

RESULTS FROM TWO PHARMACOTHERAPY TRIALS SHOW ALCOHOLIC SMOKERS WERE MORE SEVERELY ALCOHOL DEPENDENT BUT LESS PRONE TO RELAPSE THAN ALCOHOLIC NON-SMOKERS

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Abstract — Aims: To assess the role of smoking on treatment outcome in quitting alcoholics on the background of the priming or coping hypothesis (Rohsenow *et al.*, 1997). **Methods:** Data sets of placebo treated patients of the German phase III trial of naltrexone (Gastpar *et al.*, 2002) and of acamprostate treated patients of a German phase IV trial (Soyka *et al.*, 2002) were reanalyzed. Differences between smoking and non-smoking alcoholics were evaluated using χ^2 -, *t*- or ANOVA-tests, relapse rates using survival techniques with Cox regression. **Results:** Smoking alcoholics differed significantly from non-smoking alcoholics regarding sociodemographic variables (e.g. more males, more often living alone) and severity indicators of alcoholism (e.g. quantity, onset, related problems). In the naltrexone study time to first relapse was significantly longer for smoking alcoholics compared to non-smoking alcoholics (hazard ratio = 2.26; $P = 0.036$). The same effect was seen in the acamprostate study (hazard ratio = 1.34; $P = 0.015$); estimated abstinence-rates after 24 weeks were 38% for smoking alcoholics compared to 28% for non-smoking alcoholics ($P < 0.015$). **Conclusions:** Smoking was significantly associated with better outcome in recovering alcoholics included in two pharmacotherapy trials. Although the underlying mechanisms remain unclear our findings are in favour of the coping hypothesis. The results challenge the validity of the dependence syndrome.

INTRODUCTION

Epidemiological studies show that people who drink alcoholic beverages also smoke cigarettes and vice versa. About 80 to 95% of alcohol-dependent patients smoke regularly (Toneatto *et al.*, 1995; Daepfen *et al.*, 2000) and most of them are nicotine-dependent (Batel *et al.*, 1995). In explaining initiation of this special comorbid condition, it was argued that the reason for combined alcohol and tobacco consumption is that either drug might increase the desire or rewarding effects of the other or either might decrease the toxic or unpleasant (aversive) effect of the other (NIAAA, 1998). It has been proposed that with low levels of alcohol consumption the stimulant effects of nicotine may be enhanced. On the other hand, drinkers might be motivated to smoke to decrease some of the negative effects of alcohol use as nicotine is known to diminish the effects of alcohol on cognitive skills, such as arousal and mental alertness. Conversely, smokers might use the sedating effect of alcohol to mitigate aversive effects of smoking.

Two conceptual models for the relationship between tobacco and alcohol use disorders have been proposed (Rohsenow *et al.*, 1997). Some evidence supports both a shared vulnerability model (that common genetic or environmental factors underlie both tobacco and alcohol abuse) and a reciprocal influence model (that abuse of one substance predisposes an individual to abuse the other because of a number of bio behavioural processes, such as synergistic physiological effects for reward (Ericson *et al.*, 2003), cross-tolerance (Al-Rejaie and Dar, 2006a) and cuing effects (Watson and Little, 1999).

For the recovery process two mechanisms regarding the interaction of nicotine and alcohol in dual addicts may be of major importance. Due to the ‘coping’ or ‘compensatory’ hypothesis tobacco use may decrease the risk of drinking in abstaining alcoholics by providing a means of coping with urges to drink or with situations that pose a high risk for drinking (Rohsenow *et al.*, 1997). Neuropsychological compensation may occur, if alcohol craving involves depletion of dopamine or endogenous opiates, smoking may decrease this craving by stimulating the release of these substances. Common reinforcement mechanisms may also be present as social learning theories suggest that tobacco and alcohol have some common reinforcement properties, such as stress reduction and affect regulation, so that tobacco may be used instead of alcohol to provide these sources of reinforcement.

According to the ‘priming’ hypothesis tobacco use may increase the risk for drinking and urges to drink during recovery. Animal studies have shown that nicotine increases alcohol self-administration and reinstates alcohol seeking behaviour (Le *et al.*, 2003; Barrett *et al.*, 2006). It was suggested that associative learning, cross-tolerance, propositional networks or interacting neurobiological systems are elements promoting addiction (Watson and Little, 1999; Clark and Little, 2004; Rose *et al.*, 2004).

