The new ways of drinking alcohol**
Drunkorexia is a slang term that describes the practice of restricting food intake in order to drink more alcohol. Young women court danger by substituting alcohol calories for food calories.

From: American Medical Association 2004
ALCOPOPS/GIRLIE DRINKS

- More hospital admissions for acute alcohol intoxications
  - More Sexually Transmitted Diseases
  - More hormonal disorders
  - More unwanted pregnancies under twenty

Are women more vulnerable than men to alcohol’s side-effects?

Much scientific evidence says YES
**ALCOHOL & WOMEN: Clinical evidence**

- Women, on equal terms of alcohol consumption, have more elevated BAC (Blood Alcohol Concentration) values than men.

- Women, on equal terms of BAC values, show worse results on driving tests, and so are at higher relative risk than men.

- Women develop a “telescopic” effect, that is more morbidity and mortality in a shorter time and with smaller quantities of alcohol than men.

- Women who abuse alcohol have more involvement than men in legal actions and in interpersonal approaches, and are easily victims of violence.

**...Why?**

- Body Mass Index and Body Water

- Sexual hormones

- Different activity of Alcohol Dehydrogenase (ADH)
Body Mass Index and Body Water

Women's bodies have more fat than men’s and less body water
After the same alcohol intake, female BAC is significantly higher than men’s

If BAC value is normalized according to the amount of body water, gender differences are flattened (Ely et al. 1999)

Sexual hormones

Estrogens affect enzymatic activity of alcohol dehydrogenase (ADH)

Estrogens worsen inflammatory response to ethanol thus increasing the risk of alcohol epathopathies (steatosis, inflammation and necrosis)

Hormonal changes affect alcohol metabolism; some studies show that BAC varies according to the phases of menstrual cycle

Differences in hormonal pattern may be responsible for the lowered threshold of alcohol toxicity and/or of the different effects on the brain.
…sexual hormones

Long-time alcohol use affects fertility, induces early menopause and increases significantly the risk of breast cancer.

Alcohol use may be responsible for delay in menarche.

The frequency of menstrual alterations is dose-related with alcohol use.

The use of oral contraceptives may worsen alcohol liver injury by hormonal increase of intestinal-derived endotoxins.

Enzymatic activity: gastric ADH

During the so-called First Pass Metabolism (first step of ethanol metabolism) in the stomach, part of the ethanol is metabolized by the gastric isoenzyme of ADH before reaching the liver.

Gender differences:
- Activity of gastric ADH of women is significantly lower than men and is close to zero in heavy-drinking females.
- Activity is age-dependent with significant gender differences.
Age, gender and ADH activity in “social drinkers” (alcohol use < 0.4 g/Kg/die).
Source: Parlesak A. et al., 2002

Alcohol damages: liver and brain

- Over the last 40 years, much has been achieved in highlighting and treating the effects of alcohol on the liver
- Recent alcohol studies have been improving our knowledge about alcohol-related brain damages, which are often underestimated.

Alcohol related brain damage is fundamental and its long-lasting effects on individuals, and consequently on the whole society, are deeply deleterious.
ALCOHOL AND THE BRAIN

Alcohol related brain damage is a heterogeneous condition due to multiple mechanisms, and it manifests itself differently across the life-span. In particular:

- Alcohol affects the developing fetal brain, causing damages ranging from Fetal Alcohol Spectrum Disorders to Fetal Alcohol Syndrome

- Alcohol affects the adolescent brain interfering with the normal brain maturation processes and compromising future well-being

- The severity of alcohol brain damage is strongly related to other co-factors such as gender and nutrition
Alcohol, brain damage and gender differences

“The differences in brain volumes between alcoholic women and nonalcoholic women were greater than the differences between alcoholic men and nonalcoholic men.” (Hommer et al. Am J Psychiatry 2001)

• Women are at risk of blackouts and memory lapses more than men even when they assume comparable amounts of alcohol. (NIAAA, 2004)

Brain changes during adolescence

- During adolescence, brain connection and signaling mechanisms selectively change over time to meet the needs of the environment
- In this period cognitive control over high-risk behaviors is still maturing making teen agers more prone to engage in risky behaviours and more vulnerable to psychological disorders.
Are girls more vulnerable than boys to the effects of alcohol?

