Withdrawal syndrome and comorbidity in alcohol use disorder: focusing on anxiety

Summary of Ph.D. Thesis

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I. INTRODUCTION

Alcohol use disorder (AUD) and anxiety are highly comorbid and anxiety may appear in the complication of AUD. Different critical treatment points are crucial to examine AUD patients. In the present thesis, AUD patients were investigated in alcohol withdrawal syndrome (AWS) which is one of the most common complication of AUD and during rehabilitation without withdrawal. Scientific literature indicated that AUD patients with comorbid anxiety disorders show more severe AWS. In the early recovery of AUD, anxiety also maintains which is one of the most important indicator of relapse. During the early recovery phase, examination of the further comorbid conditions such as gambling involvement which is one of the most common comorbid behavior addiction in AUD is also vital. It is essential to investigate the anxiety in these critical clinical stages of AUD since it can determine the treatment planning as well as the treatment outcomes. In the present thesis, four studies were conducted where anxiety was examined comprehensively and approached differently among normal population as well as in the complication and comorbidity of AUD during different treatment points. The main goals of the studies comprising the present thesis were the following:

1. To investigate the autonomic response of moderate acute anxiety response induced by laboratory conditions in normal population comprehensively (Study 1).
2. To examine the course of AWS based on the internationally published aggregated Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) total scores using a meta-analysis (Study 2).
3. To explore the anxiety in case of one of the most common complication of AUD, during AWS and without AWS in case of comorbid gambling involvement which is one of the most common comorbid behavior addiction in AUD (Study 3 and 4).
4. To symptomatically examine the appearance of anxiety during AWS (Study 3).
5. To investigate anxiety as temperament variable among AUD patients (Study 4).
6. To investigate anxiety as temperament variable without AWS among AUD patients with comorbid gambling involvement (Study 4).
7. To compare AUD patients with and without comorbid gambling involvement regarding anxiety as temperament variable (Study 4).

II. BACKGROUND

Alcohol use disorder (AUD) is a problematic pattern of alcohol use which leads to clinically significant impairment (American Psychiatric Association, 2013). There is a great variance regarding the course of AUD. AUD could be accompanied by several comorbid states

and numerous complications can develop as consequences of prolonged AUD. Different critical treatment points are essential to examine AUD patients: alcohol withdrawal syndrome (AWS) which is one of the most common complication of AUD and the phase during rehabilitation.

Half of the AUD patients develop AWS after rapid reduction or cessation of alcohol consumption. The main leading symptoms of AWS include autonomic symptoms (e.g. sweating), tremor, nausea and/or vomiting, headache, seizures, perceptual disturbances (auditory, tactile or visual), psychomotor agitation and anxiety (American Psychiatric Association, 2013). The recognition and objectivization of the course and symptoms of AWS are essential in order to prevent the development of more severe complications. In contrast, the phase without AWS symptoms was described a more stable stage. Remission of AUD is influenced by sociodemographic (e.g. sex or age) and alcohol-related variables, level of craving, personality and comorbidity (Dawson et al., 2007; Lopez-Quintero et al., 2011; Mathew et al., 1979; Moos & Moos, 2006; Tucker et al., 2020).

Numerous comorbid conditions are common in AUD. Gambling disorder (GD) is one of the most common comorbid behavioural addictions in AUD (Di Nicola et al., 2015). Previous studies demonstrated that the occurrence of gambling involvement are prevalent in case of AUD and anxiety disorders (el-Guebaly et al., 2006). In addition, AUD is also highly comorbid with anxiety disorders (Boschloo et al., 2011; Grant et al., 2004; Vorspan et al., 2015). Acute anxiety has a comprehensive psycho-physiological response including physiological (e.g. elevated heart rate, gastrointestinal symptoms), psychological (e.g. worry and distress) and specific behavioural (e.g. avoidance) aspects. Several theories are available to describe the complex relationship between anxiety and AUD. Some previous models (e.g. the self-medication hypothesis) show that individuals use alcohol to try to manage their mental state (e.g., anxiety) (Robinson et al., 2009). According to a further theory, patients can develop anxiety due to chronic alcohol consumption (Smith & Randall, 2012). However, it was reported that if other variables (e.g. depression and/or earlier substance use) are taken into account and were controlled in the development of AUD, the early presence of anxiety was no longer a significant predictor (Goodwin et al., 2002).

