Clinical consequences of alcohol dependence syndrome: focusing on complicated withdrawal

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2. RESEARCH ARTICLES RELATED TO THE THESIS

1. Original research articles related to the thesis

1. **Kádár BK**, Gajdics J, Pribék IK, Andó B, Lázár BA. Characterization of alcohol-related seizures in withdrawal syndrome. EPILEPSIA OPEN 00:1-10. (2024)
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2. Pribék IK, **Kádár BK**, Péter L, Daróczy J, Bajsz A, Kovács CS, Demeter I, Janka Z, Urbán R, Demetrovics Zs, Lázár BA, Kovács I, Kálmán J, Andó B. Seasonality and Delirium Tremens in Hospitalized Patients with Alcohol Dependence Syndrome. EUROPEAN ADDICTION RESEARCH 29:83-91. (2023)
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2. Review article related to the thesis

1. **Kádár BK**, Pribék IK, Gajdics J, Szemelyácz J, Andó B, Lázár BA. Az alkoholmegvonásos szindróma ellátása: új perspektívák [Assessment of alcohol withdrawal syndrome: new perspectives] ORVOSI HETILAP 164: 1487-1496. (2023)
   SJR Indicator: Q4
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Cumulative impact factors of the papers related to the thesis: 8.5

3. ABRREVIATIONS

5-HT: 5-hyroxitriptophan

ADS: alcohol dependence syndrome

ARS: alcohol-related seizure

ASI: Addiction Severity Index

AUD: alcohol use disorder

AUDIT: Alcohol Use Disorder Identification Test

AWS: alcohol withdrawal syndrome

BZD: benzodiazepine

CIWA-Ar: Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised

CNS: central nervous system

COVID-19: coronavirus disease 2019

DA: dopamine

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

DT: delirium tremens

GABA: gamma-aminobutyric acid

GGT: gamma-glutamyl transferase

HPA: hypothalamo-pituitary-axis

ICD: International Classification of Disease

ICU: intensive care unit

MCV: mean corpuscular volume

NAc: nucleus accumbens

NIAA: National Institute on Alcohol Abuse and Alcoholism

NICE: National Institute for Health and Care Excellence

NMDA: N-methyl-D-aspartate

PAWSS: Prediction of Alcohol Withdrawal Severity Scale

SADQ: Severity of Alcohol Dependence Questionnaire

SAWS: severe alcohol withdrawal syndrome

SGOT: serum glutamic-oxaloacetic transaminase

SGPT: serum glutamic pyruvic transaminase

SUD: substance use disorder

VTA: ventral tegmental area

WHO: World Health Organization

2. INTRODUCTION

Alcohol dependence syndrome (ADS), one of the most common substance use problems worldwide, has great clinical significance (GBD 2016 Alcohol Collaborators, 2018). Alcohol-dependent patients usually receive a late diagnosis where various short-, mid-, and long-term consequences can be detected. Severe outcomes of ADS, such as seizure and delirium syndrome, are the most challenging complications for the healthcare system.

The course and outcome of ADS are influenced by various factors. These factors can be divided into three major groups: 1) sociological and environmental predictors ('external'); 2) demographic and 3) clinical or biological ('internal') risk factors.

Among the clinical consequences of ADS, it is important to highlight medical conditions that can be associated with serious complications. The most serious outcome is the complicated form of alcohol withdrawal syndrome (AWS). Complicated withdrawal syndrome includes alcohol-related seizures (ARS), and the most severe outcome of withdrawal syndrome with a high mortality rate is delirium tremens (DT).

The primary goal of the treatment is to prevent the development of complicated withdrawal syndrome, thus reducing the high mortality rate of ADS. Simultaneously, it is crucial for prevention to reveal the relationship between ADS, AWS, ARS, and DT, and the early recognition of risk factors for these conditions.

Therefore, the main purpose of the summarized studies in the present thesis was to assess the clinical consequences of ADS by focusing on the risk factors of complicated withdrawal.