1. More vulnerability to stress
2. More damages to cognition and memory after a shorter time of drinking alcohol
3. More vulnerability to depression
4. More vulnerability to brain changes (on account of lower volume of hippocampus)

The risk of future alcoholism increases with the amount of alcohol consumed. It was demonstrated that the risk for women increased significantly at 1-7 drinks/week. The risk for men increased significantly at more than 22 drinks/week. (Flensborg-Madsen et al 2007)
How can at-risk drinking be recognized?

TO BEAR IN MIND

• Health problems due to alcohol use are common in clinical practice but early-phase harmful drinking is frequently missed

• Men and especially women try to hide their harmful drinking and so most individuals with alcohol problems do not receive formal alcohol treatment.
TOOLS

• **Questionnaires**: are very useful to evaluate patterns of drinking but are affected by subjectivity

• **Biomarkers**: selected laboratory markers of alcohol abuse are invaluable tools to identify at-risk drinking. Up till now, no biomarker alone has been suitable to make the diagnosis of alcohol abuse.

THE STATE OF THE ART

Many studies about alcohol biomarkers included only male subjects, but results have been generalized to both sexes.

Gender studies are needed and, in particular, studies during pregnancy have to be promoted to define sex-specific limits.
BIOMARKERS OF ALCOHOL ABUSE

• **MARKERS OF EXPOSURE**: blood ethanol, methanol, acetaldehyde, ethanol metabolites

• **MARKERS OF EFFECT**: acetaldehyde adducts, modified hematological- enzymatic- immunological parameters

• **MARKERS OF SUSCEPTIBILITY**: genetic polymorphisms (CYP3E1, ADH, Serotonin transporters, Dopamine receptors )
BLOOD ALCOHOL

- Short half-life

- Metabolic rate depending on age, sex, body mass index, general health status, and environmental conditions

- Gender differences may be strongly significant at the same alcohol intake.

BAC after the same alcohol intake
Gamma Glutamyl Transferase

- Good Sensitivity: increases with alcohol abuse.
- Low specificity: increases also in the case of non-alcoholic epatopaties, diabetes, obesity. It’s inducible by drugs as barbiturates, antiepileptics, anticoagulants.

It returns to reference limits after 20-30 days of withdrawal.

During pregnancy, GGT values may become low even in alcoholic women

Mean Corpuscolar Volume

Good sensitivity: it’s increased by direct toxic action of ethanol on the production of precursors and on erythrocytes morphology. It returns within limits after almost three months of withdrawal.

Low specificity: its increase may be due also to vitamine B12 and folate deficiency, liver diseases, tabagism, hypothyroidism, reticulocytosis.
Carbohydrate Deficient Transferrin

-A very popular marker of alcohol abuse. CDT increases in case of alcohol abuse

In MEN: effective marker with high specificity and sensitivity

In WOMEN: less effective. Iron deficiency and hormonal status play a significant role in gender differences.
- Female CDT decreases after menopause and when contraceptives are used.
- Female CDT increases in pre-menopausal phase.
- Female CDT changes in different menstrual phases and reaches the maximum level during menstruation
- During pregnancy CDT increases independently of alcohol intake

CDT, Pattern of alcohol use and gender differences

MEN: CDT increase depends both on drinking intensity (drinks per day) and frequency (days per month).

WOMEN CDT increase depends on intensity much more than on frequency.

Importance of “binge drinking” as further risk factor
Blood Lipid Profile

- It’s modified by alcohol intake according to dose, individual susceptibility, genetic factors and diet.

Generally, alcohol abuse generates:

- **Triglycerides**
- **HDL cholesterol**

Immunity

Alcoholics frequently suffer from infectious diseases, auto-immune diseases and have increased rates of some cancers. All these indicate that alcohol impairs the immune system.

The adducts formed by proteins with aldehydes and hydroxyl radicals stimulate immunological responses both for IgA and IgG. IgA titres are elevated in 69% of alcoholic liver diseases.
Clinical studies

Recent studies have demonstrated that, both in vivo and in vitro, ethanol impairs the maturation of dendritic cells and compromises the immuno-defences.


Promising biomarkers

- **FAEE** (Fatty Acid Ethyl Esters): non oxidative metabolic products resulting from the interaction between alcohol and fatty acids. FAEE are sensitive and specific markers to distinguish social drinkers from abusers. They are present also in meconium.

