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

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I. ABBREVIATIONS

AUD: alcohol use disorder

AUDIT: Alcohol Use Disorders Identification Test

AWS: alcohol withdrawal syndrome

BMI: body mass index

BZD: benzodiazepine

BT: body temperature

CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol, Revised

CO: Cooperativeness

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

GAD: generalized anxiety disorder

GABA: γ-aminobutyric acid

GBA: gut-brain axis

GD: gambling disorder

GI: gastrointestinal

GSI: Global Severity Index

GSR: galvanic skin response

HA: Harm Avoidance

HPA axis: hypothalamic-pituitary-adrenal axis

HR: heart rate

nBZD: non-benzodiazepine

NS: Novelty Seeking

PS: Persistence

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RD: Reward Dependence

SAM-system: sympathetic-adrenal-medullary system

SCL-R-90: Symptom Checklist Revised

SD: Self-directedness

ST: Self-transcendence

STAI: Spielberger State Anxiety Inventory

TSST: Trier Social Stress Test

II. SCOPE AND AIMS OF THE PRESENT THESIS

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: alcohol withdrawal syndrome (AWS) which is one of the most common complication of AUD and during rehabilitation.

Scientific literature indicated that AUD patients with comorbid anxiety disorders show more severe alcohol withdrawal syndrome. In the early recovery, anxiety also maintains which is one of the most important indicator of relapse. Furthermore, patients with comorbid AUD and anxiety disorders have an increased risk for developing gambling disorder which is one of the most common comorbid behavioral addiction in AUD. Thus, it is essential to examine the anxiety in these critical clinical stages of AUD such as AWS and early recovery phase. During the early recovery phase, examination of the further comorbid conditions such as gambling involvement is also vital. Investigation of anxiety is crucial since it can determine the treatment planning as well as the treatment outcomes.

In the present thesis, four studies were conducted where the appearance of anxiety was examined comprehensively and defined differently among normal population as well as in the complication and comorbidity of AUD during different treatment points. For this purpose, the present thesis aimed to address three main aims. Our first aim was a comprehensive investigation of anxiety in a normal population, the second was to explore the anxiety level during alcohol withdrawal syndrome with a tool validated by our research group and the third major aim was to examine anxiety among treatment-seeking AUD patients and comorbid gambling involvement.

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 Study 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 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).

III. BACKGROUND

1. THE CLNICAL COURSE OF ALCOHOL USE DISORDER REGARDING COMPLICATIONS AND COMORBIDITIES

Alcohol use disorder (AUD) is defined as a problematic pattern of alcohol use which leads to clinically significant impairment. Several risk factors were identified for developing AUD (e.g. biological, psychological and/or environmental variables (American Psychiatric Association, 2013). The prevalence of alcohol use disorder is dominant worldwide and epidemiological studies demonstrated that AUD was the most prevalent substance use disorder globally ('The Global Burden of Disease Attributable to Alcohol and Drug Use in 195 Countries and Territories, 1990–2016', 2018). Similarly, studies also emphasized the high prevalence of the alcohol consumption and alcohol use disorder in Hungary (Horvat et al., 2018; Paksi et al., 2011; World Health Organization, 2018).

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 without AWS symptoms.

Several complications can develop as a result of prolonged alcohol use disorder (Maciel, 2004) including the acute withdrawal and delayed consequences such as chronic cognitive disorders (e.g. Wernicke encephalopathy or Korsakoff-syndrome) (Noble & Weimer, 2014). Alcohol withdrawal syndrome is one of the most common complication of AUD which occurs among half of the AUD patients (American Psychiatric Association, 2013). The prevalence of the symptoms of AWS is particularly high among AUD patients admitted for detoxification and rehabilitation (up to 86%) (Caetano et al., 1998). AWS can develop after rapid reduction or cessation of alcohol (American Psychiatric Association, 2013) and the first symptoms appears within 6-24 hours (Hall & Zador, 1997). The intensity and severity of AWS are different during the course of AWS (Maciel, 2004). The authors agreed that the clinical description of AWS divides the first 6-72 hours according to the symptom severity and the chance of the appearance

of severe complications from the complete course of AWS, which may take 2 weeks (Haber et al., 2009). 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). AWS may lead to severe consequences such as withdrawal seizures and delirium tremens (McKeon et al., 2008). Delirium tremens represents the most fatal and prolonged form of alcohol withdrawal which includes autonomic disarray, hallucinations and disorientations. Since delirium tremens is characterized by high degree of mortality therefore it is vital to monitor the patients at risk and to prevent its development (Noble & Weimer, 2014). It can be seen that AWS occurs commonly among AUD patients therefore the recognition and objectivization of the course and symptoms of AWS are essential in order to prevent the development of more severe complications.

Furthermore, the phase without AWS symptoms is described a more stable stage. In general, recovery is defined as a „process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential" (SAMHSA, 2012). Several recovery pathway are available from recovering without treatment through peer resources to professional treatment. There are sex differences regarding help-seeking and men have higher help-seeking rates compared to women (Tucker et al., 2020). During recovery phase, craving is an essential factor and it was described by a strong predictive impact on potential relapse. In general, craving is a core feature in AUD. It refers to the urge or desire to relive the previously experienced psychoactive substance (UNDCP & WHO, 1992) and it can maintain for months after the last intake (Mathew et al., 1979). Remission of AUD is influenced by sociodemographic features such as sex or age, alcohol-related variables (e.g. the length of the AUD), personality and comorbidity (Dawson et al., 2007; Lopez-Quintero et al., 2011; Moos & Moos, 2006; Tucker et al., 2020).

AUD is highly comorbid with several somatic (e.g. cerebrovascular, pulmonary and metabolic disorders) and psychiatric disorders (e.g. personality disorders, internalizing disorders, schizophrenia, mood disorders and other addictive disorders) (Abebe et al., 2021; Castillo-Carniglia et al., 2019). The co-occurrence of AUD and behavior addictions (e.g. compulsive buying, internet addiction, exercise addiction and sexual addiction) are high (Di Nicola et al., 2015), especially gambling disorder (GD) shows a particularly elevated comorbidity with AUD. AUD and GD were described by shared aetiology, neurobiological characteristics (Grant et al., 2006), psychiatric comorbidity (Petry et al., 2005), vulnerability factors (Slutske et al., 2000) and psychological risk factors (Aluja et al., 2019). Gambling

disorder is a persistent, recurrent and maladaptive gambling behaviour which changes the personal, family or professional life of the individual (American Psychiatric Association, 2013). According to the DSM-5, it is visible that the diagnostic categories of AUD and GD overlap. The most significant similarities in clinical symptoms of these disorder are tolerance, craving, withdrawal syndrome, adverse consequences (existential/ work-related disadvantages), high relapse, low treatment participation, loss of control, higher impulsivity and disfunctions in disinhibitory control (Andó et al., 2016). Lifetime prevalence of excessive gambling such as problem and pathological gambling varies between 1.1-6.5% according to a population-based study from Europe. In Hungary, the prevalence of problem gambling was 1.9% and the rate of pathological gambling was 1.4%. The frequency of alcohol drinking was associated with the severity of gambling behavior: while those who drank alcohol once a week in the previous year, 1.4% showed problem gambling and 0.9% had pathological gambling, those who drank more than once a week showed 4.8% and 4.5%, respectively (Kun et al., 2012). In addition, AUD is highly comorbid with anxiety disorders (Boschloo et al., 2011; Grant et al., 2004; Vorspan et al., 2015).

2. THE APPEARANCE OF ANXIETY IN ALCOHOL USE DISORDER

2.1. The definition of anxiety and the prevalence of anxiety in alcohol use disorder

Anxiety is a mental health concern worldwide and shows comorbidity with a numerous psychiatric disorders therefore recognizing and treating comorbid conditions of anxiety is essential. According to the concept of anxiety based on DSM-5, anxiety is “the apprehensive anticipation of future danger or misfortune accompanied by a feeling of worry, distress, and/or somatic symptoms of tension” (American Psychiatric Association, 2013, pp. 818).

The comorbid association between anxiety and addictive disorders has already been confirmed by several previous studies (e.g. nicotine dependence, cannabis use disorder, opiate dependence, internet disorder, gambling disorder and alcohol use disorder etc.) (Ho et al., 2014; Lorains et al., 2011; Vorspan et al., 2015). Previous studies emphasized a particularly strong relationship between anxiety and alcohol use disorders (Boschloo et al., 2011; Grant etal., 2004; Vorspan et al., 2015). According to the literature, the co-occurrence of alcohol use disorder and anxiety disorder was described by high prevalence. The co-occurrence of these disorders was 23.45% in the United States (Grant et al., 2004). However, this association is bidirectional, anxiety disorders can lead to alcohol use disorders and vice versa (Kushner et al., 1999). For instance, one-quarter to one-half of the patients with anxiety disorders reported a lifetime history of an alcohol or substance use disorder (Kaufman & Charney, 2000). In addition,

patients with AUD had three times more likely to have an anxiety disorder (Burns & Teesson, 2002). Regarding anxiety disorders, especially social anxiety disorder has a high degree of comorbidity with AUD; the lifetime prevalence of social anxiety disorder was 2.4% in AUD (Schneier et al., 2010). The high co-occurrence of AUD and anxiety is visible therefore it is vital to explore the manifestation of anxiety in AUD since the psychological and somatic effects were often more severe in case of comorbidity (Pasche, 2012).

2.2. The psycho-physiological response of anxiety

Acute anxiety has a comprehensive multidimensional psycho-physiological response which includes complex physiological, psychological and specific behavioural aspects. Although anxiety could be a natural adaptive reaction, a pathological state may develop therefore coping with the challenges and/or stressful events can be difficult (Steimer, 2002). During experiencing acute anxiety, immediate and comprehensive consequences of the autonomic nervous system appear which are the most common perceived response (Steimer, 2002). Cardiovascular (e.g. tachycardia, pain in the chest and arrhythmia), respiratory (e.g. breathlessness and choking sensation), gastrointestinal (e.g. nausea and diarrhea), urinary, neurological (e.g. vertigo and trembling) and dermatological symptoms (e.g. hyperhidrosis) may occur during anxiety response (Perrotta, 2019). Based on the DSM-5, common psychological effects of anxiety are worry, distress and feelings of tension (American Psychiatric Association, 2013).

In case of the psycho-physiological responses of anxiety, it is crucial to highlight the relationship between anxiety and stress response. Stress is a non-specific response of the body to any kind of encumbrance and its trigger factors are called stressors (Selye, 1973). The physiological response of the stressors is a complex phenomenon and anxiety can considered as part of a maladaptive psychological response to stress (Friedman et al., 1992; Liu et al., 2017). While the hypothalamic-pituitary-adrenal (HPA) axis is responsible for the long-term response in chronic stress (Selye, 1950, 1984), sympathetic-adrenal-medullary (SAM) system is activated during acute stress. It was documented that the increase of the heart frequency and body temperature or reduced galvanic skin response are common responses to acute stress induction (Civitello et al., 2014; Kirschbaum et al., 1989; Marazziti et al., 1992). Furthermore, previous studies demonstrated that anxiety and stress response have a substantial impact on the gastrointestinal area which is measurable non-invasively with the electrical activity of the GI smooth muscles (Homma, 2005; Riezzo et al., 1996).

In conclusion, these studies highlighted that anxiety has multifaceted effects which was examined from many aspects in the scientific literature. The further accent of these effects is particularly important because the chronic presence of anxiety can lead to the development of various clinical disorders.

2.3. The background and the significance of alcohol use disorder and anxiety

The relationship between anxiety and AUD was explained by several models which investigated these associations from several perspectives. Firstly, it is important to mention some earlier theories, namely the stress-reducing effect of alcohol (Sher & Levenson, 1982) or the tension reduction hypothesis and the self-medication hypothesis (Robinson et al., 2009). Based on these theories, alcohol consumption acts as negative reinforcements (Pasche, 2012) i.e. individuals will tend to avoid behaviours and environments which induce this negative state (De Witte et al., 2003). Drinking alcohol may suppress and prevent the appearance of the physiological and mood changes. Consequently, alcohol intake was often perceived as advantageous which provided substantial reinforcement therefore the individual will seek environments and develop behaviours aiming drinking alcohol (De Witte et al., 2003). However, several articles suggested the elevated physiological (e.g. heart frequency) (Cofresí et al., 2020) and subjective feelings of anxiety during alcohol intake (Logue et al., 1978). Considering the self-medication hypothesis which had received the most attention in the literature (Smith & Randall, 2012), drinking to cope could be described as a potential marker for developing AUD (Anker & Kushner, 2019; Pasche, 2012).