Experimental (Palfai *et al.*, 2000; Cooney *et al.*, 2003; Colby *et al.*, 2004) and treatment studies (Bobo *et al.*, 1998; Patten *et al.*, 2000) have been done in last years investigating the impact of nicotine deprivation or smoking cessation on alcohol urges or subsequent use with inconsistent findings. There is still little knowledge about the question whether smoking habits in alcoholics might improve or deter the natural course of alcoholism or treated outcome, respectively. Of course, there is no doubt about the devastating effects of cigarette smoking on pulmonary, cardiac and vascular function and on cancer induction; even more alcoholics are known to die from smoking-associated diseases than from drinking-related causes (Hurt *et al.*, 1996). But the issue

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whether the course of alcoholism in smoking alcoholics differs in contrast to non-smoking alcoholics has not been well studied.

Preliminary data of an earlier study by our group had indicated that smoking could possibly aid in preventing relapse to drinking in alcoholics (Schmidt and Smolka, 2001). In a small group of 63 alcoholics 33% of those smoking compared to 20% of those not smoking remained abstinent after 12 month of treatment; in addition, smokers tended to be abstinent longer from alcohol (173 days) than non-smoking alcoholics (114 days). To independently test whether smoking is associated with better treatment outcome we analysed two data sets that were provided from two pharmacotherapy trials on relapse prevention: (i) the phase III study of the German naltrexone trial (Gastpar *et al.*, 2002) and (ii) the phase IV study of the German acamprosate trial (Soyka *et al.*, 2002). In both studies alcoholics had been treated for maintaining abstinence; smoking habits had been left untargeted so far. In this study the focus was (a) on clinical characteristics possibly different in smoking alcoholics and non-smoking alcoholics and (b) on possible differences regarding relapse and their time pattern in smoking alcoholics and non-smoking alcoholics.

METHODS

Subjects

Study I was a randomized controlled multicenter trial of 171 detoxified patients, 97.7% had met the DSM-III-R-criteria for alcohol dependence (Gastpar *et al.*, 2002). The study had been designed to compare the outcome of treatment over 12 weeks in 84 patients randomized to naltrexone and 87 patients to placebo and over another 12 weeks of aftercare when the patients were kept drug-free. Data records of 87 placebo treated patients of the German naltrexone study had been obtained from the Dupont company, Wilmington, U.S.A. Forty-four of these 87 patients (51%) could be analyzed for this study due to data available for total study time of 24 weeks as completers.

Study II was a postmarketing study of acamprosate including 753 patients (intent-to-treat) who had met DSM-III-R-criteria for alcohol dependence (Soyka *et al.*, 2002). All patients received 1332 to 1998 mg acamprosate per day according to body weight and received several forms of psychotherapy (individual, group, behavioural, brief intervention or family focussed). Data records were provided by the Merck-Lipha Company, Darmstadt, Germany. Since 196 of 753 patients had fundamental missing data due to several reasons, mostly to attrition, our analysis between smoking- and non-smoking-characteristics was based on 557 patients. This group also allowed conducting a multivariate analysis of relapse predictors. For 364 of these subjects data for the complete 24 week-study was available. For the remaining 193 patients who dropped out after the first relapse, available data allowed to us analyze timing and quantity of drinking in further detail. In the naltrexone study we focussed on placebo patients to evaluate outcome unaffected by drugs; as there was no choice or chance to repeat this strategy in the acamprosate study, findings were taken for cross-validation.

Both studies had been approved by the local ethical committees.

Outcome parameters

For both studies we defined the time to first relapse as primary outcome variable with relapse defined as any consumption of alcohol (different definition as compared to the original naltrexone study). Secondary outcome variables were defined as the proportion of days with alcohol consumption during the study and the amount of alcohol consumed (in grams of alcohol per week).

Statistics

All statistics were done with SPSS 10.5. Differences between smoking alcoholics- and non-smoking alcoholic-variables at study entry were tested for significance by means of χ^2 -, *t*- or ANCOVA-tests (to control for gender).

In study I we used survival analysis to test for differences regarding time to relapse between smoking alcoholics and non-smoking alcoholics. Although we had only one factor (smoking status), we applied Cox regression analysis to better compare results with those from study II. For the two secondary outcomes (proportion of days with alcohol consumption during the study and the amount of alcohol consumed) we used *t*-tests.