2.1. ALCOHOL DEPENDENCE SYNDROME

2.1.1. Epidemiology and basic concepts of alcohol dependence syndrome

Alcohol use disorder (AUD), one of the most common forms of addictions and substance use disorders (SUD) (Horvat et al., 2018; Paksi et al., 2021; World Health Organization, 2018). The term AUD was introduced by the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), whereas ADS is used for the same diagnostic category in the 10 and 11 versions of the International Classification of Disease (ICD) (World Health Organization, 2016, 2019). Although it is a spectrum disorder, conditions of varying severity persist chronically without treatment, and mild cases can often become serious. For instance, a mild form of ADS can develop into a

severe form with regard to occurrence of internal and external risk factors. Whether it is an ADS caused by another psychiatric disease (‘dual disorder’) or a primary addiction, patients diagnosed with ADS place a heavy burden on the health and social care system as well as the economy (World Health Organization, 2018).

AUD or alcohol dependence is a significant public health problem worldwide; therefore, modern treatment is essential. The prevalence of ADS in Europe is 3.7 percent, four times higher among men than among women, but at the same time, the gender difference shows a decreasing trend (World Health Organization, 2018). In Hungary, according to the WHO report, nearly 1 million inhabitants (10%) have ADS (World Health Organization, 2018).

Because ADS is a spectrum disorder, the harmful or hazardous use of alcohol comprises the first stage of the development of the disorder, where a subgroup has ADS. However, in this group, there are two distinct subpopulations: patients with psychiatric diagnosis and ADS (“dual disorder”) and patients without psychiatric diagnosis but with ADS. This group can be referred to as primary addiction (Heilig et al., 2021; Volkow et al., 2020). Although ADS is a heterogeneous population, both primary and secondary forms share common neurobiological and psychological trajectories (Koob & Volkow, 2016).

2.1.2. Neurobiological and neurochemical background of alcohol dependence syndrome

Many neurobiological, psychological, and environmental factors play a role in ADS development. The importance of different psychological factors, such as novelty seeking, reward dependence, and impulsivity in the development and maintenance of ADS has been demonstrated (Cloninger et al., 1993; Foulds et al., 2017; Kovács et al., 2017). In addition to these psychological factors, well-defined neurobiological abnormalities have been identified (Koob & Volkow, 2016). These neurobiological changes cannot be considered as direct or indirect consequences of drug use. Nora Volkow and her colleagues revealed the main neuroanatomical structures and neurochemical abnormalities that play a role in the development and maintenance of ADS and other addictions (Koob & Volkow, 2016). In certain stages of addiction (pre-occupation, intoxication and negative), abnormalities of the prefrontal cortex, ventral striatum and the brainstem have been revealed, and these disturbances are primarily associated with shifts in the γ-aminobutyric acid (GABA), dopamine (DA), and opioid systems (Kumar et al., 2009; Volkow et al., 2007). In addition, it is worth emphasizing that in the case of ADS, chronic alcohol use also has significant mid-

and long-term neurochemical effects, which are responsible for the development of the short- and long-term consequences.

Chronic alcohol exposure changes both pre- and postsynaptic GABAergic transmission and GABA receptor expression. Downregulation of these receptors is one of the most marked changes and plays a pivotal role in both the maintenance of dependence and the development of complications (Krystal et al., 2003; Kumar et al., 2009).

The long-term inhibition of glutamate receptors, an inhibitory effect that primarily affects N-methyl-D-aspartate (NMDA) receptors, leads to receptor upregulation, which plays a primary role in the overactivity of the central nervous system (CNS) during withdrawal syndrome (Krystal et al., 2003; Kumar et al., 2009).

Moreover, the GABAergic inhibition of DAergic neurons in the ventral tegmental area (VTA) ceases under the influence of alcohol; consequently, the amount of DA in the mesolimbic system increases (Brodie, 2002; Volkow et al., 2007). This change persists during chronic alcohol use: the firing frequency of VTA DAergic neurons and basal DA levels in the nucleus accumbens (NAc) are increased (Brodie, 2002; Koob & Volkow, 2016; Volkow et al., 2007). In addition, increased peripheral and central noradrenalin activity was observed because of chronic alcohol use (Becker, 1998). Along with this, the activity of the hypothalamic-pituitary-adrenal (HPA) axis also changes: long-term alcohol use increases the release of corticotropin-releasing factor (CRF), thereby fundamentally increasing the activity of the HPA axis (Lee et al., 2001). The role of 5-HT and its receptors in the symptoms associated with alcohol use is not as significant as that of the other two monoamines; however, it is important to note that chronic alcohol use reduces the amount of 5-hyroxytriptophan (5HT) in certain brain regions, and indirectly through the serotoninergic receptor, alcohol affects DAergic neurotransmission (Becker, 1998; Maldonado, 2017).

