



Faculty of Psychology
University of Basel

Therapeutic and Psychosocial Interventions in the Treatment of Alcohol-Dependent Patients: Findings from Clinical Research

A cumulative dissertation

by

Sandra E. Müller

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Prof. Dr. rer. nat. Rolf Stieglitz (Referee)

Prof. Dr. med. Gerhard Wiesbeck (Co-Referee)

Prof. Dr. phil. Jens Gaab (Chairman)

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Declaration of Independence

The three published articles below form the basis for the cumulative dissertation to attain the degree of Doctor of Philosophy. Hereby I confirm that the present work is originally written by me, in my own words and without any unauthorized aid. Statements of others or citations are indicated. All published articles are peer-reviewed and are written in collaboration with the co-authors mentioned on the articles. Further the contents of the publications are not published elsewhere. There is no conflict of interest.

The first article represents the main results of the study founded by the Swiss Federal Office of Public Health (FOPH). The second article is a secondary analysis of an original pharmacological trial. The third article is an original questionnaire study which was published in an open access journal. All three published articles are added in the appendix.

1. Article

Mueller SE, Petitjean SA, Wiesbeck GA. (2012). Cognitive behavioral smoking cessation during alcohol detoxification treatment: A randomized, controlled trial. *Drug and Alcohol Dependence*, 1;126(3):279-85.

2. Article

Mueller SE, Petitjean S, Boening J, Wiesbeck GA. (2007). The impact of self-help group attendance on relapse rates after alcohol detoxification in a controlled study. *Alcohol and Alcoholism*, 42(2):108-12.

3. Article

Mueller SE, Degen B, Petitjean S, Wiesbeck GA, Walter M. (2009). Gender differences in interpersonal problems of alcohol-dependent patients and healthy controls. *International Journal of Environmental Research and Public Health*, 6(12):3010-22.

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Abbreviations

5-HT	5-Hydroxytryptamine (Serotonin)
AA	Alcoholics Anonymous
ANOVA	Analysis of variance
APA	American Psychological Association
AT	Autogenic training
AUDIT	Alcohol Use Disorder Identification Test
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
CAGE	Cut down drinking, Annoying, Guilty, Eye opener
CBT	Cognitive behavioral therapy
CG	Control group
CO-level	Carbon monoxide level
DALY	Disability-adjusted life years
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
EG	Experimental group
EtG	Ethyl glucuronide
FLAGS	Feedback, Listen, Advice, Goals, Strategies
FTND	Fagerström Test for Nicotine Dependence
ICD-10	International Classification of Diseases and Health Problems
IIP-64	Inventory of Interpersonal Problems
GABA	Gamma-amino butyric acid
HAMA	Hamilton Anxiety Rating Scale
HAMD	Hamilton Depression Rating Scale
LAT	Lesch Alcohol Typology
MALT	Munich Alcoholism Test
MANOVA	Multivariate analysis of variance
nACh	Nicotinic acetylcholine
NMDA	N-Methyl-D-Aspartate (Glutamate)
OR	Odds ratio
ppm	Parts per million
PTSD	Post-Traumatic Stress Disorder
SFA	Schweizerische Fachstelle für Alkohol und Drogenfragen
SFQ	Social functioning questionnaire
SUD	Substance use disorder
VAS	Visual analogue scale
WHO	World Health Organization
YLL	Years of life lost due to premature death
YLD	Years of life lost due to illness and disability

Abstract

Alcoholism is a chronic and severe disease that impairs life-quality and causes problems in health, in psychological, and in social issues over time. In the past very few treatment services were available for alcoholism. Nowadays, since alcohol dependence is defined as a psychiatric disease treatment offers have augmented. Despite multiple treatment facilities abstinence rates or successful long term treatment outcomes are still modest. This raises the question if treatment methods can be improved by adapting or tailoring treatments more to patients' individual need, like in personalized medicine, where patients' individual characteristics provoke different treatment implications.

Alcoholism is a disease heterogeneous in appearance and in its consequences. Thus reasons for alcohol drinking, the expected effects of alcohol and the course of drinking patterns are very different among alcohol dependents. Therefore it seems clear that there cannot be a standardized, uniform treatment for alcoholism which is adequate for everyone. Personalized treatments for alcoholism including different aspects with different implications for treatment are needed. Hence, the present cumulative dissertation consists of three publications from clinical research addressing different aspects in the treatment of alcoholism, which play an important role and have impact on treatment outcomes as well as on future research.

In the first article the feasibility and effectiveness of a voluntary smoking cessation offer was investigated parallel to an alcohol detoxification treatment. Outcomes in smoking quit rates were modest, but a clear advantage in the reduction rate of cigarettes was found in the CBT condition. Furthermore, it was found that the sub-group of heavy smokers benefited the most of the CBT intervention.

The second article investigated the impact of self-help group attendance, namely 12-step programs predominantly Alcoholics Anonymous on relapse rates. There was only a slightly better outcome for patients attending a 12-step group involvement regularly as an aftercare group exclusively in the first month after treatment discharge.

In the third article self-perceived interpersonal problems were examined finding that alcohol-dependent patients exhibited a higher burden of interpersonal problems in general compared to healthy controls. Furthermore, alcohol-dependent women exhibited in total more and different dimensions of interpersonal problems compared to alcohol-dependent men.

All these results from clinical research may help to adapt treatments in a way, so that patients benefit more. A higher attraction of the treatment may lead to a higher participation and probably to a higher compliance. Findings may help to improve quality of therapies, best in the sense of a personalized treatment, which in turn may improve outcomes.

1. Theoretical Background

1.1. Etiology

There is not one consistent model on the development of alcohol dependence, but several different models exist. Clear is, that monocausal models are not sufficient in explaining the genesis of a substance use disorder, because there are more contradicting results regarding monocausal models in the past, such as only nurture or only nature models. Today, rather multi-factorial models are accurate. In many psychiatric diseases the diathesis-stress model is used to explain the development of the disease. The diathesis represents a disposition or a vulnerability, which is related to hereditary factors. The stress represents the influence of environmental factors, such as risk factors that contribute to develop a substance use disorder and protective factors that diminish the risk to develop a substance use disorder. Genetic factors for a direct heredity of alcoholism can be excluded, but there are some distinctive marks where a genetic influence is highly likely. In research different methods have been established to investigate genetic impacts, such as twin studies, adoption studies, studies on high-risk groups and association studies. Regarding environmental influences it was found that the cultural norms, the availability of alcohol products, the prize, social classes, religious settings, urbanity and social values and norms play an important role. The genesis of an alcohol problem is multifactorial and corresponds most closely to a bio-psycho-social model that explains the development and the maintaining of the substance use disorder. There is a multiplicity of models hereinafter only one will be briefly shown, namely the model of Kűfner (1981). It corresponds to a vicious circle of alcoholism consisting of three circles, the *somatic*, the *inner-psychic* and the *psychosocial* circle. Every circle can lead by its own to continued substance use. The *somatic* one due to withdrawal symptoms, the *inner-psychic* due to learned patterns, for example that substance use helps to reduce anxiety, and the *psychosocial* circle due to social pressure or established social habits. The product alcohol is individually linked with its expected effect, namely sedation, relaxation or stimulation. The actual problems of an individual, e.g., conflicts with others, contribute as a causative factor and lead to substance use due to the expected effect of alcohol to solve the causative factor. Another important point is the underlying psychiatric comorbidity, (e.g., depression, sleep disorders, social phobia, post-traumatic stress disorder (PTSD), etc.) assuming that at least some patients use alcohol to relief symptoms of the underlying psychiatric disorder, in the sense of the self-medication hypothesis. For every patient the meaning and importance of each circle for maintaining substance use have to be identified and worked out, because the weighting of the circles are very individual (Figure 1).

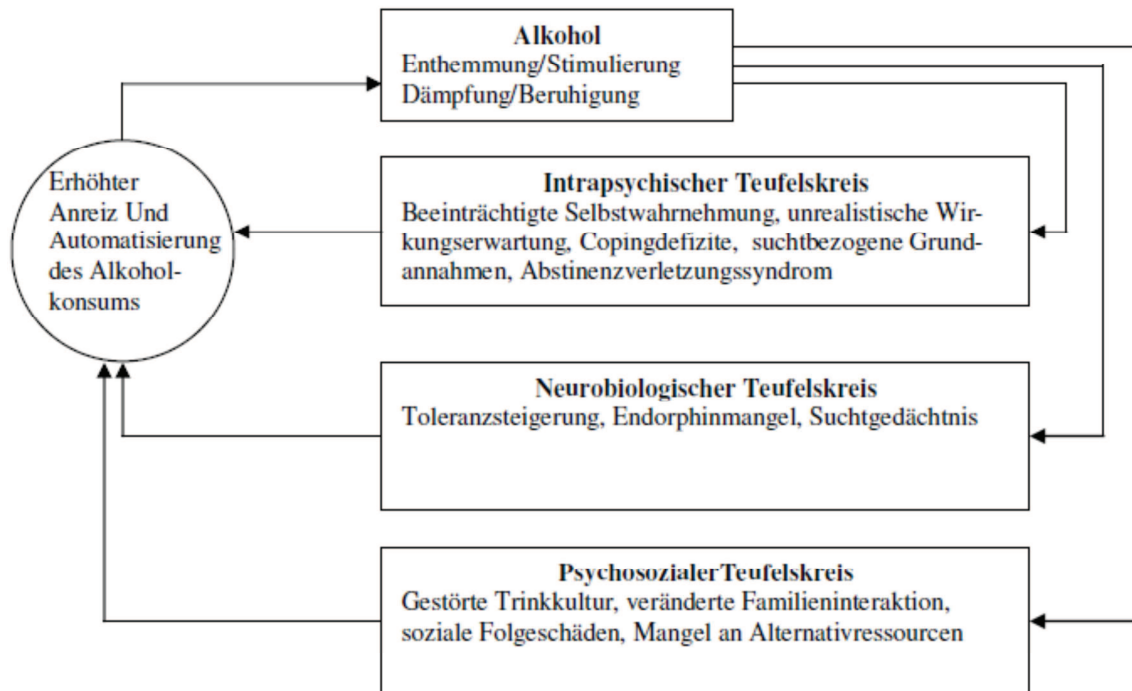


Figure 1. Vicious circle model of alcohol dependence (based on Kufner & Bühringer, 1996)

1.2. Epidemiology

Methods to quantify

To determine rates of alcohol use disorders, namely prevalence or incidence is difficult due to various reasons. In general there exist indirect and direct methods to estimate prevalence. The indirect method measures all sold alcohol and links it to the proportion of drinking patterns in society. The proportion of drinking patterns resembles a log-normal distribution curve, namely that a relatively small proportion of drinkers drink the biggest part of all sold alcohol. The prerequisite is that this relationship is calculable and quite similar over countries. Despite some criticism this is internationally accepted. The numbers of per capita consumption of alcohol are published regularly by the World Health Organization (WHO). For example the per capita consumption calculated in pure liters of alcohol from 2003-2005 was 12.8 for Germany, 10.9 for Switzerland, 3.4 for Turkey (the lowest) and 16.5 for Czechia (the highest). That means that the higher the use the higher is the proportion of heavy drinkers. The direct method for epidemiological studies is directly asking persons about the frequency and amount of alcohol use. It seems that information regarding the amount of drinking was unreliable compared to frequency which was more reliable (Kraus, 1996). It is assumed that the taboo of alcohol problems raises the number of unreported alcohol problems which biases the direct method, why usually the indirect methodology is used.

Drinking patterns: non-problematic, hazardous and problematic

To distinguish between low risk and hazardous drinking and to quantify drinking amounts the WHO established the term *standard drink*. A standard drink is defined as a specific amount of an alcoholic beverage containing 10 g pure alcohol (ethanol), which corresponds to 3 dl beer, 1 dl wine or 0.2 cl spirits in Europe with slight variations all over the world.

According to the WHO guidelines *low risk drinking* is defined as drinking daily not more than 20 g pure alcohol (2 standard drinks) for women and not more than 40 g pure alcohol (4 standard drinks) for men. Swiss Health Interview Surveys state that about 93% of the Swiss population is drinking alcohol at low risk according to the WHO. About 4% are assessed to drink at medium risk (20-40 g/d for women and 40-60 g/d for men) and about 3% drink at a high risk level (>40 g/d for women and >60 g/d for men), which is clearly hazardous to health (SFA, 2009). In surveys asking for drinking patterns more than one million citizens were found to be problematic drinkers. Out of the problematic drinkers about 782'000 are assessed to drink episodically too much alcohol, about 105'000 drink chronically too much alcohol and about 155'000 drink chronically and episodically (risk cumulates) to much alcohol (Wicki & Gmel, 2005). It is estimated that about 250'000 people are alcohol-dependent in Switzerland. About the half of all sold alcohol per year is consumed by a minority of citizens (~12%) and about 17% of the Swiss population is not (or just once in a year) drinking alcohol (SFA, 2009).

The transition from problematic to dependent alcohol consume pattern is fluent and should be thoroughly diagnosed by using the international criteria for substance use disorders.

Criteria for substance use disorders are defined in the International Classification of Diseases and Health Problems (ICD-10) or in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). In this work the criteria of dependence will be referred to ICD-10 only.

1.3. Diagnostic criteria of alcohol use disorders

The alcohol dependence syndrome is a cluster of physiological, behavioral and cognitive aspects which have developed over time from chronic substance use behavior. It leads to desire to use substances even if not intended and substance use will gain a higher priority in dependent individuals compared to behaviors which had a higher value before. The WHO defines substance use disorder as a mental and behavioral disorder due to psychoactive substance use according to the following diagnostic guidelines. According to ICD-10 the diagnosis of dependence should usually be made only if three or more of the following diagnostic criteria have been present together during the previous year (Table 1).

There is a fluent continuum from non-problematic drinking, to hazardous or risk drinking, to misuse patterns up to dependence. As substance use dependence is defined in Table 1, the substance misuse in ICD-10 is defined as harm to health or harm to social adjustment

without any signs of alcohol tolerance, psychological withdrawal or compulsive use. To detect persons in an early stage with a hazardous or problematic alcohol use screening instruments such as the CAGE (Cut down drinking – Annoying – Guilty – Eye opener) or the AUDIT (Alcohol Use Disorder Identification Test) can be used. The CAGE screening test consists of 4 questions, if 2 questions are positively affirmed a problematic alcohol use pattern is highly likely. The AUDIT consists of 10 questions with a maximum of 40 points, if men have more than 8 points and women more than 6 points problematic alcohol use is highly likely.

Table 1

Diagnostic criteria of substance use dependence according to ICD-10

I	A strong desire or sense of compulsion to take a substance (Craving)
II	Difficulties in controlling substance-taking behavior in terms of its onset, terminations or levels of use (loss of control)
III	A physiological withdrawal stated when substance has been ceased or reduced, or use of the same (or a closely related) substance with the intention to relief or avoid withdrawal symptoms
IV	Evidence of tolerance, such that increased doses of the substance is required to achieve effects originally produces by lower doses
V	Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
VI	Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning

The process of developing an alcohol problem varies widely and might follow the above described stages of drinking patterns but must not coercively. The process of developing a substance use problem normally lasts years and is characterized to be subtle and longsome. This might be one of the reasons why persons need long time to realize that they may have a substance use problem and to admit having a substance use problem is even more difficult. Another reason may be the social perspective, in which alcohol dependence is still seen as a problem of a weak will and not as a disease. Already in the 18th century a Scottish doctor named Trotter described the relationship of high and chronic alcohol use and consequent physical and psychological problems, which was kind of the first concept of an alcohol disease. It still took two centuries until in the mid of the 20th century Jellinek again postulated that alcohol dependence has to be seen as a disease and achieved that in 1968 alcohol dependence got accepted as a disease in Germany and Switzerland.

1.4. *Burden of diseases*

Hence WHO started to measure lost years of healthy life in *disability-adjusted life years* (DALY's) which combines *years of life lost due to premature death* (YLL) with *years of life lost due to illness and disability* (YLD). In the international ranking of the 10 leading risk factors regarding DALY's in high-income countries tobacco use is with 10.7% on the first place followed by alcohol use on the second place with 6.7% (WHO, 2009). Both risk factors are preventable or reducible with appropriate interventions such as early prevention, information about health damages and appropriate treatment offers. In the past alcohol-related mortality was studied more frequently than alcohol-related morbidity (Rehm et al., 2001). In fact, alcohol use has stronger links to morbidity and disability than to mortality (Murray & Lopez, 1997). Other estimates state that every alcohol-attributable death is accompanied by about 30 years of life lost (Centers for Disease Control and Prevention, 2004).

Physical, psychological and social consequences of chronic alcohol use

Chronic and high use of alcohol causes various problems with regard to physical health, psychological well-being and social issues. Regarding physical health consequences the highest risk due to chronic alcohol use is found in damages to liver, pancreas, heart diseases, cardiovascular system and gastrointestinal system. High risks due to chronic alcohol use are also found in the human nervous system, with polyneuropathy in the peripheral system and Wernicke-Korsakov encephalopathy, amnesic syndromes, general brain atrophy or cerebellar atrophy in the central nervous system. To a lesser proportion but relevant, chronic alcohol use affects all kind of neuropsychological functions, above all impaired executive functions such as working memory, planning and problem solving, attentional control and response inhibition (Noel et al., 2001; Ratti et al., 2002), further, fluency and decision-making deficits (Fernandez-Serrano et al., 2010) are reported as well. In general, ethanol has toxic effects on the human body and brain. In the brain ethanol influences various neuronal sites such as N-Methyl-D-Aspartat (NMDA)-, Gamma-amino butyric acid (GABAA)-, 5-hydroxytryptamine₃ (5-HT₃)-, and Nicotinic acetylcholine (nACh)-receptors regulating the mesolimbic dopaminergic system. Nevertheless, chronic changes in neurotransmitters in the brain influence human behavior and psychological well-being. Regarding psychological problems due to chronic alcohol use it is discussed, that impaired cognitive functions influence behavior, well-being and future plans. Coping strategies are also impaired showing that subjects with chronic alcohol use are less stress resistant and weaker in problem solving than controls. In a subset of alcohol dependents chronic alcohol use is found to lead to aggressive behavior. It is postulated that chronic and long-term use of alcohol influences personality structure, in extreme cases it can lead to an alcoholic change in personality. To a

lesser extent but relevant, temporary changes in mental condition of chronic drinkers compared to controls are found for example in increased depressive symptomatology, in reduced self-esteem, in lower tolerance for frustration, and in increased psychopathy scores in attitude and behavior. Beside physical and psychological problems alcohol-dependent persons are accompanied by a variety of social problems such as finances, domicile living, work-site-place problems, conflicts with law and difficulties in social interactions with family, friends and other persons. Social problems negatively impact psychological well-being and generate stress which in turn may constitute a reason to drink alcohol again. Against this background the importance and need of an integrative and personalized treatment becomes evident.

Comorbid diseases in alcohol-dependent patients

Alcohol problems share a high comorbidity with other psychiatric diseases. The simultaneous occurrence of a substance use disorder and a psychiatric disease is called dual diagnosis. A large US epidemiological study revealed life-time prevalence rates of psychiatric diseases of about 22.5%, of alcohol use disorders about 13.5% and of drug use disorders about 6.1%. In the sample of psychiatric diseases 29% had a concurrent substance use disorder, which is about 2.7 times increased compared to persons without a psychiatric disease. In the sample of alcohol use disorders the dual diagnosis of drug use disorders or psychiatric diseases is about 45% (Regier et al., 1990). A European epidemiological study with data of six countries shows pairwise associations of 12-months mental disorders in general population. Persons with alcohol dependence were 27.7% more likely to exhibit a comorbid psychiatric disorder in general, a so-called dual diagnosis, with a higher proportion of women (58.2%) compared to men (18.0%). The highest odds ratio (OR) for axis I dual diagnosis among alcohol dependencies are generalized anxiety disorders OR 11.2 (3.8-32.9), agoraphobia OR 10.7 (3.0-38.5), panic disorder OR 6.8 (2.2-21.1), major depression OR 6.7 (3.1-14.3), specific phobia OR 3.3 (1.3-8.4) and post-traumatic stress disorder OR 3.1 (1.0-9.5) (Alonso et al., 2004a). An Indian study showed that incidence of substance use disorders (SUD) remained quite stable over the last two decades, but the probability of additional SUD has increased (Venkatesan & Suresh, 2008). Highly worrying for example is, that about 80-90% of all alcohol dependents are tobacco smokers, which increases morbidity and also mortality, as today is known that alcohol dependents are more likely to die due to tobacco-related diseases (Hurt et al., 1996). Beside comorbid axis I disorders (dual diagnosis) and additional substance use disorders in patients with SUD there is also a higher prevalence of axis II disorders. Verheul and colleagues (2001) compared axis II disorders (personality disorders; *not other specified* were excluded) in different samples and found that in general population there is a prevalence of about 10.0-14.8%, compared to psychiatric patients with 45.2-80.0%,

compared to patients with SUD with 34.8-73.0% of axis II disorders. Table 2 shows a more specific and detailed list of axis II disorders in patients with SUD summarized from 6 studies. Taken together, there is a high prevalence of comorbid psychiatric diagnoses in patients with SUD. Those two disorders are relative to each other and may subjectively help or facilitate the burden of one disorder and maintain the other disorder. In treatment it is important to address both disorders at the same time, otherwise if only one disorder will be treated the risk that the other disorder increases, e.g., impairment of psychiatric disease if only SUD is treated or higher probability of relapses in SUD if only the psychiatric disease is treated. In the past many health centers had a main therapy focus and patients with dual diagnoses were send back and forth and in turn showed bad outcomes, e.g., high rate of re-admissions or crisis interventions (Moggi & Donati, 2004; Petitjean, 2005). This shows the importance to treat both disorders in dual diagnosed patients to achieve a sustained successful outcome. With the increased offer of integrative treatment centers in the last years for patients with dual diagnosis, this fact has gained importance and has started to be taken into account.

Table 2

Prevalence rates of DSM-III-R Axis II disorders reported in published studies among individuals with SUD and in general population (Verheul, 2001).