In study II which had a much larger sample size multivariate statistics were applied to control for differences between smoking alcoholics and non-smoking alcoholics at study entry. To identify variables associated with time to first relapse Cox regression analysis was used. We initially entered all variables that (i) were significantly different between smoking alcoholics and non-smoking alcoholics on study entry; (ii) were indicators of personality (NEO-FFI-dimensions); (iii) were indicators of compliance for pharmacotherapy and of compliance for psychotherapy (that could be rated by therapists as 'good' (= 1), 'median' (= 2) or 'poor' (= 3)). Using the backwards procedure we then removed all variables with non-significant effect ($P < 0.05$). The impact of smoking on secondary outcome variables were tested using ANOVA statistics with only those variables identified by the Cox regression statistics as being associated with time to first relapse.

RESULTS

Study I

In this study, 26 of 44 patients (59%) were smoking alcoholics and 18 (41%) were non-smoking alcoholics. Both groups did not differ regarding their mean age but—by definition—regarding smoking (Table 1). One major difference between smoking alcoholics and non-smoking alcoholics was related to alcohol intake: significantly more daily standard-drinks had been recorded in the month prior to study entry for smoking alcoholics than non-smoking alcoholics (Table 1).

Survival analysis revealed that time to first relapse to alcohol was significantly longer in smoking alcoholics than in non-smoking (hazard ratio = 2.26; $P = 0.036$). Relapse

Table 1. Sample characteristics study I

	All (N = 44)	Non-smoking alcoholics (N = 18)	Smoking alcoholics (N = 26)	P
Gender (female)	25%	33%	19%	0.288
Age (years)	44.8 (±9.7)	46.3 (±9.2)	43.7 (±10.2)	0.393
# Cigarettes/day	15.0 (±15.0)	0.0 (±0.0)	25.4 (±9.9)	0.000
Standard drinks/day	5.7 (±4.6)	3.6 (±2.0)	7.1 (±5.3)	0.004

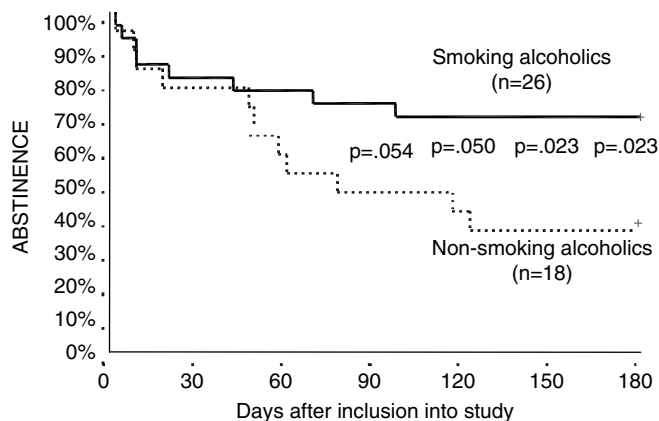


Fig. 1. Study I: Abstinence-rates in smoking alcoholics and non-smoking alcoholics of the German phase III naltrexone study (placebo-treated patients only; *P*-values relate to χ^2 -tests (one-sided).

rates were already substantially lower 3 month after inclusion into the study in smoking alcoholics compared to non-smoking alcoholics (27% vs 50%; $P = 0.054$) and also at later time points (Fig. 1). The proportion of abstinent days was also significantly higher in smoking alcoholics compared to non-smoking alcoholics during total study time (after 3 months: 84 [±13] vs [89 ± 6]; $P = 0.048$; 6 months: 165 [±18] vs 152 [±28]; $P = 0.06$). In spite of nearly two-fold higher alcohol consumption before study entry observed in smoking alcoholics, alcohol consumption (standard drinks

per day) were lower in smoking alcoholics than in non-smoking alcoholics with a significant difference emerging after 3 month (0.22 [±0.69] vs 0.48 [±0.78]; $P = 0.043$) that was stable to the end of the study after 6 months (0.20 [±0.44] vs 0.67 [±0.90]; $P = 0.012$).

