# THE FINNISH FOUNDATION

# FOR ALCOHOL STUDIES

REPORT ON ACTIVITIES 2015

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*Tomi Lintonen*, Adjunct Professor

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# GENERAL OVERVIEW

In 2015, the projects funded by the Finnish Foundation for Alcohol Studies resulted in the publication of one academic doctoral dissertation, 23 original peer-reviewed articles in international and two original peer-reviewed articles in national scientific journals. Nine other papers were published.

Alcohol and drug research received 280.160 euro in support for projects. In addition, 268.511 euro was granted to projects on gambling. Ongoing contract projects will be described below under the title *Research activities*.

The Foundation kept its office at the National Institute for Health and Welfare (THL) in Helsinki.

# ADMINISTRATION

The Board of the Foundation was composed of following members: four appointed by the Ministry of Social Affairs and Health, four appointed by the Federation of Finnish Scientific Societies, and one appointed by the Finnish Alcohol Retail Monopoly. The majority of the Board must consist of academically established scientists with special expertise in alcohol research. The Executive Committee was composed of four members of the Board and two external experts. The Gambling Research Committee was appointed by the Board and consisted of one Board member, the Research Director and seven external experts.

The Foundation's Research Director *Tomi Lintonen* is the only full-time staff member. A contract between the Foundation and the National Institute for Health and Welfare (THL) provided administrative and technical support for the Foundation.

# RESEARCH ACTIVITIES

## PhD dissertations supported by the Foundation

*Esti Laaksonen: Alkoholiriippuvuuden hoitotulokseen vaikuttavat tekijät*

The estimated number of heavy consumers of alcohol is about 20 percent of population, of which 10 percent suffer from alcohol dependency. Many heavy consumers of alcohol also smoke. The effectiveness of treatments can be significantly improved with medical treatment. The problems are: how medical treatment can be utilized in practical treatment, and how to ensure treatment adherence. The aim of this study was to investigate the effectiveness of pharmacotherapies combined with a brief manual-based cognitive-behavioural intervention (CBT) in treating alcohol-dependent patients. In the large-scale clinical treatment study, which ran for 2.5 years, the effectiveness and patient response to the three drugs (naltrexone, acamprosate and disulfiram) were compared. The study used a survey drawn up guidebook for patients, Winning at last  defeating the drinking problem. In addition, we researched how the reduced alcohol consumption affects the quality of life, mood and smoking. In the study of sweet preference, we analyzed possible associations between sweet preference and efficacy of naltrexone treatment. In addition, we researched patientstreatment adherence and medication adherence to targeted naltrexone, as well as reduction of problem drinking and craving.

This combined treatment (medication and CBT) significantly reduced alcohol consumption resulting in improved quality of life. Noticeable is that compared to the other study medicines, especially during the continuous medication period, supervised disulfiram appeared superior. During the targeted medication period, there were no other significant differences between the groups except for that the abstinence days were significantly more frequent in the disulfiram group. The treatment was also associated with success in quitting smoking among patients using disulfiram. The study of sweet preference, it was significantly related to treatment measures in the naltrexone group when the outcome was relapses to heavy drinking. Our study offers a possible new explanation of the clinical observation that naltrexone is not effective for every patient. Adherence to the targeted use of naltrexone added treatment compliance and efficacy of the medicine. Patients who had less symptoms of alcohol dependence, suffered from high craving for alcohol, were unemployment, young or could not keep the drinking diary were less committed to treatment.

Problem drinking can be changed to abstinence or moderate drinking with the combination of medical therapy, CBT and good treatment commitment. The benefits of treatments are probably long-term, because part of the positive results lasted over two years. The treatment methods used in this study were usable and they can be implemented in all levels of Finnish health care. URN:ISBN:978-951-51-1319-1

Research contracts and collaborative projects

221 *Polydrug use related deaths: trends, prescription drug abuse and regulation of risks.*
Topic of this doctoral study is polydrug use related deaths. The prevalent paradigm in addiction research for the past decades has been a single substance driven orientation. Studies have concentrated on particular substances and harms they cause. However, empirically it is evident that polydrug use – concurrent or simultaneous use of licit or illicit substances - is very common. As research has concentrated on the use of single substances, polydrug use and its harms have remained little-studied. Drug-related deaths have been increasing in Finland in 2000s. This has been explained by the increase of poisonings due to prescription opioids, especially buprenorphine, often in combination with other drugs. Finland is not alone in this development as the non-medical use of prescription drugs has increased rapidly in Western countries in the past decades. This PhD study will address these themes a) by examining the trends of polydrug use deaths in Finland, b) by comparing polydrug related mortality across diverse population groups, c) by describing association between prescription drugs and polydrug deaths, and d) by exploring the users' perceptions of risks related to polydrug use. In 2016, results of the study have been presented in the Lisbon Addictions conference in Portugal and various national seminars. One peer-reviewed article has been published, one is in review and two papers are in progress. The researcher was on maternity leave January-April 2015. Researcher: *Sanna Rönkä*, University of Helsinki.