In addition, substance-induced anxiety model is also important which emphasized that anxiety develops as a consequence of heavy and chronic alcohol drinking. This model specifically highlighted that patients develop anxiety due to chronic alcohol consumption. Prolonged alcohol use disorder causes overall γ-aminobutyric acid (GABA) deficiency which can offset the effects of acute alcohol intake and can induce anxiety (Smith & Randall, 2012). The recurrence of withdrawal can cause a progressive neural adaptation (i.e. kindling) and this results in an elevated susceptibility to anxiety and if the patients reduce alcohol drinking the stress-induced negative affect will be exacerbated (Breese et al., 2005).

However, recent studies suggest no direct causal relationship between anxiety and AUD therefore their joint presence was described as a third variable. 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). This study led to the common-factor model which indicates

that common factors of the co-occurrence can be anxiety sensitivity and genetic factors (Smith & Randall, 2012). Considering genetic factors, investigations suggested that AUD and anxiety may be genetically associated (Schuckit, 1994) which propose a genetic overlap between substance use disorders and anxiety disorders such as generalized anxiety disorders (Kendler et al., 2003).

In conclusion, several theories are available to describe the complex relationship between anxiety and AUD therefore it is particularly important to gain a better understanding of the co-occurrence of these disorders.

3. ANXIETY IN WITHDRAWAL SYNDROME AND GAMBLING COMORBIDITY IN ALCOHOL USE DISORDER

Anxiety is found in high proportions in the complication and comorbidity of alcohol use disorder in different clinical stages. Therefore, investigating the relationship between anxiety and alcohol use disorder 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 in the course of AWS than patients without anxiety disorders. This can explained by the common neurochemical basis for these conditions (Johnston et al., 1991). Similarly, the findings of Thevos et al. (1991) underscore the more severe symptoms during AWS with anxiety disorders. These results suggested that patients should be carefully evaluated for potential psychiatric symptoms, especially for anxiety which may cause different prognosis and unique treatment needs during AWS (Schuckit & Hesselbrock, 2004). Therefore, the symptomatic exploration of anxiety is essential during the course of AWS.

During rehabilitation, 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 (Driessen et al., 2001). Accordingly, the severity of psychopathology was also declined 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). Examining anxiety during abstinence is important since anxiety is one of the most important indicator of relapse (Kushner et al., 2005). In case of the co-occurrence of AUD and anxiety disorder, more than twice as

many patients relapsed within 4 months after treatment (Kushner et al., 2005). Moreover, the likelihood of recovery was lowered and the likelihood of the recurrence was increased in case of comorbidity (Bruce et al., 2005). Based on the prospective study of Bruce et al. (2005), the presence of a comorbid alcohol or other substance use disorder decreased the chance of recovery from generalized anxiety disorder by nearly fivefold and the recurrence of generalized anxiety disorder was increased by more than threefold. It is visible that the co-occurrence of anxiety and AUD has a substantial impact on the treatment outcomes during withdrawal and rehabilitation. Furthermore, AUD patients with comorbid anxiety disorders reported lower rate of abstinence than without comorbidity and relapsers demonstrated more trait anxiety than abstainers (Driessen et al., 2001).

Previous studies demonstrated that the occurrence of gambling involvement is common in case of the AUD and anxiety disorders, respectively. As detailed above, gambling disorder is one of the most common comorbid behavioural addictions in AUD (Di Nicola et al., 2015). Furthermore, anxiety also plays an essential role in the development of gambling (Coman et al., 1997). If these two phenomena occur together, patients are five times more likely to develop severe gambling than individuals without concurrent diagnosis or without psychiatric disorders (el-Guebaly et al., 2006). Thus, the impact of AUD and anxiety can be identified on gambling behaviour, however, there is a lack of studies which compares AUD patients and AUD patients with GD symptoms based on the anxiety level.

These results revealed that anxiety and AUD often appear together and special attention should be paid to the exploration of anxiety in the complication and comorbidity of AUD. These studies also demonstrated that AUD with comorbid anxiety has more severe clinical characteristics and symptom severity in case of comorbidity. The findings indicated that a more severe anxiety may have a long-term consequences. In addition, it has a significant impact on the treatment considerations and planning of the adequate treatment (Johnston et al., 1991). These results suggested that if an anxiety disorder maintains alcohol use disorder, effective treatment for anxiety should reduce alcohol consumption and also reduce the likelihood of relapse after treatment (Anker & Kushner, 2019).

4. MEASURING ANXIETY IN ALCOHOL USE DISORDER IN DIFFERENT STAGES

It can be seen that anxiety appears in AUD. However, no comprehensive study has yet been conducted to summarize the measurement possibilities of anxiety in different stages of the treatment of AUD. Therefore, these several measurement tools were detailed in the Table 1

which lists the assessment tools containing anxiety indicators during the course of AWS and without withdrawal.

Table 1: List and brief description of assessment tools containing anxiety indicators in different stages of the treatment of AUD

Name of assessment tool	Description
Clinical Institute Withdrawal Assessment of Alcohol (CIWA-A)[1] (Shaw et al., 1981)	A validated 15-item scale which evaluates the AWS symptoms by the clinicians.
Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) [1] (Sullivan et al., 1989)	A 10-item tool scale based on the patient's answers as well as the clinician's observations.
Visual analogue scale of the patient's global feelings/symptoms[1] (Björkqvist et al., 1976)	The clinician evaluates the global AWS symptoms on a 10-cm "thermometer" scale where the left end of the scale represents a condition that could not be worse and the right end means the best possible condition.
Evaluating the symptoms with 3 or 5-point scale[1] (Agricola et al., 1982; Flygenring et al., 1984)	The clinician evaluates the AWS symptoms on a 3 or 5-point scale.
Abstinence Symptom Evaluation (ASE)[1] (Knott et al., 1981)	The clinician evaluates the AWS symptoms on a 3-point scale.
Modified Selective Severity Assessment (MSSA)[1] (Benzer, 1990)	A nurse evaluates the AWS symptoms on a 10-item scale. Anxiety was examined in the perspective of agitation.
Alcohol-Withdrawal Scale (AWS)[1] (Wetterling et al., 1997)	A nurse evaluates the AWS symptoms on a 11-item scale.
Alcohol Withdrawal Symptoms Checklist (AWSC)[1] (Pittman et al., 2007)	A 14-item instrument for rating the symptoms of AWS on a 4-point scale. The patients are asked to evaluate their symptoms within the last day.
Mainz Alcohol Withdrawal Scale (MAWS)[1] (Banger et al., 1992)	A clinically experienced resident evaluates the symptoms of AWS with an 8-item tool on a 0-3 rating scale.
Beck Anxiety Inventory (BAI)[2] (Beck et al., 1988)	A 21-item, self-report tool measuring the anxiety symptoms which are not typical in depression. It is

	used to distinguish between depressive and anxiety symptoms.
Hamilton Anxiety Scale (HAM-A)[2] (Hamilton, 1959)	A 14-item instrument evaluating the anxiety symptoms by the clinicians on a 0-4 rating scale.
Spielberger State-Trait Anxiety Inventory (STAI)[2] (Spielberger et al., 1970)	A self-report, 40-item tool including two parts which measure the state anxiety and trait anxiety.
Temperament and Character Inventory-Revised (TCI-R)[2] (Cloninger, 1999)	A self-report questionnaire consists of 240 items and examines 4 temperament and 3 character dimensions. Harm Avoidance temperament scale indicates anxiety.
Eysenck Personality Questionnaire (EPQ)[2] (Eysenck & Eysenck, 1975)	Self-report tool which examines 3 personality dimensions and includes a Lie scale. Neuroticism scale refers to anxiety.
Big Five Questionnaire (BFQ)[2] (Costa & McCrae, 1985)	Self-report questionnaire which examines 5 dimensions. Neuroticism scale refers to anxiety.

Notes: Numbers in upper index represent the different clinical stages of the treatment of alcohol use disorder. In these treatment stages the measurement tool is suitable to evaluate the anxiety in AUD (1 – withdrawal, 2 – rehabilitation). Name of the assessment tool used in the present thesis was marked in bold.

During the acute withdrawal phase, it is difficult to evaluate anxiety due to the physical condition of the patients therefore the clinicians often should rely mainly on observing the patient, or perhaps if the withdrawal syndrome is mild, the patient's anxiety level can be determined by asking the patient. Previously, not validated tools were used to evaluate the severity and symptoms of AWS. Later, tools were developed that were validated based on psychometric analyses. Validation of tools is critical because it allows a reliable measurement of the symptoms and the course of AWS which can be used later during treatment.

Among the validated tools, the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) is a frequently utilized measurement tool (Sullivan et al., 1989) which is also recommended by international protocols and guidelines (Hoffman & Weinhouse, 2021; National Institute for Health and Care Excellence (NICE), 2017; Sachdeva et al., 2015). The 10-item tool is based on the patient's answers as well as the clinician's observations. The items contain the symptoms of AWS such as nausea and vomiting, tremor, sweating, auditory, visual and tactile disturbances, headache, orientation, agitation and anxiety. Thus, anxiety is defined

in this tool by 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 mildly anxious state, 4 score suggest moderately anxious state, 7 score imply equivalent to acute panic state. However, since the symptoms of AWS have not yet been operationalized in Hungary, 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 alcohol withdrawal syndrome, different questionnaires can be applied during the stage of early rehabilitation and anxiety is also measurable during this period. Self-report questionnaires can examine the subjective evaluation of anxiety or contain anxiety indicators. Therefore, numerous self-report tools are available for measuring anxiety which are widely used in research or clinical practice (e.g. Beck Anxiety Inventory, Hamilton Anxiety Scale and Spielberger State-Trait Anxiety Inventory) (Beck et al., 1988; Hamilton, 1959; Spielberger et al., 1970). The Spielberger State-Trait Anxiety Inventory (STAI) includes two parts: state anxiety and trait anxiety. While state anxiety represents the transitory emotion of anxiety, trait anxiety shows the disposition for experiencing anxiety. The first part measures the value of the current level of anxiety using 20 items (state anxiety) and the other measures the degree of trait anxiety which examines the disposition for experiencing anxiety (Spielberger et al., 1970). This tool was often used in research focusing on alcohol use disorder (Agabio et al., 2021; Durazzo & Meyerhoff, 2017).

Furthermore, other personality dimensions (e.g. neuroticism, low extraversion and conscientiousness) and coping strategies (e.g. high avoidance) are also essential in describing the association of AUD and anxiety (Ribadier & Varescon, 2019). Temperament and Character Inventory-Revised (TCI-R; Cloninger, 1999) is a suitable measurement tool which was developed by Cloninger who created one of the most commonly accepted framework to assess personality, the Psychobiological Model of Personality (Cloninger et al., 1993). This complex model combined psychological, neurobiological and psychopathological knowledge. For measuring this integrative framework, Cloninger developed the TCI-R, 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). Temperament dimensions were described by the "biological core" of personality which are heritable character dimensions derived by environmental, social and

cultural learning. The use of TCI-R is a relevant measurement tool in clinical practice during rehabilitation which was often measured in research focusing on alcohol use disorder (Andó et al., 2014; Angres, 2010). 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.

It is visible that there are several tools for evaluating anxiety but it is essential that the tool should be assigned to the clinical phase of the AUD and the patient's clinical condition.