Anxiety is found in high proportions in the complication and comorbidity of AUD in different clinical stages. Therefore, investigating the relationship between anxiety and AUD is pivotal among AUD patients. Anxiety is a common symptom during the course of AWS, almost 98% of alcohol dependent men had at least one anxiety symptom during drinking or withdrawal (Schuckit et al., 1990). Furthermore, it was demonstrated that AUD patients with co-existing anxiety disorders reported more severe withdrawal symptoms than patients without anxiety

disorders (Johnston et al., 1991). Without AWS symptoms, the symptom of anxiety was also elevated in case of AUD with anxiety disorders (Thevos et al., 1991). However, it was demonstrated that state anxiety was continuously decreased among AUD patients with lifetime anxiety disorders during the first 4 weeks after detoxification (Driessen et al., 2001). In case of comorbidity, the psychological and somatic symptoms were often more severe which suggested that the comorbidity complicated the treatment and the prognosis could be worsen (Pasche, 2012).

Several assessment tools are available for examining the course of AUD and there are some measurement tools which contain anxiety indicators. During AWS, Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar; Sullivan et al., 1989) is recommended by international protocols and guidelines (Hoffman & Weinhouse, 2021; National Institute for Health and Care Excellence (NICE), 2017; Sachdeva et al., 2015). This 10-item tool is based on the patient's answers as well as the clinician's observations. The items include the symptoms of AWS such as nausea and vomiting, tremor, sweating, auditory, visual and tactile disturbances, headache, orientation, agitation and anxiety. Anxiety is defined in this tool by the observation and also asking the patient ("Do you feel nervous?") (Sullivan et al., 1989). Anxiety is evaluated by a 7-point Likert scale. Patients with 0 score were described without anxiety, 1 score indicate a mildly anxious state, 4 scores suggest moderately anxious state, 7 scores imply acute panic state. However, since there is no measurement tool in Hungary to objectify AWS symptoms, it is difficult to measure the symptom of anxiety in Hungary during AWS. Objective measurements for monitoring the course, the severity and the symptoms of AWS are vital therefore introducing CIWA-Ar into Hungarian practice was an urgent task. Therefore, CIWA-Ar was translated and validated by our research group (Lázár et al., 2019).

After the course of withdrawal, anxiety is also measurable during rehabilitation with questionnaires. The Spielberger State-Trait Anxiety Inventory (STAI) includes two parts: state anxiety and trait anxiety. While state anxiety represents the current level of anxiety, trait anxiety shows the disposition for experiencing anxiety (Spielberger et al., 1970). For investigating personality, Temperament and Character Inventory-Revised (TCI-R; Cloninger, 1999) is a suitable tool, which consists of 240 items and examines 4 temperament (Harm Avoidance, Novelty Seeking, Persistence and Reward Dependence) and 3 character dimensions (Self-transcendence, Cooperativeness and Self-directedness). For examining anxiety, Harm Avoidance (HA) temperament dimension is suitable. HA was considered as a heritable bias and it also has an important role in the inhibition or cessation of behaviour (Cloninger et al., 1993). The higher HA temperament factor is characterized by worry, fear of uncertainty and fatigue

(Markett et al., 2016). These behaviors are associated with anxiety (Markett et al., 2016). Furthermore, HA is strongly correlated with high serotonergic activity (Cloninger, 1986) and it provides an ideal basis for exploring the neural background of anxiety (Markett et al., 2016). In the present thesis, HA was considered as anxiety indicator.

In conclusion, investigation of anxiety is crucial since it can determine the treatment planning as well as the treatment outcomes.