222 *The role of opioidergic receptors in the development of alcohol addiction.*
The biological mechanisms controlling alcohol intake and the development of alcohol addiction are mostly still unclear. Several different neurotransmitter systems in the brain are known to mediate the effects of ethanol. Studies conducted on alcohol preferring AA (Alko Alcohol) and alcohol non-preferring ANA (Alko, Non-Alcohol) lines of rats suggest that the opioidergic system plays a central role in alcohol addiction. By studying the different brain areas of the mesolimbic reward system, such as the nucleus accumbens and ventral pallidum, it is possible to more specifically determine the role of the opioidergic system in controlling alcohol intake. The aim of the current experiment is to clarify the role of μ- and κ-opioid receptors in controlling alcohol intake. In these studies, we used AA rats. The ventral pallidum is considered to be the final point of the reward system. During the course of the year we have studied the role of pallidal μ-opioid receptors in controlling alcohol intake. μ-Opioid receptor gene overexpressing viral vectors (AAV-MOR) were used in the study. The advantage of using AAV-viral vectors when compared to pharmacological agents is their long duration of action. We infused AAV-MOR, GFP gene expressing control vectors or vehicle into the ventral pallidum of rats that voluntarily consumed 10% alcohol solution. The effects of the treatments were studied in the limited access alcohol intake paradigm for five weeks. In addition, the effects of the systemically dosed opioid receptor antagonist naltrexone and agonist morphine were examined. Immunohistochemical staining and qPCR were used to verify the biological activity of the viral vectors. According to the results ethanol intake did not differ between the different treatment groups during the five week follow up. However, the AAV-MOR group was more susceptible to the decreasing ethanol intake effect of naltrexone than the control groups. Morphine increased ethanol intake similarly in all groups. The results suggest that the opioidergic mechanisms in the ventral pallidum seem to be important in controlling ethanol intake. Researcher: *Johanna Uhari-Väänänen*, University of Helsinki & National Institute for Health and Welfare. (johanna.uhari@helsinki.fi)

224 *Effects of gestational alcohol exposure on epigenome, gene regulation and the development of embryo.*

We hypothesize that early ethanol exposure disrupts the epigenetic reprogramming of embryo, which leads to alterations in gene regulation and embryonic development. Our aims are to reveal the molecular mechanisms, which lead to the phenotypic characteristics of fetal alcohol spectrum disorder (FASD) and to find biomarkers for FASD diagnosis as well as to develop new diagnostic criteria. Because prevention of FASD is often impossible, early diagnosis and appropriate support for development have an important role in the therapy of FASD children. We are using a mouse model of gestational alcohol exposure of which we have published a study in spring 2015 (Marjonen et al. PLoS One). The exposure period in this model is developmentally equivalent to the weeks 3-4 of human pregnancy, a time period when women are often not aware of their pregnancy. In this study, early exposure to alcohol significantly changed the DNA methylation in some CpG sites as well as the function of several genes in the hippocampi of adolescent mice. These changes were also apparent in the brain structures of the adult offspring: the hippocampi, olfactory bulbs and cerebral ventricles. In addition to hippocampi, we observed similar trend of altered gene expression in two other tissues: bone marrow and the olfactory epithelium of the snout. The results support our hypothesis of early epigenetic origin of alcohol-induced disorders: changes in gene regulation may have already taken place in embryonic stem cells and therefore can be seen in different tissue types of an adult organism. This would be significant for the challenging work of diagnosing alcohol-related damage. We have proceeded to human studies and collected samples from newborns that have been exposed to alcohol during the gestation. Our first results are highly interesting: we have observed altered epigenetic marks and gene expression in alcohol-exposed placentas, and these changes are significantly associated with the genotype of the child. Researcher: *Nina Kaminen-Ahola*, University of Helsinki. (nina.kaminen@helsinki.fi, http://environmental-epigenetics.helsinki.fi)

226 *Young people and a changing culture of crime control – policing alcohol drinking, delinquency and the use of public space.*

