

GENDER DIFFERENCES: DOES ALCOHOL AFFECT FEMALES MORE THAN MALES?

Henriette Walter, Alexander Dvorak, Karin Gutierrez, Werner Zitterl, Otto Michael Lesch

Vienna University, Department of Psychiatry

Érkezett: 2005. 05. 20.

Elfogadva: 2005. 06. 02.

NEMI KÜLÖNBBSÉGEK: ERŐSEBB AZ ALKOHOL HATÁSA NŐKNÉL MINT FÉRFIAKNÁL?

Az emberi tényező komplex, sok-sok pszichopatológiai és szociális faktor, valamint farmakológiai hatás befolyása alatt áll. Így a dependencia kifejlődése is bonyolult folyamat eredménye. A nemi tényezők is erős hatással vannak az egyes anyagok effektusára; a tolerancia, a dependencia és az addikció kialakulására, ennek megfelelően alakítandó a terápiás stratégia is. Tudott, hogy több férfi szenved alkohol dependenciában, de a nőknél több a mellékhatás és az alkohol okozta betegség, így a halálest is.

KULCSSZAVAK: nemi különbségek, krónikus alkohol dependencia, Lesch féle pontozás

SUMMARY

Human substance use is complex, being influenced by many psychopathological and sociological factors as well as the substance's pharmacological effects. Dependence development is not attributable directly to the consumed substance, but takes also all the other issues into regard. One of all these issues might be that gender represents an influencing factor and impacts on tolerance of a substance, on abuse patterns and finally on development of dependence as well as on addiction related disorders. Therapeutic programs' needs might be different too. 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 to 100 percent higher than those of men. Major impairments, diagnosis, medical and psychosocial consequences and their implication on treatment will be outlined.

EPIDEMIOLOGY

Though in all age groups women consume less alcohol than men, women may be at greater risk for adverse effects and alcohol related diseases. Also the number of alcohol drinking women is lower, with the exception of young women. Herbst (1996) could show that the prevalence rates for women in the age group between 18 and 20 years is higher (3,4%) in contrast to men of this age group (2,4%). Between 21 and 24 the rate becomes inverse (2,9% women and 7,3% men). For adults government surveys in most countries report about three times as many male than female alcoholics, but the number of female alcoholics is rising (Morhard-Klute and Soyka, 2002). According to the Munich follow-up study 13% of all adults, aged 25-64 years, have a life-time prevalence for alcohol abuse, whereby 5.1% of the fe-

male and 21% of the male population are concerned (Bronisch and Wittchen, 1992).

The medium interval from first drink to onset of dependence is shorter for women (3.0 years) than for men (3.6 years) (Dawson 1996).

DRINKING WOMEN HAVE HIGHER RISKS FOR PHYSIOLOGICAL IMPAIRMENTS

Women become more impaired than men after drinking the same amount of alcohol, even when differences in body weight are taken into account (Hommer et al. 2001; Tapert et al 2001; Péquignot et al. 1974). Drinking women have a higher risk for developing alcohol related diseases and women become intoxicated already after drinking lower quantities of alcohol than men (Walter et al. 2003). The three major explanations for this phenomenon are that:

1) Women have a lower total body water, wherefore alcohol is diluted less and blood alcohol levels may be up to 30% higher in women than in men (Ely et al. 1999);

2) Women develop more liver damage, which is associated with more liver fatty acids under alcohol (Ma et al. 1993, 1999) and a different first-pass metabolism, because of an oestrogen caused diminished gastric alcohol-dehydrogenase (ADH) activity (Saunders et al. 1981; Temple 1994). But gastric ADH decreases with age in men, so that this gender difference is found only in younger people (Seitz and Poschl 1997). The quantitative relevance of the first pass metabolism, however, is controversial, particularly because gastric ADH plays a major role at low doses of alcohol and because other first pass enzymes involved are active only at very high blood alcohol levels.

3) Fluctuations in gonadal hormone levels may affect the rate of alcohol metabolism (Saunders et al. 1981; Mello et al. 1993). It should also be mentioned, that alcohol increases the conversion of testosterone into oestradiol (Gordon 1979).

Heavy alcohol consumption leads to irregular menstruation cycles, anovulatory cycles, risk of spontaneous abortions, risk for FAE/FAS in their children, rapid serum glucose changes and a disturbance of vitamin D metabolism, resulting in an inadequate absorption of dietary calcium, which consequently raises the risk of an early development of osteoporosis (Streissguth et al. 1980, 1994; O'Keefe, Marks 1977; Adams, Hirst 1984). Additionally, liver diseases also affect bone metabolism and alcohol is also directly toxic to bone forming cells, inhibiting their activity. Intoxicating drinking patterns with ingestion of large amounts of alcohol is followed by a parathyroid hormone deficiency and an increased urinary calcium excretion.