IV. AIMS AND HYPOTHESIS

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 shows comorbidity with numerous psychiatric disorders and it is prominent in case of the co-occurrence of addictive disorders (Boschloo et al., 2011; Grant et al., 2004). In clinical settings, anxiety could be observed in different critical stages among AUD patients: in alcohol withdrawal syndrome (AWS) which is one of the most common complication of AUD and during rehabilitation. Furthermore, AUD is highly comorbid with other behavior addictions especially the prevalence of gambling disorder in AUD is particularly high.

In the present thesis, four studies were conducted where the appearance of anxiety was examined and approached differently among normal population as well as in the complication and comorbidity of AUD during different clinical stages. Anxiety was observed in normal population using a physiological device and a self-report questionnaire during an anxiety-provoking situation which emphasized the comprehensive effect of anxiety. In case of the AUD, different measurement tools examining anxiety were assigned in each phase to take into account the patient's clinical condition. Therefore, self-report questionnaire and clinician-rated assessment tool were used. These different measurement methods allowed for a complex and comprehensive understanding of anxiety in both normal and clinical populations.

This thesis aimed to address three main aims. Our first aim was a comprehensive physiological investigation of anxiety in normal population, the second was to explore the

anxiety level during alcohol withdrawal syndrome, and the third major aim was to examine anxiety among treatment-seeking AUD patients and comorbid gambling involvement.

Aim 1: Regarding the previous literature, it is visible that the human 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 (Study 1). On this notion, the following hypothesis was formed:

H1: The body responds comprehensively and immediately to the anxiety situation that appears in the body's autonomic response. 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. In the clinical phase of AUD, patients were examined during withdrawal syndrome and early recovery phase. It is essential to extend the examination of anxiety for these critical phases of AUD patients regarding anxiety since scientific literature demonstrated the co-occurrence of anxiety and AUD (Boschloo et al., 2011; Grant et al., 2004).

For monitoring the severity of AWS, the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) is the most recommended tool based on the national guidelines and protocols. For this purpose, the course of AWS was evaluated by a meta-analysis with aggregated CIWA-Ar total scores. Hence, the change of the CIWA-Ar scores was examined therefore the ecological validity of the tool was also tested (Study 2). Since CIWA-Ar was not a standardized measurement tool in Hungary therefore it has been validated by our research group. 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). On this notion, the following hypotheses were formed:

H2: CIWA-Ar is an ecological valid tool and the course of alcohol withdrawal syndrome can be followed using CIWA-Ar. It was hypothesized that the CIWA-Ar total score results in decreasing values (Study 2).

H3: Anxiety follows the course of AWS based on the CIWA-Ar scores therefore anxiety is continuously decreasing during alcohol withdrawal (Study 3).
H4: Anxiety is one of the most substantial symptom in the acute phase of AUD during alcohol withdrawal syndrome (Study 3).

Aim 3: In the early recovery phase, elevated anxiety may maintain during abstinence even without AWS symptoms. The examination of anxiety is essential since anxiety can be a risk factor for subsequent relapse among AUD patients (Kushner et al., 2005). Therefore, it is also important to examine the emergence of anxiety during rehabilitation phase of AUD patients. Furthermore, patients with comorbid AUD and anxiety disorders have an increased risk for developing gambling disorders. The personality structure of the patients becomes measurable in this phase therefore this period is suitable for examining anxiety as a temperament variable. Thus, the personality structure was examined during rehabilitation using questionnaire. At this treatment stage, we used one of the most commonly utilized self-report personality questionnaire, the Temperament and Character Inventory-Revised (TCI-R; Cloninger, 1999) where Harm Avoidance temperament scale was considered as anxiety indicator.

Although one of the most common comorbid behavioral addiction in AUD is gambling disorder, to our best knowledge, literature specifically 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 involvement was examined comparing to a normative sample. Then, these two AUD groups were compared and the anxiety as temperament variable was also explored. On this notion, the following hypotheses were formed:

H5: The Harm Avoidance temperament factor is elevated among AUD patients and AUD patients comorbid with GD symptoms, compared to the normative sample (Study 4).
H6: Harm Avoidance temperament factor shows even higher values in AUD patients comorbid with GD symptoms (Study 4).

V. METHODS AND MATERIALS

1. STUDY 1: Measuring state anxiety among normal population

1.1. Participants and procedure

In Study 1, the autonomic effects of the stress-induced anxiety were examined comprehensively on rat and human sample in a translational framework. However, in the

present thesis only the human results were discussed. This investigation was carried out in the Department of Psychiatry, University of Szeged. It was conducted in air-conditioned examination rooms, the temperature was set to 24 °C. Twenty-one healthy volunteers were recruited between 21 and 26 years. Convenience sampling was used during the enrolment and the participants did not receive any remuneration for the study. Written informed consent form was obtained. The study lasted approximately 90 minutes per individual.

Body mass index (BMI) below 18 or above 30, major psychiatric disorders, current medication (except contraceptives), current drug and/or alcohol consumption and scores greater than two standard deviations on Global Severity Index measured by Symptom Checklist Revised (SCL-R-90), chronic diseases were considered as exclusion criteria. The final sample size was 16 because 5 participants were excluded regarding the exclusion criteria (measurement error, outlier on GSI, pharmacotherapy and BMI index).

Before starting the investigations, participants refrained from eating 2 hours for ensuring the standardization of the initial GI parameters. Water was provided during the study if it was necessary. After the baseline questionnaires, weight, height and abdominal circumference were gathered. Then, SMEMG/HR/BT/GSR Holter device measuring anxiety was applied which recorded the physiological parameters real-time and simultaneously. Following the application of the SMEMG/HR/BT/GSR Holter device, the Trier Social Stress Test (TSST) protocol started (Kirschbaum et al., 1989). During TSST, a moderate acute social stress was induced in laboratory conditions. The TSST protocol began at 3 p.m. considering the circadian rhythm of the subjects (Hu et al., 2018; Sharma et al., 2020). The protocol consisted of three phases: resting phase, stress induction and recovery phase. Every phase lasted 20 minutes. Following the resting phase, a three-member selection committee was introduced as behavioural analysts and it was announced that the selection committee would interpret the nonverbal behaviour of the participants and the performance would be recorded by a video camera to conduct further analysis. Then the subject had to prepare alone for 10 minutes (anticipatory stress phase) for a 5-minute job interview simulation in front of the selection committee. During the job interview, the participants had to make an introduction to the selection committee and convince them that the participant was the right choice for a dream job (first stress situation). Afterwards, the participant had to perform an arithmetic task for 5 minutes and had to count loudly from 1022 by 13 as fast and as accurately as possible (second stress situation). The TSST protocol ended with the recovery phase and the participant was informed that the video camera was not turned on during the study and the speech and math performances were not recorded (Kirschbaum et al., 1989) (Figure 1).

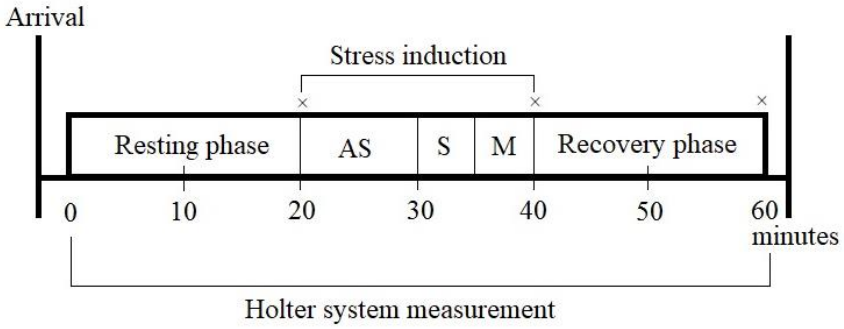

Figure 1: The Trier Social Stress Test protocol

Abbreviations: AS = Anticipatory Stress phase (10 min speech preparation), S = Speech task (5 min), M = Arithmetic task (5 min), × = measuring state anxiety with Spielberger State Anxiety Inventory

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Human Investigation Review Board, University of Szeged (ethical approval number: 134/2017).

1.2. Measures

SMEMG/HR/BT/GSR Holter device measuring anxiety

The measurement procedure with the Holter device is painless and completely harmless. On the abdominal surface, the smooth muscle electromyographic (SMEMG), electrocardiographic (ECG) and body temperature changes (BT) of the participants were recorded non-invasively and simultaneously. The signals were detected by a thermometer combined electrode pair fixed on the abdominal dermal surface of the participants. The waves detected through the electrodes were amplified by the transducer analogue amplifiers and digitized by appropriate A/D conversion. Before positioning the combined electrodes, abdominal circumference was measured. As a standard, 10% of the abdominal circumference was considered as the measurement distance from the baseline (navel). A pea-sized amount of EEG conductive paste was positioned to each electrode using a medical spatula. Subsequently, the electrodes were applied in a triangle shape on the abdominal wall, the highest vertex of the triangle was the electrode measuring BT. The Holter system was placed in a sealable pouch fixed to a belt and the device recorded the biological parameters during the stress protocol. Furthermore, galvanic skin response (GSR) was recorded non-invasively which reflected the sweat gland activity as an autonomic nerve response. GSR measurement was carried out with 10-μm gold-plated silver electrodes fixed with Velcro on the non-dominant index and middle

fingers of the subjects. Conductive paste was used on the skin surface before positioning the electrodes (Figure 2).

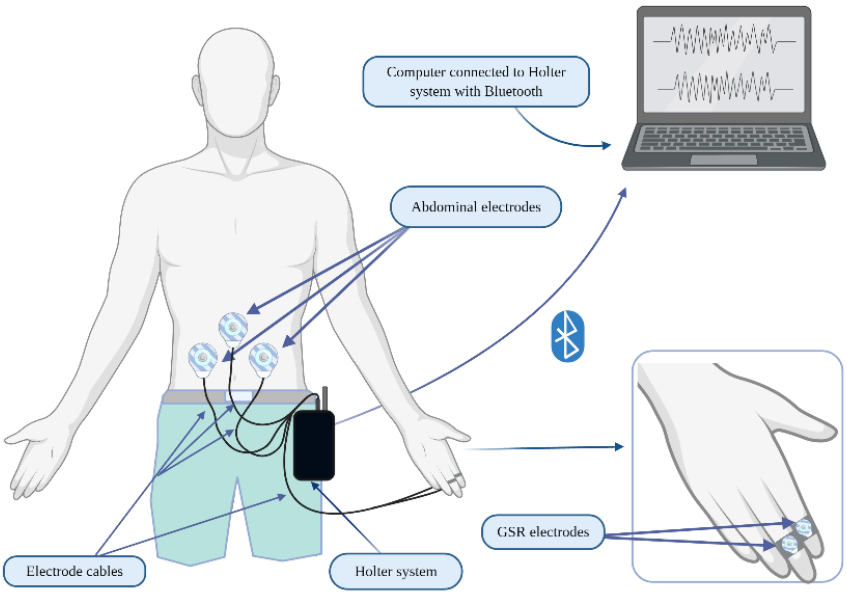

Figure 2: A schematic figure of the Holter system. The figure represents the abdominal and galvanic skin response (GSR) electrodes, which were connected to the Holter device with Bluetooth. Created with Biorender.com.

Spielberger State Anxiety Inventory (STAI)

For measuring state anxiety, Spielberger State Anxiety Inventory (STAI; Sipos et al., 1994; Spielberger et al., 1983) was used. This self-report questionnaire consists 20 items and participants have to decide to agree with the statement on a 1-4 Likert-scale. STAI was applied at three time points in TSST protocol therefore STAI was applied after the resting phase, during stress induction and after the recovery phase.

Symptom Checklist Revised (SCL-R-90)

The questionnaire contains 90 items and the participants fill the questionnaire based on how they detected their psychological symptoms in the past week. Based on the questionnaire, the Global Severity Index (GSI) was calculated and high scores on GSI indicate the current level of distress of the participants (Derogatis, 1977; Unoka et al., 2004).