III. AIMS AND HYPOTHESES

It has been well documented that the body responds immediately during an anxiety situation (American Psychiatric Association, 2013; Steimer, 2002). Thus, it is essential to explore the biological and psychological implications of anxiety. Anxiety is prominent in case of the co-occurrence of addictive disorders (Boschloo et al., 2011; Grant et al., 2004). Furthermore, AUD is highly comorbid with other behavior addictions especially the prevalence of gambling disorder (GD) in AUD is particularly high. In clinical settings, anxiety could be observed in different critical stages among AUD patients. In the present thesis, AUD patients were examined in alcohol withdrawal syndrome (AWS) and during rehabilitation by different ways. Based on these and the theoretical background detailed above, the present thesis was based on four empirical studies with the following aims:

Aim 1: It is visible that the body has a comprehensive response on the anxiety (American Psychiatric Association, 2013; Steimer, 2002). Therefore, our first aim was to investigate the autonomic response of acute anxiety in normal population comprehensively. On this notion, (*i*) it was hypothesised that the myoelectric waves of the stomach, small intestine, large intestine as well as the heart frequency, body temperature show higher values and the galvanic skin response results in lower levels during anxiety-provoking situation among normal population (Study 1).

Aim 2: In the clinical sample, AUD was investigated in two steps: during AWS and early recovery phase without AWS symptoms. For this purpose, the course of AWS was evaluated by a meta-analysis with aggregated to Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) total scores. Hence, the change of the CIWA-Ar scores was examined therefore the ecological validity of the tool was also tested. On this notion, it was hypothesised that (*ii*) CIWA-Ar is an ecological valid tool and the course of AWS can be followed using CIWA-Ar resulting in decreasing values (Study 2). Since CIWA-Ar was not a standardized tool in Hungary therefore it has been validated by our research group (Lázár et al., 2019). This provides the possibility for objectifying the symptoms of AWS. Consequently, the

symptoms of AWS were examined focusing on the anxiety based on a symptomatic examination (Study 3). It was hypothesised that (*iii*) anxiety follows the course of AWS based on the CIWA-Ar scores resulting continuously decreasing values during AWS (Study 3) and (*iv*) anxiety is one of the most substantial symptom in the acute phase of AUD, during AWS (Study 3).

Aim 3: In the early recovery phase, elevated anxiety may maintain during abstinence even without AWS symptoms. During rehabilitation, the personality structure of the patients becomes measurable. We used a frequently utilized self-report personality questionnaire, the Temperament and Character Inventory-Revised (TCI-R; Cloninger, 1999), where Harm Avoidance temperament scale indicated anxiety. Although one of the most common comorbid behavioral addiction in AUD is GD, to our best knowledge, literature comparing AUD patients with and without GD symptoms based on personality structure is scarce. For this purpose, the anxiety of AUD patients with and without GD symptoms was examined compared to a normative sample. Then, the AUD patients were compared to AUD patients with GD symptoms regarding anxiety as temperament variable. On this notion, it was hypothesised that (*v*) the Harm Avoidance temperament factor is elevated among AUD patients and AUD patients comorbid with GD symptoms, compared to the normative sample (Study 4). Furthermore, (*vi*) it was theorized that Harm Avoidance temperament factor shows even higher values in AUD patients comorbid with GD symptoms (Study 4).

IV. METHODS

1. Study 1: Measuring state anxiety among normal population

In Study 1, the autonomic effects of the stress-induced anxiety were examined comprehensively on normal population. Twenty-one healthy volunteers were recruited who participated in the Trier Social Stress Test (TSST; Kirschbaum et al., 1989) which is a situational task for inducing moderate acute stress in laboratory conditions. During the TSST protocol, participants evaluated their anxiety level with the self-report Spielberger State Anxiety Inventory (STAI) questionnaire three times (resting phase, stress induction and recovery phase). Furthermore, physiological parameters were also examined throughout the TSST protocol with a Holter device that measured 6 parameters simultaneously and non-invasively (the myoelectric waves of stomach, large intestine and small intestine, heart frequency, body temperature and galvanic skins response). The magnitude and the changes of the electrical activity of the gastrointestinal parameters were defined by power spectrum density

(PsD_{max}). STAI scores were assessed by repeated-measures ANOVA and Wilkoxon signed-rank tests were used to analyse physiological parameters.