Personality disorders	Treated addicts		General population	
	Range	Median	Range	Median
Antisocial	3.0-27.0	22.9	0.2-3.0	2.2
Borderline	5.0-22.4	17.7	1.1-1.7	1.7
Paranoid	3.2-20.7	10.1	0.4-1.8	1.7
Avoidant	2.0-18.4	6.0	1.1-5.2	1.3
Passive-aggressive	0.0-11.6	6.0	1.7-3.0	1.8
Narcissistic	0.7-17.0	5.3	0.0-3.9	0.0
Dependent	1.7-8.1	4.6	0.4-1.7	1.5
Obsessive-compulsive	0.7-10.7	4.4	1.7-2.6	2.2
Histrionic	1.4-11.9	3.3	1.3-3.0	1.7
Schizoid	0.0-4.0	1.3	0.4-0.9	0.7
Schizotypal	0.0-7.0	0.6	0.0-3.0	0.7

1.5. Treatment of alcohol dependence

In total 2.5 million persons were estimated having an alcohol problem with need to be treated in Germany 1996. Of these about 200'000 (8.3%) received an alcohol specific treatment (outpatient or inpatient) and about 600'000 (24%) were treated in general hospitals per year.

Specific inpatient alcohol treatment is even less, per year 30'000 (1.2%) alcohol dependents are treated in residential recovery treatment and about 62'000 (2.5%) go through an inpatient detoxification treatment (Feuerlein et al., 1998). There is evidence that the majority of individuals affected by alcohol use disorders never receive formal alcohol treatment (Cohen et al., 2007) or use the health system ineffectively. Further it is estimated that about 70% of alcohol dependents consult once a year their general practitioner, of which a large part fail to identify or ask about substance use.

Early detection of alcohol problems and easy access to alcohol-specific treatments would be desirable, because in general alcohol dependents come about fourteen years too late into residential recovery treatment (Weissinger, 2012). What are the factors that such a small proportion of patients come into alcohol-specific treatment and how could this number be improved? On the one hand this might be the social stigma of alcohol dependence which is still seen as a problem of a will weak instead of a disease in society. On the other hand, the insight that one has already developed an alcohol problem is mostly a long way of finding. In this insight process the ambivalence of alcohol use and its consequences play a key role. Alcoholism can affect everyone, independently of social status, intelligence and financial income and does not represent the typical stereotype of a poor and homeless person.

Stages of change model

Every person with a problematic alcohol use stands at another point of view regarding its individual change process. Considering these individual differences Prochaska and DiClemente (1983) designed the stages of change model which is still wide spread in treatment for substance use disorders (Figure 2).

The very first stage is named *pre-contemplation*, where subjects do not worry about their substance use and don't see it as a cause of their problems. The positive effects of alcohol use still outweigh the negative consequences. In the following *contemplation* stage the relationship of alcohol use and its consequent problems getting realized. Persons start to consider their substance use and work with their ambivalence of ongoing use or stop. In the *determination/preparation* stage persons have recognized that changing their behavior would yield to lesser problems and get ready to seek help. In the *action* stage persons have decided to change and start to enforce concrete aims such as consult a doctor or start a therapy. In the *maintenance* stage subjects try the changes make to stabilize, e.g., sustain abstinence with aftercare attendance and continue their lives as recovering alcoholics. If a relapse occurs subjects are in the *relapse* stage and the circular process restarts. In every stage different forms of interventions are adequate.

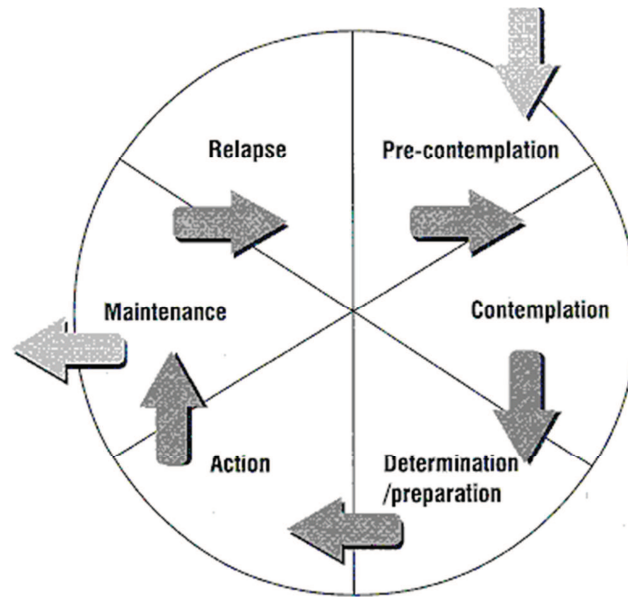


Figure 2. The stages of change model (based on Prochaska & DiClemente, 1983)

In the *pre-contemplation* stage the interventions are mainly consultancy. The reflection of self-perception with an external perspective may help to change the own opinion about drinking, which might be achieved by using diagnostic instruments or biological parameter such as liver function tests. To avoid resistance by patients from further persuasion attempts should be refrained. Better is to give information and education about the nature of substance use disorders, thus patients can build their own opinion and may change their attitude regarding their substance use under the protection of self-esteem. In the stage of *contemplation* it is important to support patient's critical self-reflection with emotional and matching arguments. In this stage it is likely to work with pro-contra lists which may help to work out the ambivalence regarding substance use and in turn support the decision for further steps. In the *preparation* stage patients know about their substance problem and want to receive recommendations about how to change or what treatment would be suitable. In the *action* stage, where persons undergo an outpatient or inpatient treatment, it is important to consolidate awareness of the problem, to increase the personal coping strategies and to show further ways of problem solving. In the *maintenance* stage it is important that patients attend aftercare, containing relapse prevention, learn how to handle relapses, mediate that relapses are a part of the longer exit process and that there is no all-or-nothing thinking about relapse or abstinence. In the *relapse* stage patients should be motivated to stop drinking again and show ways how to do so. The stages of change model shows that adequate interventions are changing with the individual development of insight and growing knowledge about the own substance use disorder. At every stage different treatment approaches are needed.

Prevention and early intervention

Taking together, there is only a small fraction of alcohol dependents receiving alcohol specific treatments in their lives, let alone being identified as a problematic drinker. Early detections and interventions would be desirable in the sense of prevention. General practitioner could use screening instruments, such as CAGE or AUDIT to detect problematic alcohol use, but mostly there is a lack of time during consultations or insufficient knowledge about screening instruments. Another approach is to look at typical symptoms or somatic comorbidities, such as gastrointestinal complaints, gastritis, pancreatitis, fatty liver or investigate liver functioning tests. If a positive indication is found a brief intervention should be applied, such as *Feedback, Listen, Advice, Goals and Strategies* (FLAGS) which may help people to take their alcohol problem seriously. Brief interventions in substance use disorders are known to be effective (Wilk et al., 1997). All kind of early interventions should be guided by the principles of motivation interviewing.

Therapies and treatment goals for alcohol use disorders

In the last years there was an enormous development of evidence-based treatments for alcohol use disorders. In the past abstinence or sobriety was the one and only goal for people with alcohol use disorders, today treatment goals are more differentiated, because it is important to adapt treatment goals to patients' possibilities and needs. The lifelong abstinence is still recommended, but a kind of ideal norm, which is not adequate to everyone. If abstinence is impossible due to patients' abilities or other problems the approach of harm reduction is indicated (Körkel et al., 2005). Other possible treatment goals in therapy for alcohol use disorders are for example promotion of insight into illness, provide knowledge about the disease, motivation to change drinking behavior, support to build up alcohol-free episodes, motivation to treat consequent and concomitant diseases of alcohol dependence. Therapy recommendations for alcohol use disorders are based upon the severity of the alcohol problem and patients' treatment goal. For example if persons exhibit a hazardous or problematic drinking pattern a counseling center may be recommended first. If there are physical withdrawal symptoms a medically based detoxification treatment is indicated. If there are concomitant severe physical or psychiatric diseases mostly an inpatient setting is indicated, otherwise an outpatient medically based detoxification treatment can be recommended. Most patients entering a detoxification treatment are ambivalent about their alcohol use, there are negative consequences due to alcohol use, but there are also positive causes or expectancies to consume alcohol again. For this reason establishing and promoting motivation to change substance use plays a key role in treatment and should not be a

premise. Treatments should have low threshold, thus more persons may be motivated to enter alcohol-specific treatments.

The modern treatment approach is integrative and interdisciplinary. Different treatment blocks overlap and interact with each other in a useful way. Treatment blocks will be individually tailored to patients' severity of disease and needs in the sense of a personalized treatment. Basically and prototypically there are four main pillars in the treatment of alcohol dependence, namely motivation for abstinence, withdrawal treatment, maintaining abstinence (relapse prevention) and lasting abstinence.

The pulse or recommendation to start a treatment for alcohol dependence mostly comes from other persons, such as family, friends, general practitioners, employers or psychotherapists. Individuals then mostly go to counseling or information briefing in specialized institutions. Afterwards a medically based detoxification treatment follows, which normally lasts about 2-3 weeks. After this a residential recovery lasting up to 3 months is the most effective treatment for alcohol use disorders. At the end of every treatment aftercare is very important to stabilize, maintain abstinence and prevent relapses. In the course of alcoholism relapses are rather the rule than the exception. Thus it is important to discuss reasons and conditions that may trigger relapses early in therapy. Aftercare is mostly held in outpatient settings and can consist of different elements, such as self-help groups, individual counseling, psychotherapy, regular alcohol breath tests or regular liver functioning tests.

Evidence-based treatments in the therapy for alcoholism

Literature regarding evidence-based treatments for alcohol dependence has enlarged in the past. Pharmacological drugs such as acamprostate, naltrexon and disulfiram for relapse prevention have proven to support abstinence or to reduce relapses (Wiesbeck, 2009), however, they are recommended to be embedded in other non-pharmacological interventions or outpatient therapies, used alone their effectiveness is rather low. Beside pharmacological drugs there is a variety of effective non-pharmacological interventions for alcohol dependence which are listed in Table 3. The purpose of all non-pharmacological interventions is to increase motivation, enhance competence to maintain abstinence or reduce hazardous use and in turn to re-gain self-competence to control alcohol use.

Table 3

Non-pharmacological interventions in alcohol disorders according to AWMF guidelines*

Type of intervention	Evidence grade**
Brief interventions	A
Motivational Interviewing	A
Behavioral psychotherapy	A
Cognitive behavioral psychotherapy	A
Social skills training	A
Relapse prevention	A
Self-help groups	B
Psychodynamic therapy	B
Interpersonal therapy	B
Couple or family therapy	B
Relaxation techniques in combination with other treatment elements	B
Behavior contracts or contingency management	B
Socio therapy	C
Occupational therapy	C
Relaxation, Movement, and Sport therapy	C
Exposition training	C
Psychoeducation as a component of a complex treatment	C

*AWMF = Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

**Evidence grades are classified into three steps in accordance with the American Psychological Association (APA). Evidence grade A is empirically good investigated, with meta-analyses and systematic reviews. Evidence grade B is investigated in general with controlled studies and follow-up studies. Evidence grade C is based on experts' opinions and descriptive studies.

2. Introductions

2.1. Tobacco smoking as an additional burden in the course of alcoholism (Article 1)

Tobacco smoking is very common and widely-used among alcohol dependents. Studies find up to 70-95% of alcohol dependents with comorbid tobacco dependence (Batel et al., 1995; Bien & Burge, 1990; Burling & Ziff, 1988) compared to general population with 25-30% of tobacco dependents (WHO, 2011). Alcohol-dependent smokers smoke more and show a more severe tobacco dependence than smokers without substance use disorders (Hughes & Kalman, 2006; Marks et al., 1997). Increased smoking is connected to increased alcohol drinking and vice versa (Barrett et al., 2006; Burton & Tiffany, 1997; Daepfen et al., 2000) indicating a strong interconnection of these two substances. Tobacco smoking itself is related to a number of severe health risks such as vascular diseases and carcinoma (Schmidt et al., 2006), but in combination with alcohol dependence health risks are synergistic especially in the upper aero-digestive tract (Pelucchi et al., 2006). For example, alcohol-dependent smokers sustain a 35 fold risk to get carcinoma in pharynx or larynx (Zeka et al., 2003). Moreover, results of a large mortality survey study reveal that alcoholics die rather due to tobacco-related diseases than due to alcohol-related diseases (Hurt, et al., 1996). Despite these alarming health consequences there is only little interest and commitment on this topic in treatment and research. This might be explained by some myths about smoking cessation in alcohol dependents. For example there exists the assumption that alcohol-dependent smokers are less motivated to quit smoking compared to smokers without an alcohol problem. Another assumption is that smoking cessation during alcohol treatment may impede alcohol abstinence (Gulliver et al., 2006). Both arguments were refuted by literature. Alcohol dependent smokers are not less motivated to quit (DiFranza & Guerrera, 1990), but there is evidence that it seems to be more difficult to stop smoking for alcohol dependent smokers than for smokers without an alcohol problem (Burling et al., 1997; Cooney et al., 2007; Hughes & Kalman, 2006). Furthermore literature does not report any negative effects of smoking interventions for threatening alcohol abstinence (Cooney, et al., 2007; Hurt et al., 1994; Metz, Kroger, et al., 2005; Saxon et al., 2003). Moreover, smoking cessation can even have a preventive, beneficial effect on alcohol outcomes (Baca & Yahne, 2009; Batra et al., 2011; Bobo et al., 1998; Grant et al., 2007; Kohn et al., 2003; Tsoh et al., 2011). Smoking cessation rates of patients with SUD in residential recovery treatment are consistently higher than in addiction treatment centers (Prochaska et al., 2004). Studies with active interventions in comparable residential settings reveal short-term smoking cessation rates of 9-22% (Hurt, et al., 1994; Kalman et al., 2001; Metz, Kröger, et al., 2005; Saxon et al., 1997) and 6-month follow-up outcomes of 2-18% (Baca & Yahne, 2009; Burling et al., 2001; Gariti et al., 2002; Metz, et al., 2005).

2.1.1. Research questions (Article 1)

There is little research in the field of smoking cessation among alcohol dependents especially in randomized-controlled trials. Therefore the aim of the present study was to investigate whether a cognitive behavioral treatment (CBT) of smoking cessation is superior compared to autogenic training (AT) during alcohol detoxification treatment regarding smoking outcome. The detoxification treatment was chosen to reach a high number of alcohol-dependent patients in an early stage of treatment, to sensitize for burdens of smoking and motivate for smoking cessation.

It was first hypothesized that CBT smoking intervention yields in higher smoking cessation rates than AT approach. Second, it was hypothesized, that the CBT group yields in a higher reduction rate of 50% or more compared to AT. Both hypotheses were analyzed directly after intervention and 6 months later. Finally, it was hypothesized, that smoking cessation would not impede alcohol outcomes 6 months later.

2.2. Self-help group attendance as a factor in the course of alcoholism (Article 2)

The first half year after treatment for alcoholism contains the highest risk of relapses (Körkel, 1996). One-year relapse rates in residential settings after alcohol detoxification and motivational treatment are quite high of about 84% (Bechert et al., 1989; Veltrup, 1995) while relapse rates after alcohol recovery treatment are ranging from 53-57% (Funke et al., 2001; Missel et al., 1997). To attenuate relapse rates and stabilize abstinence patients are recommended to make use of outpatient support the so-called aftercare. Aftercare should be personalized, i.e. arranged for individual needs consisting of different elements supporting alcohol abstinence like self-help groups, community addiction counseling, physician, and psychotherapist. The comparison of different aftercare modalities revealed that patients who obtained no aftercare at all had the poorest alcohol outcomes (Ouimette et al., 1998). One of the oldest and global widespread self-help groups for alcoholism is the Alcoholics Anonymous (AA). Findings in literature are inconsistent. While some report positive effects of participation in AA on drinking outcomes (Connors et al., 2001; Emerick et al., 1993; Gossop et al., 2003; Watson et al., 1997) others found no positive impact of AA on drinking outcomes (McLatchie & Lomp, 1988; Montgomery et al., 1995). Furthermore, there are two meta-analyses about AA attendance and drinking outcomes, which both did not find unequivocal effectiveness for AA regarding drinking outcome (Ferri et al., 2006; Tonigan et al., 1996). These discrepancies might also be explained by the existence of a wide range of AA groups all over the world. There are findings indicating that differences exist within AA organizations, because they differ from place to place in group processes, members, and atmosphere (Montgomery et al., 1993). Other criticism of studies focusing on AA is the low

study quality and the lack of biological markers to corroborate alcohol abstinence (Tonigan, et al., 1996). Regular AA attendance once a week is associated with superior drinking outcomes (Gossop, et al., 2003; Ouimette, et al., 1998) whereas increasing the frequency of more than weekly shows no additional benefit (Watson, et al., 1997). Regular aftercare attendance is associated with lower levels of substance use at 6-month (Arbour et al., 2011). This is supported by findings that the duration over time is more important than the frequency of AA attendance, where rapid entry into AA followed by a longer participation after detoxification promise better 1- and 8-year outcomes (Moos & Moos, 2004).

2.2.1. Research question (Article 2)

There is a large body of literature about 12-step programs such as AA attendance and drinking outcomes with heterogeneous results (Ferri, et al., 2006; Tonigan, et al., 1996). Further study quality and the lack of biological corroborated alcohol abstinence were criticized by some authors. Due to this, the idea was to investigate a data-pool without the above mentioned limitations. For this, data from an original placebo-controlled pharmacological study with alcohol dependent patients was re-analyzed. The question was whether alcohol-dependent patients who regularly attend AA meetings show better alcohol outcomes, i.e. more abstinent days, compared to patients' not attending AA meetings after detoxification treatment.

2.3. Gender as a factor in the course of alcoholism (Article 3)

In alcoholism there is a gender difference of about 3:1 (Papst & Kraus, 2008) with a higher proportion of alcohol-dependent men (Alonso et al., 2004b). Surveys in hospitals discovered 25% of male and 4% female patients on internist or surgical units and 28% male and 8% female patients on gastrointestinal units regarding alcoholic-related diseases. One fourth (24.6%) of the number of direct alcohol-related mortality in 1993 in Germany were women (Feuerlein, 1996). As there is a higher proportion of men suffering from alcoholism, research on alcoholism has focused predominantly on men in the past, resulting in an under-representation in research addressing alcohol-dependent women. In the beginning of alcoholism treatment men and women seem to have similar severe alcohol problems (Glenn & Parsons, 1991; Greenfield, 2002; Greenfield et al., 2000). No differences in frequency of binge drinking, in indicators of tolerance or in numbers or latencies to relapse were found between genders. However, women are more likely to have poorer prognostic characteristics for treatment outcome than men (Foster et al., 2000; Glenn & Parsons, 1991). Alcohol-dependent men tend to drink greater amounts of alcohol with an earlier onset of heavy drinking than women (Grella, 2003; Ross, 1989). Other results indicate that women were

heavier drinkers than men with respect to the index of drinking to intoxication (Rubin et al., 1996). On the one hand, the volume of alcohol distribution in the female body is lower than in a male body, on the other hand, the “first pass” effect and with it the alcohol metabolism is reduced in women compared to men (Walter, 2004). Findings of observational follow-up studies on gender differences postulate that the time interval from regular alcohol use to the first hospitalization in women is significantly shorter than in men (Diehl et al., 2004). Despite a later onset and a shorter duration of alcohol use women seem to have equally neurological and internal medicine complications as men (Diehl, et al., 2004). For example women have a higher vulnerability to develop liver cirrhosis than men and have a higher risk to die due to liver cirrhosis, being 19.8% for women and 15.6% for men (Feuerlein, et al., 1998). Despite a shorter total time of alcohol exposition in alcohol dependent women, atrophic changes in the brain are seen in the same extent as in alcohol dependent men (Diehl, et al., 2004; Hommer et al., 2001).

Several studies found that alcohol-dependent women have a higher overall rate of psychiatric comorbidity, especially affective disorders (Alonso, et al., 2004a; Hesselbrock, 1991) and score higher on depressive symptoms than men (Foster, et al., 2000; Glenn & Parsons, 1991). This is in line with results of studies investigating factors preceding relapse episodes. Women are more likely to relapse in response to negative emotional states and interpersonal influences while men tend more to relapse in response to positive affect and social pressure (Connors et al., 1998; Zywiak et al., 2006). Reasons for drinking alcohol, social stressors or problems, expectations on alcohols effect and benefits of alcohol use differ between genders. Compared to controls alcohol-dependent women differ in terms of coping styles, personality variables and in interpersonal conflicts, which appear to be an additional risk factor for alcohol-dependent women (Conte et al., 1991; Walitzer & Dearing, 2006). Interpersonal problems lead to frustration and psychological distress in interactions and relationships, which lead to maintain substance use (Walter et al., 2005), which then sustains interpersonal problems. Furthermore interpersonal problems affect all kind of relationships, as well as the therapeutic alliance which in turn has an influence on treatment outcome.

2.3.1. Research question (Article 3)

Since very few studies have directly addressed the issue of interpersonal problems in alcohol dependents by gender, the present study aimed to corroborate the reported differences in literature by using a structured and validated questionnaire to assess self-perceived interpersonal problems. It was hypothesized that first of all alcohol-dependent patients perceive themselves as having more interpersonal problems compared to healthy controls independent of gender. Further it was hypothesized that in particular alcohol dependent women suffer from different interpersonal problems than alcohol-dependent men.

3. Methods

3.1.1. Study design, subjects, and procedure (Article 1)

Cognitive behavioral smoking cessation during alcohol detoxification treatment (Article 1)

The study design is a prospective, randomized and controlled clinical trial, in a residential detoxification unit in the Psychiatric University Hospital of Basel in Switzerland. To our knowledge this is one of the first studies regarding smoking cessation in alcohol dependents with a randomized and controlled design in German speaking countries.