1.3. Statistical analysis

Evaluation of the myoelectric signals of the GI tract, HR, BT and GSR parameters were performed by Easy Chart software (MDE GmbH, Walldorf, Germany). Regarding the GI tract, a digital cutter was applied to extract the motion artefacts whose edge values were given by

motion-free artefacts. Therefore, high-amplitude values resulting from motion did not distort the GI signals (Szűcs et al., 2018). Fast Fourier transformation (FFT) was used to evaluate the recorded values of the GI parameters and it required at least a 20-minute measurement period in each phase. Furthermore, HR and GSR values were gathered in every 5 minutes during the three phases. The values of each stage were aggregated so both HR and GSR could be described by a single mean value during the three phases. To examine the changes in BT, stress induction 0 min (t_0) was compared to stress induction 20 minutes (t_{20}). In addition, changes also were contrasted between the stress induction and the recovery phase regarding GI tract, HR and BT. In case of BT, stress induction 20 minutes (t_0) was compared to the subsequent 20 minutes of the recovery phase (t_{20}). The results were considered statistically significant if $p < 0.05$.

The magnitude and the changes of the electrical activity of the GI parameters were defined by power spectrum density (PsD_{max}), HR was described by bpm (beats per minute) and BT was characterized by °C. Furthermore, GSR was defined by kOhm.

The results were analysed by IBM SPSS Statistics 24 software (IBM Corp, 2016). State anxiety was evaluated by repeated-measures ANOVA during the TSST protocol. Values greater than one standard deviation in the physiological parameters were considered as outliers and were therefore excluded from the analysis. Wilcoxon signed-rank tests were analysed in terms of the biological parameters (stomach, colon, small intestine, HR, BT and GSR) between the resting phase and stress induction. Furthermore, changes between stress induction and the recovery phase were calculated by further Wilcoxon signed-rank tests regarding the physiological variables (stomach, large intestine, small intestine, HR and BT).

2. STUDY 2: Examining the course of alcohol withdrawal syndrome and the ecological validity of CIWA-Ar

2.1. Search strategy and study selection

In Study 2, the course of alcohol withdrawal syndrome was examined with the aggregated CIWA-Ar total scores using meta-analysis that allowed the analysis of the ecological validity of the measure. This systematic review-based meta-analysis were presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) statement, and its reporting was in accordance with the guidelines of meta-analyses in epidemiology described by Stroup and his colleagues (Stroup et al., 2000). Four scientific databases (PubMed, ScienceDirect, Web of Science and Cochrane Registry) were systematically searched by three authors in our research group to determine studies published before January 31, 2020, which documented the severity of AWS with the

CIWA-Ar in patients treated with AWS. The full-text search was conducted without filtering, "ciwa" was used as the key search term.

A total of 1054 articles were identified for potential inclusion in the quantitative meta-analysis. The previously identified scientific articles were listed for critical revision of a professional researcher team expert in the methodology of meta-analyses, the course and pharmacotherapy of AWS and in clinical psychometrics.

During applying the exclusion criteria, duplicates (N = 209) and grey literature (e.g. correspondence, editorial letters, conference abstracts and RCT registrations) (N = 176) were excluded. Non-English papers (N = 58) and publications not connected to AWS (N = 62) were also selected out. Since the comorbid somatic state may have an impact on the course and treatment of AWS, investigations of specific populations were removed (N = 5). These were the following: Spies et al. (1995, 1998) and Kong et al. (2017) have investigated alcohol dependent patients with carcinoma, Illig et al. (2001) have explored the unexpected emergence of AWS following aortic surgery and Talbot (2011) has examined patients developing Wernicke's disease. Articles (N= 70) using different versions of the CIWA-Ar (CIWA-Benzodiazepine, CIWA-A or other modified versions) were also removed. Non-empirical studies (e.g. reviews, table of contents, case reports, appendixes, indexes, author indexes, abbreviations, protocols and guidelines etc.) were also excluded (N = 219). Papers not monitoring the course of AWS (e.g. only one assessment point was reported since the CIWA-Ar was used as a screening test) (N = 71) were selected out and articles that lacked the use of the CIWA-Ar total scores (N = 92) were also removed. Therefore, when we found a publication that was potentially eligible for inclusion for our study but did not include the necessary means and standard deviations, we tried to contact the corresponding author two times over two months to ask them to provide these missing data. Additionally, 12 papers fell out due to non-eligibility based on medication.

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]). Finally, reference lists of studies identified were hand-searched for possible inclusion. After applying all the exclusion criteria aforementioned, 11 studies met the previously set criteria for inclusion in the quantitative meta-analysis and two subgroups were identified based on pharmacotherapy (Figure 3).

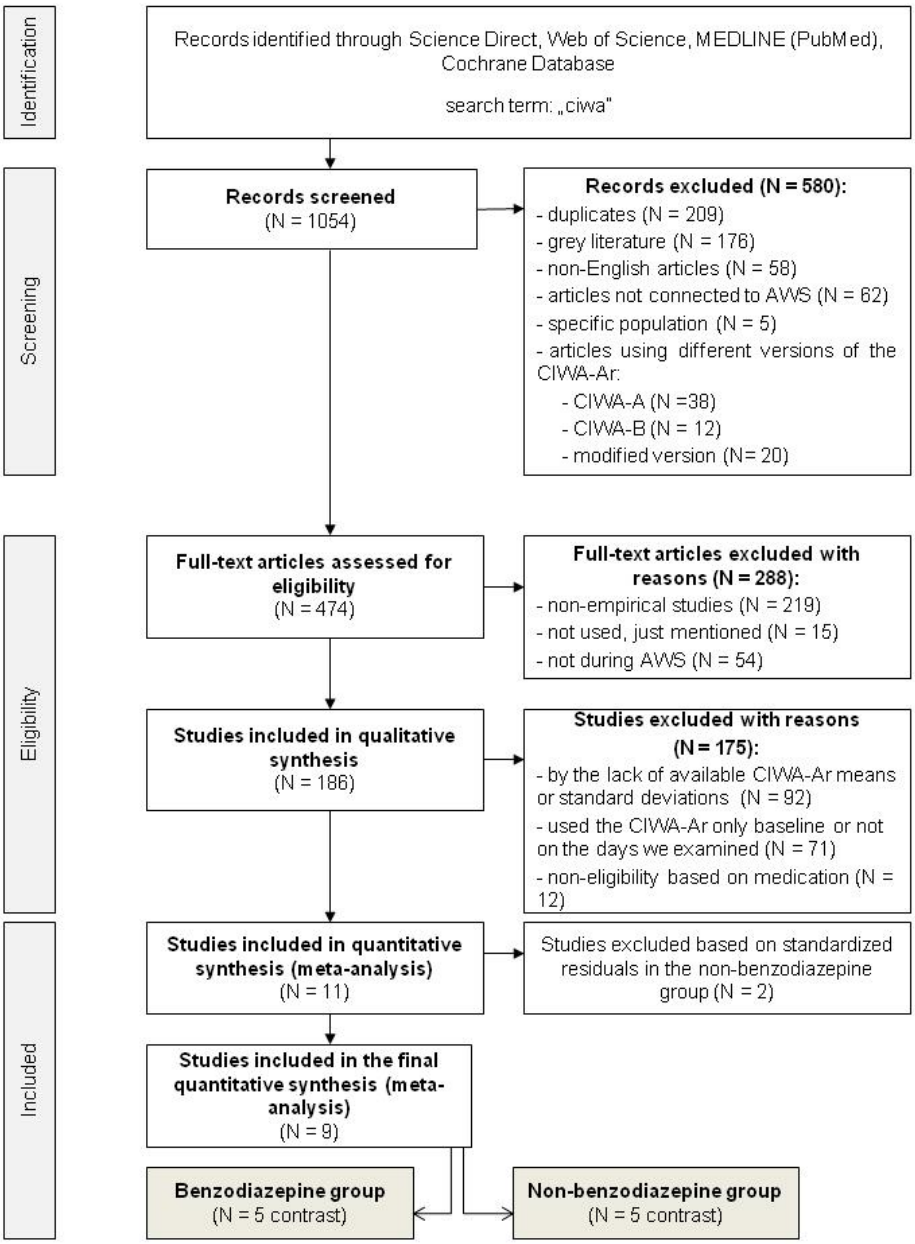

Figure 1: The PRISMA flow diagram

2.2. Statistical analysis

All analyses were made with using the Comprehensive Meta-Analysis Software 3.0 (*Comprehensive Meta-Analysis Software (CMA)*, 2020). Analyses were assessed using a random-effects model. We also conducted existence of publication bias, calculation of effect sizes and moderator analysis. The means and standard deviations of the CIWA-Ar total scores monitoring the course of AWS were gathered for the calculations. The demographic (gender and age) and alcohol-specific data (alcohol consumption in grams, duration of alcohol consumption and alcohol dependence) were also collected. However, these data were

documented differently in the papers and many were lacking therefore these collected data could not be analysed as moderator variables in the final analysis.

The unit of data analysis was the comparison of the cumulative mean CIWA-Ar scores of two phases of the course of AWS treatment. The means and standard deviations of the first 9 days of AWS treatment were gathered from each study and were separated into two measurement intervals which reflects the first and last phase of AWS. The first phase of AWS was day 1-3, the last phase of AWS was day 4-9 and the means of these days were averaged. If there were missing daily data, then averaging was done without them. In the study of Johnston et al. (1991), only 1, 2, 7 days were documented therefore for the first phase, we calculated the means and standard deviations of day 1 and 2, and the second phase was the seventh day. Similarly, in the study of Addolorato et al. (1999), the means and standard deviations of the CIWA-Ar total scores of day 1, 2 and 3 were calculated for the first phase and day 4 and 5 were calculated for the second phase. Sengul et al. (2009) documented only data of day 1, 4 and 7 of the CIWA-Ar scores therefore the day 1 mean and standard deviation were the unit of analysis of the first phase and the means and standard deviations of CIWA-Ar scores of day 4 and 7 were averaged for the second phase. In case of some studies reporting only the CIWA-Ar total score of day 1 and 7, only the CIWA-Ar total score of the first day was used for the first phase and the CIWA-Ar total score of the 7^{th} day was used for the second phase (Cavus et al., 2012; Heberlein et al., 2010, 2014, 2015, 2017; Sönmez et al., 2016). Furthermore, three studies (Addolorato et al., 1999; Chourishi et al., 2010; Girish et al., 2016) yielded two comparison pairs for analysis therefore a total of 10 comparison pairs were contrasted.

Publication bias was determined several methods. Firstly, it was estimated based on visual/graphic examination of the funnel plots as well as Egger's regression (Egger et al., 1997) and Begg and Mazumdar's rank correlation test (Begg & Mazumdar, 1994) were calculated to determine publication bias. If the *p*-value was < 0.05 in the Begg and Mazumdar test and the *p*-value was < 0.1 in the Egger's test, significant asymmetry was detected. In addition, the study was considered an outlier (Shiffler, 1988) if the standardized residual of a study was greater than 3.29. Consequently, two studies (Chourishi et al., 2010; Girish et al., 2016) were removed based on the aforementioned standardized residuals. Therefore, the previously identified 9 studies yielded 10 comparison pairs for the present meta-analysis (Pribék et al., 2020).

Heterogeneity was evaluated with the Q-test and I^2 test to explore the consistence of the results of the studies. In the sample, a statistically significant, considerable heterogeneity was considered with a significant *p*-value in the Q-test and value over 75 in the I^2 test.

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

3.1. Participants and procedure

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. The study was carried out at the Department of Psychiatry, University of Szeged. Thirty patients admitted with alcohol withdrawal syndrome were included between 18 and 65 years from the inpatient addictology unit. Written informed consent was obtained from each participant.

During the baseline assessment, demographic (gender, age) and alcohol consumption-related (number of addiction treatments and the quantity of the last beer, wine and spirit intake) questions were gathered. Alcohol withdrawal syndrome was assessed by Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) which was translated and validated by our research team. The validation process was detailed in the study of 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.

The study was ethically approved by the Human Investigation Review Board, University of Szeged (28/2018, SZTE).

3.2. Measures

Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar)

Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) measures the severity and the symptoms of AWS. The scale was assessed based on a clinician-rated scoring on a Likert-scale and the scores of 0–8, 9–15 and 16 or more indicate mild, moderate and severe withdrawal syndrome. The 10-item tool contains the symptoms of AWS such as nausea and vomiting, tremor, sweating, auditory, visual and tactile disturbances, headache, orientation, agitation and anxiety. The maximum score is 67, where the higher score shows more severe AWS . Considering the Anxiety item, anxiety was 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, 7 scores imply acute panic states (Sullivan et al., 1989). In this study, the Hungarian validated version was used which was translated and validated by our research group (Lázár et al., 2019).