2. Study 2: Examining the course of AWS and the ecological validity of CIWA-Ar

In Study 2, the course of AWS was examined with the aggregated Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar; Sullivan et al., 1989) total scores using meta-analysis that allowed the analysis of the ecological validity of the measure. Empirical publications were included in case they reported sample size, the means and standard deviations of the CIWA-Ar in patients with clinical diagnosis of AWS and used evidence-based treatments (benzodiazepine [BZD] and non-benzodiazepine [nBZD] groups). The unit of data analysis was the comparison of the cumulative mean CIWA-Ar scores of two phases of the course of AWS treatment: day 1-3 and day 4-9. Four scientific databases were searched with the search term "ciwa" which yielded 1054 results. After applying all exclusion criteria, 11 empirical study met the criteria to be included for quantitative analysis of aggregated empirical data. All analyses were made with using the Comprehensive Meta-Analysis Software 3.0 (*Comprehensive Meta-Analysis Software (CMA)*, 2020) using random-effects model. Existence of publication bias and calculation of effect sizes were also conducted. Moderator analysis was calculated for examining the moderator effect of male proportion and age on the change in CIWA-Ar total score.

3. Study 3: Exploring the potential role of anxiety in the course of alcohol withdrawal syndrome

In the Study 3, the potential key role of anxiety was examined in the course of AWS which is one of the most common complication of AUD therefore symptomatic analysis of AWS were performed. Firstly, the CIWA-Ar was translated and validated involving 30 treatment-seeking AUD patients diagnosed with alcohol withdrawal syndrome (Lázár et al., 2019). CIWA-Ar was applied 6 times therefore the tool was administered every 2 days for 10 days in a structured way via interviews and observations conducted by a trained clinician. Following the validation, the potential role of anxiety was examined based on symptomatic analysis. Firstly, the means and standard deviations of CIWA-Ar item scores were evaluated focusing on the Anxiety item. Then, the changes of the items were further analysed with Friedman's ANOVA during the 6 measurements. Furthermore, psychometric measurements were also tested (Cronbach alpha and item-total correlations).

4. Study 4: Anxiety in alcohol use disorder and comorbid gambling involvement

In the Study 4, the comorbidity of AUD and gambling involvement was examined during rehabilitation, with a specific focus on anxiety as a temperament variable. A comprehensive assessment was completed including 104 AUD patients without clinically significant intellectual disability (IQ 70+) measured with the Wechsler Adult Intelligence Scale, 4th Edition (Wechsler, 2008). Alcohol Use Disorders Identification Test (AUDIT) was used to measure the severity of AUD (Allen et al., 1997; Gerevich et al., 2006) and South Oaks Gambling Scale (SOGS) was applied for evaluating the gambling involvement (Gyollai et al., 2013; Lesieur & Blume, 1987). Temperament and Character Inventory-Revised (TCI-R) was used for measuring the personality dimensions and anxiety was evaluated as the temperament factor of Harm Avoidance (Cloninger, 1999; Rózsa et al., 2004, 2005). Patients were classified as AUD and AUD+GD in the presence of comorbid gambling involvement using two-step clustering algorithm. Firstly, one-sample t-tests were used to contrast the T-scores of the Hungarian normative sample (T-Score: 50, SD = 10) and the AUD and AUD+GD groups. Then, one-way analysis of covariance (ANCOVA) was conducted to compare the T-scores of the AUD and AUD+GD groups with the AUDIT score as a covariate. Finally, Hedge's g was analysed for determining the effect sizes of the groups.

V. RESULTS

This present thesis summary reports the most relevant statistical analyses of the study.

1. Study 1: The autonomic response of anxiety among healthy volunteers

In the study 1, 7 men and 9 women participated (N = 16) and the mean age of the subjects was 23.56 years (SD = 1.315). During the stress-induced anxiety situation, the STAI scores showed significant changes in the three phases ($F(1.46, 21.91) = 18.18$; $p < 0.001$). The STAI total score evaluated after the stress induction was significantly higher than the total STAI total score measured after the resting phase ($p < 0.001$) and the recovery phase ($p < 0.001$).