Patients were eligible if they were diagnosed as alcohol dependent according to ICD-10 criteria, were regular daily smokers, were motivated to quit or reduce their tobacco use, were between 18 and 65 years old and stayed long enough to complete study intervention. Patients were excluded if they took medication supporting a smoking stop (e.g., Varenicline, Bupropion), participated in another smoking cessation treatment, were pregnant, had insufficient German language knowledge or were mentally not capable to understand study information. Additional SUD or psychiatric disorders were not excluded, to ensure a convenience sample of alcohol dependents in residential psychiatric detoxification wards. Of 237 eligible alcohol-dependent patients 103 patients participated in the study of these 53 patients were randomly allocated to the experimental group receiving CBT intervention and 50 patients to the control group receiving AT intervention.

The study consisted of an intervention phase, conducting five 30min-group sessions (CBT or AT) within 1-2 week parallel to alcohol detoxification treatment. Before and in the end of the intervention phase a baseline and post-treatment interview was made. After 6 months all patients were re-invited for a follow-up interview.

3.1.2. Data Assessment (Article 1)

The baseline interview consisted of demographic variables, history of psychiatric diseases and SUD in family, ICD-10 criteria for alcohol dependence and a smoking anamnesis.

Smoking anamnesis at baseline consisted of questions such as age of smoking onset, years of smoking, past quit attempts, pack years and the Fagerström Test for Nicotine Dependence (FTND; Bleich et al., 2002) to assess the severity of tobacco dependence. The severity of alcohol dependence was measured by asking the number of standard drinks prior to admission and by using the Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993). To assess craving scores for both substances a visual analogue scale (VAS) ranging from 0 to 100 was used. Similar VAS was used to measure *importance* and *self-efficacy* to quit smoking during study time. Additionally questions regarding the stages of change model, namely *preparation* and *action* stage (Prochaska & DiClemente, 1983) were asked.

Smoking status was recorded by the number of cigarettes per day and by breath carbon monoxide (CO-level) measurements. After intervention and at follow-up urinary cotinine

(nicotine metabolite) was measured to verify nicotine exposure. To corroborate self-reported alcohol use at 6-months follow-up the biomarker ethyl glucuronide (EtG) was determined in urine.

3.2.1. Study design, subjects and procedure (Article 2)

The impact of self-help group attendance on relapse rates after alcohol detoxification in a controlled study (Article 2)

To test the impact of self-help group attendance a re-analysis of an original placebo-controlled pharmacological study was made. Of the original study only data of the placebo group was analyzed to avoid any interaction with the active pharmaceutical medication. In total 78 patients of the original placebo sample were selected of which 50 belonged to the experimental group attending a self-help group regularly and 28 patients without attending any self-help group. Patients were recommended to attend a self-help group but were free to decide if they wanted to. Patients were eligible if they were diagnosed with an alcohol dependence according to DSM-III criteria and had a score of >11 in the Munich Alcoholism Test (MALT; Feuerlein et al., 1980). To control for comorbidity patients with scores of > 18 on the Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) or scores of > 16 on the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) were excluded. Patients came to study sessions every second week during the first half year, in the following half year study sessions took place every eight week. Attendance of self-help groups (AA) and data of alcohol abstinence based on self-report and on biochemical parameter such as alcohol breath-test and liver enzymes were recorded regularly at study sessions. Any use of alcohol was counted as relapse.

3.2.2. Data assessment (Article 2)

For baseline measurements the MALT, the HAMD and the HAMA were used. The MALT measures problems and consequences due to alcohol use and gives an impression if there is a suspicion of alcohol misuse and reaching higher scores, gives a hint regarding the severity of the alcohol problem (Feuerlein, et al., 1980). The HAMD is a self-rating questionnaire measuring actual depressive symptoms (Hamilton, 1960) and the HAMA is a self-rating questionnaire measuring actual symptoms of anxiety (Hamilton, 1959). The social functioning questionnaire (SFQ) was used to assess social functioning in everyday life situations, where low scores indicate better social functioning (Tyrer et al., 2005). Patients had to fill out HAMD, HAMA and SFQ in regular study session at 3, 6, and 12 months after study start.

3.3.1. Study design, subjects and procedure (Article 3)

Gender differences in interpersonal problems of alcohol-dependent patients and healthy controls (Article 3)

The study was an inpatient, observational and controlled questionnaire study, with alcohol-dependent patients in the end of the detoxification treatment. The experimental group consisted of 85 alcohol-dependent patients (48 males and 37 females), which were recruited from the alcohol detoxification unit in the Psychiatric Hospital of the University of Basel. They were eligible if they were diagnosed according to the DMS-IV criteria of alcohol dependence, without suffering from other substance dependencies, except tobacco dependence. The control group consisted of 62 healthy participants (35 males, 27 females) working in the health sector and were eligible if they were between 18 and 65 years.

3.3.2. Data assessment (Article 3)

The study based on three questionnaires in a fixed sequence. First, a psychologist or assistant doctor interviewed the patient by using the Lesch's Alcohol Typology (LAT; Lesch et al., 1990). Afterwards the patient had to fill out two more questionnaires, namely the Alcohol Use Disorder Identification Test (AUDIT; Saunders, et al., 1993) and the Inventory of Interpersonal Problems (IIP-64; Horowitz et al., 1994) in a paper-and-pencil format. The procedure lasted about 50 minutes. The LAT categorizes alcohol dependents into four subtypes. Typ I is described as the so-called *allergy-model* suffering from intense alcohol dependence and exhibiting a severe alcohol withdrawal syndrome. Typ II alcohol-dependents use alcohol as a self-medication because of its anxiolytic effects and try to *reduce anxiety or conflicts*. Typ III also uses alcohol in terms of self-medication but to *reduce depressive symptoms*. Typ IV alcohol dependents show pre-morbid cerebral defects or behavioral disorders preexisting in childhood, the so-called *alcohol drinking as adaption* model. The IIP-64 is the core instrument of the study. It is a 64-item questionnaire to assess self-perceived distress in interpersonal relationships. There are four dimensions with eight anchor-subscales arranged in a circumplex model. There are two main axes, namely affiliation and dominance. The horizontal axis describes how much friendliness a person displays to someone else, on the one anchor naming *overly nurturant*, referring to love or strong affiliation and on the other anchor named *cold*, referring to hostility, coldness and hate. The vertical axis describes dominance in relation to others with the upper anchor of *domineering* and the lower end of the anchor the term *submissive*. The third dimension ranges from the anchor named *vindictive* to the opposed anchor named *exploitable*. The last dimension ranges from the anchor *socially avoidant* to the opposed end named *intrusive*. For a more detailed description of the IIP-64 please consider methods in the published article (Appendix).

4. Statistical Analyses

All data was first analyzed for extreme outliers and for normal distribution. If normal distribution was given appropriate analyses in regard to the nature of data (categorical, ordinal or continuous variables) and their type of comparison (independent or dependent data) were conducted. If not other specified, statistical differences were tested with Chi-square tests for categorical data, non-parametric tests for ordinal data and ANOVA's for continuous data. Unless otherwise stated all calculations were held as intention-to-treat analyses. The level of significance was set at $p=0.05$ if not other specified. All calculations were performed by using the Statistical Package of the Social Sciences (SPSS for Windows, versions: 11.0 (Article 1)/ 14.0 (Article 2)/ 19.0 (Article 3))

3.1. Article 1 – Smoking cessation parallel to alcohol detoxification

To analyze changes over time in the two groups (EG and CG) and for sub-group analyses, repeated measurement ANOVA's were used. To evaluate impact of variables such as severity of tobacco dependence, a covariate was included in the repeated measurement ANOVA's. Because the total sample size was rather small to detect a statistical difference effect sizes were calculated to confirm the clinical significance, i.e. clinical advantage. For this the formula $\epsilon = \frac{x_u - x_l}{\sigma_u}$ (Bortz, 2005) was used, where an effect size of $\epsilon \geq 0.80$ indicates a strong effect, $\epsilon \geq 0.50$ a medium effect and $\epsilon \geq 0.20$ a weak effect.

3.2. Article 2 – Impact of self-help groups

For a continuous analysis over time of abstinent days to the first day of relapse a non-parametric Kaplan-Meier survival analysis (log-rank test) between the two groups was made. Analyses of relapses were based on intention-to-treat method, i.e. drop-outs were counted as relapses. To find out whether there are predictive variables for relapses at baseline, a stepwise logistic regression analysis was made. For changes over time in variables such as HAMD, HAMA, and SFQ repeated measurement ANOVA's were conducted.

3.3. Article 3 - Self-perceived interpersonal problems

Because normal distribution was not given, raw data was first transformed to z-scores and additionally the p-level was adjusted to $p=0.010$ for a more conservative analysis. Due to a high intercorrelation of the IIP-64 dimensions and the hazard of multiple testing the multivariate analysis MANOVA was chosen to detect differences in IIP-64 subscales.

5. Summary of the results

5.1. Cognitive behavioral smoking cessation during alcohol detoxification treatment: A randomized, controlled trial. (Article 1)

Baseline characteristics were similar between experimental and control group, only a slight trend of more cigarettes per day in the control group was seen (EG: 25.5 vs. CG: 30.5; $p=.066$). Directly after intervention 6 patients were smoke-free (EG: $n=4$ (7.5%) versus CG $n=2$ (4%)). At 6-month follow-up 3 patients (2.9%) were smoke-free of which all belonged to the CG. There was no difference between the groups regarding tobacco abstinence rates at any time during study. Tobacco abstinence was corroborated with CO-levels for every patient and with urinary cotinine at 6-month follow-up. However, 25 patients achieved a reduction of $\geq 50\%$ of their initial tobacco use directly after intervention of which 17 patients (32%) belonged to the CBT and 8 patients (16%) to the control group, which reached statistical significance ($\text{Chi}^2=3.617$, $p=.046$). In both groups a decrease in the number of daily cigarettes from baseline to after intervention was observed ($t(86)=7.193$; $p<.001$), with the experimental group achieving a significantly higher reduction of daily cigarettes than the control group (16.4 vs. 23.4; $t(86)=-2.317$, $p=.023$). Effect sizes corroborated a stronger effect for the reduction of cigarettes in the EG with $\epsilon = 0.77$ compared to a medium effect in the CG with $\epsilon = 0.49$. CO-levels decreased parallel to the number of cigarettes with a trend in favor of the EG but without reaching significance ($p=.076$). At 6-month follow-up there were 16 patients (15.5%) showing a successful smoking reduction of which 6 patients (11.3%) belonged to the EG and 10 patients (20%) to the CG again without reaching significance. The self-reported reduction of the cigarettes was corroborated by a mean CO-level of 14.9 ppm (parts per million) for patients reporting successful reduction compared to 31.8 ppm for patients failing a reduction ($F(1,56)=16.339$, $p<.001$). CO-levels from baseline to 6-month follow-up declined over time ($F(1,56)=9.434$, $p<.001$) in both groups with a medium effect of $\epsilon = 0.56$ for the EG compared to a small effect of $\epsilon = 0.18$ for the CG.

Attitudes regarding a smoking quit were rated by patients over study time and effects were found comparing baseline to post-intervention. The EG rated the *importance* (81.9 vs. 71.4, $t(83)=2.107$, $p=.039$) and *self-efficacy* (70.5 vs. 54.1, $t(83)=2.775$, $p=.007$) to quit smoking significantly higher compared to the CG directly after intervention, while at baseline no difference was found between the groups. Similarly, direct after intervention the EG agreed significantly more often being in the stage of *preparation* to stop smoking (79.5% vs. 51.2%, $\text{Chi}^2=7.754$, $p=.005$) and being in the stage of *action*, i.e. “having made quit attempts lately” (52.3% vs. 23.3%, $\text{Chi}^2=7.777$, $p=.005$) compared to the CG. After 6 months these effects were diminished.

Since it is known from literature, that the severity of tobacco dependence plays a role regarding successful quit attempts, sub-group analyses were made according to tobacco severity. All patients with a baseline FTND score of ≥ 7 were classified as *heavy smokers* (n=54; EG: n=30, CG: n=24) and patients with a FTND score of < 7 were classified as *moderate smokers* (n=49; EG: n=23, CG: n=26). As expected, *heavy smokers* compared to *moderate smokers* smoked more cigarettes per day, had a higher CO-level, had a higher pack year score and reported higher craving scores for cigarettes. Regarding alcohol use *heavy smokers* reported of more standard drinks per day compared to *moderate smokers* (24 vs. 15, $t(92) = -3.32, p < .001$) prior admission. Regarding tobacco use, *moderate smokers* reported significantly more often about cessation attempts during the past year (17 (34.7%) vs. 7 (13%), $p = .009$) and scored significantly higher in the self-efficacy score (47 vs. 62, $F(1, 101) = 6.061, p = .016$) regarding a future smoking quit than *heavy smokers*. To analyze changes in the number of cigarettes over time a repeated measurement ANOVA was calculated including the covariate *heavy versus moderate smokers*. The within-factor *cigarette* was significantly reduced over time ($F(1,84) = 20.827, p < .001$), the between-factor *treatment group* $F(1, 84) = 7.004, p = .010$) and the covariate revealed significance ($F(1,84) = 20.811, p < .001$), indicating a significant influence of the severity of tobacco dependence. Due to this finding repeated measurement models were calculated separately for each severity group. In *moderate smokers* only the within factor *cigarette* reached significance ($F(1, 39) = 24.253, p < .001$) whereas in *heavy smokers* the within factor *cigarette* ($F(1,44) = 27.902, p < .001$) and the between factor *treatment group* ($F(1,44) = 13.261, p = .001$) reached significance. This indicated a higher likelihood for heavy smokers in the CBT condition to achieve a reduction in the number of cigarettes directly after intervention, whereas in the group of moderate smokers' treatment group allocation seemed not to have a significant impact. After 6 months these effects were leveled out (Figure 3).

For analyses of alcohol use 44 patients were eligible, of which 42 patients had valid urine samples. No difference was found in self-report regarding alcohol use in the last 7 days between the groups with 19 patients reporting abstinence (EG: n= 10, CG: n= 9) and 25 reporting alcohol use (EG n= 12, CG n= 13). In analyses of urine samples 21 (50%) were found to have a positive EtG indicating alcohol use in the last 3 days. Combining self-report with urine samples resulted in 17 patients being verifiably abstinent from alcohol. This corresponds to a relapse rate of 80.5% (86/103) after 6 months (intention-to-treat analysis). There was no evidence that cigarette reduction affects alcohol use outcomes.

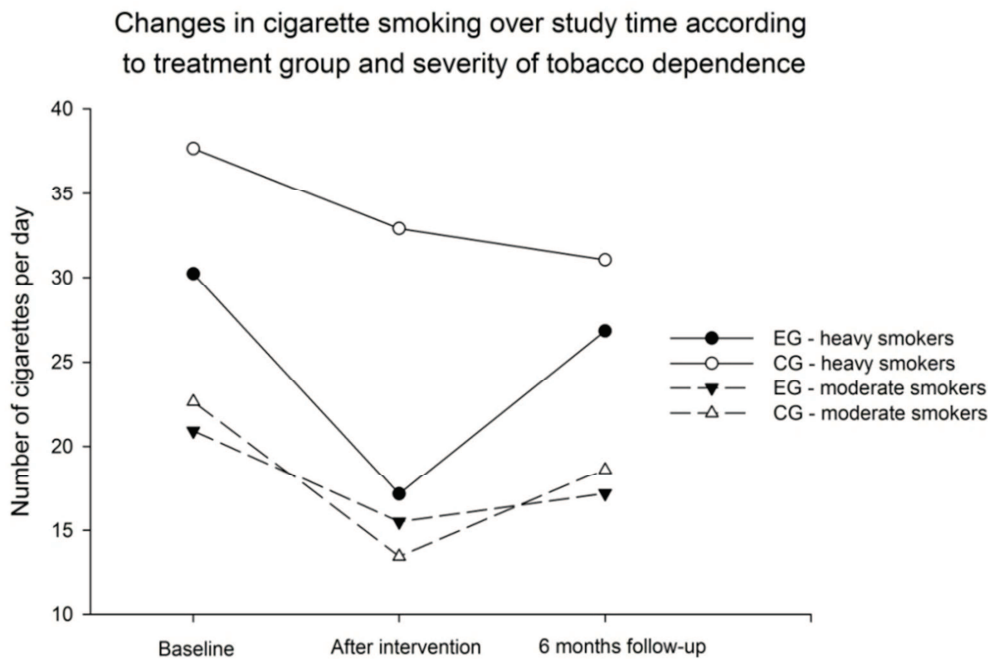


Figure 3. Changes in number of cigarettes over study time according to treatment groups and severity of tobacco dependence. EG = experimental group, CG = control group.

5.2. *The impact of self-help group attendance on relapse rates after alcohol detoxification in a controlled study (Article 2)*

Except the social functioning questionnaire (SFQ) score no baseline differences could be found between the EG attending self-help group meetings, predominantly AA, and the CG without any support. The EG exhibited a lower SFQ score with 13.8 indicating a better social functioning level compared to the CG with a SFQ score of 15.8 ($t(76)=2.51, p=.037$).

Comparison of relapses over time by using the Kaplan-Meier method revealed no significant differences, but a strong trend (log-rank, $p=.106$) in favor for EG. There was a lower relapse rate after 1 month for the EG with 14% (7 out of 50) compared to the CG with 28% (8 out of 28). After 3 months relapse rates were 40% for the experimental and 42% for the control group, after 6 months 56% versus 50% and after 1 year 64% versus 64.3% respectively. Taken together there was a slight advantage in the first month for attending AA's but the positive effect leveled off over time. To check whether the difference of social functioning at baseline may impact outcomes the SFQ score was adjusted and again no differences in relapse rates after 1 year could be detected. Afterwards a completer analysis (per protocol analysis) was calculated where again no difference in relapse rates after 1 year could be found. Changes in HAMD, HAMA and SFQ over time were analyzed using repeated measurement ANOVAs, finding that SFQ improved in both groups ($F(2,84)=7.61, p < .001$) exposing the factor *time in the study* as significant. To find out if any pre-treatment variable might have a predictive

value regarding relapses after 1 year, a stepwise logistic regression was conducted with four baseline variables including, age, HAMA, HAMD and SFQ. The logistic regression revealed a one-variable solution with an Odds Ratio of 1.359 (95% CI = 1.010, 1.829; $p=.043$) for HAMD the depression score at baseline. The goodness of fit accounted with Nagelkerke $R^2=0.12$ for only 12% of the variance of the total model, with an overall prediction rate of 67.1%.

5.3. Gender Differences in interpersonal problems of alcohol-dependent patients and healthy controls (Article 3)

Regarding demographic variables none of the variables differed between gender except that alcohol-dependent men were significantly more often unmarried with 41.7% ($n=20$) compared to alcohol-dependent women with 13.9% ($n=5$). No differences were found in the quantity, frequency or severity of alcohol use except question 4 in the AUDIT “How often during the last year have you had the impression not being able to stop drinking once you had started” was significantly more often confirmed by alcohol-dependent women than by alcohol-dependent men ($Z = -1.97, p = 0.049$). Alcohol-dependent men reported more often about violations of the law than alcohol-dependent women, 41.7% ($n=20$) compared to 19.4% ($n=7; \chi^2=4.66, p=0.031$). Reported life-time depressive episodes were significantly higher in alcohol-dependent women 86.5% ($n=32$) compared to alcohol-dependent men 68.8% ($n=33; \chi^2 = 3.65, one-tailed, p = 0.047$). Differences were neither found in LAT nor in family history of substance use. Current depressive episodes at admission were similar between gender with men ($n=15, 31.3\%$) and women ($n=14, 37.8\%$). Beside the reported gender differences no other baseline differences were found. Comparing dimensions of the Inventory of Interpersonal Problems (IIP) of alcohol dependents to healthy controls by using a MANOVA an overall group effect was found (multivariate $F(8,138) = 3.144, p=0.003$), namely five out of eight dimensions differed significantly between the groups (*vindictive, cold, socially inhibited, self-sacrificing, intrusive*). When comparing alcohol-dependent men with healthy men, the overall effect did not reach significance, but one significant univariate effect was found for the dimension *too cold* ($F(1,82)=7.404, p=0.008$), meaning that alcohol-dependent men perceive themselves as *colder* than healthy men do (Figure 4). Comparing the female groups regarding IIP-dimensions a significant overall effect was found (multivariate $F(8,55)=2.979, p=0.008$) and four out of eight dimensions reached significance. Alcohol-dependent women scored significantly higher on dimensions of being *too vindictive* ($F(1,63)=8.739, p=0.004$), *too socially inhibited* ($F(1,63)=8.532, p=0.005$), *too self-sacrificing* ($F(1,63)=14.198, p<0.001$), and *too intrusive* ($F(1,63)=10.283, p=0.002$) compared to female controls (Figure 4). To control for the possible confounding effects of the higher proportion of reported life-time depressive episodes in alcohol-dependent women, this variable was used as a covariate in the MANOVA. No effect due to life-time depressive

episodes was found with regard to gender differences in IIP-dimensions. Finally gender differences of the healthy samples in IIP dimensions were analyzed using a MANOVA without finding any significant differences.