3.3. Statistical analysis

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 tested focusing on the Anxiety item therefore the Cronbach alpha values were calculated in case of the total CIWA-Ar scores and after deleting the Anxiety item. In addition, item-total correlations were also conducted in case of the first three measurements. If the value of Cronbach Alpha is above 0.7, the questionnaire is reliable in the sample (Tavakol & Dennick, 2011).

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

4.1. Participants and procedure

In the Study 4, the comorbidity of AUD and gambling involvement was examined, with a specific focus on anxiety as temperament variable. As part of a comprehensive research project, patients receiving inpatient treatment for addictive disorders were assessed for eligibility at the Department of Psychiatry, University of Szeged. A total of 104 patients were enrolled in the study. Patient were enrolled who met the criteria for DSM-5 diagnosis of AUD (American Psychiatric Association, 2013). Patients were included if their general intellectual level was above intellectual disability (IQ 70+) measured with the Wechsler Adult Intelligence Scale, 4th Edition (Wechsler, 2008). Neurological diseases, any psychosis spectrum disorders, history of progressive neurodegenerative disorders or reported acute severe intoxication were exclusion criteria. For a detailed description of inclusion criteria and patient enrolment, see Kovács et al. (2020). Written informed consent was obtained from each participant.

Six patients were excluded from the study. In this sense, one patient was excluded from the sample due to untimely termination of treatment, another patient was selected out due to the unsuccessful completion of the Temperament and Character Inventory, Revised (TCI-R; Cloninger, 1999; Rózsa et al., 2004, 2005) and four patients were excluded due to scoring low on the validity scale of the TCI-R. Based on the aforementioned exclusions, the final sample size was 98. According to the South Oaks Gambling Scale scores (SOGS; Gyollai et al., 2013; Lesieur & Blume, 1987), gambling disorder (GD) symptom severity proved to be the dominant clustering variable. Based on the clusters, two groups were formed: the AUD group (n = 68) included patients without GD symptoms (scoring 0 on the SOGS), and the AUD + GD group (n = 30) comprising AUD patients with comorbid GD symptoms (scoring 1 or above on the SOGS).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Investigation Review Board, University of Szeged (ethical approval number: 49/B-53/2016KK).

4.2. Measures

Addiction-related and demographic variables and intelligence

Addiction Severity Index (ASI) was assessed for demographic (age, gender and education) and addiction-related information (lifetime alcohol intake in years and age onset of regular alcohol consumption). It is a partially structured interview which evaluated 7 major psychiatric topics including major problematic areas covering topics of alcohol, drugs, general medical history, employment status, social and familial situation, legal issues and previous psychiatric history, focusing on the details of lifetime and recent addictive problems (McLellan et al., 1980; Rácz et al., 2005).

Furthermore, Alcohol Use Disorders Identification Test (AUDIT) was also used to measure drinking behaviour, the level of alcohol intake and the existence of problems connected to excessive alcohol consumption (Allen et al., 1997; Gerevich et al., 2006).

Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV) was assessed the patient's cognitive ability and intelligence. It evaluated four domains including Processing Speed, Working Memory, Perceptual Reasoning and Verbal Comprehension (Rózsa & Kő, 2008; Wechsler, 2008). In the Study 4, the WAIS-IV cumulative score generated from the values of the four subdomains was used.

South Oaks Gambling Scale (SOGS)

South Oaks Gambling Scale (SOGS) was assessed to measure pathological gambling severity found in the DSM-3 (Gyollai et al., 2013; Lesieur & Blume, 1987). Scores between 1 and 4 suggest problematic gambling, however, patients with 1 or 2 points on the SOGS are characterized with minimal or few gambling problems (Gyollai et al., 2013). Schaffer and Hall (1996, 2001, 2002) have suggested that participants with any level of gambling symptoms below the diagnostic cut-off point (SOGS scores of 1–4) should belong to the "at risk" or "problematic" gambling group, while Weinstock, Ledgerwood, and Petry (2007) recommended that SOGS ≥1 indicate symptomatic gamblers. SOGS scores of 5+ show probable pathological gambling. SOGS was administered via interview conducted by a trained clinician to avoid the identification of false positive results on the tool (i.e. scoring above 0 on the SOGS when the underlying condition of clinical and/or subclinical GD is absent).

Temperament and Character Inventory-Revised (TCI-R)

Personality dimensions were measured by Temperament and Character Inventory-Revised (TCI-R) which distinguishes 4 temperament (Persistence [PS], Reward Dependence [RD], Harm Avoidance [HA] and Novelty Seeking [NS]), and 3 character (Self-transcendence [ST], Cooperativeness [CO] and Self-directedness [SD]) factors (Cloninger, 1999; Rózsa et al., 2004, 2005). Harm Avoidance temperament factor was considered as anxiety indicator.

4.3. Statistical analysis

The results were analysed by IBM SPSS Statistics 24 software (IBM Corp, 2016). To determine clusters of the total sample, cluster analysis of variables evaluating addiction severity and personality was conducted. Clusters of gambling symptom severity and personality dimensions were identified using Two-Step Clustering algorithm, with the use of hierarchical clustering design. The Bayesian information criterion (BIC) was performed to single out the most applicable cluster solution, where smaller values of the BIC indicate the better model. Based on the SOGS scores, GD symptom severity proved to be the dominant clustering variable therefore two groups were formed according to the clusters: the AUD group incorporating patients without GD symptoms (scoring 0 on the SOGS), and the AUD+GD group comprising AUD patients with comorbid GD symptoms (scoring 1 or above on the SOGS).

Independent-samples t-tests were performed for exploring group differences of continuous variables and Chi-square tests were utilized for comparing categorical demographic data.

TCI-R T-scores of patients were analysed according to the age groups and gender of the Hungarian normative scores (Rózsa et al., 2004, 2005). 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.

VI. RESULTS

1. STUDY 1: Measuring state anxiety among normal population

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). In addition, 6 participants (37.5%) completed secondary and 10 subjects (62.5%) had higher education.

Repeated-measures ANOVA was used to examine the changes in scores between the resting phase and stress induction in the STAI questionnaires. Based on the Mauchly's sphericity, sphericity is not satisfied ($\chi 2(2) = 6.456$, $p = 0.04$) and the degrees of freedom of the ANOVA were corrected by the Greenhouse-Geisser method ($\varepsilon = 0.73$). The means of the three phases differed significantly ($F(1.46, 21.91) = 18.18$; $p < 0.001$). The Bonferroni post hoc analysis showed that 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 ($p < 0.001$) (Figure 4A).

The SMEMG signals were transformed to spectra by FFT analysis to emphasize the different PsD_{max} values for the segments of the GI tract. The SMEMG, HR, BT and GSR measurements were performed between the resting phase and stress induction. The values of the PsD_{max} in the stomach were higher during the stress induction than in the resting phase ($Z = -1.977$; $p = 0.048$). However, no significant difference was showed regarding the myoelectric waves of the large intestine during stress induction ($Z = -0.659$; $p = 0.51$). The myoelectric waves of the small intestine showed higher values during stress phase than in the resting phase ($Z = -2.045$; $p = 0.041$). Consistence with the GI tract, HR also showed higher during the stress induction compared to the resting phase ($Z = -3.464$; $p < 0.001$). Similarly, the BT of the participants was also significantly higher during stress induction compared to the resting phase ($Z = -2.628$; $p = 0.009$). In addition, GSR decreased by 65% during the TSST ($Z = 2.919$; $p = 0.004$). These results demonstrated that the STAI total scores changed with the physiological variables (stomach, small intestine, HR, BT and GSR) simultaneously except for the large intestine (Figure 4BCDE).

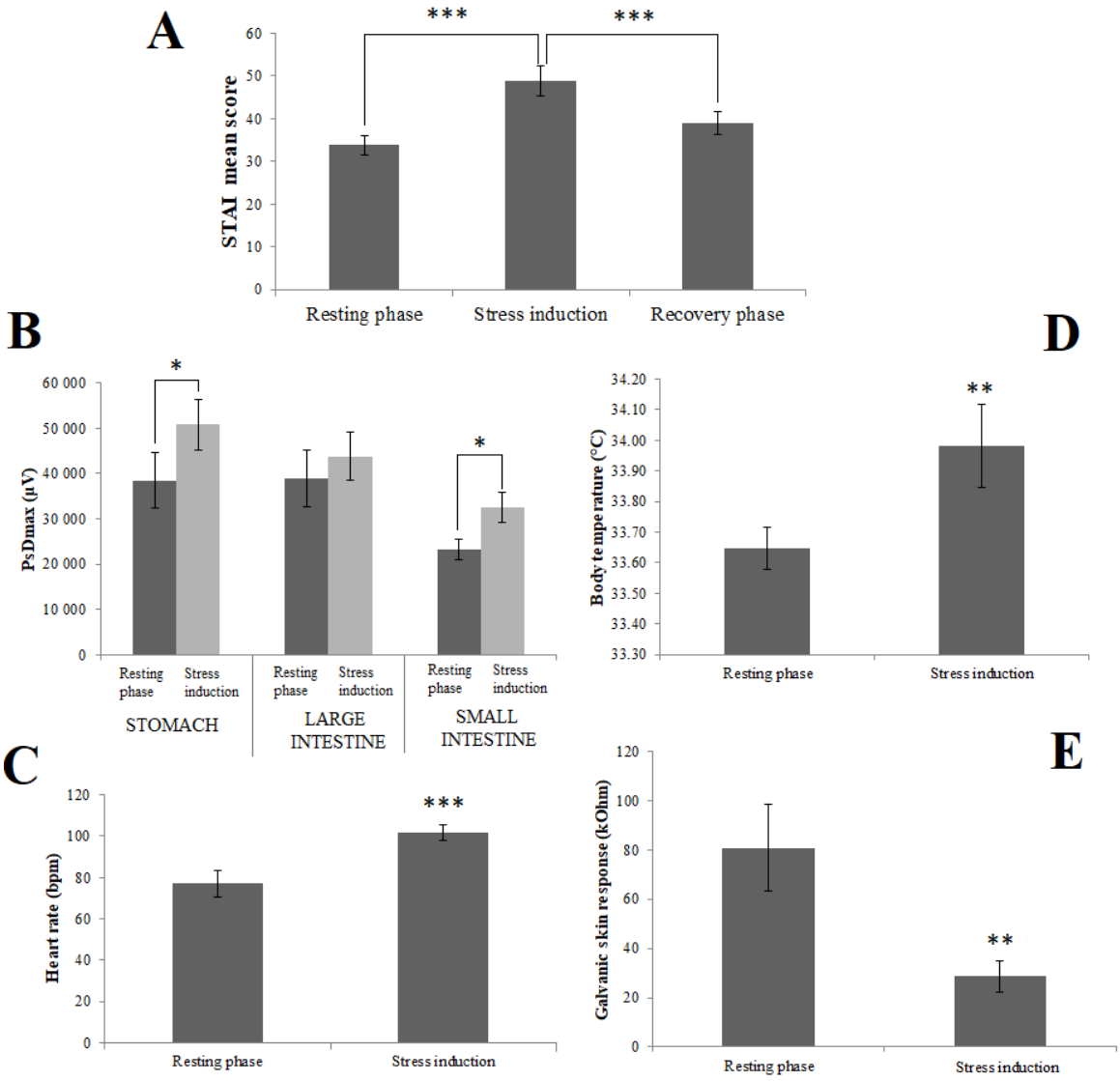

Figure 2: Changes in total scores of STAI (A) during the TSST protocol. The myoelectric waves of the gastrointestinal tract (B), heart rate (C), body temperature (D) and galvanic skin response (E) during the resting phase and stress induction of TSST protocol. Columns represent mean, error bars represent standard error of mean (SEM). **Abbreviations**: bpm = beats per minute; PsDmax = Power spectrum density maximum value of the Fast Fourier Transformation (Unit: µV2); TSST = Trier Social Stress Test; (#: $p < 0.05$; **, ##: $p < 0.01$; ###;***: $p < 0.001$)

Following the stress induction, recording the examined parameters were continued in the second resting phase therefore the potential changes in the recovery phase were also examined. Gastric PsD_{max} values decreased significantly in the recovery phase ($Z = –2.103$; $p = 0.035$). No significant differences were detected in the recovery phase in terms of the myoelectric waves of the large intestine ($Z = –0.568$; $p = 0.570$). Concerning the PsD_{max} values of the small intestine, a significant decrease was showed between the stress induction and the

recovery phase (Z = –2.271; p = 0.023). HR significantly decreased in the recovery phase (Z = –2.845; p = 0.004). In regard to BT, an increase in the level of tendency was observed in the recovery phase (Z = –1.962; p = 0.050).