This sociological PhD research examines encounters between underage young people, police and private security guards. It studies young people's perceptions of social control directed towards youth delinquency, alcohol use and free time activities. The starting point for the study was an observation that police control of underage young people has intensified, although youth delinquency and alcohol use have not increased. Furthermore, the private security sector's role in policing young people in a city space has extended. Central criminological discussions for this study are citizens' trust in the crime control system and control selectivity. Prior research has focused mainly on adult perspectives and on police control. This study aims to offer new insights by focusing on young people and by including also private security. The main questions are: First, are some groups disproportionately targeted for formal social control (social selectivity hypothesis)? Second, how do young people constitute perceptions of trust and legitimacy toward control agents? How can trust be constituted between young people and control agents in adversarial situations where control agents intervene in alcohol use? Finally, the study explores differences in youths' perceptions between the police and security guards to understand how people formulate perceptions of trust. The study consists of 4 articles and a summary article (3 articles published by the end of 2015). It uses mixed methods approach. Two sub-studies draw on a youth survey (N=5826, aged 15 to 16). Multivariate regressions examine which factors increase the likelihood of police interventions (article 1, Saarikkomäki & Kivivuori 2013) and security guard interventions (article 2, Saarikkomäki & Kivivuori 2014). The results support the social selectivity hypothesis. The findings show that police and security guard interventions disproportionately target lower class city youths. This finding holds when delinquency and alcohol use were controlled for. Additionally, delinquency and heavy drinking increased the likelihood of interventions. The study indicates that it is highly common for

youths to encounter both public and private policing agents. Another two sub-studies draw on qualitative focus group data (9 interviews, 31 young people aged 14 to 17). The study analyses how trust is constructed between young people and control agents. The 3rd article analyses narratively young people's stories of fair and unfair encounters where police and security guards intervene in underage alcohol use. The key difference was related to how authorities treat people. Fair narratives highlighted friendly, peaceful and predictable interactions and mutual respect. Intervening to alcohol use in city space did not challenge trust when young people perceived that the control agents' work task legitimated the intervention. Unfair narratives consisted of aggressive and unfriendly treatment. Prior procedural justice research has failed to notice the importance of the emotional state of the control agents: ideal control agents had an ability to be empathetic and to control their negative emotions. The findings highlight the importance of fair treatment in constituting trust between young people and adult society. (Saarikkomäki 2015.) The 4th article analyses how trust and legitimacy are constituted by comparing youths' perceptions of police and security guards. Good relations between young people and adult society are important because if young people perceive unfairly treated, it can increase conflicts and enhance feelings of not being a valued part of society. The project began in 2011 and from May 2012 it continued as a research contract project. During 2015, the third article of the PhD was finalized and published. In addition, the researcher wrote a Finnish article aimed primarily for people working with young people. The researcher has continued to analyse the focus group data and she has drafted the 4th article manuscript (plan to submit spring 2016). In addition, the researcher started to draft the summary article of the PhD study. The findings were presented in conferences, e.g. Annual Sociology Conference and Annual Conference of Finnish Youth Research Society. The researcher gave lectures in Open University of Helsinki and in University of Turku. The researcher participated in the media training supported by the Foundation (organized together with the council of Finnish foundations). Researcher: *Elsa Saarikkomäki.* (elsa.saarikkomaki@helsinki.fi)

227 *Association between parental substance abuse problems and their children's cumulative risk factors for social deprivation at adolescence.*

This sociological dissertation study examines from different perspectives disadvantage that is related to parental substance abuse, and the intergenerational transmission of disadvantage from parents to children. The study is based on the findings of an increase in alcohol consumption in Finland over the last forty years, especially among women who are at parenting age, and the more prevalent drug use and the stabilization of higher drug use level than before during the 1990's. Harmful parental substance use in the child's living environment can significantly affect the child's wellbeing, and it can also become entangled with other problems, such as parental mental health disorders and the family's financial difficulties. The aim of this study is to find out associations between parental substance abuse and child's risk factors for health, social and economic disadvantage from birth to 20 years of age. The study is based on an extensive administrative register data of a total birth cohort of children born in 1991, and their biological parents. The data allows the follow-up of the cohort until year the 2011. The methods applied in analysis are statistical analysis suitable for longitudinal data. In 2015, the study was funded by the research contract. During this period, two article manuscripts were written and the results of the research project were presented at two international conferences. One of the article manuscripts describes how parental substance abuse is associated with dissolution of the families. The other manuscript focuses on the association between parental substance abuse and educational attainment of the children by the age of 20 years. Results of the research project were presented at the conference of Kettil Bruun Society in Munich, Germany on June 1, 2015 with the title "Fragility of families with parental substance abuse". In addition, results

were presented at the KBS Thematic Meeting on alcohol's harm to others in Helsinki on September 16, 2016 with the title "Effect of parental substance abuse on educational attainment of children". During the year 2016, the aim is to write the fifth article manuscript and the summarizing article of the thesis. Researcher: *Marke Jääskeläinen*, University of Helsinki. (marke.jaaskelainen@thl.fi)