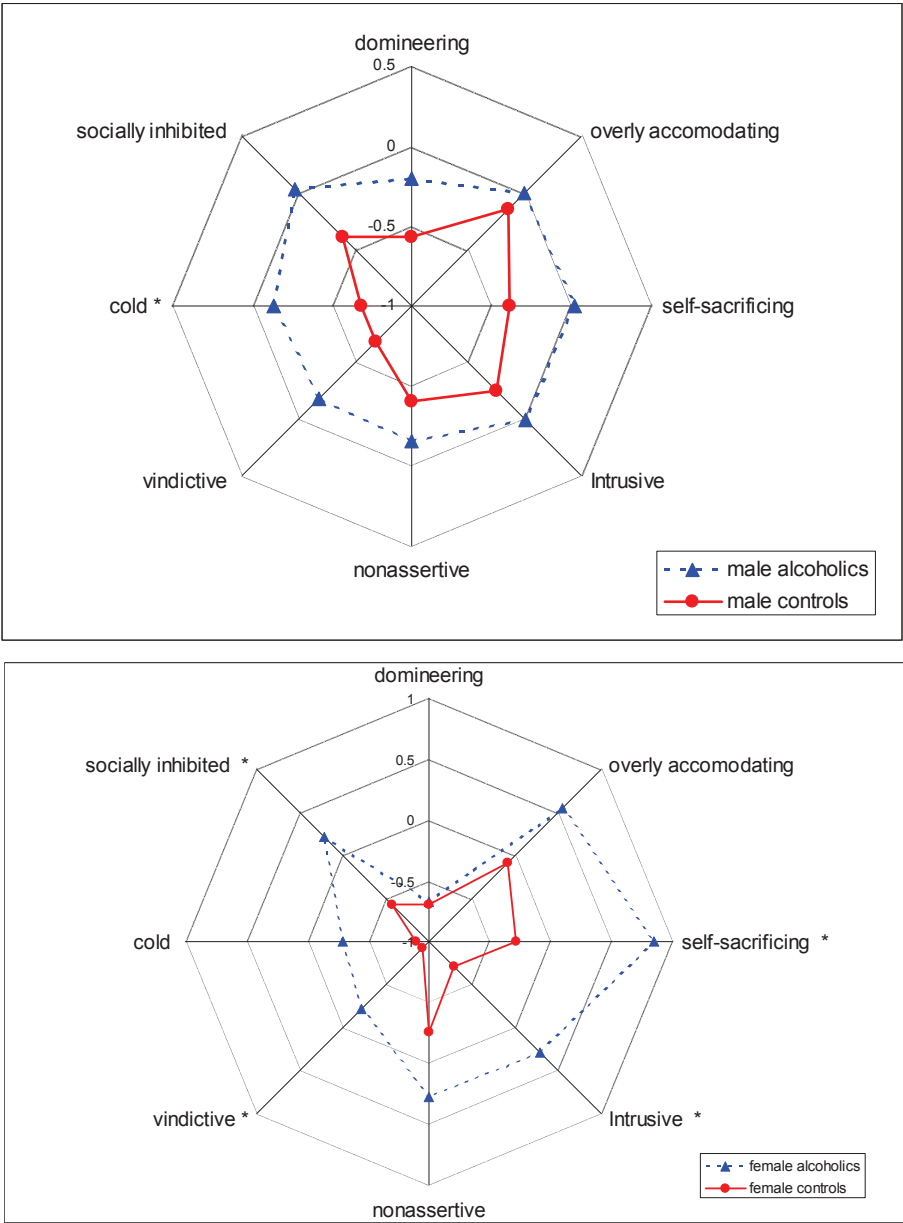


Figure 4. Circumplex model of interpersonal problems according to the IIP-64 dimensions. Above figure shows the circumplex model for alcohol-dependent men versus healthy men and the figure below for alcohol-dependent women versus healthy women. Note different scales.

6. Discussion

These studies highlight various important aspects that should be considered in the treatment for alcohol use disorders. The aim of these research projects was to contribute to the knowledge and improvement of effective treatments in alcoholism. Three parameters were elucidated, namely the feasibility of smoking cessation parallel to an alcohol detoxification treatment, the importance of self-help group attendance to reduce alcohol relapses and gender differences in self-perceived interpersonal problems of alcohol-dependent patients compared to controls.

Article 1: Though modest, the smoking quit rate of 2.9% after 6 months was in line with the literature reporting tobacco quit rates from 2-18% after 6 months in patients with SUD (Baca & Yahne, 2009). This was clinically relevant, since costs per treatment are very economical compared to health gains and prevention of premature death (West, 2007). Regarding the tobacco reduction rate of $\geq 50\%$ there was a significantly higher proportion of patients in the CBT compared to AT group achieving the reduction directly after intervention. However, after 6 month follow-up this effect was disappeared. Though the first hypothesis of a higher quit rate in CBT could not be supported in this sample, the second hypothesis of a superior outcome for the CBT group in reducing their cigarettes was confirmed, at least for short-term outcomes. CBT is a promising approach in short-term outcomes, but long-term outcomes seem not promising, which is in line with published data (Carmody et al., 2012; Prochaska, et al., 2004) furthermore there is evidence that smoking cessation in SUD has a lack of long-term success (Baca & Yahne, 2009; Burling, et al., 1997). Both experimental and control group achieved to reduce their cigarettes with a clear advantage for CBT in short-term outcomes. This might be explained by the study participation as every patient was motivated to change smoking behavior. Another factor might be hospitalization per se, where a study without any smoking intervention showed that heavy smokers tend to decrease and moderate smokers tend to increase their cigarettes after alcohol detoxification (Aubin et al., 1999). Another study found in a 21-day detoxification treatment that patients receiving a smoking intervention achieved to reduce their cigarettes, whereas the control group without an intervention tends to increase the amount of cigarettes (Olbrich et al., 2008). It might be speculated, that AT even as a non-evidence based method (Marques-Vidal et al., 2011) helped a subset of smokers as a stress-relief method and patients who smoke due to stress-relief may benefit from AT. The present reduction rate of 15.5% without any group difference after 6 months is modest, but clinically significant in respect of harm reduction, since there is evidence supporting that cigarette reduction increases probability for future cessation attempts (Hughes & Carpenter, 2006).

Beside the positive effect of reduction in the CBT group in short-term outcomes, also attitudes regarding a smoking quit changed significantly from baseline to post-intervention.

Only the CBT group reported an improvement in *importance* and *self-efficacy* regarding a smoking quit after study intervention. Similarly the CBT group reported more often being in the stage of *preparation* and being in the stage of *action* to stop smoking soon compared to the CG directly after intervention. These changes in attitudes may reflect activation in the quit smoking process probably due to the active discourse about smoking behavior in the CBT group.

After 6 months, no difference in alcohol use or sobriety between the groups was found, suggesting that smoking interventions did not jeopardize alcohol outcomes. This is in line with other reports (Baca & Yahne, 2009; Prochaska, et al., 2004) and supported the third hypothesis, that smoking cessation has no negative impact on alcohol outcomes.

There is evidence that patients with low FTND scores are more likely to quit smoking by themselves (Bobo et al., 1996; Karam-Hage et al., 2005). Therefore the present sample was divided to *heavy* and *moderate smokers*. There was no difference in AUDIT scores or in additional SUD but *heavy smokers* reported significantly more standard drinks prior admission than *moderate smokers*, which is in line with research and symbolizes the strong interrelationship of both substances (Barrett, et al., 2006; Daeppen, et al., 2000). Present analyses showed that primarily *heavy smokers* in the CBT condition reduced the number of cigarettes significantly compared to all other groups. *Moderate smokers* did not differ in the reduction rate between the CBT and the AT condition. However, the benefit for *heavy smokers* of the CBT approach did not sustain at 6 months follow-up. Nevertheless, it may be assumed that *heavy smokers* profit the most of the CBT approach and that *moderate smokers* seem not to need intense support for smoking cessation.

The present participation rate of 43.5% reflected a high interest for smoking cessation interventions in alcohol dependents and gave evidence for the feasibility of smoking interventions parallel to an alcohol detoxification treatment, which might constitute an ideal window of opportunity. Moreover the rather high participation rate and interest for smoking cessation in the present study underlined the statement that “offering smoking interventions in substance use disorder treatments is an obligation” (Prochaska, 2010) and ought to be a moral responsibility in health care systems (West, 2007).

In conclusion, there existed a high acceptance and interest of patients regarding a smoking cessation parallel to alcohol detoxification treatment. Smoking reduction outcomes and motivational processes regarding a smoking quit were significantly increased in the CBT condition directly after intervention, indicating a successful harm-reduction intervention by CBT. Especially alcohol-dependent heavy smokers profited the most from CBT.

Article 2: Regarding the impact of self-help groups no clear advantage for AA or 12-step group involvement could be shown. Exception was a slight trend in the first month compared to the non-attendance group, this effect, however, did not maintain over study time. Possible confounders for this rather negative result might be the low sample size and the

heterogeneity of AA groups themselves, their group processes, members and atmosphere (Montgomery, et al., 1993). Despite this rather negative finding of AA attendance, regular self-help group attendance is proven to support alcohol abstinence, is associated with reduced substance use (Arbour, et al., 2011) and constitutes an important factor in aftercare for SUD patients. Calculation of possible predictive variables revealed that the HAMD score at baseline has a slight predictive value regarding alcohol relapse. Interestingly, as patients with a score of > 18 on the HAMD were excluded from study, it seemed that already sub-clinical scores of depression might have an impact on relapses. Furthermore, the present results indicate an improvement of the social functioning level in both groups over study time, which might be associated to study adherence. The groups differed in scores of social functioning at baseline. The group attending AA meetings exhibited better social functioning levels than the group not attending self-help group meetings. This may reflect that patients with a weaker social functioning level hesitate to attend a self-help group, due to a lower self-esteem regarding their social skills. In conclusion there was a slight advantage for participants attending AA groups regarding alcohol relapse in the first month. However, this trend did not sustain over time. Furthermore, participants with sub-clinical scores of depression seem to have a slightly higher likelihood to relapse, but both groups showed an improvement of social functioning over study time. Overall, the finding supported the importance of aftercare (e.g., self-help groups) for patients with alcohol use disorders.

Article 3: The present findings revealed that alcohol-dependent patients exhibit a higher burden of self-perceived interpersonal problems than healthy controls. Further analyses revealed that this difference in interpersonal problems was mainly mediated by alcohol-dependent women. Alcohol-dependent women have a higher burden in four IIP dimensions compared to only one IIP dimension in alcohol-dependent men. Alcohol-dependent women rated themselves as higher loaded in the dimensions *too socially avoidant*, *too self-sacrificing*, *too vindictive* and *too intrusive* compared to healthy women. Thus alcohol-dependent women fall overall in the friendly-submissive region of the IIP-64 circumplex model. Alcohol-dependent men reported a higher burden of the dimension *too cold* compared to healthy men. Furthermore, alcohol-dependent men reported more often to be unmarried or single, whereas alcohol-dependent women were more likely to be in relationships. There is a high concordance of alcohol use in couples and women are more likely than men to have a partner who drinks even more than they do (Graham & Braun, 1999). Against this background, it may be assumed that alcohol-dependent women perceive more marital stress or conflicts in their relationship which in turn may aggravate interpersonal problems. This might explain the present finding of a higher burden in IIP dimensions for alcohol-dependent women. Another factor for a higher burden of interpersonal problems in women may be the depressive symptomatic. Prior research has shown that alcohol-dependent women are more likely to suffer from overall psychiatric

comorbid disorders, especially affective disorders (Alonso, et al., 2004a). In the present findings no gender difference was found regarding current depressive episodes, however, alcohol-dependent women reported of more life-time depressive episodes compared to alcohol-dependent men. Therefore, life-time depressive episodes were included as covariate in the analyses of the IIP dimensions to control for possible influence, but no impact of life-time depressive episodes could be found. Aubry and colleagues (2004) found that alcohol-dependent women compared to alcohol-dependent men exhibit overall a lower self-image, which may be associated with depressive episodes. It is conceivable that lower self-images influence the perception of interpersonal problems, namely that persons with lower self-images are searching causes for problems primarily by themselves, which in turn may improve depressive symptomatic and sustain interpersonal problems such as the friendly submissive interaction style found in alcohol-dependent women. Altogether, the factor low self-image, depressive symptoms and perceived interpersonal problems are strongly interconnected and influence each other. Mäkelä et colleagues (2000) found in a representative sample of the Finnish population that women reported more commonly that drinking had helped them to sort out interpersonal problems at home or at work-place and helped to express their feelings, whereas men reported more often that alcohol use helped them to be funnier, wittier and to get closer to the opposite sex. This finding implies that the use of alcohol between genders could have a different functional mechanism. Whether alcohol use in alcohol-dependent women is a cause or a consequence regarding interpersonal problems cannot be stated here, however, alcohol-dependent women compared to alcohol-dependent men have a higher burden of interpersonal problems. In conclusion, alcohol dependents differ from healthy controls regarding self-perceived interpersonal problems. Among alcohol dependents there is a gender difference, namely that alcohol-dependent women exhibit more self-perceived interpersonal problems on different dimensions than alcohol-dependent men. Further alcohol-dependent women reported of more depressive episodes in life-time and reported more often being in relationships than alcohol-dependent men.

7. Conclusions

All findings of the above mentioned studies have an impact on treatment for alcohol use disorders and may help to improve effectiveness.

Literature states that the duration of residential treatment and treatment satisfaction emerged as significant predictors of aftercare attendance (Arbour, et al., 2011; Moos & Moos, 2004). The first article, where a high interest in smoking cessation intervention parallel to alcohol detoxification treatment was apparent and almost 50 percent of all screened alcohol dependents took part in the smoking cessation study, reflected patients' request. Moreover it

shows that a combined treatment is feasible and highly accepted. Moreover, it might represent an ideal window of opportunity for smoking cessation. Voluntary offers of smoking cessation in detoxification units may increase treatment satisfaction and length of patients' stay, what in turn may enhance aftercare attendance according to Arbour's finding. Furthermore it is discussed that dealing with one substance use disorder may help to overcome another substance use disorder. Formal strategies for recovering substance abusers are quite similar across substances such as recognition of high-risk situations, dealing with craving, handling triggers or emotional states that may lead to substance use. Against this background it is possible that learned strategies for abstinence of one substance might be likely to be transferred to other abusing substances. Another important point is, if a person achieved a success, e.g., abstinence or controlled use in regard to harm reduction, this may impact self-efficacy positively to change concomitant substance use or related behaviors. A further aspect to be considered in treating alcohol use disorders is the difference in self-perceived interpersonal problems between alcohol-dependent men and women, which may influence treatment and should be taken into account. Against this background it is conceivable, that women and men interact differently due to their self-perceived interpersonal problems. This may impact all kinds of treatment settings in single and in group settings. For example, in therapeutic group sessions such as relapse prevention it is conceivable that women first give preferences to others or hesitate to say their own opinion due to their friendly submissive interaction style found in the IIP article compared to alcohol-dependent men. Also in gender mixed detoxification units it is conceivable that alcohol-dependent women have a higher likelihood to take sooner duties than alcohol-dependent men, which in turn keep up their interaction style. Beside the behavioral interactions, also themes and topics differ strongly between men and women. Therefore, gender-tailored groups would give the opportunity to discuss gender specific themes, e.g., sexuality or alcohol-related violence, more in detail and without any fears of opinions of the opposite sex. Very important is to take these gender differences into account in single settings, with respect to the therapeutic alliance, as it is known that therapeutic alliance is one of the most effective factors for a successful therapy (Orlinsky et al., 1994). It follows from this that gender differences have considerable impact on alcohol-related outcomes and may help to enhance treatment effectiveness when taken into account.

Gender differences of self-perceived interpersonal problems play a role in self-help groups with regard to atmosphere and contents as well. One solution would be to recommend gender-specific self-help groups, e.g., self-help groups for women only. This will probably result in a higher self-help group attendance and could strengthen group adherence and affiliation. Affiliation with a self-help group is important, especially affiliation with AA and has found to be more predictive for maintaining abstinence than AA attendance alone (Longabaugh et al., 1998; Montgomery, et al., 1995; Morgenstern et al., 1997). To reach a

strong affiliation with self-help groups different aspects such as the feeling being respected and accepted by group members improves group affiliation and atmosphere, what in turn enhances trust to speak openly about personal problems and substance use. This may be easier in homogeneous groups, like gender-specific groups. There exist gender-specific self-help groups but they are still very rare. Another possibility would be that patients with a high burden of specific interpersonal dimensions get some pre-sessions to improve the problematic dimensions before entering a self-help group which might lead to higher attendance rate. Further, interpersonal encounters in self-help groups are important for mutual support, for example to meet positive role models and to draw hope from statements or behaviors of others. Most patients with SUD suffer from social withdrawal, therefore it seems important to improve interpersonal encounters and relationships, where group settings provide an ideal basis.

7.1. Limitations

Article 1: The number of participants varied widely over study time. Sometimes many patients were interested to participate at once and sometimes almost no one entered the study. This might be related to the mouth-to-mouth propaganda as the study ran within one building. As participants knew each other they talked about experiences of the study and get aware of the different group contexts. Study explanation stated two different group interventions which are intended to be compared and for every group intervention a rationale of effectiveness was given. Nevertheless about 3 persons in the control group doubted that their intervention would really help them to stop smoking. Another weak point might be the difference in the durations of hospitalization. Most participants in the study were hospitalized for about 3 weeks according to the standard duration of a qualified alcohol detoxification treatment. As a central concern in the treatment of alcoholism patients were motivated for an ongoing treatment (in- or outpatient) thus some of the participants continued their stay in a residential recovery treatment. Those had a longer time of stabilization and support, which might influence alcohol and tobacco outcomes. Further, the external generalization cannot be drawn specifically to alcohol-dependents, as the study aimed for a convenience sample where psychiatric comorbidities and additional SUD were included.

Article 2: On the one hand it can be argued that voluntarily self-help group attendance leads to a selective sample where patients with a higher motivation for abstinence rather attend a self-help group compared to patients not that motivated. On the other hand to coerce someone to visit a group is contra productive if the inner attitude to visit a group is dismissive and negative. Thus the selective sample is probably more in accordance to reality than a proper randomized controlled trial where everyone ought to attend a self-help group.

A further advantage of this re-analysis was that the expectation of the patient was focused on the pharmacological medication rather than on self-help group attendance. Another point is that the length of observation might be too short, because other findings started to find positive effects after 18 months but not after 12 months (Thurstin et al., 1987) and findings of Moos and Moos (2004) give evidence that the duration of AA participation is more important than frequency. Last but not least, due to the secondary analysis only the placebo group of the original study was analyzed to avoid any medication effects, thus, the sample size is rather low, limiting the external validity of the results.

Article 3: The finding of gender differences in interpersonal problems are based on one questionnaire filled out by the patients themselves. It would be desirable to assess patients' interpersonal dimensions additionally from a good-known external person, such as family member or friend, to first match self- and foreign-perspective of a person. Further as the sample size was rather low and the thesis rather exploratory the present results should be replied by using other measurements or behavioral experiments in real settings to confirm these gender differences.

7.2. Clinical implications and future research

The therapy study investigating smoking cessation was done in a realistic clinical setting with patients undergoing an inpatient alcohol detoxification program. In comparison to experimental studies, where everything is tried to be under control representing an almost unnatural setting, therapy studies have the strength to test an investigation in a realistic setting with real patients. As a high interest and acceptance for smoking cessation was found in patients, smoking interventions proved its feasibility parallel to an alcohol detoxification. The advantage of the study is the high external validity, because the present study investigated a convenience sample in a typical clinical sample of psychiatric patients with alcohol use disorders. As smoking cessation does not jeopardizes alcohol outcomes this should be implemented as a standard offer in substance use treatments. To prove evidence of the integrated smoking cessation in an existing treatment, this should be investigated with a higher sample size, more in detail according to different settings (e.g., outpatient) and with different samples (e.g., methadone maintenance patients).

Overall, attendance of aftercare is very important in alcohol use disorders in relation to reduce relapses and give mutually support. Thus, the most important point is to motivate patients to attend aftercare sessions regularly. Future research could investigate whether gender-specific groups show a higher ongoing attendance rate and whether group affiliation and adherence is stronger compared to gender-mixed self-help groups. Thereafter substance use outcomes of gender-specific and gender-mixed groups could be compared. Another idea would be to develop and investigate specific treatment modules for preventing depressive

symptomatology at the end of alcohol detoxification treatment due to the finding in article 2 that even sub-clinical scores of depression might increase the likelihood of alcohol relapses. All these offers should be voluntary and be tailored to the individual needs of the patient.

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9. Publication List 2007-2012

Sandra Müller, M. Sc.
ZAE / UPK Basel

2012	IF
Mueller SE , Petitjean SA, Wiesbeck GA. (2012). Cognitive behavioral smoking cessation during alcohol detoxification treatment: A randomized, controlled trial. <i>Drug Alcohol Depend.</i> , 1;126(3):279-85.	3.383
2011	
Schaller G, Lenz B, Friedrich K, Dygon D, Richter-Schmidinger T, Jacobi A, Mueller SE , Maihöfner C, Sperling W, Kornhuber J. (2011). Repetitive transcranial magnetic stimulation influences mood in healthy male volunteers. <i>J Psychiatr Res.</i> , 45(9):1178-83.	3.827
Meister L, Alawam K, Dudley E, Taurines R, Müller SE , Walter M, Höppner J, Teipel S, Donev RM, Eckert A, Wiesbeck GA, Thome J. (2011). Pilot study of the application of magnetic bead protein profiling to the study of biomarkers in addiction research. <i>World J Biol Psychiatry.</i> , 12 Suppl 1:80-4.	5.564
2010	
Dürsteler-MacFarland KM, Fischer D, Mueller S , Moldovanyi A, Wiesbeck GA (2010). Symptom complaints of patients prescribed either oral methadone or injectable heroin. <i>J. Subst. Abuse Treat.</i> , 38(4): 328-337.	2.902
Wurst FM, Mueller SE , Petitjean S, Euler S, Thon N, Wiesbeck GA, Wolfersdorf M (2010). Patient suicide: a survey of therapists' reactions. <i>Suicide Life Threat Behavior</i> , 40(4): 328-336.	1.454
Müller-Schweinitzer E, Müller SE , Reineke DC, Kern T, Carrel TP, Eckstein FS, Grapow MT. (2010). Reactive oxygen species mediate functional differences in human radial and internal thoracic arteries from smokers. <i>J Vasc Surg.</i> , 51(2):438-44.	3.517
2009	
Mueller SE , Degen B, Petitjean S, Wiesbeck GA, Walter M. (2009). Gender differences in interpersonal problems of alcohol-dependent patients and healthy controls. <i>Int J Environ Res Public Health.</i> , 6(12):3010-22.	1.33 (unofficial IF)
2008	
Müller SE , Weijers HG, Böning J, Wiesbeck GA. (2008). Personality traits predict treatment outcome in alcohol-dependent patients. <i>Neuropsychobiology.</i> 57(4):159-64.	2.15
Savaskan E, Müller SE, Böhringer A, Schulz A, Schächinger H. (2008). Antidepressive therapy with escitalopram improves mood, cognitive symptoms, and identity memory for angry faces in elderly depressed patients. <i>Int J Neuropsychopharmacol.</i> , 11(3):381-8.	4.378
2007	
Mueller SE , Petitjean S, Boening J, Wiesbeck GA. (2007). The impact of self-help group attendance on relapse rates after alcohol detoxification in a controlled study. <i>Alcohol Alcohol.</i> , 42(2):108-12.	2.691
Savaskan, E., Müller, S. E. , Böhringer, A., Philippsen, C., Müller-Spahn, F. and Schächinger, H. (2007). Age determines memory for face identity and expression. <i>Psychogeriatrics</i> , 7: 49–57.	1.21

10. Appendix - Publications of the cumulative dissertation

1. Article

Mueller SE, Petitjean SA, Wiesbeck GA. (2012). Cognitive behavioral smoking cessation during alcohol detoxification treatment: A randomized, controlled trial. *Drug and Alcohol Dependence*, 1;126(3):279-85.