2.1.3. Diagnosis of alcohol dependence syndrome

In addition to the specific short- and long-term effects of alcohol use, ADS is characterized by the same neuropsychiatric features as any other SUD. ADS and other SUDs are characterized by the following: 1) impaired control, 2) social impairment, 3) risky use of the substance, 4) craving, 5) tolerance, and 6) withdrawal symptoms (American Psychiatric Association, 2013).

The diagnosis of ADS is a clinical diagnosis based on DSM-5 and/or ICD-10 and -11 criteria (American Psychiatric Association, 2013; World Health Organization, 2016, 2019). Although specific biomarkers such as elevated liver enzymes, gamma-glutamyl transferase [GGT],

serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], SGOT/SGPT quotient, thrombocytopenia, and elevated mean corpuscular volume (MCV) have been revealed (Goodson et al., 2014; Wood et al., 2018), there are no specific biological tests for the diagnosis of ADS. However, the use of questionnaires and psychodiagnostics tools, such as Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2016), the Alcohol Use Disorder Identification Test (AUDIT) (Allen et al., 1997; Gerevich et al., 2005), the Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell et al., 1979, 1983) and Addiction Severity Index (McLellan et al., 1992; Rácz et al., 2002) play a pivotal role in screening and monitoring individuals with alcohol use problems. SCID-5 is a semi-structured interview based on the DSM-5 criteria that helps clinicians in the diagnosis of ADS (First et al., 2016). AUDIT is a screening tool and is routinely used during the follow-up of patients (Allen et al., 1997). While SADQ and ASI are useful in the detailed analysis of the severity of patients diagnosed with ADS (McLellan et al., 1992; Rácz et al., 2002; Stockwell et al., 1979, 1983).

The main treatment goals are to decrease the harmful use of alcohol, prevent relapse, and prevent hospital admission that results in potential alcohol withdrawal symptoms and possible severe, life-threatening complications.

2.1.4. Clinical consequences of alcohol dependence syndrome

Short- and long-term consequences must be expected because of the neural and metabolic side effects of chronic alcohol exposure. The long-term consequences of ADS, such as toxic encephalopathy and thiamine deficiency syndromes (Wernicke encephalopathy, Korsakoff syndrome) are diseases that mainly affect the social care system and are preventable (Hammoud & Jimenez-Shahed, 2019; Sarkar et al., 2017). The care and follow-up of these symptoms is mainly the responsibility of the psychiatric/addiction care system. Neurological and internal diseases such as polyneuropathy, certain liver diseases, reflux disease, acute hemorrhagic gastritis, and certain tumors fall under the scope of allied professions. Among the short- and medium-term complications, AWS should be highlighted.

Alcohol-dependent individuals with regularly or irregularly presenting AWS comprise a special subpopulation. However, we lack any data on the exact proportion of this subgroup. Various reports have shown that approximately 20% of patients with ADS receive treatment, and approximately 50% of alcohol-dependent patients are affected by withdrawal symptoms during their life (Maldonado et al., 2014; Schuckit, 2014).

2.2. ALCOHOL WITHDRAWAL SYNDROME

AWS is a potentially life-threatening complex neuropsychiatric disorder, and its treatment requires internal medicine, neurological and psychiatric knowledge. As mentioned above, more than half of the patients diagnosed with ADS suffer from AWS (Maldonado et al., 2014; Schuckit, 2014). Furthermore, it has been revealed that the incidence of AWS in intensive care units is approximately 30% (Suchyta et al., 2008).

Based on the occurrence of severe clinical consequences, two forms of AWS can be separated: uncomplicated and complicated or severe alcohol withdrawal syndrome (SAWS). Approximately 10%–20% of hospital admissions with AWS are characterized by a complicated form of AWS, where seizures or delirious symptoms occur (Maldonado et al., 2014).