Study II

In the larger study II, 364 subjects of 557 alcoholics were smoking alcoholics (65%) and 193 (35%) non-smoking alcoholics (Table 2). However, smoking alcoholics and non-smoking alcoholics showed significant differences in more domains than in study I. Smoking alcoholics had begun heavy drinking about 2 years earlier and were 4 years younger at index treatment than non-smoking alcoholics, there were differences regarding gender (more males in smoking alcoholics than non-smoking alcoholics) and marital status (e.g. more smoking alcoholics living alone than non-smoking alcoholics). Smoking alcoholics had met more DSM-III-R criteria for alcohol dependence than non-smoking alcoholics, had more alcohol withdrawal treatments prior to index treatment, had been more often arrested by police and reported more frequently prior imprisonment. However, there were no differences concerning personality traits assessed with the NEO-FFI at study entry (Table 3), regarding level of education or being employed between both groups (data not shown).

Treatment conditions led to a more than 10-fold reduction of frequency and quantity of alcohol consumption. Smoking alcoholics reported fewer days per week with alcohol consumption compared to non-smoking alcoholics (0.42

Table 2. Sample characteristics study II

	All (N = 557)	Non-smoking alcoholics (N = 193)	Smoking alcoholics (N = 364)	P
Gender (female)	29%	40%	22%	0.000 ^c
Age (years)	43.6 (±8.7)	46.2 (±9.2)	42.3 (±8.1)	0.000 ^a
Living on its own	33%	22%	38%	0.000 ^b
Employed	53%	58%	51%	0.104 ^b
Onset of heavy drinking (age)	20.4 (±8.3)	21.9 (±9.7)	19.6 (±7.3)	0.045 ^a
Duration of alcohol dependence (years)	10.4 (±6.9)	9.9 (±6.8)	10.7 (±6.9)	0.646 ^a
Days with alcohol consumption/week	6.1 (±1.7)	5.8 (±1.9)	6.2 (±1.5)	0.002 ^a
Standard drinks/week	192 (±129)	152 (±111)	214 (±132)	0.000 ^a
Inpatient detoxification	71%	64%	74%	0.007 ^b
DSM-III-R criteria fulfilled (#)	7.3 (±1.6)	7.0 (±1.7)	7.4 (±1.6)	0.010 ^a
Drunken arrest	13%	8%	16%	0.025 ^b
Imprisonment	6%	2%	8%	0.013 ^b

^a Given *P*-values (two-tailed) refer to ANCOVA statistics (adjusted for gender).

^b Logistic regression (adjusted for gender).

^c χ^2 -tests.

Table 3. NEO-FFI scores (study II)

	All (<i>N</i> = 557)	Non-smoking alcoholics (<i>N</i> = 193)	Smoking alcoholics (<i>N</i> = 364)	<i>P</i> *
Neuroticism	2.07 (±0.64)	2.04 (±0.64)	2.09 (±0.64)	0.189
Extraversion	2.10 (±0.50)	2.13 (±0.50)	2.08 (±0.50)	0.567
Openness	2.27 (±0.46)	2.31 (±0.43)	2.25 (±0.47)	0.196
Agreeableness	2.46 (±0.42)	2.53 (±0.41)	2.42 (±0.42)	0.128
Conscientiousness	2.66 (±0.50)	2.72 (±0.48)	2.63 (±0.51)	0.072

* *P* (adj. for gender).

Table 4. Variables significantly associated with time to relapse (study II; *N* = 557; Cox regression)

	B	S.E.	Wald	df	Sig	R	HR
Compliance pharmacotherapy	0.96	0.08	148.3	1	0.0000	0.196	2.62
Compliance psychotherapy	0.62	0.15	16.5	1	0.0000	0.062	1.85
Smoking status	0.29	0.12	5.9	1	0.0148	0.032	1.34
Neuroticism (NEO-FFI)	0.22	0.09	5.8	1	0.0158	0.032	1.24
Earlier withdrawal treatment	0.27	0.13	3.9	1	0.0469	0.023	1.30

(±0.71) vs 0.55 (±0.97) days per week) and also lower amounts of alcohol (10.2 (±23.0) vs 10.9 (±25.6) drinks per week).

