



Snips from the journals

Update on alcohol

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Alcohol use disorders and the course of depressive and anxiety disorders (1).

The aim of this study was to determine whether the course of depressive and/or anxiety disorders is conditional on the type (abuse or dependence) or severity of comorbid alcohol use disorders. The participants of this study were part of an ongoing cohort study in the Netherlands, aimed at examining long-term course of depressive and anxiety disorders in the adult population (18-65 years), and were recruited from the community, primary care and outpatient care. A total of 1369 participants were included at baseline, which consisted of the following groups: a healthy control group, people with a past history of depressive and/or anxiety disorder, and people with current depressive and/or anxiety disorder. Baseline assessment included a face-to-face assessment and a standardised psychiatric interview. Follow up assessment occurred after 2 years, again in the form of a face-to-face assessment. The presence of a depressive or anxiety disorder at baseline was established using the CIDI version 2.1, based on DSM-IV criteria. This assessment was repeated at 2-year follow up, and participants were considered to have a persistent disorder if they met DSM-IV criteria for depressive and/or anxiety disorder in the 6 months prior to the 2-year follow up assessment. Alcohol use disorder was diagnosed at baseline according to DSM-IV criteria again using the CIDI. Participants' alcohol use disorder status was categorized as- no lifetime alcohol use disorder (reference category), remitted disorder or current alcohol use disorder (remitted disorder was the presence of alcohol use disorder in the past, upto 6 months prior to baseline assessment). Those with remitted or current alcohol use disorder were categorized as follows: remitted alcohol abuse, current alcohol abuse, remitted alcohol dependence, current alcohol dependence.

The results showed that, participants with alcohol dependence at baseline (either remitted or current), had a significantly higher risk of having a persistent depressive and/or anxiety disorders at 2 year follow up (OR 1.42, 95% CI 1.02-1.97) for remitted alcohol dependence, and (OR 1.69, 95% CI 1.04-2.75) for current alcohol dependence at baseline, compared to participants with no lifetime alcohol use disorder. However alcohol abuse at baseline (either remitted or current) did not show a significant association with the presence of persistent depressive and/or anxiety disorders at 2-year follow up. When the findings for those with current alcohol dependence at baseline was analyzed by alcohol dependence severity, only participants with severe current alcohol dependence at baseline (meeting 6-7 diagnostic criteria) showed a significantly higher risk of depressive and/or anxiety

disorder at 2-year follow up, when compared to those with no lifetime alcohol use disorder (OR 17.15, 95% CI 2.27-129.51). This association remained significant after adjusting for other factors such as baseline severity of depression and anxiety, psychosocial factors and treatment factors.

This study differentiates between alcohol abuse and dependence, and reports a significant association between current dependence as well as a history of alcohol dependence, but not abuse and the presence of persistent depressive and/or anxiety disorders at 2-year follow up. The large participant sample, and the prospective study design are particular strengths of this study. Based on their findings, the authors highlight the importance of integrating addiction treatment to general mental health services, especially for those with depression and/or anxiety disorders and alcohol dependence, particularly current severe alcohol dependence. Limitations of the study include the relatively smaller number of participants with severe alcohol use disorders. The study findings also do not shed light on the possible reasons for the increased risk of persistent depressive/anxiety disorders in those with alcohol dependence.

The cardio-protective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis (2).

Referred to as a J-shaped curve, several meta-analysis of observational epidemiological studies seem to show evidence for a cardio-protective association between average alcohol intake and ischaemic heart disease (IHD) risk. The aim of this review was to quantify the dose-response relationship between average alcohol consumption and IHD, stratified by sex and IHD endpoint (mortality vs morbidity).

The authors used strict inclusion criteria to identify high quality observational studies, particularly those which reported analyses stratified by sex and end-point suitable for investigation of a curvilinear relationship (for identification of a cardio-protective or detrimental association at different levels of alcohol intake). They also considered bias in reported effect estimates because of differentially defined reference groups. The authors conducted a systematic search of Medline and Embase electronic databases and Web of Science (1980-2010), to identify studies.

Forty four papers were included in the final review, a majority of them originated from the US, UK and Japan. Continuous dose-response meta analysis for men

showed that the risk function followed a J-curve, with a nadir (lowest point of the curve, i.e. lowest IHD risk) at 31g/day, and with the reversion point being reached at 63g/day, for IHD mortality. Regarding morbidity for men, a declining curve was seen, with a nadir of 69g/day, which then leveled off. For women however, a steep J-curve was seen both for IHD mortality and morbidity. The nadir and reversion points for both IHD mortality and morbidity were substantially lower for women (11g/day and 14g/day respectively), compared with men.