Simultaneously with self-report anxiety level, physiological parameters in the resting phase and stress induction phase were compared. During stress induction, while PsD_{max} values of the stomach ($Z = -1.977$; $p = 0.048$) and the small intestine ($Z = -2.045$; $p = 0.041$) were significantly higher, PsD_{max} values of the large intestine did not show significant changes ($Z = -0.659$; $p = 0.51$). Furthermore, heart frequency ($Z = -3.464$; $p < 0.001$) and body temperature showed significantly higher values ($Z = -2.628$; $p = 0.009$) and galvanic skin response was significantly reduced ($Z = 2.919$; $p = 0.004$) compared to resting phase. These findings indicated

that an acute autonomic response appeared simultaneously as the occurrence of an elevated anxiety in normal population.

2. Study 2: Examining the course of AWS and the ecological validity of CIWA-Ar

In the final analysis, nine studies were analysed which yielded 10 comparison pairs. A total of 423 patients were examined in this analysis. Publication bias was not explored in the groups according to the Begg and Mazumdar tests (BZD [Kendall's tau = –0.5, $p = 0.221$], nBZD [Kendall's tau = –0.5, $p = 0.22$]) and the Egger's test for intercept also indicated symmetry (Intercept = –4.774, $p = 0.177$). Due to the methodological differences in the studies, a significant heterogeneity was expected and significant heterogeneity was found (Q_w (9) = 32.946, $p < 0.001$; $I^2 = 72.68$).

Based on the random effects model, a significant decrease between the two measurement intervals was showed, which meant a decrease of the CIWA-Ar scores during the course of AWS (d = –0.945; CI: $–1.140 < \delta < –0.750$; $p < 0.001$). Finally, a moderator analysis was performed, however, neither the proportion of men (coefficient: 0.02; p = 0.48) nor age (coefficient: 0.10; p = 0.216) had a significant moderating effect on the change in CIWA-Ar total score.

3. Study 3: Exploring the potential role of anxiety in the course of alcohol withdrawal syndrome

In the Study 3, 24 male and 6 women patients were participated (N = 30) and the mean age of the enrolled participants was 45.7 years (SD = 9.5). Considering the course of the AWS, the Anxiety item decreased significantly during the six measurements based on the Friedman's ANOVA calculations ($p < 0.001$). The further 9 items were also decreased significantly during the six measurements ($p < 0.001$) except for the Orientation item ($p = 0.152$). According to the means and standard deviations of the six measurements, anxiety appeared as a central symptom in AWS. In this sense, Anxiety item showed the second highest mean value until day 6^{th}, then had an average score approximately equal to Tremor on day 8^{th}, and then, although low on day 10 but it had the highest mean of symptoms. Consequently, the decrease in the score of Anxiety item was slow and the symptom of anxiety was more stable in the course of AWS.

CIWA-Ar is a valid and reliable tool specifically at the beginning of the withdrawal phase, during the first three measurements (Lázár et al., 2019). Therefore, only these measurements were evaluated in the following psychometric analysis of the Anxiety item. The item-total correlation analysis showed that the Anxiety item had a strong correlation coefficient especially during the first measurement (r = 0.793). According to the Cronbach's alpha values,

the internal consistency was decreased if the Anxiety item was deleted. In case of the first measurement time, the Cronbach alpha was lowered from 0.732 to 0.644. These decrease was further observed regarding the second and third measurement times, respectively. It can be concluded that anxiety plays a decisive role in the AWS, and without the Anxiety item, the reliability of the tool decreases.