229 *Neuroinflammation in mouse models of alcohol consumption.*
Immune system has been shown to modulate acute and chronic effects of alcohol, and neuroinflammation might be important also in development of alcoholism. Immune system related genes display expression changes in alcoholic brain samples postmortem. Recent preclinical research shows a connection between neuroimmune signaling and alcohol consumption. For example, knockout mouse models of immune system genes show changes in alcohol consumption. Our aim is to investigate how strengthening of this signaling influence ethanol consumption and sensitivity, and how it modifies brain reward system. We have utilized lipopolysaccharide (LPS) for inflammation challenge, a model that has been shown to increase long term free-choice alcohol consumption in C57Bl/6J mice. However, we found that LPS-treatment reduced ethanol consumption at highest ethanol concentrations in a similar 24-h 2-bottle free-choice drinking test (with ascending ethanol concentrations) in contrast what was reported earlier by others. Therefore, we wanted to test the effect of LPS also in a drinking in the dark (DID) -model. Utilizing this 4-h drinking model, we found that alcohol concentration has an impact on the effects of LPS, an increase in consumption was observed only when 20% (v/v) ethanol was used, not when 15% ethanol was used. We saw that LPS (1 mg/kg) -treatment was able to increase long term 20% ethanol consumption as ethanol consumption remained elevated at least two months. Interestingly, low doses of LPS, given repeatedly during abstinence periods between drinking sessions, also increased alcohol consumption. Our results indicate that the model of increased alcohol consumption by LPS-inflammation challenge needs modifications between different laboratories. Utilizing this model, we have also repeated known decreasing effects of naltrexone and minocycline on ethanol consumption. However, it was evident that at least a part of the decreasing effect on alcohol consumption by minocycline was caused by a general decrease in liquid intake. In future experiments we will continue to study the effect of a single and repeated doses of LPS on 20% ethanol consumption in the DID-model and search for a valid LPS-ethanol-interaction protocol to be used in other behavioral studies. The effect of neuroinflammation on ethanol reward will be studied in conditioned place preference and changes in brain reward thresholds will be analyzed with intracranial self-stimulation method. This PhD thesis aiming research began in April 2013. Researchers: *Mira Lainiola* and *Anni-Maija Linden*, University of Helsinki, Institute of Biomedicine, Pharmacology.

231 *Role of GDNF in incubation of alcohol craving.*
Withdrawal from alcohol leads often to relapse even after long periods of abstinence. It is known that there can be intensive craving for alcohol and that craving can last long periods. Drug and alcohol craving methods are well established with laboratory rats. In rats it has been observed that rat's response to cues increases over time after withdrawal from self-administration. The phenomenon is termed incubation of drug craving. Our first aim was to set up and validate a novel method to study alcohol craving in mice by using IntelliCage. The use of fully automated IntelliCage is a new approach to study addiction related behavior in mice. One of the advantages of IntelliCage is that the mice are group housed, and therefore they drink and live in social environment. In many other models the laboratory animals are isolated and single-housed. Self-administration, following extinction and relapse paradigms in mice are still not

well developed. Mice pose enormous possibility for studies in the field of neurobiology of addiction and many studies could be conducted in mice that cannot be conducted in rats. It is good to remember that gene modifications are much more diverse in mice as well as they are rather cost efficient. We have studied differences in alcohol, alcohol and sweetener, sweetener, and water on drinking related behavior in mice, as well as extinction responses on withdrawal days 1 and 10. We have found that sweetened alcohol increases craving after withdrawal as compared to alcohol or sweetener alone. We have started to study the role of glial cell line-derived neurotrophic factor (GDNF) in alcohol craving. GDNF is a protein that has survival promoting properties in dopamine neurons and effects on dopamine neurotransmission. It has been shown that GDNF has effects on behavioral responses of abused drugs and alcohol, but its role in alcohol craving is not fully clear. Researchers: FM *Maryna Veremieva*, FaT *Mikko Airavaara*, LT *Vootele Voikar*. Collaborators: FaT T. *Petteri Piepponen*, FT *Jaan-Olle Andressoo*.