Rivier (1996) found in a series of rat studies, that alcohol over-stimulates the hormonal cascade of the hypothalamus–pituitary–adrenal (HPA) axis far more in females than in males. One of the last hormones in this cascade is cortisol. Chronically increased cortisol release can produce mild brain damage (Wright 1978). White and especially gray matter differences were found by Hommer et al. (2001) to be present in alcoholic women. Furthermore irritations of the HPA-axis are related to symptoms of the spectrum of affective disorders. Cornelius et al. (1995) and Greenwood (1999) could show, that the scores for suicidal risk, impulsivity, low self esteem, cognitive performance and negligence are higher in de-

pressed alcohol dependent patients when compared to depressed non-alcohol dependent patients.

Out of all these reasons the World Health Organisation recommends a maximum of 20 g/day alcohol for a low risk intake in women (Bühringer et al. 2000).

DIAGNOSTIC DISTRIBUTION AND THERAPEUTIC RELEVANCE

Typologies show mainly, that the proportion of negative affect alcoholics is greater in women (14,6%) than in men (8%) (Cloninger et al. 1998, Kendler et al 1992, Heath et al. 1997). In 250 alcohol dependent patients, the distribution of the 4 types according to Lesch was investigated. In the types I and II the male/female ratio was nearly equal. Significantly more female patients could be attributed to type III (24,8% females versus 12,0% males). Type III patients drink episodically, are social drinkers, rather depressed (either episodes or a predominance of depressive personality traits), with frequent suicidal tendencies, ingesting alcohol for “self-treatment” of negative affects or to get “access” to inner perceptions and feelings (Lesch et al. 1988, 1996). This finding is in line with the results of Schutte et al as well as Skaff et al, who found in alcohol dependent women more symptoms of depression than in alcohol dependent men (Schutte et al. 1995; Skaff et al. 1999). Type IV comprised significantly more males (29,6% males versus 11,2% females) (Sperling et al. 2000). This unequal distribution underlines the necessity of taking gender differences into account for therapy planning and to pay special attention even to discrete symptoms from the affective spectrum.

A multicenter placebo controlled study on flupenthixol (n=281) applied the Lesch typology in 134 patients (Wiesbeck et al. 2001). The distribution of female patients was nearly equal for the types I to III (Type I: 31.3%; Type II: 29.7%; Type III: 28.8% female patients), whereby the low overall number of female patients has to be regarded. Of importance is that no female patient could be attributed to type IV. This finding of a lack of women in type IV, underlines Sperling's results. In the types I and III flupenthixol administration doubled the relapse rates for men and women. In type II this applies only for men. There was no negative influence of flupenthixol on type II alcohol dependent women (Lesch-Type II patients are anxious or phobic, but not depressed). In the over-

all results of the placebo group female patients had a far higher relapse rate (64.3%) than male patients. The flupenthixol group did not show these differences (male relapsers: 70.1%, female relapsers 74.3%). If we suppose that the placebo group may mirror the natural illness course, we can interpret, that the female study attendants indeed had a worse natural illness course than male study attendants. These results indicate gender as being one of the major factors important for consideration in therapeutic strategies.

SOCIAL AND TREATMENT FACTORS

Feuerlein et al (1999) state, that in 30% of alcohol dependent women a drinking partner can be found. Treatment centers are under-utilised by women (Dawson, 1996a). Beckmann and Amaro found, that women experience more difficulties when entering alcoholism treatment settings (Beckmann and Amaro 1986). Barriers for women seem to be the social stigma and the fear to lose the right to care for their children, once an alcohol problem is identified (Poland et al. 1993).

For therapy women in contrast to men, are less frequently motivated by their partners, but more frequently by their parents or children. One of the most striking gender differences in this respect is a much stronger impact of friendship for women than for men in all aspects of functioning (Skaff et al. 1999). Better children's health and good child-parent relationships were found to be consistent predictors of subsequent mother's reduced drinking and better psychic states (Timko et al. 2000).