2. STUDY 2: Examining the course of alcohol withdrawal syndrome and the ecological validity of CIWA-Ar

2.1. Publication bias and heterogeneity

Symmetric funnel plots were examined in the BZD (Figure 5) and nBZD subgroups (Figure 6) based on the results of the visual/graphic examination. Similarly, the Egger's test for intercept also indicated symmetry (Intercept = –4.774, p = 0.177). Publication bias was not explored neither in the BZD group (Kendall's tau = –0.5, p = 0.221) nor in the nBZD (Kendall's tau = –0.5, p = 0.22) group according to the Begg and Mazumdar tests. These results indicate that no evidence of publication was detected in the present meta-analysis.

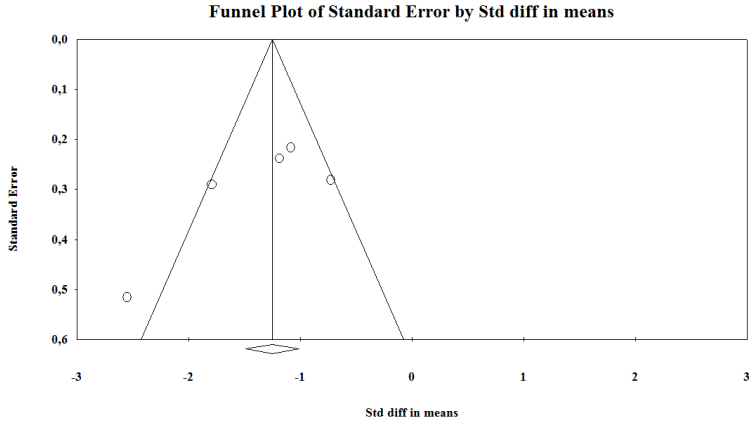

Figure 5: Funnel plot of standard error by standardized mean differences in the benzodiazepine (BZD) group

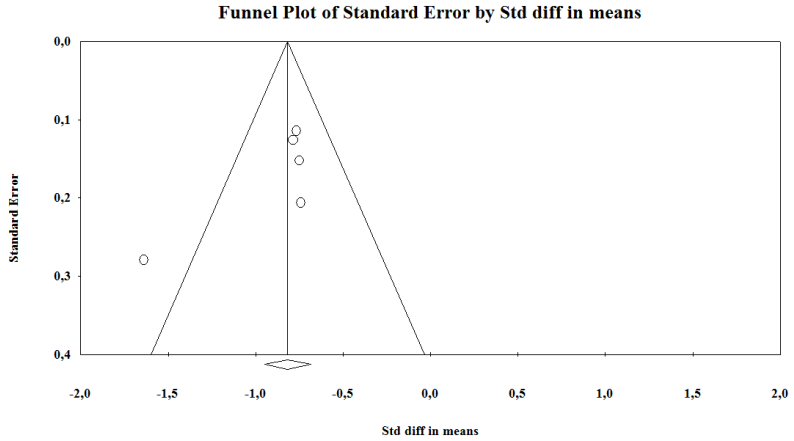

Figure 6: Funnel plot of standard error by standardized mean differences in the non-benzodiazepine (nBZD) group

Due to the methodological differences in the studies, a significant heterogeneity was expected therefore a random effects model was conducted to analyse the summary effect estimates. In the sample, significant heterogeneity was found (Q_w (9) = 32.946, $p < 0.001$). The I^2 test indicated a moderate level of heterogeneity in the overall sample ($I^2 = 72.68$).

2.2. Analysis of the aggregated CIWA-Ar total scores in the meta-analysis

Nine studies met the inclusion criteria and yielded 10 comparison pairs. A total of 423 patients were examined in this analysis. 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 < δ < –0.750; $p < 0.001$) (Figure 7).

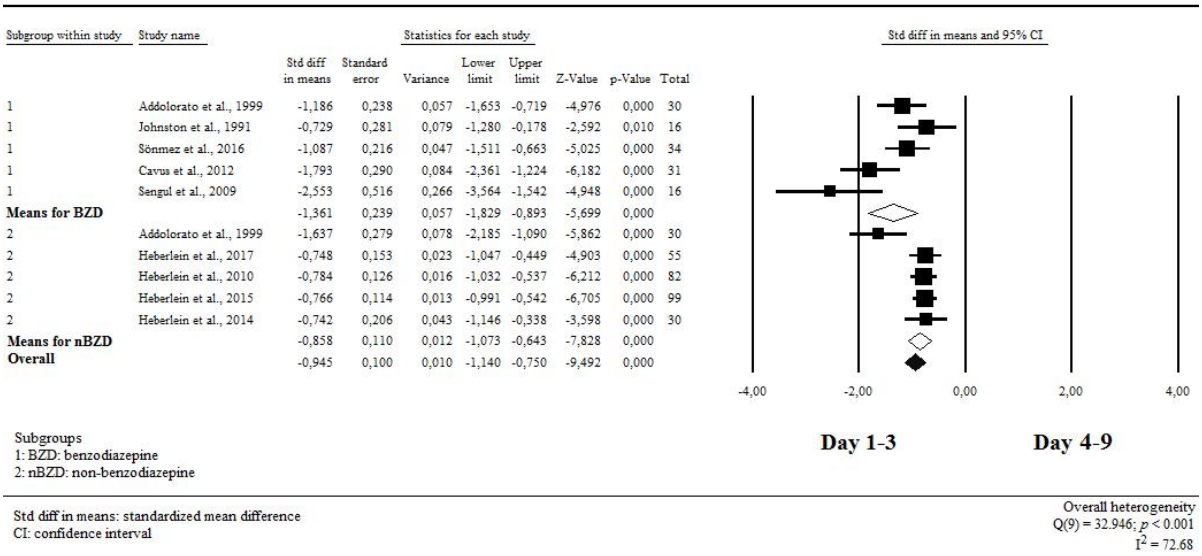

Figure 7: Forest plot of standardized difference in means for the overall sample

For exploring the role of the proportion of males and age in the samples, moderator analysis was conducted; data regarding the proportion of males were available for 10 comparison pairs and 9 reported ages. Based on the model, no significant effect was detected, therefore the proportion of males (coefficient: 0.02; $p = 0.48$) and the age (coefficient: 0.10; $p = 0.216$) did not have any moderating effect concerning the change of the total CIWA-Ar 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 alcohol withdrawal syndrome. In this sense, Anxiety showed the second highest mean value until day 6th, then had an average score approximately equal to Tremor on day 8th, and then, although low on day 10 but it had the highest mean of symptoms (Figure 8). Consequently, the decrease in the score of Anxiety item was slow and the symptom of anxiety was more stable in the course of AWS.

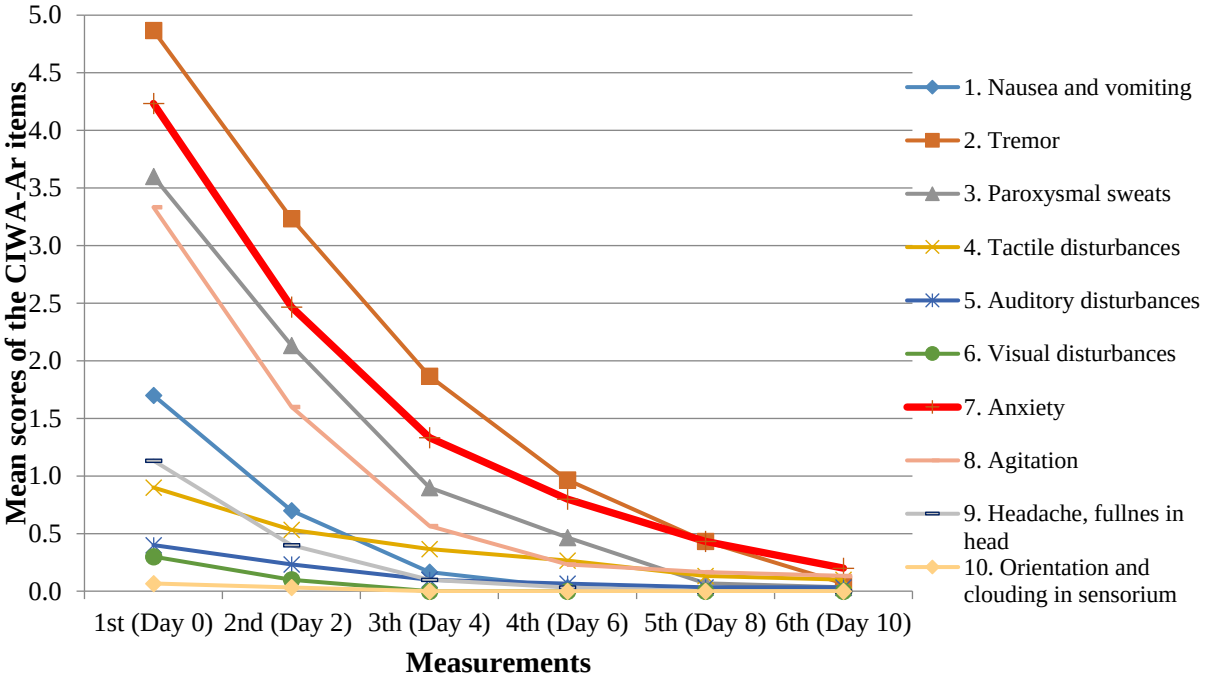

Figure 8: The mean scores of the CIWA-Ar items during the 6 measurements (A). Red represents the Anxiety item. **Abbreviations**: CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol, Revised

The validation process of CIWA-Ar through reliability and validity indicators was detailed in the study by Lázár et al. (2019) which demonstrated that CIWA-Ar is a valid and reliable tool specifically at the beginning of the withdrawal phase, during the first three measurements. Since the CIWA-Ar was more reliable and valid in the first phase of AWS therefore only these measurements were evaluated in the following psychometric analysis of the Anxiety item. The item-total correlation analysis showed that 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 measurements, respectively (Table 2). Based on these results, it can be concluded that anxiety plays a decisive role in the alcohol withdrawal syndrome and without the Anxiety item, the reliability of the tool decreases.

Table 2: Item-total correlation values of the Anxiety item and Cronbach Alpha values after item deletion during the first 3 measurements

Measurements	Item-total correlation of the Anxiety item of CIWA-Ar	Cronbach Alpha of the CIWA-Ar if Anxiety item was deleted	Cronbach Alpha of the CIWA-Ar
1.	0.793	0.644	0.732
2.	0.523	0.705	0.745
3.	0.502	0.655	0.704

Abbreviations: CIWA-Ar: Clinical Institute Withdrawal Assessment of Alcohol, Revised

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

4.1. Grouping and personality profiles according to cluster analysis of the sample

In the Study 4, 74 men and 24 women patients participated (N = 98). Firstly, we conducted a two-step analysis with all temperament and character variables measured with the TCI-R, severity of alcohol misuse assessed by the AUDIT and gambling symptom severity assessed with the SOGS as predictor variables. Based on the results, two clusters were identified where gambling symptom severity proved to be the most important predictor. Silhouette measure of cohesion and separation was fair (si = 0.3). Therefore, based on the results of the cluster analysis, two groups (AUD and AUD+GD) were formed. According to the overall median scores of TCI-R dimensions, the AUD group showed higher scores of CO, RD, PS and SD, and lower scores of NS and HA compared to the AUD+GD group.