4. Study 4: Anxiety in alcohol use disorder and comorbid gambling involvement

Firstly, AUD and AUD+GD groups were compared to the normative sample regarding HA which was considered as anxiety indicator. Based on the results, the AUD ($t = 3.073$, $p = 0.003$, Hedges' $g = 0.384$) and the AUD+GD group ($t = 4.319$, $p < 0.001$, Hedges' $g = 0.756$) scored higher on HA than the Hungarian normative sample scores. In case of group comparisons of the AUD and AUD+GD groups, controlled for the AUDIT scores, the HA indicating anxiety was significantly higher in the AUD+GD group ($F(82, 14) = 6.683$, $p < 0.001$, Hedges' $g = 0.409$) than in the AUD group.

VI. DISCUSSION

Alcohol use disorder and anxiety (AUD) have a strong relationship (Boschloo et al., 2011; Grant et al., 2004; Vorspan et al., 2015). The present thesis aimed to focus on the comprehensive assessment of anxiety among normal population as well as in the complication and comorbidity of AUD during different treatment points. Anxiety was approached by different way. In the Study 1, the acute autonomic and comprehensive effects of anxiety were demonstrated in normal population which resulted in a more physiologically elevated condition during anxiety-provoking situation. In a clinical sample, AUD was investigated in different clinical stages regarding anxiety therefore alcohol withdrawal syndrome (AWS) and early recovery phase were examined, respectively. It was reported that the course of AWS can be followed appropriately (Study 2) and the symptoms of AWS became measurable by the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) which was validated by our research group. It was also demonstrated that anxiety appeared substantially in the whole clinical process of AUD which was examined by the present studies: it occurred in the acute phase (AWS) as a central symptom (Study 3) and it was also markedly observed in the patient's personality structure in the next phase of recovery (rehabilitation). Furthermore, if AUD was also associated with a comorbid state (gambling involvement), anxiety was described by higher values (Study 4).

The first hypothesis (*i*) that the body responds comprehensively and immediately to the anxiety situation that appears in the body's autonomic response, was confirmed. Based on the results of the self-reported STAI questionnaire, it was demonstrated that anxiety level was elevated during the stress induction of Trier Social Stress Test (TSST; Kirschbaum et al., 1989). This increase in anxiety level also appeared parallel with physiological reactions (myoelectric waves of stomach and small intestine, heart rate, body temperature and galvanic skin response). The current results emphasized that a comprehensive autonomic response was demonstrated in a stress-induced anxiety situation and specifically the gut-brain axis (GBA) has an essential role. GBA allows bidirectional communication between the central nervous system and the gastrointestinal tract through neural and humoral pathways (De Palma et al., 2014). These alternations of the parameters contribute to understand the anxiety-provoking mechanisms. It is proposed that detecting the physiological responses of anxiety is essential especially among patients with various psychiatric disorders. For instance, stress and anxiety may participate in the development of affective and alcohol use disorder and play a crucial role in the course of these disorders (Becker, 2012; Goodwin et al., 2002) therefore examining anxiety level is a key issue regarding psychiatric disorders.

The second hypothesis (*ii*) was confirmed that Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) is an ecological valid tool and the course of AWS can be followed using CIWA-Ar. According to the results of the meta-analysis, the aggregated CIWA-Ar total scores followed the course of AWS which suggested that our findings showed a significant decrease of CIWA-Ar total scores during the course of AWS. These results indicated that CIWA-Ar appropriately monitored the course of AWS which showed the ecological validity of this measure. Based on the results, CIWA-Ar was suitable for detailed symptomatic examination of AWS. According to the symptomatic analysis of CIWA-Ar, the third hypothesis (*iii*) was confirmed that anxiety appeared and followed the course of AWS. Furthermore, the fourth hypothesis (*iv*) was also confirmed since anxiety was one of the most substantial symptom during AWS. The value of anxiety was particularly high since it was the second highest score of the CIWA-items at the beginning of AWS. Furthermore, anxiety reduced throughout the course of AWS and its decrease was stable. Moreover, if the Anxiety item was not considered in case of analysing the internal consistency of CIWA-Ar, the reliability of the measurement also weakened.