Cox regression analysis on the 557 subjects in study II revealed that five of the 19 variables initially included in the model were significantly associated with time to first relapse (χ^2 Overall = 311; *df* = 5; *P* = 0.0000): besides 'smoking status' these were 'compliance to pharmacotherapy', 'compliance to psychotherapy', 'neuroticism' (NEO-FFI), and 'earlier withdrawal treatments' (Table 4). Less compliance to pharmacotherapy as well as to psychotherapy had the most significant impact and increased risk for relapse (HR = 2.62; HR = 1.85 respectively); higher neuroticism and number of previous detoxifications led also to increased risk (HR = 1.24; HR = 1.30 respectively). Interestingly, many indicators of alcoholism severity, as e.g. number of DSM-III-R-criteria fulfilled, duration of the disease or drinking quantity parameters were not related to treatment outcome.

Using Cox regression analysis including these significant five covariates estimated abstinence-rates were 38% for smoking alcoholics compared to 28% for non-smoking alcoholics at the end of the study (*P* = 0.015; Fig. 2). Using ANOVA statistics we found that the number of drinking days (per week) was significantly associated with the five covariates identified above (R^2 : = 0.338; *F* = 54.6; *df* = 5; *P* = 0.000). All variables including smoking status (*F* = 10.7; *df* = 1; *P* = 0.001; η^2 = 0.02) but not 'neuroticism' were significant (Table 5); in case of predicting drinks per weeks only 'compliance to pharmacotherapy' (*F* = 72.0; *df* = 1; *P* = 0.000; η^2 = 0.119) and 'earlier withdrawal treatments' (*F* = 7.4; *df* = 1; *P* = 0.007; η^2 = 0.014) were significant (Table 6).

DISCUSSION

Smoking comorbidity in alcoholism or dual addiction on alcohol and nicotine receives an ongoing high interest in

Table 5. Multivariate analysis of variables significantly associated with drinking day per week (study II; *N* = 557)

	<i>F</i>	<i>df</i>	<i>P</i>	η^2
Compliance pharmacotherapy	121.3	1	0.000	0.185
Compliance psychotherapy	13.0	1	0.000	0.024
Smoking	10.7	1	0.001	0.020
Earlier withdrawal treatments	9.7	1	0.002	0.018
Neuroticism (NEO-FFI)	3.4	1	0.068	0.006

R^2 = 0.338; *F* = 54.6; *df* = 5; *P* = 0.000.

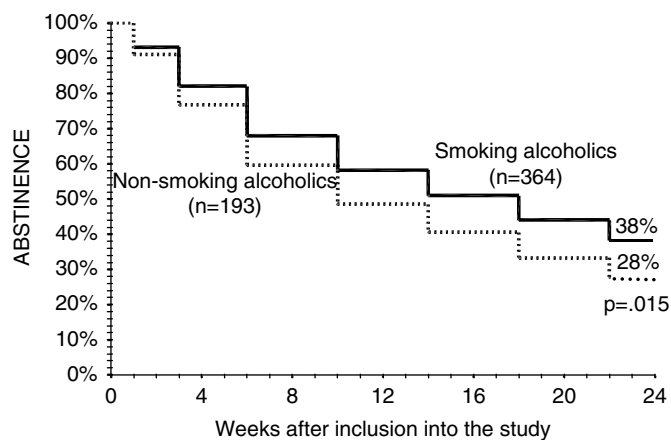


Fig. 2. Study II: Estimated abstinence-rates in smoking alcoholics and non-smoking alcoholics in a German phase IV acamprosate study (all patients on acamprosate; corrected for the factors 'compliance to pharmacotherapy', 'compliance for psychotherapy', 'neuroticism' (NEO-FFI) and earlier withdrawal treatments; *P* value: two-sided by Cox regression).

recent years (Ait-Daoud *et al.*, 2006; Meyerhoff *et al.*, 2006). In this context, two major results from our study warrant discussion.

First, our data analysis revealed that smoking alcoholics and non-smoking alcoholics in both samples were clinically

Table 6. Multivariate analysis of variables significantly associated with drinks per week (study II; $N = 557$)

	F	df	P	η^2
Compliance pharmacotherapy	72.0	1	0.000	0.119
Earlier withdrawal treatments	7.4	1	0.007	0.014
Smoking	2.1	1	0.149	0.004
Neuroticism (NEO-FFI)	1.7	1	0.191	0.003
Compliance psychotherapy	0.9	1	0.356	0.002

$R^2 = 0.197$; $F = 26.1$; $df = 5$; $P = 0.000$.

different in many aspects. Smoking alcoholics were more often male, more often living alone, had begun heavy drinking earlier, had about twice as much alcohol drinks at index time and had more conflicts with law. These observations are consistent with one of the largest sample contrasting smoking alcoholics and non-smoking alcoholics by Daepfen *et al.*, 2000 also indicating that smoking alcoholics suffer from a more severe form of alcohol dependence and more alcohol-related life problems independent of some additional diagnoses, e.g. as antisocial personality disorders. However, our data did not substantiate smoking alcoholics to be more often unemployed or of lower education—an observation that may due to different socio-cultural backgrounds of the samples.