4.2. Group differences and gambling prevalence in the sample

The AUD and AUD+GD group differed only in the severity of alcohol consumption assessed with the AUDIT. The AUD+GD group scored significantly higher on the AUDIT total scores (Table 3). In the AUD+GD group, the prevalence of patients with problematic gambling

symptoms was 53.33% (n = 16), while the prevalence of patients with probable GD was 46.67% (n = 14).

Table 3: Sample characteristics of study groups

	AUD (n = 68)	**AUD+GD (n = 30)**	
Age (SD)	45.15 (9.60)	46.60 (11.53)	$t(96) = -0.648$, $p = 0.615$[b]
Sex (Male%)	72.1%	83.3%	$X^2(2) = 0.974$, $p = 0.244$)[a]
Education% (primary/secondary/higher)	5.9%/70.6%/23.5%	10.00%/73.3%/16.7%	$X^2(2) = 1.431$, $p = 0.232$)[a]
Start of alcohol misuse in years (SD)	25.28 (*9.49*)	22.70 (*11.72*)	$t(96) = 1.151$, $p = 0.253$ [b]
Lifetime alcohol consumption in years (SD)	16.96 (*9.86*)	21.40 (*11.74*)	$t(96) = -1.928$, $p = 0.057$ [b]
SOGS Total (SD)	0 (*0*)	4.83 (*3.54*)	
WAIS-IV Total IQ (SD)	92.57 (*14.99*)	90.33 (*16.28*)	$t(96) = 0.664$, $p = 0.508$ [b]
AUDIT Total (SD)	23.51 (*7.43*)	28.03 (*6.36*)	**$t(96) = -2.893$, $p = 0.005$** [b]

Abbreviations: AUD: alcohol use disorder patient group, AUD+GD: alcohol use disorder patient group with gambling disorder symptoms; SOGS Total: South Oaks Gambling Scale total score; WAIS-IV Total IQ: Wechsler Adult Intelligence Scale IV total score; AUDIT Total: Alcohol Use Disorders Identification Test cumulative score. [a]Chi-square test, [b]Independent sample t-test

4.3. Comparison of normative sample scores and patient group differences in TCI-R dimensions

Regarding anxiety which was indicated by the HA temperament factor, 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 (T-score for each dimension is 50, SD = 10). Furthermore, the AUD group showed significantly higher NS (t = 2.458, p = 0.018, Hedges' g = 0.294) and lower SD (t = −5.463, $p < 0.001$, Hedges' g = −0.663) scores than the Hungarian normative sample scores, while the AUD+GD group scored higher on NS (t = 4.160, $p < 0.001$, Hedges' g = 0.553) and resulted in significantly lower scores of PS (t = −2.205, $p = 0.036$, Hedges' g = −0.433), CO (t = −2.896, $p = 0.007$, Hedges' g = −0.687)

and SD (t = −4.988, $p < 0.001$, Hedges' g = 0.928) than the T-scores of the Hungarian normative sample.

In case of group comparisons of the AUD and AUD+GD groups, controlled for the AUDIT scores, there was significant difference between the anxiety indicator HA variable (F(82, 14) = 6.683, $p < 0.001$, Hedges' g = 0.409), and significant difference on the level of tendency between RD (F(70,26) = 1.712, $p = 0.064$, Hedges' g = 0.411) between group scores of AUD and AUD+GD.

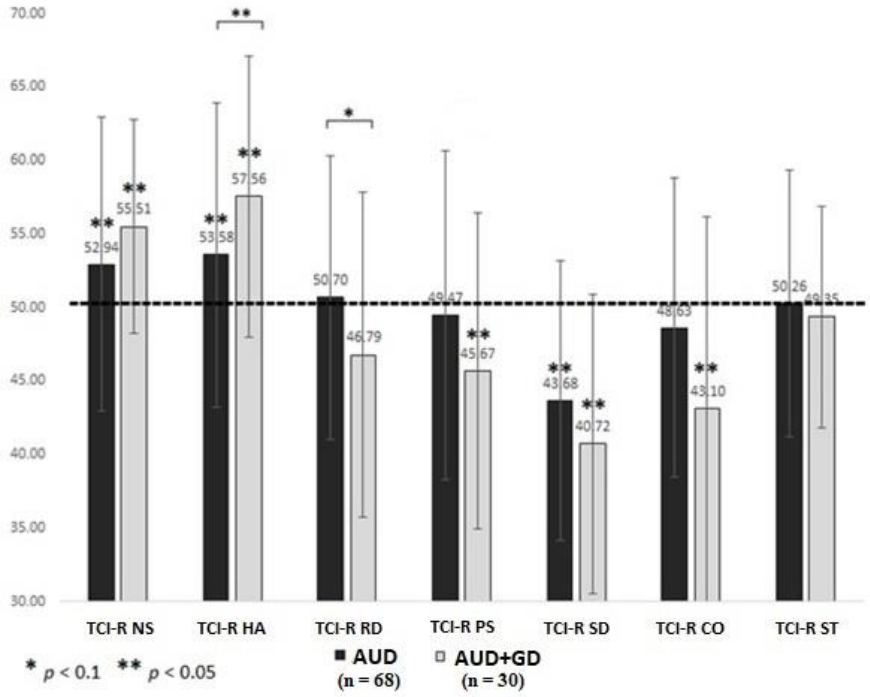

Figure 3: TCI-R dimensions in AUD and AUD+GD group compared to normative sample T-score. */** indicate difference from normative sample T-scores, brackets with significance indicate significant difference between patient groups. **Abbreviations**: AUD: alcohol use disorder patients without gambling symptoms; AUD+GD: alcohol use disorder patients with gambling symptoms; TCI-R NS: Temperament and Character Inventory Novelty Seeking subscale T-scores; TCI-R HA: Temperament and Character Inventory Harm Avoidance subscale T-scores; TCI-R RD: Temperament and Character Inventory Reward Dependence subscale T-scores; TCI-R PS: Temperament and Character Inventory Persistence subscale T-scores; TCI-R SD: Temperament and Character Inventory Self-directedness subscale T-scores; TCI-R CO: Temperament and Character Inventory Cooperativeness subscale T-scores; TCI-R ST: Temperament and Character Inventory Self-transcendence subscale T-scores; dashed line: Hungarian normative sample T-scores.

VII. DISCUSSION

Alcohol use disorder and anxiety (AUD) have a strong relationship based on the scientific literature (Boschloo et al., 2011; Grant et al., 2004; Vorspan et al., 2015). The course of AUD has different stages which results in a heterogenous physiological and psychological patterns. Different critical treatment points were examined in AUD patients: in alcohol withdrawal syndrome (AWS) which causes an acute physiologically demanding state and during rehabilitation without AWS symptoms where the patient's condition is more stable. Our findings suggested that the comorbid conditions and the anxiety symptoms were associated regarding the clinical course of AUD.

In the present thesis, four studies were conducted where the appearance of anxiety was examined comprehensively and defined differently among normal population as well as in the complication and comorbidity of AUD during different treatment points. Several measurement tools examining anxiety were assigned in each phase due to the different clinical characteristics of the stages. 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 clinical sample, AUD was investigated in different clinical stages regarding anxiety therefore alcohol withdrawal syndrome and early recovery phase were examined, respectively. It was reported that the course of alcohol withdrawal syndrome 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 as indicated by Harm Avoidance (HA) temperament factor was described by higher values (Study 4).

The first hypothesis (H1) 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 considerably during the Trier Social Stress Test (TSST; Kirschbaum et al., 1989). TSST was used since it provides a moderate laboratory social stress situation which incorporated speaking and arithmetic tasks in front of a three-member staff provoking anxiety and several studies used similar situations to induce elevated anxiety (de Wit et al., 2003;

Phillips & Giancola, 2008). Furthermore, earlier studies reported that TSST accompanies with higher level of anxiety therefore our results are consistent with the previous studies (Abe et al., 2020; de Wit et al., 2003; Erquicia et al., 2020; Trotman et al., 2019). 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). In our study, the stomach and small intestine showed the highest sensitivity to gastrointestinal myoelectric activation during anxiety-provoking tasks. According to the literature, acute stress (e.g. mirror drawing test and arithmetic task) can increase gastric myoelectric activity among healthy participants (Homma, 2005; Riezzo et al., 1996). Although the colon did not show a significant difference during stress induction, previous literature suggested that stress showed a moderate increase in colon motility (Rao et al., 1998) and the intestinal transit was shorter in generalised anxiety disorder compared to healthy controls (Gorard et al., 1996). According to the recent literature, it draw attention to the relationship between anxiety/stress and gastrointestinal symptoms. The theoretical basis of this association is based on the gut-brain axis (GBA) which allows bidirectional communication between the central nervous system and the GI tract through neural and humoral pathways (De Palma et al., 2014). Individuals with gastrointestinal symptoms are commonly reported by patients with anxiety disorders (Fadgyas-Stanculete et al., 2014; Haug et al., 2002). In general, constipation, nausea, diarrhea and abdominal distress are often in these diagnoses (Fadgyas-Stanculete et al., 2014; Haug et al., 2002). However, the relationship between the GI diseases and anxiety are bidirectional since functional GI diseases may maintain the anxiety symptoms and lead to reduced quality of life (e.g. negative impact on work) (Fadgyas-Stanculete et al., 2014).

Furthermore, as acute stress elevated the activity of the sympathetic nervous system, there was also an increase in values of heart rate (HR) which was also appeared in our study. Thus, it can be concluded that HR increased during stress-induced anxiety which is in line with the previous studies (Jezova et al., 2004; Trotman et al., 2019) and this increase was simultaneous with the gastrointestinal tract. Examining changes in HR is essential because anxiety and the emergence of stress can lead to cardiovascular disease (Lagraauw et al., 2015). The stress induction of TSST protocol elevated the mean HR by 33.4%, which is similar with the previously published data (Jezova et al., 2004; Jönsson et al., 2010; Kirschbaum et al., 1989; Kudielka et al., 2004).

In addition, acute stress induction elevates body temperature (BT) through human thermoregulation, which is a multifaceted process under the regulation of the central nervous system (Vinkers et al., 2013). Thus, similar to previous results, BT also increased in the stress-

induced anxiety situation, i.e., the body temperature of the subjects elevated by 0.35 degrees. Since body temperature was tested less frequently on a human sample, the results are inconsistent in the previous literature. For instance, increased axillary BT was recorded during psychological stress induction (Marazziti et al., 1992) but the temperature measured at the periphery (upper arm skin) did not elevate significantly during the TSST (Vinkers et al., 2013). However, BT was examined on the abdominal surface in our study so it seems that the abdominal surface is also suitable for measuring anxiety induced by stress induction.

During the stress induction of TSST, galvanic skin response (GSR) decreased which was applied as a further physiological tool to measure stress level, and it also provided real-time monitoring during the study. GSR is one of the most commonly used measurement for assessing the activity of the sweat glands and evaluating the level of anxiety and stress response. Numerous supportive literature are available which concluded that anxiety and acute stress have a great impact on the functions of the sweat gland (Allen etal., 2014; Guez et al., 2016; Jezova et al., 2004; Robert-McComb et al., 2015). Therefore, our results are consistent with the previous studies (Allen et al., 2014; Guez et al., 2016; Jezova et al., 2004; Robert-McComb et al., 2015).

In the last 20-minute period, the subjects could take a rest in the recovery phase according to the TSST protocol. During this phase, the participants continuously calmed down and the physiological parameters normalized, as indicated by the decreased values of HR and GI tract contractions.

The current results emphasized that a comprehensive autonomic response was demonstrated in a stress-induced anxiety situation and specifically the gut-brain axis had an essential role. These alternations of the parameters also contribute to understand the stress-induced anxiety mechanisms. It is proposed that the understanding and 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.