- **EtG** (Ethyl Glucoronide): direct metabolite of alcohol can be detected in blood (36h), urine (5 giorni) after heavy alcohol use, and hair

- **PEth** (Posphatidylethanol): an abnormal phospholipid formed in cell membranes in the presence of ethanol. It’s a candidate as a higly specific and sensitive alcohol marker detectable in blood
**PROTEOMICS**

Proteomics allows us to know the mechanisms of alcohol-related brain damage at the level of protein expression.

Recent studies identified alteration of the protein expression profiles in each brain region.

(Matsumoto I, Alc&Alc 2009)

**EDAC INDEX**

- Early
- Detection
- Alcohol
- Consumption

- It’s a mathematical combination of the results of routine laboratory analyses (GGT, MCV, AST/ALT..), since there is no “gold standard” method of diagnosis.
... the environment

- Nutrition
- Pollution

Alcohol and nutritional factors

Deficiency of Thiamine (Vitamin B1)
Thiamine (Vitamin B1)

- Water soluble vitamin synthesized by plants and microorganisms but not by mammals, including man

- Thiamine is present in the organism as free thiamine (T), monophosphate ester (TMP), diphosphate ester (TDP) and trifososphate ester (TTP), which play major roles as coenzymes in three major enzymatic complexes:
  - Piruvate dehydrogenase
  - Alfa-ketoglutarate dehydrogenase
  - Transketolase

Alcohol and thiamine deficiency (TD)

Brain receives energy from aerobic oxidation of glucose and so it’s the first organ affected by TD

- TD produces heavy brain damage as the Wernicke-Korsakoff syndrome, but clinical symptoms of TD are frequently ill-defined and most cases of WKS are diagnosed only post-mortem

- In western countries, thiamine deficiency (TD) is due in most cases to alcohol abuse in consequence of poor nutrition, decreased absorption, liver diseases, and impaired phosphorilation
Whole blood samples from a series of patients diagnosed as alcohol dependent by DSM IV, were examined.

Their age of onset of heavy drinking (21.3 ys for males and 32.5 for females) was significantly different (p<0.005).

The mean age of men and women was close (males= 45.5 ys; females= 47.6) so that the duration of females’ heavy drinking was about ten years shorter than males’, with a tendency towards a gender effect (p=0.07).

T and TDP in alcoholics resulted significantly lower than controls (p<10^-5). So TDP can be proposed as an effective alcohol biomarker to be used in combination with other well-established markers such as MCV, CDT, GGT.

Differences were found between male and female alcoholics and were confirmed by the analysis of ROC curves.

Thiamine deficiency may be enhanced during pregnancy by poor nutritional status (e.g. due to hyperemesis gravidarum) and may be a further risk for alcohol teratogenic effects (Fetal Alcohol Spectrum Disorders, FASD).

Alcohol damage on female health seems stronger than on male (AUC), notwithstanding shorter duration of female alcohol abuse. This is consistent with the so-called “telescoping effect”.

ROC curves: gender differences

T and TDP ROC curves: females AUC were greater than male ones (p<0.0005)

Alcohol and pollution
Lead is one of the more toxic metals to human health. It may increase in chronic alcohol abuse, because of a reduced availability or activity of regulatory essential nutrients and substances. In the last decade lead levels in the general population lowered in consequence of many regulatory limits.

**EFFECTS**

- Prenatal and postnatal development are compromised significantly by long exposure.
- Cognitive performance is affected, and even the risk of developing psychiatric disease such as schizophrenia is debated.
- It was demonstrated that lead exposure, like prenatal exposure to alcohol, affects cognitive performances severely in children and may trigger antisocial behavior in adolescence.

*Today, can alcohol abuse still be considered a risk factor of lead toxicity?*

---

**Lead Level & reference values: gender differences**

Mancinelli R et al. (Alcohol & Alcohol, in press 2009)
In a nutshell…

- **Thiamine** is an effective antidote against lead intoxication, but this vitamin is dramatically reduced in alcoholics, because of both malnutrition and impaired phosphorilation. Thiamine deficit is more severe in alcoholic women,
- **Lead**: is higher in the alcoholic population. Among alcoholic women it results almost threefold the reference value

**Alcohol abuse, thiamine deficiency, and high lead levels are worse in women and can have synergic teratogenic effect.**

Alcohol and pregnancy

In western countries prenatal alcohol exposure is the first preventable cause of mental retardation and of many physical and neurological permanent disabilities (FASD) in children.