Concerning treatment outcome women tend to be more abstinent in self control systems, to have a higher abstinence rate during the first year of follow up and a lower abstinence rate later on (Brennan et al. 1993). After three months of follow up the fact of being married was found to be protective for men, while it might represent a risk factor for women (Schneider et al. 1995). Leonard and Roberts (1998) investigated the effects of alcohol on aggressive couples and found more negative behaviour and more negative reciprocity. Under the influence of alcohol the husbands, but not the wives, increased their problem-solving attempts.

The most potent predictive factors for early substance experimentation among young women in alcoholism treatment were adolescent impulse control problems or distinct acting-out behaviours (Walton and Gombert 1994).

Brennan et al. (1993) focused on gender differences and life contexts of late-life problem drink-

ers: Late-middle-aged women with drinking problems consumed less alcohol, had fewer drinking problems, and reported more recent onset of drinking problems than did their male counterparts. They also used more psychoactive medications, were more depressed, and were less likely to seek alcoholism treatment. Consistent with a gender role perspective on alcohol abuse, problem-drinking women had more family-related and fewer financial stressors than did problem-drinking men. Contrary to expectation, however, problem-drinking women reported more support from children, extended family members and friends, than did problem-drinking men. Moreover, women who continued to have drinking problems over a one-year interval reported some unexpected short-term benefits at follow-up, including reduced spouse stressors. Women who had remitted at follow-up experienced less spouse support, and more family-related stressors and depression than did remitted men. They also lost support from extended family members over the 1-year interval. The results suggest a need for screening and treatment efforts tailored more closely to the life circumstances of women with late-life drinking problems. Brennan et al. further found in 1999, that late middle aged women reduce drinking mainly because of health problems, whereas men's reduction of alcohol consumption was related mainly to the presence of financial stressors (Brennan et al. 1999).

DISCUSSION AND OUTLOOK

Alcohol research involving humans as well as animals has been dominated by investigations of males. Only recently the effort has increased to include women in study populations (Kendler et al. 1992) and also to study the behavioural and biological mechanisms for alcohol intake in female animals (Devaud et al. 1998). Early conclusions from these studies document increased vulnerability of women regarding alcohol induced damage. Within a shorter period of drinking and with less overall intake of alcohol, females are more vulnerable to the development of liver cirrhosis and brain damage due to alcohol abuse (Norton et al. 1987). These effects can occur even in moderate drinkers (Harper et al. 1990). The reasons for differential risk for the consequences of alcohol intake for males and females still need more explanations. Social factors, which have played a part in concealing problems associated with alco-

holism of women as well as the research focus on males, have limited larger studies of alcohol abusing or dependent women. This deficiency has resulted in a deficit of information regarding the drinking women in our society.

Alcoholism research has begun to recognise the importance of gender related aspects and is on the way to contribute to a more individual and specific treatment for all population members. The application of diagnostic subgroups might be one basic step in this direction, rendering more homogeneous patient groups for all kinds of further investigations. Our data from studies, using the Lesch alcoholism typology, show a preponderance of female patients in type III, which has a clear impact on therapeutic strategies for alcohol dependent women (Lesch et al. 2001). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) indicates the following areas, that need further research: (1) male/female patterns alcohol

intake, (2) determining the genetic bases of gender differences in alcoholism, (3) investigation of the hormonal influences on female/male responses to alcohol, (4) role of neurotransmitters and peptide systems in sex-related differences in alcohol intake and/or response to alcohol intake. Further investigations, focussing on gender differences in motivation to enter and adhere to treatment programs, as well as in basis research. A focus on gender differences in therapy research could lead to a development of gender specific therapeutic interventions.

Author's address:
Prof. Dr. H. Walter
Medical University of Vienna
Department of Psychiatry
Waehringer Guertel 18-20;
A-1090 Vienna, Austria
e-mail: henriette.walter@meduniwien.ac.at