2. Article

Mueller SE, Petitjean S, Boening J, Wiesbeck GA. (2007). The impact of self-help group attendance on relapse rates after alcohol detoxification in a controlled study. *Alcohol and Alcoholism*, 42(2):108-12.

3. Article

Mueller SE, Degen B, Petitjean S, Wiesbeck GA, Walter M. (2009). Gender differences in interpersonal problems of alcohol-dependent patients and healthy controls. *International Journal of Environmental Research and Public Health*, 6(12):3010-22.



Cognitive behavioral smoking cessation during alcohol detoxification treatment: A randomized, controlled trial

S.E. Mueller*, S.A. Petitjean, G.A. Wiesbeck

Division of Substance Use Disorders, Psychiatric Hospital of the University of Basel, CH-4012 Basel, Switzerland

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ABSTRACT

Background: Among alcohol-dependent subjects tobacco smoking is very common and causes a variety of health risks. Therefore, it is necessary to reach this high-risk population early with appropriate smoking interventions.

Methods: Smokers in alcohol detoxification treatment were offered to participate in a smoking cessation study. A total of 103 patients was enrolled and randomly assigned to either the experimental group (EG) receiving a cognitive behavioral smoking cessation treatment (CBT) or the control group (CG) receiving autogenic training. Smoking outcomes were measured by self-report and carbon monoxide levels, directly after intervention and 6 months later, where additionally alcohol outcomes were recorded.

Results: There were no differences in smoking quit rates directly after intervention. However, patients in the EG were significantly more likely to reduce their daily cigarette use compared to CG ($p = .046$). Sub-group analyses revealed that heavy smokers (FTND score ≥ 7) seemed to profit most in the EG regarding cigarette reduction. After 6 months, these positive effects had leveled out. No evidence was found that smoking cessation might jeopardize alcohol outcomes.

Conclusions: Results suggest that alcohol-dependent smokers are interested in smoking interventions even during alcohol detoxification. CBT is promising in short-term smoking outcomes and in the approach of harm reduction, however, long-term effects are desirable. These findings underline the feasibility and the importance to provide smoking cessation interventions to patients in alcohol detoxification treatments.

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1. Introduction

Tobacco smoking is related to a number of severe vascular health risks and carcinoma (Schmidt et al., 2006). Alcohol dependence on its own is harmful, but in combination with tobacco smoking health risks on the upper aero-digestive tract are synergistic (Pelucchi et al., 2006). Alcohol-dependent heavy smokers sustain a 35 fold higher risk to get carcinoma in pharynx or larynx (Zeka et al., 2003). Every alcohol-attributable death is accompanied by about 30 years of life lost (CDCP, 2004). Among alcohol-dependent patients 70–95% have a comorbid tobacco dependence (Batel et al., 1995; Bien and Burge, 1990; Burling and Ziff, 1988; John et al., 2003) compared to 25–30% in general population (WHO, 2011). Increased smoking is connected to increased alcohol drinking and vice versa

(Barrett et al., 2006; Burton and Tiffany, 1997; Daepfen et al., 2000) indicating the strong interconnection of the two substances.

Despite these alarming consequences, this problem gained only little interest in research because of the myth that alcohol-dependent patients are less motivated to quit smoking. Literature gives evidence that alcohol-dependent smokers find it more difficult to stop smoking than smokers without an alcohol problem (Burling et al., 1997; Cooney et al., 2007; Hays et al., 1999; Hughes and Kalman, 2006). The assumption the difference may be the motivation to quit smoking can be denied. In a self-report study 81% of alcohol-dependents tried to quit smoking but succeeded in only 7% compared to 49% of smokers without an alcohol problem (DiFranza and Guerrero, 1990). Furthermore, tobacco smoking is suggested to be the lesser evil than alcoholism (Gulliver et al., 2006). In fact, tobacco smoking exhibits almost no harmful short-term consequences but most alcoholics die due to tobacco related long-term consequences (Hurt et al., 1996). Another myth is that smoking cessation is suggested to impede alcohol sobriety (Gulliver et al., 2006). However, literature predominantly concludes that there are no negative effects of smoking interventions for threatening abstinence (Cooney et al., 2007; Hurt et al., 1994; Metz et al., 2005a;

* Corresponding author at: Division of Substance Use Disorders, Psychiatric Hospital of the University of Basel, Wilhelm Klein-Str. 27, CH-4012 Basel, Switzerland. Tel.: +41 61 325 53 33; fax: +41 61 325 55 83.

E-mail address: Sandra.Mueller@upkbs.ch (S.E. Mueller).

Saxon et al., 2003). Smoking cessation can even have a preventive, beneficial effect on alcohol outcomes (Baca and Yahne, 2009; Batra et al., 2011; Bobo et al., 1998; Grant et al., 2007; Kohn et al., 2003; Prochaska et al., 2004; Tsoh et al., 2011).

Smoking cessation rates among patients with substance use disorders (SUD) in recovery are consistently higher than in addiction treatment centers (Prochaska et al., 2004). Studies with active interventions in comparable residential treatments reveal short-term cessation rates of 9–22% (Hurt et al., 1994; Kalman et al., 2001; Metz et al., 2005b; Saxon et al., 1997) and 6 months follow-up outcomes of 2–18% (Baca and Yahne, 2009; Burling et al., 2001; Gariti et al., 2002; Metz et al., 2005b).

In the present study, we compared the efficacy of a cognitive behavioral smoking cessation (CBT) to that of autogenic relaxation training (AT) during alcohol detoxification treatment. First, we hypothesized that the CBT intervention would yield in significantly higher smoking quit rates than AT. Second, we hypothesized that the reduction of 50% or more would be higher in CBT than in AT. Both hypotheses were investigated directly after intervention and 6 months later. Finally, it was hypothesized that smoking cessation would not jeopardize alcohol outcomes 6 months later.

2. Methods

2.1. Study design and procedure

The study was a prospective, randomized, controlled clinical trial consisting of an intervention phase and a 6-month follow-up. Inpatients were screened for a smoking anamnesis and motivated to participate in a smoking cessation study simultaneous to alcohol detoxification treatment. Oral explanation and written study information was given to interested patients. After providing signed informed consent, patients were randomly allocated to either experimental group (EG) receiving cognitive behavioral smoking cessation (CBT) or control group (CG) receiving the relaxation technique autogenic training (AT). With patients in both groups baseline interview took place within the first week, followed by the intervention phase including five 30-min group-sessions in the last 2 weeks ending with a post interview. After 6 months all participants were invited to follow-up interview.

The EG received a modified version of a manual guided CBT program (Batra and Buchkremer, 2004) with additional information regarding the harm of concomitant use of alcohol and tobacco. The CBT program included regular CO-level measurements in every session, dealt with motivational processes, education about nicotine and its effects, psychological factors in addiction, a stop date if patients intended to quit and elements of relapse prevention. The CG practiced AT, a non-evidence based method regarding smoking cessation (Marques-Vidal et al., 2011). Both groups were clinically supervised and received treatment as usual. Patients intending to quit smoking were offered transdermal nicotine patches (NR-patch 21 mg) only during inpatient stay independent of group allocation. All assessments and intervention sessions were conducted by two psychologists trained in CBT with 3 years of experience in addiction treatment. The study was approved by the local ethic committee and registered in www.clinicaltrials.gov with the identification number NCT00963482.

2.2. Participants

Participants were recruited from a 21-day inpatient alcohol detoxification unit at the Psychiatric Clinic of the University of Basel, Switzerland from July 2007 to August 2010. The psychiatric hospital has a total smoking ban since 2007. Because the detoxification ward has locked doors, a smoking room without any chairs or comfort is available. Patients were eligible if they were alcohol-dependent according to ICD-10 criteria (Dilling et al., 2005), tobacco smokers, motivated to either stop or reduce their tobacco use, between 18 and 65 years old, and staying long enough to complete study intervention (>10 days). Participants were excluded if they took medication supporting smoking cessation (e.g., Varencline, Bupropion), simultaneously participated in another smoking cessation treatment, were pregnant, had insufficient German language knowledge or were mentally not capable to understand study information. Additional psychiatric disorders and SUD were not exclusion criteria as the sample was intended to be a convenience sample. As the trial was primarily designed to study the effectiveness of CBT, medication supporting smoking cessation was excluded in order not to be biased by smoking quit medication, but none of the participants had to be excluded for that reason.

2.3. Study assessment

The Fagerström test for nicotine dependence (FTND; Bleich et al., 2002) was used to assess the severity of tobacco dependence. Additionally, the number of smoked cigarettes per day and the parameter pack years, indicating the inhaled tobacco

doses over the years, were asked. Alcohol dependence was classified by using the ICD-10 criteria. Alcohol use was measured by asking the amount of standard drinks per day prior treatment and by using the alcohol use disorder identification test (AUDIT; Saunders et al., 1993). To measure tobacco and alcohol craving at baseline visual analogue scales (VAS) ranging from 0 to 100 with the anchor “no craving at all” up to “the strongest craving I know” were used. Attitudes such as *importance* to quit and *self-efficacy* regarding smoking cessation were measured by VAS at baseline, after intervention and at follow-up. Moreover, questions regarding the stages of change model (Prochaska and DiClemente, 1983) concerning the stage *preparation* “Are you seriously planning to stop smoking soon?” and the stage *action* “Have you tried stop smoking lately?” were asked. Breath carbon monoxide (CO) level was measured using a portable Bedfont Smokerlyzer to corroborate smoking status at baseline, after intervention and at follow-up. A level of 10 ppm or more indicated a regular tobacco smoker, levels below 10 ppm referred to smoking abstinence. Urine samples to verify nicotine exposure by urinary cotinine (nicotine metabolite) were taken after intervention and at 6-month follow-up and to detect any alcohol use in the past 3 days the biomarker ethyl glucuronide (EtG) was determined in urine only at follow-up in urine.

The main variable of interest was the smoking cessation rate, defined as smoking zero cigarettes and having a breath carbon level of less than 10 ppm. At 6-month follow-up self-report of smoking in the last 7 days (7-day point-prevalence), CO-level and cotinine were used to verify tobacco abstinence. Reduction rate was defined as reducing the amount of cigarettes by 50% or more compared to initial use.

2.4. Data analysis

For comparison of nominal data such as drop-outs or dichotomous variables Chi² calculations were used. All comparisons of continuous data were calculated using one-way ANOVAs or independent *t*-tests. Within-group comparisons of continuous variables were performed using dependent *t*-tests or repeated measurement ANOVAs, as used for sub-group analyses. Because the sample size was too small to detect a statistical difference effect sizes were calculated to confirm the clinical significance, i.e. clinical advantage according to the formula $\epsilon = (x_u - x_l) / \sigma_u$ (Bortz, 2005). An effect size of $\epsilon \geq 0.80$ indicates a strong effect, $\epsilon \geq 0.50$ a medium effect and $\epsilon \geq 0.20$ a weak effect. All tests of significance were reported as two-tailed using alpha level of 0.05. All calculations were held as intention-to-treat analysis if not other specified. Statistical analyses were calculated by using the software SPSS version 19.0 for Windows.

3. Results

3.1. Recruiting process and baseline characteristics

Of 237 eligible alcohol-dependent patients 103 patients (43.5%) gave their written informed consent (Fig. 1). The intervention phase was completed by 87 patients (84.5%). The follow-up interview was attended by 58 patients (56.3%; EG: *n* = 25, CG: *n* = 33) without any group difference (Chi² = 3.708, *p* = .054). No difference in drop-outs was observed at any time. Baseline characteristics were similar in both groups (Table 1). The only trend was, that EG referred to smoke 25.5 cigarettes compared to CG with 30.5 cigarettes per day, without reaching statistical significance (*p* = .066). According to the first item of the FTND ‘smoking the first cigarette within 30 min of awakening’ (Pomerleau et al., 1990) 80.6% were defined as physical highly nicotine dependent.

3.2. Smoking outcomes after intervention (short-term outcomes)

After the intervention 6 patients (5.8%) achieved the status smoke-free, without any group difference (EG: *n* = 4 (7.5%) vs. CG: *n* = 2 (4%)) as presented in Fig. 2. All six patients were male and their breath carbon monoxide level was on average 2.5 ppm, corroborating smoking abstinence. Five out of 6 patients made use of the NR-patch offer. After the intervention 25 patients (24.3%) achieved the 50 percent reduction of tobacco use (EG: *n* = 17 (32%) CG: *n* = 8 (16%)) reaching statistical significance (Chi² = 3.617, *p* = .046; Fig. 2). CO-levels did not differ between the groups reaching reduction (EG = 13.2 ppm vs. CG = 13.3 ppm). The 6 smoke-free patients were also included in the smoking reduction analysis.

Though in both groups a decrease of the number of cigarettes was observed (*t*(86) = 7.193, *p* < .001), the EG reduced their daily cigarettes significantly more than the CG (16.4 vs. 23.4;

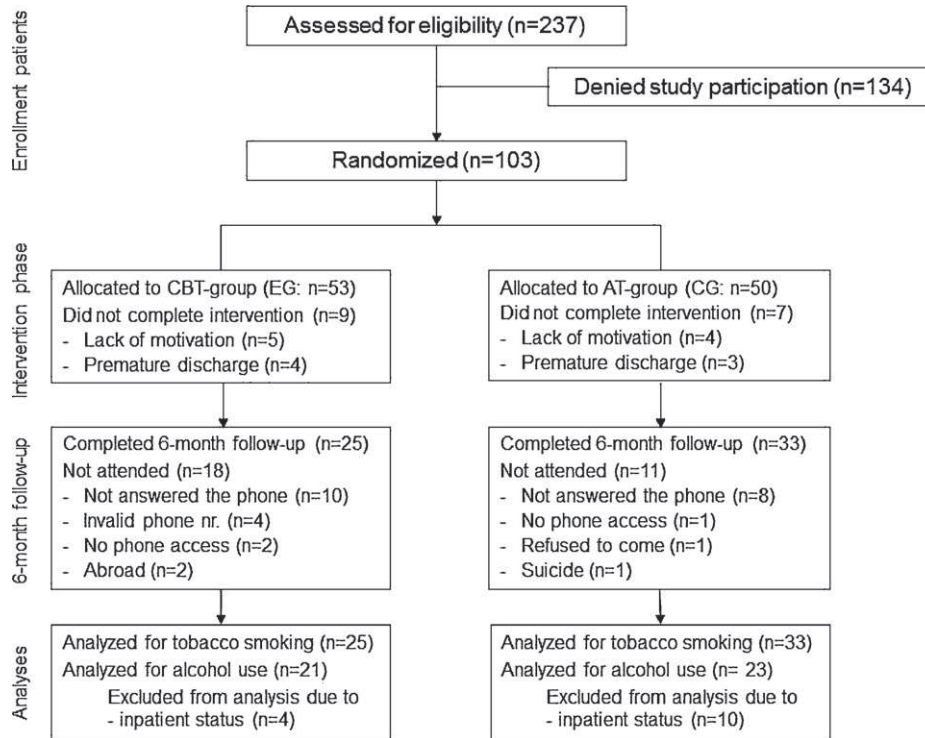


Fig. 1. Recruiting process according to CONSORT.

$t(86) = -2.317, p = .023$; Fig. 3). Calculated effect sizes for successful cigarette reduction revealed a strong effect in the EG with $\epsilon = 0.77$ and a medium effect in the CG with $\epsilon = 0.49$.

CO-levels decreased significantly over time ($t(85) = 5.272, p < .001$), with a trend in favor of the EG ($p = .076$) but without significant difference between both groups (Fig. 4). Effect sizes regarding CO-levels showed stronger effects in the EG ($\epsilon = 0.74$) than in the CG ($\epsilon = 0.30$). Totally 24 patients (23.3%) used NR-patches (EG: $n = 14$, CG: $n = 10$), between 1 and 10 days (EG: $n = 9$, CG: $n = 9$) and between 21 and 63 days (EG: $n = 5$, CG: $n = 1$).

3.3. Smoking outcomes at 6-month follow-up (long-term outcomes)

At 6-month follow-up 3 patients (2.9%) reported tobacco abstinence during the last 7 days corroborated by a mean CO-level of

3 ppm. These 3 patients (1 female) belonged to the CG (6%). The woman was smoke-free, but reported to use 7 nicotine gums a day. One man just stopped smoking the week before follow-up by using NR-patches and the other man was smoke-free since the intervention using NR-patches continuously. This was the only one with a cotinine level of 0 ng/l. Three other patients (EG: $n = 2$, CG: $n = 1$) reported smoke-free days in the last week. In total 16 patients (15.5%) showed a successful smoking reduction 6 months later, of which 6 patients belonged to the EG (11.3%) and 10 patients to the CG (20%) without significant difference (Fig. 2). CO-levels corroborated the smoking reduction rate, with a mean CO-level of 14.9 ppm for patients reporting successful reduction compared to 31.8 ppm for patients failing a reduction ($F(1,56) = 16.339, p < .001$).

The number of cigarettes at 6 months was similar in both groups (EG = 21.8, CG = 25.4), corresponding to effect sizes of $\epsilon = 0.33$ and $\epsilon = 0.36$ compared to study start (Fig. 3). Repeated measurement

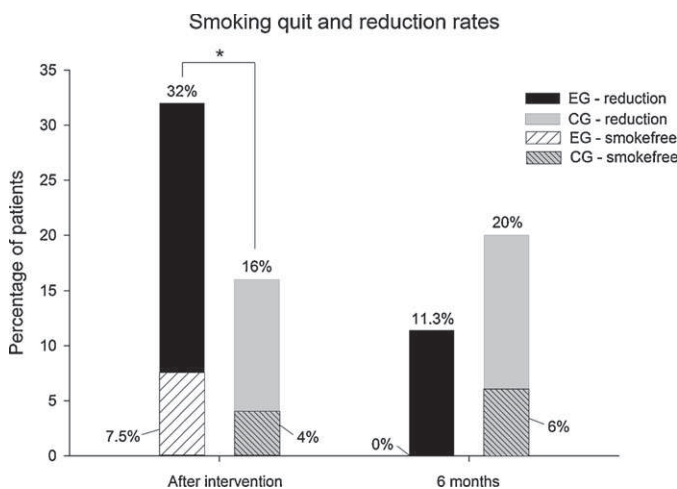


Fig. 2. Smoking quit and reduction rates according to treatment groups after intervention and after 6 months. * $p = .046$; EG, experimental group; CG, control group.

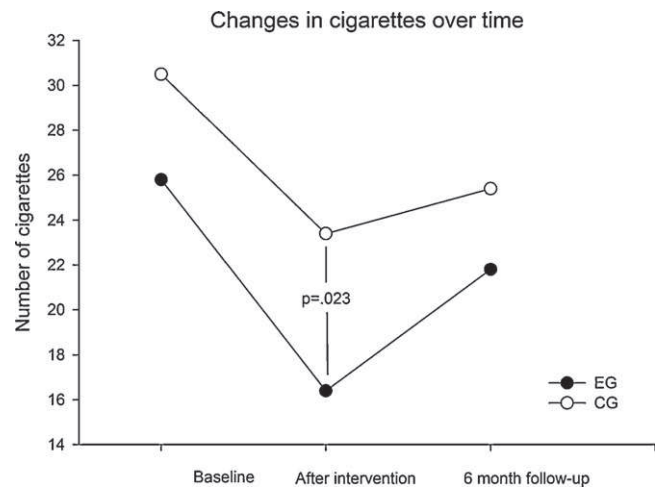


Fig. 3. Changes in the number of daily smoked cigarettes over study time. EG, experimental group; CG, control group.

Table 1
Baseline characteristics.

	Experimental group (EG, n = 53) N (%)	Control group (CG, n = 50) N (%)
Female	16(30.2)	14(28.0)
Marital status		
Unmarried	29(59.2)	19(41.3)
Married	11(22.4)	16(34.8)
Divorced/separated	9(18.4)	11(23.9)
Education		
Standard school (9 years)	9(18.4)	14(30.4)
Job training after school	24(49.0)	17(37.0)
Secondary school (≥ 12 years)	15(30.6)	14(30.4)
Something else	1(2.0)	1(2.2)
Positive family history of alcohol dependence		
Fathers	12(26.1)	15(34.9)
Mothers	3(6.3)	4(9.1)
Positive family history of tobacco dependence		
Fathers	30(65.2)	34(79.1)
Mothers	16(33.3)	12(27.3)
Additional substance use disorders (SUD) ^a	22(41.5)	27(54.0)
Daily alcohol consumption before entry	39(81.3)	39(84.8)
Abstinent episode from alcohol		
0–1	18(45.0)	15(40.5)
2–5	15(37.5)	10(27.0)
>5	7(17.5)	12(32.4)
	Mean (SD)	Mean (SD)
Age (years)	44.0 (11.0)	44.0 (9.0)
BDI	14.1 (10.2)	11.6 (7.4)
Age of onset smoking (years)	17.8 (5.8)	18.0 (5.8)
Years of smoking total	25.7 (11.0)	24.9 (9.5)
FTND	6.2 (2.4)	6.4 (2.5)
Number of cigarettes	25.5 (12.1)	30.5 (14.2)
CO-level (ppm)	32.9 (15.8)	32.8 (18.6)
Pack years	33.9 (20.0)	34.0 (18.2)
Nicotine craving (VAS)	50.8 (24.2)	57.1 (28.0)
Age of onset of the alcohol problem	32.2 (9.8)	30.7 (10.7)
Duration of alcohol problem (years)	11.75 (9.5)	13.95 (9.9)
AUDIT	24.3 (9.3)	23.8 (8.1)
Standard drinks per day	19.5 (13.3)	20.2 (15.0)
Alcohol craving (VAS)	13.3 (21.6)	11.3 (18.0)

^a For additional SUD's current and remitted SUD's were counted, misuse patterns were excluded. BDI, Beck Depression Inventory; FTND, Fagerström test for nicotine dependence; ppm, parts per million; VAS, visual analogue scale (0–100); AUDIT, alcohol use disorder identification test.