2.2.1 Neurochemical background and symptoms of alcohol withdrawal syndrome

Overall, AWS can be characterized by overactivity of the CNS. From a neurochemical and neurophysiological point of view, the symptoms are based on glutamate-induced excitation, the cessation of GABAergic action, excessive adrenergic action, hyperactivity of the HPA axis, and the resulting dysfunction of dopaminergic and serotonergic transmission (Jesse et al., 2017). Typical symptoms of AWS can be separated into two larger groups: 1) psychiatric and neurological symptoms (anxiety, agitation, tremors), which are mainly explained by the intense glutamate effect and dopamine imbalance and 2) the symptoms associated with the overactivity of the autonomous nervous system (tachycardia, blood pressure increase, nausea, headache) are mainly explained by the high adrenergic effect and the overactivity of the HPA axis (Becker, 1998; Hall & Zador, 1997; Maldonado, 2017).

2.2.2. The course of alcohol withdrawal syndrome and the basic concept of complicated withdrawal

The withdrawal symptoms appear approximately 8–24 h after the last alcohol consumption. The literature organizes the withdrawal syndrome in different ways in terms of the quality and severity of symptoms. In the case of uncomplicated withdrawal, which occurs in nearly 80% of patients, it is mostly mild– moderate withdrawal symptoms that do not require inpatient care. Another common feature of uncomplicated AWS is that seizure and/or signs of DT are not present. When seizures and/or signs of DT with symptoms of withdrawal occur, complicated AWS can be detected (Goodson et al., 2014; Hall & Zador, 1997; Maldonado, 2017; Wood et al., 2018).

In addition to the non-complicated and complicated classification, withdrawal syndrome can be described as a symptom spectrum disorder. It is worth mentioning that while mild and moderately severe withdrawal does not pose a risk for the development of seizures and DT, severe AWS is a clear risk factor for the development of DT and seizures, and it can even be assumed that delirium syndrome is the most severe form of the withdrawal symptom group (Jesse et al., 2017; Maldonado et al., 2014).

Generally, anxiety, nausea and vomiting, and tremors are the first and most common symptoms of withdrawal syndrome. As withdrawal syndrome worsens, symptoms associated with vegetative hyperactivity appear, such as paroxysmal sweats, increased blood pressure, tachycardia, nausea, headache, and severe anxiety and psychomotor agitation due to intense CNS activity. However, relevant reliable literature data clearly draw attention to the special importance of risk factors for seizures and DT during the care of patients with AWS (Becker, 1998; Hall & Zador, 1997; Maldonado, 2017).

2.2.3. Risk factors of alcohol withdrawal syndrome

During the past few decades, papers published in the field of withdrawal syndrome have focused on the assessment of risk factors for SAWS or complicated withdrawal syndrome (Wood et al., 2018).

However, the importance of medical history and laboratory biomarkers has been indicated (Jesse et al., 2017). Blood ethanol concentration, hypokalemia, thrombocytopenia, MCV, GGT, and SGOT/SGPT ratio higher than 2 are relevant biomarkers for future episodes of withdrawal syndrome (Jesse et al., 2017; Wood et al., 2018). Furthermore, previous episodes of AWS are the most robust predictors of the occurrence of withdrawal symptoms (Jesse et al., 2017).

In addition to medical history and biomarkers, questionnaires such as the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) (Lázár et al., 2019; Sullivan et al., 1989), the Richmond Agitation-Sedation Scale (Sessler et al., 2002), and the Prediction of Alcohol Withdrawal Severity Scale (PAWSS)(Maldonado et al., 2014) play a pivotal role during the risk assessment and treatment of AWS.

2.2.4. Diagnosis and treatment of alcohol withdrawal syndrome

AWS diagnosis is based on clinical signs not explained by other disorders (American Psychiatric Association, 2013). Furthermore, the diagnosis of ADS and auto- and

heteroanamnestic data are helpful in separating symptoms from other neurological or internal medicine disorders.