REFERENCES

- Adams MA, Hirst M (1984) Adrenal and urinary catecholamines during and after severe ethanol intoxication in rats: A profile of changes. *Pharmacology, Biochemistry and Behavior* 21/1: 125-131
- Beckmann LJ, Amaro H (1986) Personal and social difficulties faced by women and men entering alcoholism treatment. *J Stud Alcohol* 47/2: 135-145
- Brennan PL, Moos RH, Kim JY (1993) Gender differences in the individual characteristics and life contexts of middle-aged and older problem drinkers. *Addiction*, 88/6: 781-90
- Brennan PL, Schutte KK., Moos RH. (1999) Reciprocal relations between stressors and drinking behavior: a three-wave panel study of late middle-aged and older women and men. *Addiction* 94/5: 737-749
- Bronisch T-H, Wittchen HU. (1992) Lifetime and 6-month prevalence of abuse and dependence of alcohol in the Munich Follow-up Study. *Europ Arch Psychiatr Clin Neurosci* 241: 273-282
- Bühringer G, Augustin R, Bergmann E, Bloomfield K, Funk W, Junge B, Kraus L, Merfert-Diete C, Rumpf H-J, Simon R und Töppich J. (2000) Alkoholkonsum und alkoholbezogene Störungen in Deutschland. Band 128 der Schriftenreihe des Bundesministeriums für Gesundheit. Baden-Baden: Nomos.
- Cloninger CR, Bayon C, Svrakic DM (1998) Measurement of temperament and character in mood disorders: a model of fundamental states as personality types. *J Affect Disord*, 51/1:21-32.
- Cornelius J, Salloum I, Cornelius M, Fabrega H, Ehler J, Ulrich R, Thase M, Mann J (1995) Disproportionate suicidality in patients with comorbid major depression and alcoholism. *Am J Psychiatry* 152/3: 358-364
- Dawson D. (1996) Gender differences in the probability of alcohol treatment. *J Substance Abuse* 8/2: 311-225
- Dawson D (1996a) Gender differences in the risk of alcohol dependence: United States, 1992. *Addiction* 91/12: 1831-1842
- Devaud LL, Fritschy JM, Morrow AL (1998) Influence of gender on chronic alcohol-induced alterations in GABAA receptors in rats. *Brain Res*,15;796/1-2:222-30
- Ely M, Hardy R, Longford NT and Wadsworth MEJ. (1999) Gender differences in the relationship between alcohol consumption and drink problems are largely accounted for by body water. *Alcohol and Alcoholism* 34/6: 894-902
- Feuerlein, W., Dittmar F, Soyka M. (1999) Wenn Alkohol zum Problem wird. Georg Thieme Verlag, Stuttgart
- Gorwood, Ph. (1999) Alcooldépendence et depression. *La Revue du praticien* 49: 391-394
- Gordon GG, Vittek J, Ho R, Rosenthal WS, Southren AL, Lieber CS. (1979) Effect of chronic alcohol use on hepatic testosterone 5-alpha-A-ring reductase in the baboon and in the human being. *Gastroenterology* 77/1: 110-114
- Harper CG, Smith NA, Kril JJ (1990) The effects of alcohol on the human brain: A neuropathological study. *Alcohol and Alcoholism* 25:445-448
- Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, Statham DJ, Dunne MP, Whitfield JB, Martin NG (1997) Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychol Med.*, 27/6:1381-1396.
- Herbst K (1995) Repräsentativerhebung 1994 zum Konsum und Mißbrauch von illegalen Drogen, alkoholischen Getränken, Medikamenten und Tabakwaren. In: Deutsche Hauptstelle gegen die Suchtgefahren. Jahrbuch SUCHT 1996. Neuland, Geesthacht.
- Hommer DW, Momenan R, Kaiser E, Rawlings R. (2001) Evidence for a gender-related effect of alcoholism on brain volumes. *The American Journal of Psychiatry* 158/2: 198-204
- Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ. (1992) A population-based twin study of alcoholism in women. *JAMA* 268:1877-1882
- Leonard KE, Roberts LJ. (1998) The effects of alcohol on the marital interactions of aggressive and nonaggressive husbands and their wives. *Journal Abnorm Psychol* 107/4: 602-607
- Lesch OM, Dietzel M, Musalek M, Walter H, Zeiler K. (1988) The course