ANOVA revealed that in both groups the CO-level declined over time ($F(1,56)=9.434, p<.001$), without any group difference (Fig. 4). Effect sizes of CO-levels showed a medium effect of $\varepsilon=0.56$ for the EG and a small effect of $\varepsilon=0.18$ for the CG.

3.4. Attitudes regarding smoking cessation

At study start variables such as *importance* and *self-efficacy* as well as *preparation* and *action* to quit smoking did not differ between EG and CG. Directly after the intervention, however, the EG rated the score *importance* to quit significantly higher than the CG (81.9 vs. 71.4, $t(83)=2.107, p=.039$) and exhibited significantly higher self-efficacy scores compared to the CG (70.5 vs. 54.1, $t(83)=2.775, p=.007$). After the intervention participants in the EG also were significantly more likely to agree being in the stage of *preparation* with 79.5% vs. 51.2% ($\text{Chi}^2=7.754, p=.005$) and approved having made significantly more attempts to stop smoking (stage *action*) compared to the CG (52.3% vs. 23.3%, $\text{Chi}^2=7.777, p=.005$). At 6 months follow-up, however, all these effects leveled out.

3.5. Subgroup analyses regarding smoking severity

Sub-group analyses were conducted to analyze if severity of tobacco dependence has an impact on smoking outcomes. According to the FTND score ≥ 7 , 54 patients (52.4%) were classified as heavy smokers (EG: $n=30$, CG: $n=24$) and 49 patients (FTND < 7 ; 47.6%) as moderate smokers (EG: $n=23$, CG: $n=26$). Heavy smokers differed from moderate smokers in baseline variables, such as cigarettes per day (33.4 vs. 21.8; $F(1,93)=22.162, p<.001$), CO-level (36.8 ppm vs. 28.5 ppm; $F(1,99)=6.198, p=.014$), pack years (41 vs. 26.2; $F(1,93)=16.691, p<.001$) and tobacco craving score (60.6 vs. 46.3; $F(1,93)=7.552, p=.007$) confirming the validity of these group assignments. Heavy and moderate smokers differed neither in the number of additional SUD nor in the AUDIT score, but they differed significantly in the number of daily standard drinks prior to admission (24 vs. 15, $t=-3.32, p<.001$). Moderate smokers were significantly more likely to refer about a cessation attempt during the last 12 months (17 (34.7%) vs. 7 (13%), $p=.009$) and scored significantly higher in the *self-efficacy* score regarding a smoking quit (47 vs. 62, $F(1,101)=6.061, p=.016$) at baseline compared to heavy smokers.

Generally, no differences in the smoking quit or reduction rate ($\geq 50\%$) were found between heavy and moderate smokers. A repeated measurement ANOVA was computed to analyze the number of daily cigarettes by using heavy vs. moderate smokers as a covariate. The within-factor cigarette was significantly reduced over time ($F(1,84)=20.827, p<.001$), the between-factor treatment group ($F(1,84)=7.004, p=.010$) and the covariate revealed significance ($F(1,84)=20.811, p<.001$), indicating an important influence of the severity of tobacco dependence. Due to this finding repeated measurement models were calculated separately for each severity group. Among moderate smokers the within-factor number of cigarettes was significantly decreased ($F(1,39)=24.253, p<.001$), without any group difference. However, among heavy smokers, not only the within-factor number of cigarettes ($F(1,44)=27.902, p<.001$) but also the between-factor treatment group ($F(1,44)=13.261, p=.001$) reached significance, indicating considerably higher likelihood to reduce cigarettes in the EG. After 6 months these effects were leveled out (Fig. 5).

3.6. Alcohol outcomes at 6-month follow-up

Totally 44 out of 58 (75.9%; EG: $n=21$, CG: $n=23$) patients were included in the analyses of 6-month alcohol outcomes. The remaining 14 patients (24.1%) were excluded due to

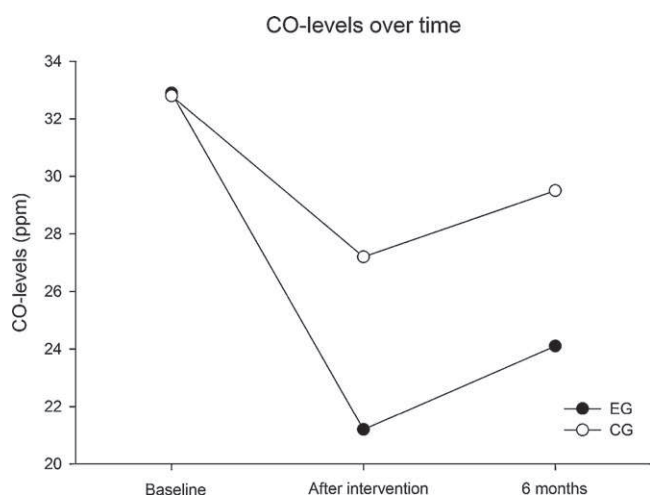


Fig. 4. Changes in CO-levels by treatment group over study time. EG, experimental group; CG, control group.

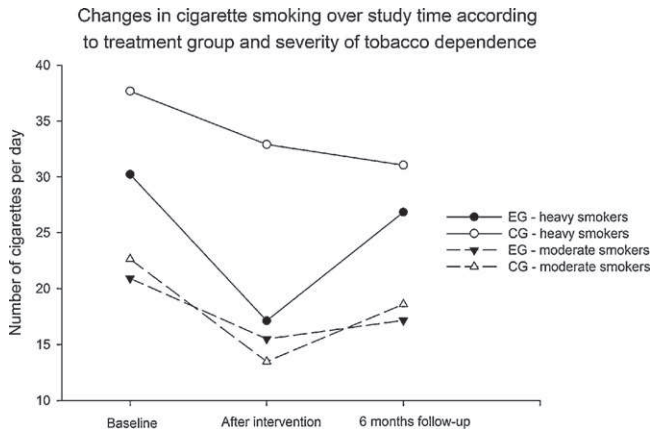


Fig. 5. Changes in number of cigarettes over study time according to treatment groups and severity of tobacco dependence. EG, experimental group; CG, control group.

re-hospitalization at this time, which would not reflect the natural history of alcohol use.

Urine samples (42 valid) revealed in 50% positive EtG results ($n=21$) indicating alcohol use in the past 3 days. No difference in self-report regarding alcohol use was found, 19 patients (EG: $n=10$, CG: $n=9$) reported abstinence and 25 reported alcohol use (EG: $n=12$, CG: $n=13$) in the past 7 days. Combining these two variables resulted in 17 patients being verifiably abstinent from alcohol at follow-up. Per protocol analysis revealed a relapse rate of 61.4% (27/44) while an intention-to-treat analysis revealed a relapse rate of 80.5% (86/103) after 6 months. No difference in alcohol use regarding group allocation was found. Further calculations whether a successful smoking reduction might influence 6-months alcohol outcomes were made. Eleven out of 44 patients achieved a post treatment smoking reduction, 5 were abstinent and 6 were drinking alcohol again.

4. Discussion

The present study revealed short-term and 6-month follow-up cessation rates without any group difference. Thus, our primary hypothesis that the EG yielded in higher smoking quit rates could not be supported. Though modest, the 7-day point-prevalence quit rate of 2.9% after 6 months was in line with the literature reporting tobacco quit rates from 2 to 18% at 6 months (Baca and Yahne, 2009). It also was clinically significant since costs per treatment are very economical compared to health gains and prevention of premature death (West, 2007).

Focusing on the reduction rate directly after intervention there was a significantly higher proportion of patients achieving the reduction rate of $\geq 50\%$ in the EG compared to the CG, suggesting superiority of CBT in near-term smoking outcomes. However after 6 months this effect was attenuated, confirming our second hypothesis of a superior smoking reduction outcome in CBT only partially, namely in near-term outcomes. The fact, that both groups achieved to reduce the number of cigarettes with a better outcome in CBT, may be explained by different factors. All patients enrolled in this study were motivated to change their smoking behavior. Furthermore, the placebo effect might have influence in both groups, namely if someone participates in a study *it has* to help. Finally, hospitalization per se might have played a role. In a 21-day detoxification treatment study (Olbrich et al., 2008) the active group receiving a smoking intervention reduced their cigarettes while the control group tended to increase their cigarettes. Another study found evidence that without any smoking intervention moderate smokers tend to increase and heavy smokers tend to decrease their

amount of cigarettes smoking after detoxification treatment (Aubin et al., 1999). The present smoking reduction rate of 15.5% after 6 months is also clinically significant in the respect of harm reduction, which is thought to rather increase probability for future cessation attempts (Hughes and Carpenter, 2006).

In the present study heavy smokers reported of more standard drinks prior to admission than moderate smokers reflecting the strong interrelationship of both substances supporting Barrett et al. (2006) and Daepfen et al. (2000). In the relatively small follow-up sample no differences in alcohol outcomes at 6 months were found, suggesting that smoking interventions did not jeopardize alcohol outcomes. This was in line with other reports (Baca and Yahne, 2009; Prochaska et al., 2004) and supported our third hypothesis that smoking cessation have no negative impact on alcohol outcomes.

The present participation rate of 43.5% is comparable to other inpatient settings addressing tobacco smoking in substance abusers, ranging from 24 to 40% in SUD patients (Batra et al., 2011; Saxon et al., 1997). This rate reflected a high interest and feasibility of smoking interventions even in alcohol detoxification treatment and underline the statement “offering smoking interventions in substance use disorder treatments is an obligation” (Prochaska, 2010), and ought to be a moral responsibility in health care systems (West, 2007).

The benefit of CBT in this study was predominantly seen in near-term smoking reduction outcomes, but it was also reflected by positive changes of attitudes regarding a smoking stop. Short-term outcomes showed increased values of *importance* and *self-efficacy* regarding a smoking stop in EG compared to CG. The CBT program seemed to activate motivational processes probably due to an active discourse about smoking behavior. The lack of effect after 6 months can be explained by the fact that measuring attitudes is a picture of a particular moment and that patients who just tried to quit and failed are frustrated as reflected in the scores of motivational processes.

The severity of tobacco dependence has an influence on smoking cessation because patients with low FTND scores are more likely to quit smoking by themselves (Bobo et al., 1996; Karam-Hage et al., 2005). Calculated sub-group analyses in this study revealed that heavy smokers in the EG reduced their daily cigarette use significantly more compared to all other groups, while moderate smokers in both groups reduced their daily cigarettes slightly. It might be speculated that moderate smokers who are motivated do not need intense support. However, after alcohol detoxification without smoking intervention heavy smokers tend to reduce their smoking while moderate smokers increase their smoking (Aubin et al., 1999). Against this background it could be expected that heavy smokers would reduce their cigarettes after detoxification, but it was the CBT that helped heavy smokers in the EG to reduce smoking significantly more than those in the CG. On the other hand moderate smokers in the present study also achieved to reduce their daily cigarettes, reflecting the support of the study or patients' motivation.

The 6 months quit rate of 2.9% and the result with zero % in the EG was rather low. However, as the study population was a convenience sample, open for almost all alcohol-dependent patients, regardless of psychiatric comorbidities or severe somatic diseases the sample had a high burden of morbidities. Smoking cessation in a detoxification ward with locked doors is difficult. One influencing factor is that there are patients staying involuntarily who may affect the group dynamic negatively. Another factor is that patients often report that cigarette smoking helps them to cope with stress due to withdrawal symptoms. Nevertheless in the study course CBT showed superiority in short-term reduction outcomes, especially in heavy smokers and in increasing motivational processes. It might be speculated, that the positive effects of CBT only

sustain, when patients are in active CBT treatment and that positive effects of CBT were just lost some time before follow-up. It might be speculated that even as non-evidence based method AT have helped a subgroup of smokers, e.g., stress-relief smokers and thus elevated the smoking cessation rate in CG. Nevertheless the present results show successful near-term but not long-term smoking outcomes which is in line with recently published data (Carmody et al., 2012; Prochaska et al., 2004). Moreover it underlined the problem that smoking interventions in SUD have a lack of long-term success (Baca and Yahne, 2009; Burling et al., 1997; Cooney et al., 2007).

In conclusion, the present results revealed a high acceptance and interest of patients in smoking cessation even during an alcohol detoxification treatment. The smoking reduction rate and motivational processes regarding a smoking quit were significantly increased after intervention in the EG compared to the CG indicating a successful harm-reduction intervention by CBT. Especially alcohol-dependent heavy smokers profited from cognitive-behavioral smoking cessation offers. CBT is a promising approach in short-term outcomes, but further research is needed to achieve similar benefits regarding long-term outcomes.

The high proportion of patients interested in smoking cessation during alcohol detoxification treatment and the fact that it seems not to influence alcohol outcomes should encourage clinical practitioners to offer both treatments to their patients and that a detoxification treatment can be seen as a window of opportunity for smoking interventions.

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Contributors

Gerhard Wiesbeck and Sylvie Petitjean designed the study and wrote the protocol for the FOPH. Sylvie Petitjean and Sandra Mueller planned and organized the study. Bigna Degen and Sandra Mueller were responsible to run the study. Sandra Mueller undertook the statistical analyses and wrote the first draft of the manuscript. All authors made substantial contributions and approved the final manuscript.

Conflict of interest

No conflict declared.

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THE IMPACT OF SELF-HELP GROUP ATTENDANCE ON RELAPSE RATES AFTER ALCOHOL DETOXIFICATION IN A CONTROLLED STUDY

S. E. MUELLER^{1*}, S. PETITJEAN¹, J. BOENING² and G. A. WIESBECK¹

¹Psychiatric University Clinics, Wilhelm Klein-Strasse 27, CH-4025 Basel, Switzerland

²Addiction Research Group, Department of Psychiatry, University of Wuerzburg, Fuechsleinstr. 15, D-97080 Wuerzburg, Germany

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Abstract — Aims: Self-help groups such as Alcoholics Anonymous (AA) are widely recommended for aftercare of alcohol-dependent persons, even though scientific knowledge of its effectiveness is inconsistent. The aim of the present analysis was to elucidate whether persons attending AA groups regularly after detoxification have lower relapse rates within 1 year, compared to persons without self-help group attendance. **Methods:** Data for the present analysis were derived from the placebo-group of a multi-centre study in Germany (Wiesbeck *et al.*, 2001). Patients were free to choose either self-help group attendance ($N = 50$) or no support ($N = 28$). **Results:** After 1-month of follow-up, there was a lower relapse rate in patients attending a self-help group as compared to the control group, a difference, however, that leveled off during the following months. Moreover, relapse rates did not differ significantly at any point of time between both groups. Levels of social functioning improved in both groups over 1 year. **Conclusions:** The present study was unable to show an advantage of self-help group attendance in reducing relapses compared to the control group.

INTRODUCTION

Empirical research on alcoholism and its treatment corroborates that in the disorder of alcoholism relapses are rather the rule than the exception and that the first half year after treatment contains the highest risk of relapses (Körkel, 1996). After the first month following an alcohol detoxification, relapse rates range between 19% for inpatients and 34% for outpatients and increase to about 46 and 48% respectively, after 6 months (Hayashida *et al.*, 1989). It is presumable, therefore, that after an alcohol detoxification, any subsequent outpatient support could endorse abstinence. In addition, comparison of different aftercare modalities revealed that patients who obtained no aftercare had the poorest drinking outcome (Ouimette *et al.*, 1998).

There is a widespread belief in the effectiveness of Alcoholics Anonymous (AA) in the treatment of alcoholism, even though scientific findings are inconsistent. While positive effects of participation in AA on drinking outcomes have been reported (Emerick *et al.*, 1993; Watson *et al.*, 1997; Connors *et al.*, 2001; Gossop *et al.*, 2003), other studies found no positive impact of AA on drinking outcomes (McLatchie and Lomp, 1988; Montgomery *et al.*, 1995). Accordingly, a meta-analysis of 74 studies revealed that AA experience and drinking outcome are rather heterogeneous (Tonigan *et al.*, 1996) and the recently published Cochrane meta-analysis did not find an unequivocal effectiveness for AA regarding drinking outcome (Ferri *et al.*, 2006). These discrepancies could be due to the existence of a wide range of different self-help groups. Apart from various group approaches, several findings indicate that differences exist even among AA organizations, because they differ from place to place in group processes, members, and atmosphere (Montgomery *et al.*, 1993). However, all self-help groups share important

similarities such as the reference to a non-professional, peer-operated organization, where group members give and receive advice. Furthermore, participation in a self-help group provides the opportunity to meet others who have had similar experiences and problems, thereby being supportive and helpful in sharing their own experiences and expanding the social network with likeminded and non-drinking persons. In spite of all cultural differences, AA groups act on the same basic principles, namely, the twelve steps, worldwide. These twelve steps include the belief in a higher power, such as God, which helps in recovering. So, it could be argued that religious people would benefit more when attending AA, but a study revealed that atheists and agnostics benefited equally as did people with religious belief; thus, belief in God appears not to impact AA-related benefit (Tonigan *et al.*, 2002).

Regular AA attendance once a week seems to be associated with superior drinking outcome (Fiorentine, 1999; Gossop *et al.*, 2003; Ouimette *et al.*, 1998). However, no additional effect can be obtained when the frequency of attendance is increased to more than twice a week (Watson *et al.*, 1997). Thurstin *et al.* (1987) found higher rates of abstinence for AA attendees only after 18 months, but not after 12 months. These findings are supported by studies of Moos and Moos (2004) suggesting that for a better alcohol-related outcome, the duration over time is more important than the frequency of AA attendance. In those studies it could be demonstrated that a rapid entry into AA and a longer participation after detoxification promise better 1- and 8-year outcomes (Moos and Moos, 2004).

Taking the points of criticisms in Tonigan's meta-analysis (Tonigan *et al.*, 1996) into account, that most AA studies are of a low study quality and miss biological markers to corroborate abstinence, the aim of the present analysis was to investigate the impact of AA on abstinence within the bounds of a large pharmaceutical study. This implies two advantages, namely (i) biomedical parameters were used to corroborate patients' self-reported abstinence and (ii) participants' expectation of change was focused on drug effectiveness rather than on the additional AA participation.

*Author to whom correspondence should be addressed at: Psychiatric University Clinics, University of Basel, Wilhelm Klein-Strasse 27, CH-4025 Basel, Switzerland. Tel: +41 61 325 53 33; Fax: +41 61 325 55 83; E-mail: sandra.mueller@upkbs.ch

METHODS

Data were obtained from a randomized, placebo-controlled pharmacological study conducted in 13 alcohol treatment centres in Germany (Wiesbeck *et al.*, 2001). To avoid any interaction with pharmaceutical medication, only patients from the placebo-group were included in this analysis. Patients had to join the study for at least 30 days and had to either visit a self-help group or receive no treatment (control group). On the basis of these criteria a total of 78 patients was selected, of whom 50 patients had visited a self-help group regularly and 28 patients had no additional treatment.

In the original study, patients had to fulfil at least six DSM-III-R criteria for moderate or severe alcohol dependence and had to reach a score of ≥ 11 in the Munich Alcoholism Test (Feuerlein *et al.*, 1980). For comorbidity of depression and anxiety disorders, a cut-off score of >18 on the Hamilton depression rating scale (Hamilton, 1960) and a cut-off score of >16 on the Hamilton anxiety rating scale (Hamilton, 1959) respectively, were used as exclusion criteria. The social functioning questionnaire (SFQ) was used to assess social functioning in everyday life situations (Tyrer *et al.*, 2005). Low scores indicated better social functioning than high scores, whereas a score of more than 10 stood for poor social functioning. Conditions for participation in this study were the absence of severe physical, neurological and psychiatric disorders requiring specific medication and the intention to remain abstinent in future. Data of abstinence were based on self-reports and on biological parameters such as alcohol breath-test and liver enzymes. Any alcohol consumed was counted as a relapse.

After alcohol detoxification, patients were recommended to attend a self-help group but were free to decide whether they wanted to attend a self-help group or not. Offered self-help groups were AA or other 12-step-programmes, whereas other approaches like relapse-prevention or cognitive behavioural programmes were excluded from this analysis. Patients in self-help groups attended the meetings once a week. The study consisted of a 6-month medication period followed by a medication-free 6-month period. During the first half year participants had to visit their investigator every second week to receive their i.m. placebo injection. Additionally, every 4th week, participants had a physical examination, with blood samples taken for laboratory tests and filled self-report questionnaires to corroborate abstinence from alcohol. In the medication-free second half year, the same visits took place every eighth week. Follow-ups, where participants had to fill questionnaires such as Hamilton Anxiety Inventory (HAMA), Hamilton Depression Inventory (HAMD) and social functioning questionnaire (SFQ), took place after 3, 6, and 12 months. None of these visits included any therapeutic intervention.

Statistical analysis

The main interest during the year was focused on abstinence, which was operationalized by the relapse rate as a dichotomous variable. To investigate relapse rates at follow-ups, chi-square tests were used. To reveal relapse rates over time a Kaplan-Meier survival analysis (log-rank test) was used.