The study findings suggest some form of cardio-protective association between alcohol and ischaemic heart disease morbidity and mortality. However, for both sexes these findings were associated with a statistically significant heterogeneity for most models, and relatively wide confidence intervals, and therefore a cardio-protective association between alcohol use and ischaemic heart disease cannot be assumed for all drinkers. Furthermore while the nadir (maximum cardio-protective association) for morbidity and mortality in men was located at an average intake between 33-69 g/day, these levels are by no means safe from a clinical and public health perspective, since they have been shown to be detrimentally associated with many other disease outcomes. Forming clinical advice for individuals to start drinking for health purposes based on epidemiological evidence alone cannot be advocated because too many questions on confounding factors remain unanswered. Further research regarding the heterogeneity associated with these findings, as well as regarding the overall benefit-risk ratio of average alcohol consumption in relation to ischaemic heart disease and other diseases is indicated.

Mortality in people with depressive, anxiety and alcohol use disorders in Finland (3).

This study examined mortality levels associated with depressive, anxiety and alcohol use disorders. The study employed a data-set from the Health 2000 study, which consisted of a nationally representative sample of the Finnish population aged 30 years and over (n=7419). The participants underwent baseline assessments (home interview and examination) in 2000-2001, where they were assessed for psychiatric morbidity, somatic morbidity, socio-demographic factors and health behaviours (such as smoking). Psychiatric morbidity was assessed using the Munich version of the Composite International Diagnostic Interview (CIDI) and psychotic disorders were screened and examined by using the Structured Clinical Interview for DSM-IV (SCID-I). Follow up and mortality data was collected from Statistics Finland, upto the end of 2008.

Results showed that after controlling for socio-demographic factors, health status and smoking, both depressive (Hazard ratio HR=1.97, 95% CI 1.15-3.39) and alcohol use disorders (HR=1.72, 95% CI 1.10-2.71) showed a statistically significant association with higher mortality. Mild/moderate and severe depressive symptoms (as measured by the Beck Depression Inventory) were also associated with increased

mortality, after controlling for confounders. A majority of the deaths occurred in the 50-70 year age group, but those with mental disorders had a higher risk of death at a younger age (30-50years). Interestingly, the presence of an anxiety disorder or alcohol use disorder was also associated with an increased risk of death by unnatural causes (suicide/ homicide/ accident).

The findings of this study suggest that those with alcohol use disorder or depression have a 2.3-2.6 fold increased risk of death, after controlling for confounders such as smoking status, and somatic health status. Limitations of the study include the relatively short period of follow up, and the fact that the elderly (>80 years) were oversampled (2:1) in the initial study sample, which may have led to a bias in the results. Furthermore, the study results do not offer an explanation as to the cause of increased mortality in those with depressive or alcohol use disorders.

K(Ca)₂ channels: novel therapeutic targets for treating alcohol withdrawal and escalation of alcohol consumption (4).

A relapse is the most challenging clinical problem encountered during treatment of alcohol dependency. Current evidence suggests that chronic and repeated episodes of alcohol exposure and withdrawal causes changes in the glutamatergic function in key brain regions in addiction circuitry. Chronic ethanol exposure and withdrawal produces morphological changes in dendritic spines, and leads to increased activity of glutamate (an excitatory neurotransmitter) and NMDA receptors (glutamate receptors), in the brain. It is hypothesized that this enhanced glutamatergic function and associated neuronal hyperactivity may drive the expression of ethanol seeking behaviours. The authors of this paper review evidence for K(Ca)₂ channels as a novel potential target for reducing glutamatergic hyperactivity that occurs with chronic alcohol exposure and withdrawal.

K(Ca)₂ are calcium activated potassium channels found in many areas of the brain, including the cerebral cortex, hippocampus, amygdala, as well as in areas involved in the brain's reward circuitry, such as the nucleus accumbens and ventral tegmental area. K(Ca)₂ channels influence levels of intracellular calcium levels, and thus influence neuron membrane potentials. Based on laboratory studies, the authors report that continuous ethanol exposure leads to a down regulation of K(Ca)₂ activity in the brain. Administration of a substance which increased K(Ca)₂ channel activity in the brain caused reduction of withdrawal symptoms and withdrawal convulsions in mice, and also reduction of epileptiform firing in hippocampal neurons. The authors present K(Ca)₂ channels as a novel therapeutic target for treating alcohol withdrawal and dependence. Furthermore, based on animal studies, the authors also suggest that enhancing activity of K(Ca)₂ channels in the mesolimbic reward circuitry maybe useful in reducing motivation to consume alcohol in those with chronic alcohol exposure.