The fifth hypothesis (*v*) was confirmed that the Harm Avoidance (HA) temperament factor was elevated among AUD patients with and without GD symptoms compared to normative sample. In general, in the background of the anxiety indicator assessed by high HA

can be explained by the use of alcohol as a self-medication opportunity to help reduce and relieve the negative emotions of the subject (Robinson et al., 2009). Similarly, it is conceivable that persons often gamble because they would like to avoid negative emotions therefore this will be a self-regulation as well as a coping mechanism for the individual (Ledgerwood & Petry, 2010).

The sixth hypothesis (*vi*) was confirmed that Harm Avoidance temperament factor showed even higher levels values in AUD patients with GD symptoms compared to AUD patients. Based on the fourth and fifth hypotheses, it was demonstrated that anxiety indicated by HA appeared markedly in the AUD group and AUD+GD group compared to the normative sample, and if there is also comorbid GD involvement in AUD patients, the level of anxiety is even higher. These results showed a new perspective which is suitable to demonstrate the personality constellations which are focusing on the maladaptive effect among AUD patients with GD involvement. Thus, anxiety also occurs, which can be explored in another form. Individualized treatment is essential which emphasizes the exploration of the comorbid anxiety symptoms during rehabilitation. These findings are suitable to develop a multimodal treatment approach, which specifically focus on the role of personality structure to reduce the development of relapse and have beneficial effects on treatment outcomes (Crescentini et al., 2015; Ledgerwood & Petry, 2006).

Our results highlighted the importance of examining anxiety comprehensively in case of AUD, as anxiety accompanies the clinical appearance of the complication and comorbidity of AUD. We propose a comprehensive assessment possibility to determine anxiety which includes a non-invasive physiological measurement, clinician's observations as well as self-report questionnaires. This framework highlights the complex understanding of anxiety level and provides new perspective on the prevention and treatment. Future research would also consider investigating treatment outcomes (e.g. relapse) and the role of craving, which has a strong association with anxiety and also has an impact on the potential relapse (Sinha et al., 2011). In conclusion, comorbid conditions associated with AUD are difficult to treat and untreated anxiety can affect quality of life and can contribute to relapse. Therefore, the development of adequate therapy can be considered as priority issue and targeted prevention programs are needed that specifically focuses on anxiety as a comorbid condition.

VII. SUMMARY OF THE RESULTS AND CONCLUSIONS

In the present thesis, the role of anxiety was emphasized in the clinical course of alcohol use disorder (AUD). Therefore, anxiety was examined comprehensively and defined differently

in normal and clinical sample in case of the complication and comorbidity of AUD. Four studies were conducted and several measurement tools were assigned due to the different characteristics of the participants. According to the results of the studies, novel findings of the present thesis are the following:

1. In normal population, an acute and autonomic response appeared simultaneously with the occurrence of an elevated anxiety, indicating the global and comprehensive effect of the human body on the anxiety.
2. An increased response of the stomach and small intestine appeared during an anxiety-provoked situation which supports the importance of subsequent examination of the gut-brain axis.
3. The ecological validity of the CIWA-Ar was confirmed for the first time based on aggregated CIWA-Ar scores.
4. Anxiety occurred as one of the central symptoms of alcohol withdrawal syndrome based on the symptomatic analyses, i.e. anxiety can be interpreted as an indicator of withdrawal therefore monitoring anxiety is especially important.
5. Anxiety also maintains without alcohol withdrawal syndrome and it was revealed in another form as temperament variable.
6. Anxiety is even more pronounced among AUD patients in case of symptoms of comorbid gambling involvement, which may indicate that patients with comorbid conditions are more vulnerable therefore their exposure to relapse may be even higher.

Our results highlight the importance of the comprehensive investigation of anxiety in AUD. Since the co-occurrence of AUD and anxiety causes a more severe prognosis therefore it is important to explore the comorbidity of these disorders. Treating AUD with comorbid conditions is difficult, and untreated anxiety can contribute to relapse and affect quality of life. Therefore, the treatment efficacy can increase if anxiety in AUD is taking into account and it is beneficial to use personalized therapy focusing on the anxiety level. Further research is needed in case of alcohol withdrawal syndrome to comprehensively examine anxiety and further manifestations of anxiety after rehabilitation.

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