Differences of group characteristics were analysed using a one-way analysis of variance (ANOVA). If the variances were heterogeneous, a *t*-test for independent samples for unequal variances was used. To evaluate whether there were predicting variables for relapse or not, a stepwise logistic regression was used. To observe changes such as social functioning level over time, repeated ANOVA measurements were conducted for study completers only. The scores for the measures were tested for deviation from normal distribution by means of the Kolmogorov-Smirnoff test. To justify whether differences were substantial, two-tailed post hoc power analyses were applied (Altman, 1991; Faul and Erdfelder, 1992). All calculations used an alpha significance level of 0.05 and were interpreted two-tailed. All analyses were conducted by using the statistical software program SPSS Version 11.0 for Windows. Analysis of relapses was based on intention-to-treat (ITT), i.e. drop-outs were counted as relapses.

RESULTS

There were no differences in age, scores in the MALT, or number of DSM-III-R criteria for alcohol dependence between patients in a self-help group ($N = 50$) and the control group ($N = 28$). Moreover, no difference in anxiety (HAMA) or depression (HAMD) between both groups existed at the beginning of the study. The only significant difference between both groups was the level of social functioning (SFQ), $t(76) = 2.51$, $P = .037$. Compared to the control group, patients choosing a self-help group possessed a lower score in the SFQ, indicating a better social functioning level. No differences were found between the groups concerning the number of days remaining in the study, the days until the first relapse, or drop-out rate (Table 1). At the end of the observation period, after 1 year, the study retention was 58% ($N = 29$ out of 50) for patients in self-help groups and 61% ($N = 17$ out of 28) for patients without support.

Table 1. Characteristics of the groups

	SHG ($N = 50$)		Controls ($N = 28$)	
	Mean	SD	Mean	SD
At the beginning of the study				
Age (years)	42.1	7.5	43.9	8.6
Scores of MALT	33.4	5.5	35.3	6.3
Number of DSM-III-R criteria of alcohol dependence	8.3	0.9	8.2	1.1
Smoker (%)	74	—	71	—
SFQ-score	13.8	2.9	15.8*	4.2
HAMA-score	4.4 ^a	7.6	4.9	5.9
HAMD-score	1.9 ^b	2.6	2.8 ^b	3.9
At the end of the study				
Drop-outs after 1 year (%)	42	—	39	—
Days in the study	253	112	268	98
Days to first relapse	57	70	53.7	79

* $P < .05$.

^a 1 value is missing.

^b 2 values are missing.

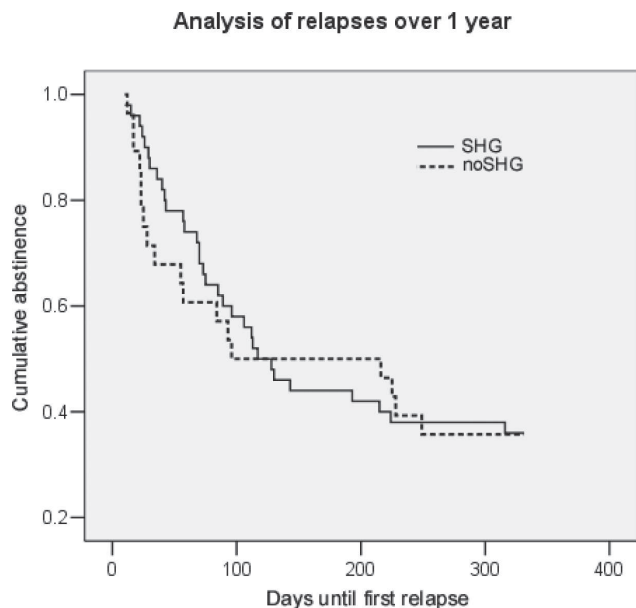


Fig. 1. Process of relapses for self-help group (— SHG) versus control condition (--- no SHG) over 1 year.

Comparison of relapsed and abstinent patients after 1, 3, 6, and 12-months follow-up revealed no differences between both groups. To take the factor time into account, a Kaplan-Meier survival analysis was conducted (Fig. 1). After 1 month, the relapse rate of the self-help group was with 14.0% ($N = 7$ out of 50) lower than that of the control group with 28.6% ($N = 8$ out of 28) which, however, did not reach significance, log-rank, $P = .106$. After 3 months, relapse rates were 40.0% ($N = 20$ out of 50) versus 42.9% ($N = 12$ out of 28) and after 6 months 56.0% ($N = 28$ out of 50) versus 50.0% ($N = 14$ out of 28). Thus the positive impact of self-help groups leveled off over time, as indicated by relapse rates of 64.0% ($N = 32$ out of 50) patients in the self-help group and 64.3% ($N = 18$ out of 28) in the control group after 1 year. A power analysis for this sample ($N = 78$) yielded a power of 0.60, calculated with an estimated magnitude of effect drawn from two studies finding a difference between self-help group attendance and control group in drinking outcome (Moos and Moos, 2004; Ouimette *et al.*, 1998). In the completer analysis, again no difference in relapse rates was found. Out of all completers, a proportion of 37.9% ($N = 11$ out of 29) in the self-help group and 41.2% ($N = 7$ out of 17) in the control group had relapsed after one year. To find out whether the difference of social functioning at baseline had a confounding impact on outcome, SFQ was adjusted. When excluding the three highest scores of the control group, SFQ did not reveal any difference anymore, $t(73) = 1.37$, $P = .175$. All the calculations on abstinence outcome were analysed again but did not reveal different results.

To check whether any pre-treatment variable might have a predictive value for relapses after 12-months, a stepwise logistic regression was conducted. Pre-treatment variables such as age, anxiety score (HAMA_{t0}), depression score (HAMD_{t0}) and social functioning score (SFQ_{t0}) were included in this analysis. The logistic regression revealed

a one-variable solution with an Odds Ratio of 1.359 (95% Confidence Interval [CI] = 1.010, 1.829; $P = 0.043$) for the depression score (HAMD_{t0}) at baseline. All other variables were excluded. The goodness of fit accounted with $R^2 = 0.12$ (Nagelkerke) for only 12% of the variance of the total model. Only 40.7% of the participants who stayed abstinent were classified correctly as abstinent, whereas 82.6% of the observed relapses were classified correctly as relapsed, with an overall prediction rate of 67.1%.

Changes in the variables HAMA, HAMD, and SFQ during the study were analysed for completers only (SHG, $N = 25$; Controls, $N = 17$). HAMA and HAMD revealed no changes due to time or group allocation. Interestingly, however, there was an improvement in the social functioning level in both groups over 1 year, as indicated by the social functioning level exposing the factor of time, but not group allocation, as significant, $F(2, 84) = 7.61$, $P < .001$, corrected for Greenhouse-Geisser because sphericity was not given (Fig. 2). To estimate the relevance of the improvement in the social functioning level from the beginning to the end of the study, a post hoc, within-subject, power analysis was calculated for each group separately. The improvement in social functioning for the self-help group yielded a power of 0.83 compared to the control group, which yielded a power of 0.75 for improvement within 1 year (Altman, 1991).

DISCUSSION

Though reports concerning the effectiveness of self-help groups are contradictory, 12-step approaches such as AA reap the benefit of a widespread belief in its effectiveness. The present analysis was performed to elucidate whether attendance in a self-help group after alcohol detoxification may enhance abstinence. However, despite a slightly lower relapse rate after 1 month in the self-help group, no positive impact of self-help group attendance on relapse rates after 1 year could be found, which is in line with the results of the Cochrane review of AA (Ferri *et al.*, 2006). The 1-year abstinence outcome of 36% found in this sample is supported by other reports on 1-year outcomes after alcohol detoxification. In an uncontrolled Indian study, 33% (Kuruville *et al.*, 2004) and in a controlled American study 43% attending AA versus 21% of the control group stayed abstinent after 1 year (Moos and Moos, 2004).

All participants of the present study attended AA meetings once a week, which is in line with the suggestion of regular AA attendance once or twice a week to support abstinence (Ouimette *et al.*, 1998; Fiorentine, 1999; Gossop *et al.*, 2003). It is possible that the duration of observation in the present study was not long enough. In their study Thurstin *et al.* (1987) found a positive effect for AA participation only after 18 months but not after 12 months. Further evidence for this has been presented by Moos and Moos (2004) supporting the hypothesis that the duration of AA participation is more important than the frequency.

The self-selection of treatment compared to random allocation can be seen as a confounding factor. But on the other hand, a randomized group allocation could lead to a coercion for participants with negative beliefs and preferences about

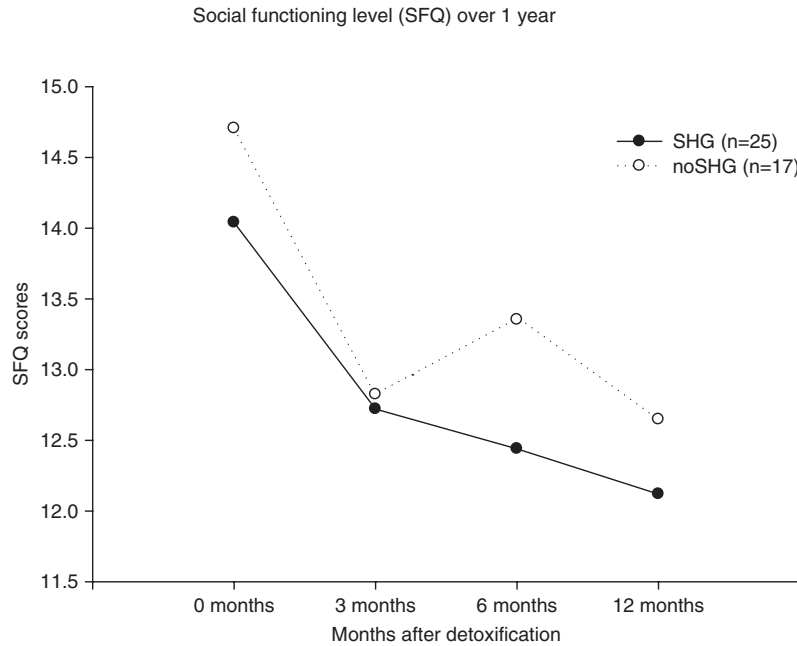


Fig. 2. Completer analysis of social functioning level for self-help group (— SHG) and control group (--- no SHG) during the observation period.

AA and bias the effect and intrinsic value of AA. In the original study, participants were allowed to choose the kind of treatment, which is more likely to reflect the real-world effectiveness in the treatment of alcoholism. Moreover, it can be presumed that self-selected treatment is associated with a higher motivation for abstinence, and enhances the probability of staying abstinent in the group of AA, which would in total rather support a possible positive effect of AA than attenuate it.

Those patients who chose AA showed even at the beginning of the study, a better social functioning level than the controls. Whether the social functioning level might have contributed to group selection, because patients with a lower social functioning level might hesitate to choose group treatment, or whether it is coincidental, remains to be clarified. Interestingly, however, there was an improvement of the social functioning level in both groups over 1 year, though empirical research reveals that an improved social functioning level is predominantly related to AA participation (Humphreys *et al.*, 2004; Moos *et al.*, 2001). The 12-step programme predicts better general friendship characteristics such as number of close friends and better substance abuse-specific friendship characteristics, (e.g. proportion of friends abstaining from drugs and alcohol) at follow-up (Humphreys and Noke, 1997) which helps to strengthen social functioning. The reported advantage of AA with regard to improving social functioning is probably reflected in the statistical power, which is a little bit higher for the self-help group than for the control group (0.83 vs 0.75). An explanation of the improvement of social functioning in both groups may be the study performance, which included many regular meetings with investigators in the first half year and loose meetings afterwards.

Looking for predictive variables of relapses, the depression score (HAMD) was found to be slightly predictive but

accounted for only 12% variance of the model. In general, this variance is too low, but considering that all persons with HAMD scores of more than 18 were excluded to control for comorbidity, it is remarkable that even sub-clinical depressive scores showed a slight predictive value. Research on relapse predictors revealed that participants with mild-to-moderate depressive symptoms were 2.9 times more likely to relapse than were non-depressive controls, while participants with severe depressive symptoms were 4.9 times more likely to relapse (Curran *et al.*, 2000). By contrast, other investigators found that neither lifetime major depression (Miller *et al.*, 1997), nor the degree of depressive symptoms are predictive of relapses (Sellman and Joyce, 1996). Further investigations are required to clarify whether sub-clinical depression scores can predict relapses in non-depressive persons.

Prior studies suggested effective variables for AA research, which were not investigated in this study. Thus, affiliation with AA has been found to be more predictive of maintaining abstinence than AA attendance alone (Longabaugh *et al.*, 1998; Montgomery *et al.*, 1995; Morgenstern *et al.*, 1997). Likewise there is evidence that increased abstinence is not mediated by AA attendance alone, but rather by a positive relationship between AA participation and self-efficacy to avoid drinking, which in turn predicts more abstinent days (Connors *et al.*, 2001). In the present analysis, there was no control for affiliation with AA or perceived self-efficacy to avoid drinking.

The strength of the present study is that data were drawn from a multi-centre, randomized, placebo-controlled trial investigating the effectiveness of a pharmaceutical drug for relapse prevention. Since the expectations of changes were focused on medication rather than on group attendance, the risk of running a self-fulfilling prophecy about the effectiveness of AA was rather low. Of further benefit was the

prospectively controlled design, i.e. no measure was biased by retrospective statements and both subjective and objective parameters about alcohol consumption were used to assess relapses.

In conclusion, the findings in this sample revealed no advantage in AA participation on drinking outcomes compared to the controls in 1 year. A limitation of the study is that the allocation of treatment was self-selected and not randomized, which might be a confounding factor, even if self-selected treatment reflects the naturalistic setting in the treatment of alcoholism more and would rather be a benefit for AA than for controls. Interestingly, however, even though patients choosing AA showed a better social functioning level at the beginning, both groups showed an improvement in social functioning at the end of the study.

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Article

Gender Differences in Interpersonal Problems of Alcohol-Dependent Patients and Healthy Controls

Sandra E. Mueller *, Bigna Degen, Sylvie Petitjean, Gerhard A. Wiesbeck and Marc Walter

Division of Substance Use Disorders, Psychiatric Hospital of the University of Basel, Wilhelm Klein-Str. 27, CH-4025 Basel, Switzerland; E-Mails: Bigna.degen@upkbs.ch (B.D.); Sylvie.petitjean@upkbs.ch (S.P.); Gerhard.wiesbeck@upkbs.ch (G.W.); Marc.walter@upkbs.ch (M.W.)

* Author to whom correspondence should be addressed; E-Mail: Sandra.mueller@upkbs.ch; Tel.: +41 61 325 53 33; Fax: +41 61 325 55 83.

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Abstract: Alcohol dependence is a heavy burden on patients, their families, and society. Epidemiological studies indicate that alcohol dependence will affect many individuals at some time in their lives, with men affected more frequently than women. Since alcohol-dependent patients often exhibit a lack of social skills and suffer from interpersonal problems, the aim of this study is to elucidate whether men and women experience the same interpersonal problems. Eighty-five alcohol-dependent patients (48 men; 37 women) after detoxification and 62 healthy controls (35 men; 27 women) were recruited. Interpersonal problems were measured with the Inventory of Interpersonal Problems (IIP-64). Additionally, alcohol-dependent patients were interviewed with the Alcohol Use Disorders Identification Test (AUDIT) and were subtyped according to Lesch's Alcohol Typology (LAT). There were no significant gender differences in the AUDIT and LAT between alcohol-dependent men and women. Interpersonal problems of alcohol-dependent men differed significantly in one out of eight dimensions from controls; alcohol-dependent men perceive themselves as colder than male controls. Alcohol-dependent women differed in four out of eight interpersonal dimensions from female controls. Alcohol-dependent women rated themselves as significantly more vindictive, more introverted, more overly accommodating and more intrusive than female controls. Results suggest that alcohol-dependent men and women suffer from different interpersonal problems and

furthermore alcohol-dependent women perceive more interpersonal problems, whereas the severity of alcohol dependence did not differ between the groups. Our findings indicate that alcohol-dependent women may profit more from a gender-specific treatment approach aimed at improving treatment outcome than alcohol-dependent men.

Keywords: alcohol dependence; gender differences; interpersonal problems; personality; sex differences

1. Introduction

Research on alcoholism initially focused predominantly on alcohol-dependent men, resulting in under-representation of women with alcohol use disorder. The first review on gender differences in alcoholism was 1992 by Jarvis and colleagues [1]; since then gender specific research in alcoholism has gained a lot of attention.

Overall men are more likely to suffer from alcohol use disorders [2]; however, relapse rates and time to relapse are similar across the genders [3]. A few studies have reported that women and men often begin treatment with similarly severe alcohol problems [4-6] but that women are more likely to have poor prognostic characteristics for treatment outcome [6,7]. In a study by Ross and colleagues [8], alcohol-dependent men reported drinking greater absolute amounts of alcohol, with earlier onset of heavy drinking than women [9]. However, there were no gender differences with respect to the frequency of binge drinking or in indicators of tolerance. In other findings, women reported more abstinent days and fewer drinks per day than men 3 months prior to the baseline measurement. However, it appeared that women were heavier drinkers than men with respect to the index of drinking to intoxication [10].

Social stressors or reasons for drinking seem to differ more than the actual characteristics of drinking across gender. For alcohol-dependent men, marriage appears to be a protective factor; when men with an alcohol disorder drink, this is likely to create marital stress. In contrast, alcohol-dependent women appear to be at greater risk if married or as a result of marital stress [3,11]. This may reflect the fact that women are more likely than men to have a spouse or partner who drinks more than they do [12]. Further, women are more likely to relapse with a romantic partner or female friends—in contrast to alcohol-dependent men, who are more likely to relapse when alone [3,10]. Overall, men with an alcohol problem had greater exposure to peers' drinking and women had greater exposure to partner's drinking [13].

A study investigating the reasons of problem drinkers compared to non-problem drinkers found that women were more likely to have experienced family and interpersonal problems, the death of someone close and emotional distress that may lead to drinking, while men were more likely to have experienced workplace problems [13]. A representative sample of drinkers in Finland revealed that women were more likely to report that drinking had helped them to sort out interpersonal problems at home or in the workplace, to feel more optimistic about life, and to express their feelings, in contrast to men who reported more commonly that drinking helped them to be funnier and wittier and to get closer to the opposite sex. Overall, men tended to perceive more hedonic benefits while women

perceived more functional benefits of drinking [14]. Factors preceding relapse episodes differ between the genders, in that women are more likely to drink in response to negative emotional states and interpersonal influences [15,16] while men, on the contrary, are more likely to relapse as a result of positive affect [15] and social pressure [16]. Other findings suggest that alcohol-dependent subjects of both genders experience predominantly negative moods. Immediately after the relapse, both genders reported a mix of negative and positive moods, with a tendency for men to report more positive moods after drinking than women [10]. These gender differences of positive and negative mood and intra- versus interpersonal conditions are expected to be reflected in Marlatt's taxonomy of high risk situations for relapse; however no gender difference was found [10].

A recent study found that the association that women report drinking more than men in response to unpleasant emotions and conflicts with others seems to be mediated by severity of depression [17]. Women with drinking problems report more depression, more psychiatric problems and are more likely to drink to relieve negative affect [18], which is supported by an European epidemiological study showing that alcohol-dependent women have a higher overall rate of co-morbid psychiatric disorders than men, especially affective disorders [19]. Two studies on gender differences in relapse to alcohol found that, at baseline, women scored higher on depressive symptomatology than men [6,7].

Alcohol-dependent patients differ from controls in coping styles and personality characteristics, while alcohol-dependent females differ greatly in terms of coping styles, personality variables and in terms of conflicts [20]. Especially for alcohol-dependent women, interpersonal conflicts appear to be an additional risk factor [3]. Problems in interpersonal relationships lead to frustration in interactions, to psychological distress and to lower quality of life, which in turn enhance the aforementioned negative social consequences and lead to maintained substance use [21], which then sustains interpersonal problems. To our knowledge, very few studies have addressed gender differences in interpersonal problems. One study investigating healthy controls failed to reveal any difference in the subscales of the Inventory of Interpersonal Problems by gender [22].

A large body of literature in alcoholism has concentrated on personality traits and it has been found, for example, that novelty seeking is a strong predictor for relapse [23-25]. Nevertheless, no integrative pattern for dependence (such as an addictive personality) could be found, and this in turn has led to the development of various alcohol typologies, such as Barbor's [26] or Cloninger's [27] typology of alcoholism. Even if the objective of all alcohol typologies is not to categorize, but to provide help in assessing the course and prognosis [28], opinions on the validity of these typologies differ considerably. Most authors emphasize that dichotomous typologies are unlikely to be complex enough to prove helpful in clinical work [29]. Therefore, more detailed methods are required to describe the interpersonal behavior style of these subjects. Dimensional approaches rather than dichotomous typologies are useful for clinical work. The strengths of the IIP-64 are that it uses a dimensional approach and assesses multiple aspects of interpersonal functioning. Patients are not allocated to single categories, but to a specific region of the underlying circumplex model, e.g., the friendly-submissive region of the circumplex, which describes the patient's distress in interpersonal interactions more precisely.

Therefore, the aim of the present study was to investigate self-perceived interpersonal problems in alcohol-dependent subjects, compared to healthy controls. The study was designed to test the following hypotheses: (1) Alcohol-dependent patients exhibit more self-perceived interpersonal

problems than healthy controls, and (2) alcohol-dependent females suffer from different interpersonal problems than alcohol-dependent males. This is expected to be due to gender differences in alcoholism with respect to triggers to relapse, comorbid psychopathology, and socioeconomic variables, as mentioned above.