This is an interesting paper which suggests novel therapeutic targets to alleviate the symptoms of alcohol withdrawal and reduce high amounts of alcohol drinking. However this is preliminary data, based only on laboratory and animal based studies, and many questions regarding the activity of K(Ca)₂ channels still remain unanswered. Future work is needed to explore if these findings will translate into efficacious pharmacotherapies for treating alcohol use disorders.

Risk assessment of moderate to severe alcohol withdrawal- predictors for seizures and delirium tremens in the course of withdrawal (5).

This re-analysis of a cohort study population examined factors associated with development of withdrawal seizures or delirium tremens, in patients admitted to an alcohol detoxification unit in Munich, Germany. The study participants consisted of a cohort of 827 adult patients, who met ICD-10 criteria for alcohol dependence. The severity of the withdrawal syndrome was determined by analogy to the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale, by a validated and standardized 11-item score. Patients received score guided pharmacological treatment with oral chlormethiazole and valproic acid or carbamazepine. For this study, data was collected by retrospectively reviewing patient charts for data on demographics, withdrawal history and alcohol/drug use, laboratory data on admission, and physical and psychiatric co-morbidity. The charts were also reviewed for reported structural brain lesions at admission (e.g. cerebral trauma or haemorrhage in the past).

In the multivariable regression model, significant predictors for withdrawal seizures among the study participants were a delayed climax of withdrawal severity since admission (OR for every increase of 10 hours: 1.23, 95% CI 1.1-1.4, P<0.001), prevalence of structural brain lesions in the patient's history (OR 6.5, 95% CI 3.0-14.1, P<0.001) and withdrawal seizures as the cause of admittance (OR 2.6, 95% CI 1.4-4.8, P=0.002). Significant predictors at admission for the occurrence of delirium tremens independent of administered therapy were lower serum potassium (OR per an increase of 1 mmol/l: 0.33, 95% CI 0.17-0.65, P=0.001), a lower platelet count (OR per an increase of 100,000: 0.42, 95% CI 0.26-0.69, P=0.001) and prevalence of structural brain lesions (OR 5.8, 95% CI 2.6-12.9, P<0.001). Patients who developed withdrawal seizures were also three times more likely to develop delirium tremens, compared to those without seizures. Based on these findings the authors suggest

development of normograms to predict the probability of developing withdrawal seizures and delirium tremens during acute alcohol withdrawal.

This study suggests that clinicians maybe able to use easily determinable parameters to stratify patients with respect to risk of developing withdrawal seizures or delirium tremens on admission. While this is a thought provoking hypothesis, several study limitations also need to be considered. First, the retrospective design may have led to bias of the results. Second, and importantly, the data was derived from a cohort of patients who were originally recruited for a different trial, namely to compare two protocol driven withdrawal schedules in the management of alcohol withdrawal, and therefore the trial criteria for patient selection, as well as differences in withdrawal treatment schedules during the trial, may have biased the results of this study.

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References

1. Boschloo L, Vogelzangs N, van den Brink W, Smit JH, Veltman AT, Beekman ATF, Phenninx BWJH. Alcohol use disorders and the course of depressive and anxiety disorders. *Br J Psychiatry* 2012;200(6):476-484.
2. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addiction* 2012;107:1246-1260.
3. Markkula N, Harkanen T, Perala J, Partti K, Pena S, Koskinen S, Lonnqvist J, Suvisaari J, Saarni SI. Mortality in people with depressive, anxiety and alcohol use disorders in Finland. *Br J Psychiatry* 2012;200(2):143-149.
4. Mulholland PJ. K(Ca)₂ channels: novel therapeutic targets for treating alcohol withdrawal and escalation of alcohol consumption. *Alcohol* 2012;46:309-315.
5. Eyer F, Schuster T, Felgenhauer N, Pfab R, Strubel T, Saugel B, Zilker T. Risk assessment of moderate to severe alcohol withdrawal- predictors for seizures and delirium tremens in the course of withdrawal. *Alcohol* 2011;46(4):427-433.