234 *Substance Abuse in the Family – Children's Experiences of Inequalities and Ambivalent Family Relations.*

In this post doc -study, interest lies in the experiences of family relations, inequalities and social class of chil-dren and young people in problem-drinking families. For the qualitative part of the study, interview data (N=30) of children and young people who have a problem-drinking parent was collected. Also interviews of adult sons of problem-drinking fathers (N=21) are used in the study. In addition, national 1987 -cohort data will be utilized in the study. During 2015, analyses and writing up the results have been in progress. Interviews of children and young peo-ple, collected in 2014 for the research project "Growing up in the Finnish Drinking Culture" have been ana-lyzed. Articles "Sons of Problem-Drinking Fathers: Narratives on the Father-Son Relationship" (in Family Sci-ence), and Pirskanen, Henna et al.: "Researching Children's Multiple Family Relations: Social Network Maps and Life-Lines as Methods" (in Qualitative Sociology Review) have been published. In addition to the qualita-tive data, the national 1987 -cohort data, into which data from different sources has been combined, is now in the usage of the study. Different analyses related to inequalities and the parents' alcohol problems will be applied to the cohort data. In 2016, analyses and writing up the results in the form of article and book chapter manuscripts will continue. In 2015, the researcher has also presented her work in several national and international seminars and con-gresses. Researcher: PhD *Henna Pirskanen*, National Institute for Health and Welfare / University of Jyväskylä. (henna.pirskanen@thl.fi)

235 *Immune response to alcohol metabolites.*

The immune defense system is activated by several alcohol metabolites. Heavy drinkers have antibodies binding to protein adducts of acetaldehyde and malondialdehyde in their serum. We have shown in our previous animal study that phosphatidylethanol, a lipid metabolite of alcohol, is immunogenic –capable of generating immune response. In our recent study we found antibodies binding to phosphatidylethanol in plasma of heavy and moderate drinkers. The aim of the study is to investigate the immunological characteristics of alcohol metabolites in humoral and cell mediated immunity. Genetic background and binding characteristics of the plasma antibodies binding to phosphatidylethanol will be analyzed and compared to the antibodies binding to structurally similar targets. The formation of phosphatidylethanol in the immune cells and the cellular functions are analyzed to understand the mechanisms of immunogenicity. Phosphatidylethanol is one of the promising markers of heavy drinking. The antibodies that are produced and characterized in this project are of interest in the development of new test systems for diagnostic use. The role of alcohol metabolites in the immune system will provide new understanding for pathogenic mechanism of alcohol related diseases. Researcher:

*Antti Nissinen*, PhD, Research Unit of Biomedicine and Research Unit of Internal Medicine, University of Oulu, (antti.nissinen@oulu.fi)

# PUBLICATIONS

## PhD dissertations

*Laaksonen E:* Alkoholiriippuvuuden hoitotulokseen vaikuttavat tekijät. University of Helsinki and University of Turku. PhD dissertation (article-based)

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http://www.qualitativesociologyreview.org/ENG/Volume32/QSR_11_1_Pirskanen_Jokinen_Kallinen_Harju-Veijola_Rautakorpi.pdf

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*Lintonen T, Karjalainen K:* Lääkkeiden päihdekäyttö on iso osa huumeongelmaa. Haaste 1:16-18

*Lintonen T, Mäkelä P, Härkönen J, Raitasalo K:* Tulevat sukupolvet eivät ole raitistumassa. Yhteiskuntapolitiikka 80(1):46-53

*Lintonen T, Niemelä S*: Kipulääkkeiden väärinkäyttö yleistyy. Suomen Lääkärilehti 70(7):376-377

*Lintonen T, Niemelä S*: Kipulääkkeiden väärinkäyttö yleistyy. Potilaan Lääkärilehti 18.2.2015

*Obstbaum Y*: Päihdehaittojen kontrollin muutos. Haaste 1:7-9

*Pitkänen T*: Päihdehoidossa alaikäisenä olleilla suuri riski kuolla nuorenna. Tiimi 5: 26-27.

*Törmä S, Pitkänen S ja Huotari K*: Sukupuolittuneet pelikentät. Naisten pelaaminen kulttuurisena ja yhteiskunnallisena ilmiönä Suomessa. Kuntoutussäätiön työselosteita 49/2015, Kuntoutussäätiö 2015.