2. Methods

2.1. Participants and Procedures

The experimental sample consisted of 85 alcohol-dependent inpatients (48 males; 37 females) recruited at an alcohol detoxification unit after alcohol withdrawal. All patients had been diagnosed as alcohol dependent according to the DSM-IV criteria [30], without any other substance use disorder except tobacco dependence. The diagnosis of a current depressive episode was distributed equally between men ($n = 15$, 31.3%) and women ($n = 14$, 37.8%). After the completed alcohol detoxification at the Alcohol Treatment Unit of the Psychiatric Hospital of the University of Basel, patients were asked to participate in a questionnaire study. Patients were interviewed by a psychologist or an assistant doctor, using three questionnaires. Questionnaires were filled out in the following sequence: First, Lesch's Alcohol Typology (LAT), the Alcohol Use Disorder Identification Test (AUDIT), and afterwards the Inventory of Interpersonal Problems (IIP-64) in paper-and-pencil format. The procedure lasted about 50 minutes. All patients provided written informed consent. The control group consisted of 62 healthy participants (35 males; 27 females) working in the health sector and were eligible if their age was between 18 and 65 years. They only filled out the Inventory of Interpersonal Problems (IIP-64) and provided written informed consent.

2.2. Materials and Measures

The Lesch Alcohol Typology (LAT) categorizes alcohol-dependent subjects into 4 subtypes, on the basis of various questions, such as family history characteristics, personal psychopathology and substance use history. Type I alcohol dependents exhibit very intense alcohol withdrawal syndrome and very intense alcohol dependence, with less other psychopathology, the so-called model of "allergy". Type II alcohol-dependent patients use alcohol as a self-medication because of its anxiolytic effects and try to reduce anxiety or conflicts. The main characteristics of the Type III alcohol dependents are depressive symptoms to which the alcohol is used as a self-medication. And last but not least, Type IV alcohol dependents show pre-morbid cerebral defects or behavioral disorders predominantly in childhood, the so-called "alcohol drinking as adaptation" model [31,32].

The AUDIT is composed of 10 questions examining the quantity and frequency of alcohol drinking and alcohol-related behaviors and consequences, in which a score of 8 or more indicates that problematic alcohol use is suspected. A high AUDIT score is related to greater severity of alcohol dependence [33].

The German version of the Inventory of Interpersonal Problems (IIP-64) is a 64-item questionnaire used to assess self-perceived distress in interpersonal relationships [34]. The scales are arranged in a circumplex model, where two orthogonal dimensions, affiliation and dominance, are the main axes.

Adjacent scales have more similarity and opposite scales have opposite qualities. The horizontal axis describes how much friendliness a person displays toward someone else and refers to nurturance, love, or affiliation, where the anchor on the right end is *excessively nurturant* and that on the left end is *cold*, referring to hostility, coldness and hate. The vertical axis quantifies the power or control someone else claims, and refers to status, agency or dominance, where the anchor on the upper end is *domineering* and the anchor on the lower end is *submissive*. Counterclockwise from the top of the circle, these subscales include: (1) *domineering, i.e.*, being too controlling or manipulative in interpersonal interactions; (2) *vindictive, i.e.*, being frequently egocentric and hostile in dealing with others; (3) *cold, i.e.*, having minimal feelings of affection for, and little connection with other people; (4) *socially avoidant, i.e.*, being socially avoidant and anxious and having difficulties approaching others; (5) *submissive, i.e.*, having difficulties expressing one's needs to others; (6) *exploitable, i.e.*, being gullible and easily taken advantage of by people; (7) *overly nurturant, i.e.*, being excessively selfless, generous, trusting and caring; and (8) *intrusive, i.e.*, imposing one's needs and having difficulties respecting the personal boundaries of other people. Due to the two main axes of love and dominance, the circumplex model can be divided into four regions; going clockwise, these are a friendly-dominant, a friendly-submissive, a hostile-submissive and a hostile-dominant region.

2.3. Statistical Analysis

Data analyses included the χ^2 test for categorical variables and non-parametric tests for ordinal data. If normal distribution was given for continuous variables, appropriate analyses such as one-way ANOVA were used.

The raw data of the IIP-64 were first transformed to z-scores to ensure normal distribution. As after the z-transformation, some of the IIP-64 dimensions still failed to exhibit normal distribution, the p-level was adjusted to $p = 0.010$ for a more conservative analysis. Because of the intercorrelation of the IIP-64 dimensions, a multivariate analysis MANOVA was chosen for the IIP-64 data. All statistical analyses were calculated using the statistical software SPSS version 14.0 for Windows.

3. Results

3.1. Demographic and Substance Use Characteristics

Age and gender were equally distributed between the groups. The alcohol-dependent sample had a mean age of 46 years (SD 9.5), compared to 43 years (SD 10.1) for the control sample. Gender distribution was equal in the two groups, with 48 males (56.5%) and 37 females (43.5%) in the alcohol-dependent group compared to 35 males (56.5%) and 27 females (43.5%) in the control group. There was also no significant difference between the groups with respect to age. Family status differed significantly among alcohol-dependent patients. While 20 alcohol-dependent males (24.1%) reported that they were unmarried, this was true for only five alcohol-dependent women (7.8%). No significant differences across gender were found for positive family history of alcoholism, tobacco dependence or psychiatric diseases (Table 1).

Table 1. Characteristics of gender differences in the alcohol-dependent group.

		Alcohol-dependent men	Alcohol-dependent women	p
Gender distribution; n (%)		48 (56.5%)	37 (43.5%)	n.s.
Age		44.6 (10.6)	48.5 (7.4)	n.s.
AUDIT (total score)		24.2	26.8	n.s.
Family status				
	Unmarried	20 (41.7%)	5 (13.9%)	0.022
	Living together	14 (29.2%)	16 (44.4%)	
	Separated/divorced	14 (29.2%)	15 (41.7%)	
Positive family history of				
Alcohol dependence	Yes	18 (37.5%)	17 (47.2%)	n.s.
	No	30 (62.5%)	19 (52.8%)	
Tobacco dependence	Yes	38 (79.2%)	29 (78.4%)	n.s.
	No	10 (20.8%)	8 (21.6%)	
Psychiatric diseases	Yes	13 (27.1%)	14 (38.9%)	n.s.
	No	35 (72.9%)	22 (61.1%)	
Lesch's typology				
	Type 1 (7.4%)	3 (6.3%)	1 (2.7%)	n.s.
	Type 2 (22.4%)	9 (18.8%)	10 (27%)	
	Type 3 (49.2%)	24 (50%)	18 (48.6%)	
	Type 4 (23.5%)	12 (25%)	8 (21.6%)	

No differences across gender were found in self-reported variables, such as years of pathological drinking, the first experienced withdrawal symptom (in years), loss of control in the last 3 months or the longest sober period. Alcohol-dependent men did not differ significantly from alcohol-dependent women in the AUDIT. Furthermore, when every single question of the AUDIT was compared across gender with non-parametric tests, one out of ten questions differed significantly across gender. Question 4 “How often during the last year have you found that you were not able to stop drinking once you had started” was more frequently affirmed by alcohol-dependent women ($Z = -1.97$, $p = 0.049$). The analysis of the Lesch Typology revealed that almost 50% of all patients were classified as type 3 (49.2%), the anti-depressive model of drinking. This was followed by type 4 (23.5%), type 2 (22.4%), and type 1 (7.4%) No gender difference was found regarding Lesch's typology (Table 1).

One or more accidents under the influence of alcohol were reported, with similar frequency across gender, while even violation of the law was significantly more often confirmed by alcohol-dependent men 20 (41.7%) than women 7 (19.4%) ($\chi^2 = 4.66$, $p = 0.031$). The question whether they ever experienced a depressive episode was significantly more often confirmed by alcohol-dependent women, with 32 (86.5%) versus 33 (68.8%) by men ($\chi^2 = 3.65$, one-tailed, $p = 0.047$). Sleeping disorders without the influence of alcohol was reported to be similar across genders. Moreover, there was no gender-dependent difference in the incidence of suicide attempts (one or more).

3.2. Interpersonal Problems

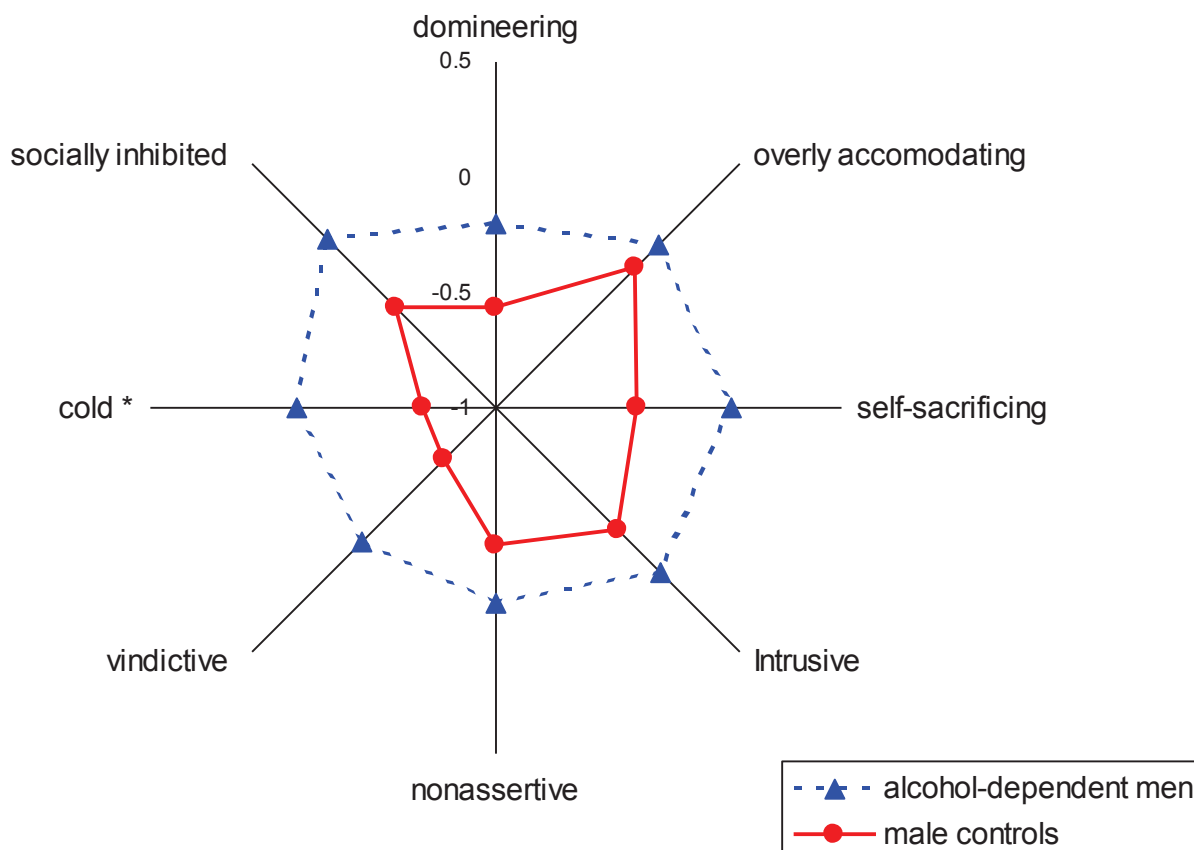
A MANOVA was performed on continuous variables of the IIP dimensions for the complete alcohol-dependent sample compared to the healthy control group; in a second step, MANOVA analyzes were performed for each gender separately. For the complete sample, an overall effect for the group was found (multivariate $F(8,138) = 3.144, p = 0.003$). Five out of eight univariate effects reached significance. All results are given in Table 2.

Table 2. Differences in interpersonal problems for the complete sample and separately for each gender.

	Alcohol-group (n = 85)	Healthy controls (n = 62)	Univ F	p
Domineering	-0.411	-0.628	2.51	0.115
Vindictive	-0.196	-0.788	14.32	>0.001
Cold	-0.203	-0.776	13.49	>0.001
Socially inhibited	0.111	-0.467	12.27	0.001
Non-assertive	0.034	-0.339	4.28	0.040
Overly accommodating	0.231	-0.228	3.68	0.057
Self-sacrificing	0.379	-0.343	14.49	>0.001
Intrusive	0.127	-0.456	9.71	0.002
Multivariate $F(8,138) = 3.14, p = 0.003$				
	Alcohol-dependent men (n = 48)	Male controls (n = 35)	Univ F	p
Domineering	-0.208	-0.573	4.25	0.042
Vindictive	-0.18	-0.685	5.85	0.018
Cold	-0.137	-0.686	7.40	0.008
Socially inhibited	0.032	-0.389	4.08	0.047
Non-assertive	-0.155	-0.405	1.34	0.251
Overly accommodating	-0.008	-0.144	0.386	0.536
Self-sacrificing	0.017	-0.390	3.18	0.078
Intrusive	0.005	-0.257	1.35	0.248
Multivariate $F(8,74) = 1.07, p = 0.394$				
	Alcohol-dependent women (n = 37)	Female controls (n = 27)	Univ F	p
Domineering	-0.674	-0.699	0.014	0.907
Vindictive	-0.216	-0.923	8.74	0.004
Cold	-0.29	-0.893	6.02	0.017
Socially inhibited	0.213	-0.569	8.53	0.005
Non-assertive	0.278	-0.253	3.12	0.082
Overly accommodating	0.54	-0.084	4.36	0.041
Self-sacrificing	0.849	-0.282	14.2	>0.001
Intrusive	0.286	-0.7133	10.28	0.002
Multivariate $F(8,55) = 2.98, p = 0.008$				

Firstly, a MANOVA of alcohol-dependent men versus healthy men was performed (Figure 1). The overall effect did not reach significance in the male group. There was one significant univariate effect for alcohol-dependent men, namely being too *cold* ($F(1,82) = 7.404, p = 0.008$).

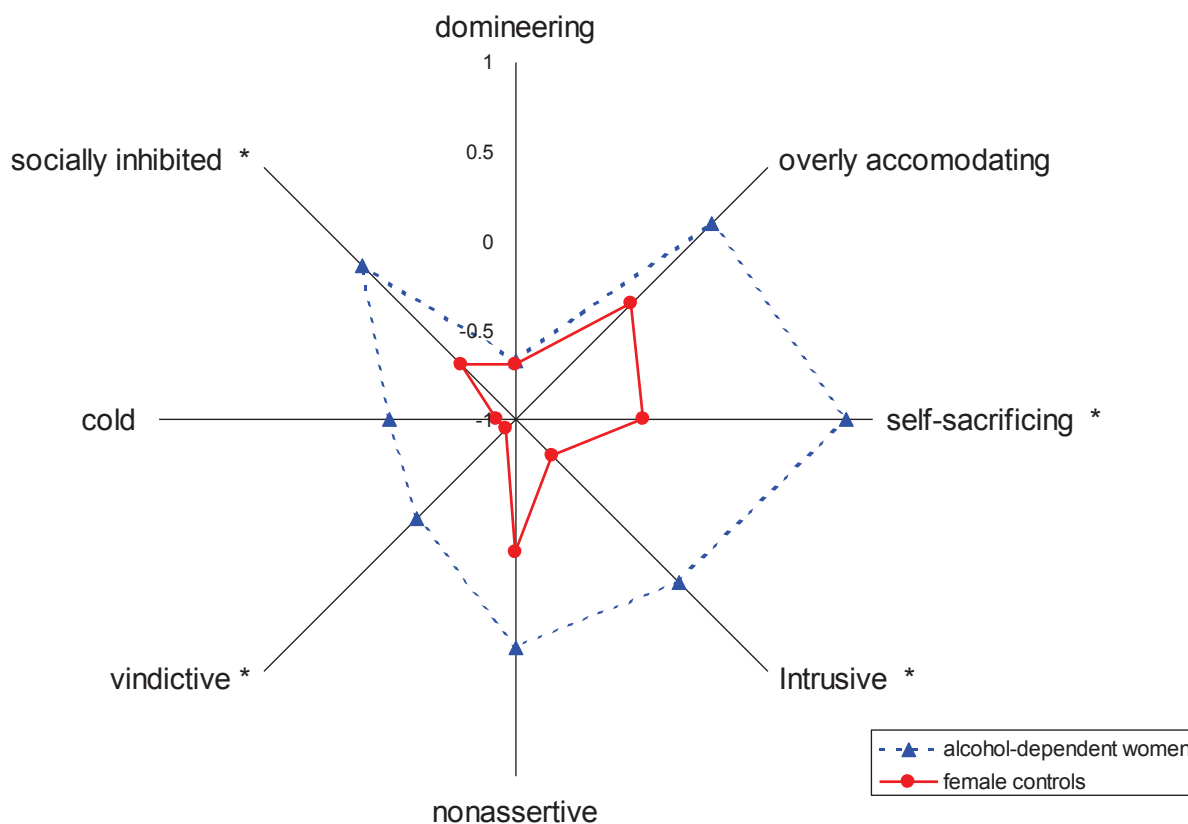
Figure 1. Circumplex model of interpersonal problems (IIP) of alcohol-dependent men vs. male controls (z-scores).



Secondly, a MANOVA of the alcohol-dependent women compared to female controls was performed (Figure 2). There was a significant overall effect in the female group (multivariate $F(8,55) = 2.979, p = 0.008$). Additionally, four out of eight dimensions in the univariate effects reached significance. Alcohol-dependent women had higher scores on being too vindictive ($F(1,63) = 8.739, p = 0.004$), being too socially inhibited ($F(1,63) = 8.532, p = 0.005$), too self-sacrificing ($F(1,63) = 14.198, p < 0.001$), and too intrusive ($F(1,63) = 10.283, p = 0.002$).

In a third step, the dichotomous variable of having a reported life-time depressive episode was used as a covariate in the MANOVA. No effect of this covariate could be found in either gender groups. Finally, the healthy control group alone was analyzed by a MANOVA for gender differences. No overall group effect for gender was found and none of the univariate dimensions reached significance.

Figure 2. Circumplex model of interpersonal problems (IIP) of alcohol-dependent women vs. female controls (z-scores).



4. Discussion

The current study revealed as an overall group effect that alcohol-dependent patients reported a higher severity of interpersonal problems than healthy controls. Further analyses revealed that this difference is mainly mediated by alcohol-dependent women, irrespective of the severity of their alcohol dependence. Alcohol-dependent women reported a higher burden in the dimensions of being too vindictive, too socially avoidant, too self-sacrificing and too intrusive compared to the female controls. Overall, it can be stated that alcohol-dependent women are in the friendly-submissive region, whereas alcohol-dependent men cannot be classified to any region of the IIP dimensions. In contrast, alcohol-dependent men did not differ in the overall effect from male controls; however, in the dimension of being too *cold* alcohol-dependent men scored significantly higher than male controls. Because no differences between male and female alcohol-dependent patients regarding a current depressive episode were found, the gender differences in interpersonal problems could not be mediated by current depressive episodes.

In this study, no differences across gender regarding characteristics of alcohol use could be found, except that women more frequently reported they failed to stop drinking once started. This finding is supported by the results of Rubin and colleagues [10], who reported that alcohol-dependent women drank more often to intoxication than their male counterparts, when gender and weight were taken into account. Another significant difference across gender was the family status. Alcohol-dependent men

were more frequently single or unmarried compared to alcohol-dependent women. In this sample, alcohol-dependent women were more frequently in relationships, and prior research affirmed that women are more likely than men to have a spouse or partner who drinks even more than they do [12]. With this background, it may be assumed that alcohol-dependent women perceived more marital or family stress and more conflicts in the family, and that these aggravated interpersonal problems. This would in turn explain the present results of a higher burden of interpersonal problems in alcohol-dependent women.

Even if in this sample, the current depressive episodes did not differ across gender, although alcohol-dependent women reported more frequently life-time depressive episodes than alcohol-dependent men. This is in line with several findings that alcohol-dependent women score higher on depressive symptomatology at the beginning of treatment for alcohol and that comorbid psychiatric disorders—especially affective disorders—are more frequent in women with an alcohol use disorder [6,7,19]. Interestingly, the most frequent type of Lesch's typology was Type III, the model of drinking for its anti-depressive effect, which exhibited no gender differences. This is contradicting to the finding of Sperling and colleagues [35] that alcohol-dependent women were more likely to be classified as Type III while alcohol-dependent men were more likely to be classified as Type IV of Lesch's typology. In general, it is important to note that depressive episodes have negative influences on self-perception and interpersonal behavior. Nevertheless, findings for depressive patients with the IIP are somewhat inconsistent. Alden and Philips [36] found that depressive patients are comparable to controls, but Stangier *et al.* [37] reported that patients with a major depressive episode showed higher values on the subscales *socially avoidant*, *non-assertive*, *exploitable (overly accommodating)*, and *overly nurturant (self-sacrificing)*, compared to the normative sample. The variable of life-time depressive episode was used as a covariate in the multivariate analysis and no effect was found. Furthermore there was no difference in current depressive episodes, so that it can be stated that the present results of the IIP dimensions are probably not affected by life-time or current depressive episodes.

It might be that the gender difference in perceived interpersonal problems is due to a lower self-image in alcohol-dependent women compared to alcohol-dependent men, as was found in a study of Aubry and colleagues [38]. A lower self-image and an overall higher depressive group of symptoms can lead to a biased perception, that the subject is the source of most mistakes.

One limitation of our study is that alcohol-dependent patients were recruited shortly after alcohol detoxification. Moreover, the findings should be corroborated with a larger sample size.

In summary, the most important finding of the present study is that especially alcohol-dependent women suffer from more interpersonal problems than men. This may be caused by the variety of preceding gender differences found in alcoholism research, which may lead to more perceived or effective interpersonal problems. Neither prior research [22] nor the present analysis of the control group found gender differences in interpersonal problems of healthy controls, suggesting that the difference is not due to gender per se, but may be linked to alcohol dependence or to the consequences of chronic alcoholism. Furthermore, a large body of literature shows that alcohol-dependent women, in contrast to alcohol-dependent men, suffer from or drink due to interpersonal problems [3,13-16], supporting the present finding. These limitations notwithstanding, the results of the current study retain some significant clinical implications. This is the first examination of gender differences in

interpersonal problems of alcohol-dependent patients. It establishes that alcohol-dependent women suffer from different and more interpersonal problems than alcohol-dependent men, irrespective of the severity of alcohol dependence or affective disorder. This difference should be addressed in gender specific treatment programs to improve treatment outcome.

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