- of alcoholism. Long term prognosis in different types. *Forensic Science International*, 36, 121-138
- Lesch OM, Walter H. and Rommelspacher H. (1996) Alcohol abuse and alcohol dependence. *Bailliere's Clinical Psychiatry* (Eds. H. Rommelspacher and M. Schuckit), Chapter 3 "Drugs of abuse". Bailliere Tindall, London, Philadelphia, Sydney, Tokio, Toronto: p: 421-444
- Lesch OM, Riegler A, Gutierrez K, Hertling I, Ramskogler K, Semler B, Zoghalmi A, Benda N. and H Walter (2001) The European Acamprosate trials: conclusions for research and therapy. *J. of Biomed Science* 8/1: 89-95
- Ma X, Baraona E, Goozner BG, Lieber CS. (1999) Gender differences in medium chain dicarboxylic aciduria in alcoholic men and women. *The American Journal of medicine* 106: 70-75
- Ma XL, Baraona E, Goozner BG, Lieber CS. (1993) Alcohol consumption enhances fatty acid β -oxidation, with a greater increase in male, than in female rats. *Hepatology* 18: 1247-1253
- Mello NK, Mendelson JH and Teoh SK. (1993) An overview of the effects of alcohol on neuroendocrine function in women. In: Zakhari S. (Ed.) *Alcohol and the Endocrine System*. National Institute on Alcohol Abuse and Alcoholism Research Monograph No. 23 NIH Pub. No 93-3533. Bethesda, MD: National Institutes of Health, 1993. pp: 139-170
- Morhard-Klute V, Soyka M. (2002). *Alkoholismus bei Frauen - Epidemiologie, Klinisches Erscheinungsbild und Therapie*. *Journal für Neurologie, Neurochirurgie und Psychiatrie*. 3.Jg./1:36-41
- Norton R, Dwyer T, MacMahon S. (1987) Alcohol consumption and the risk of alcohol related cirrhosis in women. *Brit Med J* 295:80-82
- O'Keefe SJ and Marks V (1977) Lunchtime gin and tonic, a cause of reactive hypoglycaemia. *Lancet* 1/8025: 1286-1288
- Péquignot G, Chabert C, Eydoux H, Courcol MQ. (1974) Augmentation du risque de cirrhose en fonction de la ration d'alcool. *Revue de l'Alcoolisme* 20:191-202
- Poland ML, Dombrowski MP, Ager JW, Sokol RJ. (1993) Punishing pregnant drug users: enhancing the flight from care. *Drug Alcohol Depend* 31/3: 199-203
- Rivier C. (1996) Alcohol stimulates ACTH secretion in the rat: mechanisms of action and interactions with other stimuli. *Alcohol Clin Exp Res* 20/2: 240 - 254
- Saunders, JB, Davis M, and Williams R. (1981) Do women develop alcoholic liver disease more readily than men. *British Medical Journal* 282: 1140-1143
- Schneider KM, Kviz FJ, Isola ML, Filstead WJ (1995) Evaluating multiple outcomes and gender differences in alcoholism treatment. *Addict Behav* 20/1: 1-21
- Schutte KK, Moos RH, Brennan PL. (1995) Depression and drinking behavior among women and men: a three-wave longitudinal study of older adults. *J Consult Clin Psychol*. 63/5: 810-822
- Seitz HK, Poschl G. (1997) The role of gastrointestinal factors in alcohol metabolism. *Alcohol and Alcoholism* 32/5: 543-549
- Skaff MM, Finney JW, Moos RH (1999) Gender differences in problem drinking and depression: different "vulnerabilities?" *American Journal of Community Psychol*. 27/1: 25-54
- Sperling W., Frank H, Martus P, Mader R, Barocka A, Walter H. and Lesch OM. (2000) The concept of abnormal hemispheric organization in addiction research. *Alcohol Alcoholism* 35/4: 394-399
- nicotine, and caffeine use during pregnancy on infant mental and motor development at eight months. *Alcohol Clin. Exp. Res.* 4/2: 152-164
- Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, Feldman J., Mirsky AF (1994) Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring - a longitudinal prospective study. *Alcohol Clin Exp Res* 18/1: 202-218
- Tapert SF, Brown GG, Kindermann SS, Cheung EH, Lawrence RF, Brown SA. (2001) fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clin and Exp Res* 25: 236-245
- Temple, D (1994) Why women must rethink their second drink. *Search* 25: 149-150
- Timko C, Kaplowitz MS, Moos RH. (2000) Children's health and child-parent relationships as predictors of problem-drinking mothers' and fathers' long-term adaptation. *J. Subst Abuse* 11/1: 103-121
- Walter H, Gutierrez K, Ramskogler K, Hertling H, Dvorak A and OM Lesch (2003) Gender specific differences in alcoholism: Implications for treatment. *Archives of Woman Mental Health* 6:253-258
- Walton MA, Gomberg ESL. (1994) Determinants of early alcohol and drug use among young women in alcoholism treatment. *Journal of Substance Abuse* 6: 367-379
- Wiesbeck GA, Weijers HG, Lesch OM, Glaser T, Toennes PJ and Boening J. (2001) Flupethixol decanoate and relapse prevention in alcoholics: results from a placebo-controlled study. *Alcohol and Alcoholism* 36/4: 329-334
- Wright J. (1978) Endocrine effects of alcohol. *Clin Endocrinol Metab.* 7/2: 351-367