Second, smoking alcoholics though seemingly more heavily dependent on alcohol did not experience more alcohol relapses than non-smoking alcoholics in both of our samples under placebo or acamprosate. These results confirm our initial observation (Schmidt and Smolka, 2001) that is in some contrast to studies that reported a mixed role of tobacco in alcohol recovery (Abrams *et al.*, 1992; Gulliver *et al.*, 2000). Here it had been reported that alcoholics with more intense nicotine dependence developed higher urges to drink alcohol and demonstrated higher quantities and frequencies of alcohol use if they relapsed; but 58% of them reported to cope with urges to drink and relapsed less likely to alcohol use a month later (Abrams *et al.*, 1992). Another treatment study could not predict post-treatment drinking by pre-treatment smoking (Gulliver *et al.*, 2000).

It might be concluded from our study that smoking has some capacity to help alcoholics to cope with urges to drink and does not prime alcoholic drinking in weaning patients engaged in abstinence studies. Moreover, it could be inferred for the larger acamprosate group that smoking was associated with a 10% reduction in risk for relapse in alcohol recovery. However, the smoking effect for preventing relapse was modest in comparison to other factors that were evidenced to contribute much more to abstinence of the patients, like compliance to pharmacotherapy and psychotherapy with compliance being rated and not proved. This points to strategies that booster the patients' attitudes to achieve fundamentally better health conditions.

Smoking must not be left unaddressed in alcohol treatment due to the fatal effects of smoking on morbidity and mortality in general and in alcoholics in particular (Hurt *et al.*, 1996). Recent investigations came to the conclusion that sobriety is not jeopardized by various smoking cessation strategies that studied different psychological (Bowman and Walsh, 2003;

Hurt and Patten, 2003) or pharmacological approaches, e.g. nicotine replacement (Hughes *et al.*, 2003; Hurt *et al.*, 2005) or naltrexone administration (Krishnan-Sarin *et al.*, 2003; Rohsenow *et al.*, 2003). The timing of smoking cessation within the alcohol recovery process is still on debate (Kalman *et al.*, 2001; Joseph *et al.*, 2004) as well as the treatment modalities of substance-induced and substance-independent mood disorder in alcoholism (Hitsman *et al.*, 2002). It is to hope for the future that more specific substances targeting the molecular basis of this dual addiction more precisely may foster a better treatment outcome these patients urgently need (Tritto *et al.*, 2001; Owens *et al.*, 2003; Bowers *et al.*, 2005; Al-Rejaie and Dar, 2006a,b).

Our observation that addicts who were more severely dependent were less prone to relapse may challenge the validity of the dependence syndrome (Edwards and Gross, 1976). In general, a more severe clinical syndrome should be associated with less favourable treatment outcome. Interestingly, commonly used indicators of alcoholism severity, e.g. number of DSM-III-R-criteria fulfilled, duration of the disease or quantity and frequency of drinking were not related to treatment outcome in our study. Although it is beyond the scope of our initial study goal, our finding raises the question whether additional severity parameters should be developed for better predicting the course of the disease and guidance of individualized treatment approaches.

Finally, in returning to the limitations of our study it has to be noted that recruited patients were not representative for the general population of smoking alcoholics due to a lower percentage of smoking alcoholics in our samples and a possibly higher motivation for recovery of the subjects due to their informed consent to participate in a scientific study. All patients had taken pills (placebo or acamprosate); but both formulations had been balanced in smoking and non-smoking alcoholics. In smokers, we had not differentiated between never-smokers and former smokers. Our conclusion what smoking means for alcohol recovery may be weakened by applied retrospective data analysis that should be validated by a prospective study design also enabling researchers to evaluate the many drop-outs. However, it has to be taken into consideration that patients cannot be randomized to experimental tobacco exposure due to ethical considerations; in so far it might difficult to evaluate smoking independently from the smoker as both variables are intrinsically tied together in alcoholic patients.

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