Scientific literature points out the co-occurrence of anxiety and AUD (Boschloo et al., 2011; Grant et al., 2004). In the clinical phase of AUD, patients can be examined during withdrawal syndrome and early recovery phase regarding anxiety. For measuring the severity of alcohol withdrawal syndrome, Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) is recommended by the nationals guidelines and scientific literature (Hoffman &

Weinhouse, 2021; National Institute for Health and Care Excellence (NICE), 2017; Sachdeva et al., 2015). In addition, several articles demonstrated the appropriate psychometric characteristics of CIWA-Ar suggesting the robustness of the tool (Bakhla et al., 2014; Higgins et al., 2019; Pittman et al., 2007; Sullivan et al., 1989). The second hypothesis (H2) was confirmed that CIWA-Ar is an ecological valid tool and the course of alcohol withdrawal syndrome can be followed using the tool. 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. Besides reducing the symptoms of AWS, further aim during the treatment of AWS is to prevent the development of DT. During AWS, the presence of DT is connected to a worse prognosis, it may lead to death in approximately 1-5% of the patients (Schuckit et al., 1995). If the AWS is uncomplicated, the symptoms decrease continually as the syndrome progresses due to the natural process of withdrawal. However, this reduction can be facilitated by the adequate pharmacological treatment. Our results confirmed that CIWA-Ar can be used regularly by clinicians and health care professionals in health care, which can contribute to the choice of medication treatment and the monitoring of the course of AWS. Based on the results, CIWA-Ar follows the course of AWS therefore it was suitable for detailed symptomatic examination of alcohol withdrawal syndrome.

During AWS, the emergence of the symptoms are connected with negative mood state such as elevated anxiety (De Witte et al., 2003). Based on the symptomatic analysis of CIWA-Ar, the third hypothesis (H3) was confirmed that anxiety appeared and followed the course of alcohol withdrawal syndrome. The fourth hypothesis (H4) was also confirmed since anxiety was one of the most substantial symptom during alcohol withdrawal syndrome. 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 assessing CIWA-Ar, the reliability of the measurement also weakened. Considering the literature, an elevated level of anxiety, dysphoria, negative emotional state and stress is induced during alcohol withdrawal which is caused by the decrease in dopamine release in nucleus accumbens (De Witte et al., 2003). However, the symptoms can be alleviated by drinking alcohol connecting to an increase of dopamine activity in nucleus accumbens which was also examined in preclinical studies such as in rats (Weiss et al., 1996). Further neurobiological studies found a possible dopaminergic etiology which was associated mood-related symptoms during AWS

(Laine et al., 1999). In addition, changes in plasma serotonin and noradrenaline level were detailed in AWS (Patkar et al., 2003) which are also connected to the degree of anxiety.

The fifth hypothesis (H5) was confirmed that the Harm Avoidance (HA) temperament factor was elevated among AUD patients with and without GD symptoms compared to the normative sample. Harm Avoidance temperament factor which was considered as anxiety indicator was evaluated by the self-report questionnaire TCI-R, which is often used in addictive disorders to explore the personality structure (Cunningham-Williams et al., 2005; Janiri et al., 2007; Jiménez-Murcia et al., 2010, 2021; Moragas et al., 2015). Differences in personality structure have an impact on the risk of developing psychopathological conditions, including substance use, especially in the case of alcohol use disorder (Cloninger & Svrakic, 1997). Related to this, Cloninger created two subtypes of alcohol dependence that specifically drawn attention to the role of personality structure regarding differentiation (Cloninger, 1987; Cloninger et al., 1996). In Cloninger's alcohol dependence typology, while Type 1 tends to have a higher HA, Novelty seeking shows a higher value in case of Type 2 (Cloninger et al., 1996). High HA has also been reported in previous studies among AUD patients therefore our results are in a good agreement with previous articles (Andó et al., 2014; Evren et al., 2007). In general, the high anxiety indicator of AUD patients 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). In addition, the importance of anxiety was also emphasized in the present thesis since an elevated level of Harm Avoidance temperament variable was demonstrated among AUD patients with gambling involvement compared to the normative sample. Previous studies reported that higher HA was resulted in predictor of elevated psychopathology and severity of the gambling disorder (GD) (Moragas et al., 2015). Similarly, Potenza et al. (2001) demonstrated that high rates of anxiety was reported among GD patients which was caused by the gambling activities. However, a few studies did not demonstrate changes in HA values in case of gambling severity among pathological gamblers (Cunningham-Williams et al., 2005). Similarly to Cloninger's alcohol dependence typology, gambling subtypes can be also differentiated (including Behavioral Conditioned, Emotionally Vulnerable and Antisocial-Impulsive subtypes) and anxiety plays a central role in this framework: Emotionally Vulnerable group have poor emotional coping skills and these individuals are often anxious before the gambling activities which they try to alleviate with gambling (Blaszczynski & Nower, 2002). 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 (H6) was confirmed that Harm Avoidance temperament factor showed even higher levels values in AUD patients comorbid with GD symptoms compared to AUD patients. In addition, more severe alcohol consumption was reported among AUD patients with comorbid GD symptoms compared to AUD patients without GD symptoms. These findings are consistent with the previous scientific literature since several articles demonstrated the higher rates of alcohol use which was connected to concurrent GD (Blaszczynski & Nower, 2002; Kovács et al., 2020; Toneatto et al., 2002). For instance, del Pino-Gutiérrez et al. (2017) reported that alcohol consumption was a predictor of greater GD severity. In addition, it can be assumed that the patients may became more vulnerable for developing and maintain more severe symptoms in case of comorbidity. Furthermore, problem gamblers were also described with elevated general psychopathological symptoms measured with GSI than patients with substance use disorder with non-problem gambling group. At the same time, no significant differences were found regarding anxiety between the two groups (Petry, 2000). Nevertheless, to best of our knowledge, literature examining the personality structure of AUD patients with GD symptoms compared to AUD patients without GD symptoms is scarce. In the study of del Pino-Gutiérrez et al. (2017), the impact of alcohol consumption and risk of alcohol dependence was examined on gambling disorder. Although the authors found that HA was high in GD patients, it was not a significant difference regarding the alcohol consumption level. Their results showed that the high risk of alcohol dependence group did not report significantly higher HA values than the low risk or abuse group (del Pino-Gutiérrez et al., 2017).

Based on the fourth and fifth hypotheses, it was demonstrated that anxiety indicator Harm Avoidance temperament factor appeared markedly in the AUD and AUD+GD group compared to the normative sample, and if there is also comorbid GD involvement in AUD patients, the HA value 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).

Several limitations need to be taken into account when interpreting the results of this present thesis. Overall, it is worthwhile to extend the usage of different additional tools to assess a more comprehensive investigation. In case of Study 1, the investigation was a preliminary

study with a limited number of subjects therefore the sample size must be increased in the future. In case of Study 2, only the course assessed by the CIWA-Ar total scores were measured, however, other symptoms such as vital signs (e.g. blood pressure or pulse) could be a further important outcome variables regarding AWS. In the view of Study 2, since the course of AWS takes 5-10 days (McKeon et al., 2008; Mirijello et al., 2015) but only two measurement intervals (day 1-3 and day 4-9) were defined and compared statistically in this study. Several studies did not report the daily data of the CIWA-Ar scores comprehensively therefore aggregated scores could be used in the present meta-analysis. This methodological diversity resulted in a relatively smaller sample size and comparable units of data. In addition, one of the limitation of Study 2 was the significant methodological heterogeneity due to the different pharmacotherapy. Furthermore, several alcohol-related factors (e.g. duration of alcohol consumption or alcohol dependence and consumed alcohol in grams) were not detailed in all included studies therefore these data could not be incorporated in the moderator analysis due to insufficient data. Moreover, only English articles were searched and the incorporated data were only from the European region and included mainly men. Therefore, these could potentially lead language, geographical and gender bias (Grégoire et al., 1995; Holdcroft, 2007). In case of Study 2, it is important to note that the CIWA-Ar item scores were not published in the articles therefore we could not investigate the aggregated CIWA-Ar items symptomatically. In contrast, symptomatic analysis was conducted based on the means, standard deviations and psychometric calculations in case of the Study 3. Considering Study 3 and Study 4, the enrolled patients were mainly men. However, this rate is in a good agreement with earlier studies which showed that the prevalence of alcohol use disorder is higher among men and the treatment-seeking patients are mainly men (Brady & Randall, 1999). Considering the Study 4, it needs to be addressed that GD is a heterogeneous condition and the preferred type of gambling activity (e.g. slot machine or poker) can have an impact on personality structure (Moragas et al., 2015). However, because of the smaller sample size, this study did not differentiate the potential gambling subtypes. Finally, GD symptoms were defined in case of 1+ value on the SOGS. The explanation for that is that the traditional scoring of the SOGS considered a score above 0 as subclinical GD symptoms, while score ≥ 5 suggested probable GD. Nevertheless, some authors emphasized that only scores of 5+ should suggest the occurrence of GD symptoms to avoid false positive cases (Goodie et al., 2013) but others indicate that the cut-off score should be raised even higher (Stinchfield, 2002).

Our results highlighted the importance of examining anxiety comprehensively in case of alcohol use disorder, as anxiety accompanies the clinical appearance of the complication and

comorbidity of AUD. Based on our results, it can be concluded that anxiety appeared in different clinical phases of AUD, in alcohol withdrawal syndrome and also occurred without AWS symptoms in case of the comorbidity of AUD. In our studies, anxiety was explored by several measurement tools which were assigned to each stages of AUD and approached from several perspectives. 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). Furthermore, it was demonstrated that craving was also positively associated with trait anxiety and it was negatively correlated with the duration of abstinence therefore it is essential to explore its impact (Mathew et al., 1979). In conclusion, comorbid conditions associated with alcohol use disorder 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.

VIII. MAIN FINDINGS AND CONCLUSIONS

In the present thesis, anxiety was examined comprehensively and defined differently in normal and clinical sample in case of the complication and comorbidity of alcohol use disorder (AUD). A total of four studies were conducted and several measurement tools were assigned due to the different characteristics of the participants. Among normal population, the changes of state anxiety were demonstrated simultaneously with the acute autonomic response of anxiety and the essential role of the gut brain-axis was emphasized. In the treatment-seeking AUD sample, anxiety accompanied the clinical process of AUD in different forms. Thus, anxiety appeared in alcohol withdrawal syndrome (AWS) and during rehabilitation, respectively. The course and the symptoms became measurable with the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) which was translated and validated by our research group. Furthermore, CIWA-Ar was validated with aggregated CIWA-Ar scores for the first time which demonstrated that the tool is ecological valid since it followed the course of AWS. According to the symptomatic analysis, anxiety was decreased during the 6 measurements. Furthermore, the key role of anxiety was seen during AWS which was confirmed by the psychometric analyses. Early rehabilitation was also examined where

comorbid gambling involvement which is one of the most common comorbid behavioral addiction in AUD was further studied regarding anxiety. For this purpose, the anxiety of AUD patients with and without gambling involvement was examined compared to a normative sample. Anxiety was indicated as Harm Avoidance temperament scale assessed by Temperament and Character Inventory, Revised (TCI-R). It was demonstrated that Harm Avoidance was higher in the two groups compared to the normative sample. However, when the AUD and AUD+GD groups were compared, the AUD+GD group showed a significantly higher Harm Avoidance than the AUD group. Consequently, anxiety was even more pronounced among AUD patients in case of symptoms of comorbid gambling involvement. The results demonstrated that the anxiety accompanied the clinical phase of AUD appearing in a different form which may determine the treatment planning and the outcome of treatment.

In the present thesis, evaluating the anxiety was investigated comprehensively by different ways. Anxiety response was observed in normal population using a physiological device and self-report questionnaire. In case of the clinical stages of AUD and comorbid gambling involvement, tools examining anxiety were assigned in each phase. A comprehensive measurement procedure is proposed to examine anxiety in AUD patients which includes a non-invasive physiological measurement, clinician's observations as well as self-report questionnaires. This measurement procedure can provide a holistic approach for the further investigation of AUD patients.

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 during rehabilitation and it was revealed in another form as temperament variable.
6. Anxiety is even more pronounced among alcohol use disorder 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 alcohol use disorder. 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 alcohol use disorder 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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