Graphic Production: M. delle Femmine
Istituto Superiore di Sanità. Roma
Does a “safe alcohol dose” in pregnancy exist?

• Adverse effects can occur also with *moderate* drinking and a safe dose in pregnancy is not defined.
• So the unique prescription is:
  **Alcohol Abstinence During Pregnancy**

---

**Fetal Alcohol Syndrome: new evidences**
FAS: Prevalence in Italy

The epidemiology study carried out on almost 1000 children of 25 primary schools in the Lazio region (2003-2005) show that estimated prevalence of FAS was 0.4% and, the prevalence of Fetal Alcohol Spectrum Disorders (FASD) was almost 3.5%.

This exceeds previously published estimates of both FAS and FASD for the western world.


Prenatal alcohol exposure: recent studies on neurotrophic factors

Mice brain alterations were investigated for Nerve Growth Factor (NGF) and Brain Derived Neurotrophic Factor (BDNF).

It was compared chronic prenatal exposure to ethanol solution (11%) and to red wine (11%) starting 60 days before pregnancy and lasting up to pups’ weaning.

*Mancinelli R et al.. Neurotoxicology 2009
Results: in vivo

Animals exposed to only ethanol had disrupted levels of both NGF and BDNF in the hippocampus and other brain areas, impaired ChAT immunopositivity and altered cognition and emotional behavior.

Mice exposed to red wine had no change in behavior or in ChAT immunopositivity and a mild NGF decrease in the cortex.

ChAT= CholineAcetylTransferase

Mancinelli R et al.. Neurotoxicology 2009

Results: in vitro

Neuritis outgrowth in PC-12 cells exposed in the medium to ethanol, red wine and sucrose with and without NGF.

Note the high presence of neuritis in the mediums containing sucrose+NGF and red wine+NGF compared to the low presence of neuritis in the medium containing ethanol+NGF.

THE DATA SUGGESTS THAT RED WINE EFFECTS ARE LOWER THAN ETHANOL EFFECTS. THESE DIFFERENCES COULD BE RELATED TO COMPOUNDS WITH ANTIOXIDANT PROPERTIES IN THE RED WINE.

Mancinelli R et al.. Neurotoxicology 2009
...and long-lasting effects

- Long-lasting damage induced by early exposure to ethanol solution and red wine was studied to investigate differences in NGF, BDNF, HGF and VEGF in 18 month-old mice.
- **Ethanol** per se elevated significantly NGF, BDNF, HGF and VEGF in brain limbic system areas, and significantly decreased BDNF and VEGF in the liver.
- **Red wine** significantly decreased liver BDNF and VEGF in the liver and kidneys, but no damage was observed in hippocampus and frontal cortex.

HGF= Hepatocyte Growth Factor
VEGF= Vascular Endothelial Growth Factor

In summation....

**Alcohol and biomarkers**

- Early diagnosis of alcohol abuse is very difficult.
- There is not a “gold standard” biomarker that is able to discriminate by itself harmful drinking.
- Other parameters, such as blood thiamine and lead level, can be also effective markers of alcohol abuse.
- The best strategy seems to be the use of questionnaires in combination with a panel of different alcohol biomarkers.
- Everything suggests that being a woman and pregnancy are highly significant risk factors for alcohol damage.
- The most recent alcohol studies collectively show the need to improve research about gender differences and pregnancy.
**Prevention: what strategy?**

- Alcohol drinking is not quite like “Il Paese dei Balocchi” (“Toyland” in the story *Pinocchio*). As for Pinocchio in Toyland, the days after binge drinking may be very, very difficult…but unlike Pinocchio, one may not be able to leave the negative effects of alcohol behind.

---

**Information is the best prevention**

- The public, especially the young, must be informed about how alcohol affects the brain.

- All members of professions (medical, educational, …) who are likely to be responsible for public health must make a contribution and use all the available scientific tools to improve knowledge and to promote the prevention of alcohol abuse.
THANKS

Experimental research was supported by the collaborative Project ISS-NIH “Woman, health, alcohol. Risks and damages from alcohol in different woman ages: the role of abuse markers” (to RM), involving researchers from

- Istituto Superiore di Sanità (Rome),
- University “Sapienza” (Rome) and
- Istituto di Neurobiologia e Medicina Molecolare (CNR-Rome)

Gaspar Van Wittel: A view of Rome