Although there is no biological tool for the diagnosis, specific symptom assessment scales are available for the screening and follow-up of patients with withdrawal syndrome. The CIWA-A was the first symptom assessment scale for AWS which was modified and the CIWA-AR was introduced (Manikant et al., 1992; Shaw et al., 1981; Sullivan et al., 1989). CIWA-Ar is a 10-item scale that reflects the major symptoms of withdrawal syndrome, such as nausea/vomiting, tremor, paroxysmal sweats, perceptual (tactile, visual, auditory) disturbances, anxiety, agitation, headache, and disturbance of orientation and/or consciousness (Lázár et al., 2019; Pribék et al., 2021; Sullivan et al., 1989). Each item is scored using a Likert scale, with a maximum score of 67, where a higher score reflects more severe withdrawal syndrome. Several studies have suggested that CIWA-Ar has high reliability and validity (Foy et al., 1988; Lázár et al., 2019; Sullivan et al., 1989). However, it has been demonstrated that during the first phase (six days) of AWS, CIWA-Ar scores show a higher internal consistency (Lázár et al., 2019). It has also been revealed that CIWA-Ar follows the course of AWS and ecologically valid (Pribék et al., 2021; Wood et al., 2018). Nevertheless, CIWA-Ar has been translated into various languages, and guidelines such as the protocols of the National Institute for Health and Care Excellence (NICE) recommend it as a gold standard tool in the management of AWS (NICE, 2011).

Treatment of AWS is based on benzodiazepine (BZD) therapy. BZDs as potent agonists of GABA receptor type A decrease the hyperactivity of CNS (Maldonado, 2017). There are two ways to use BZDs: fix-schedule doses and symptom-triggered therapies. In recent years, several reports have suggested that considering the sedative and long-term (e.g. cognitive decline) side effects of BZDs and the longer duration of hospitalization, the symptom-triggered approach is a better choice during treatment. However, the use of symptom assessment scales, such as the CIWA-Ar, is necessary for symptom-trigged therapies (Maldonado, 2017). In addition to the efficacy of BZD treatment, previous findings revealed that some non-BZD drugs, such as antiepileptics and α2-adrenergic receptor antagonists (e.g. clonidine, dexmedetomidine), may have similar efficacy (Maldonado, 2017).

Nonetheless, despite diminishing withdrawal symptoms being one of the most important treatment goals, preventing the development of DT, the most severe consequence of AWS, bears critical importance because of its high mortality rate.

2.3. DELIRIUM TREMENS

DT is the most severe consequence of withdrawal and occurs in 5%–15% of patients with AD; its mortality can reach 5% even with optimal therapy (Maldonado, 2008; Wood et al., 2018). Although the prevention and treatment of DT is a major public health priority, it is usually overlooked and misdiagnosed.

2.3.1. The background of delirium syndrome

Delirium syndrome is a group of symptoms characterized by an acute change in consciousness, attention, and other aspects of cognition (e.g. memory deficit, disorientation). Furthermore, other psychiatric symptoms can occur during delirium, such as visual hallucinations, delusions, and severe agitation (Wilson et al., 2020).

Gibb and his colleagues revealed that the prevalence of delirium is 23% among inpatients (Gibb et al., 2020). Furthermore, a prevalence of 31.8% has been reported among ventilated and non-ventilated intensive care unit (ICU) patients (Krewulak et al., 2018). Although the prevalence of delirium has not yet been well determined because of various factors (e.g. cohorts, type of medical settings, used screening tool), its examination is of critical importance because of its association with adverse short- and long-term outcomes (e.g. malignant arrhythmia, respiratory arrest, increased post-discharge mortality).

Delirium is triggered by various causes including sepsis, stroke, hypoxia, hypoglycemia, surgery (‘post-operative’), substance toxicity (e.g. amphetamine, heroin), and substance withdrawal (e.g. alcohol) (Wilson et al., 2020). Clinical subtypes of delirium vary from hyperactive, hypoactive, and mixed. It has been revealed that hypoactive delirium is the most frequent among critically ill patients (Krewulak et al., 2018; Tiwari et al., 2023). This classification reflects only the manifestation of symptoms, however, regarding the various etiological factors, there are pathophysiological, clinical, and treatment differences between distinct subtypes of delirium syndromes.

2.3.2. The basic concept and the background of delirium tremens

A special subtype of delirium associated with AWS is DT (Schuckit et al., 1995). The term DT was proposed by Thomas Sutton at the beginning of the nineteenth century as a severe neuropsychiatric syndrome caused by excessive drinking and described with severe withdrawal symptoms, disturbance of consciousness, and tremor (Maldonado, 2008; Maldonado et al., 2014; Schuckit et al., 1995; Sutton, 1813).

The neurochemical changes that occur in withdrawal syndrome, which in the case of delirium can primarily be traced back to the disruption of the balance of the dopaminergic and noradrenergic systems, create a secondarily developing complex neural dysfunction, which leads to the disruption of the vigilance and integrity of consciousness (Gibb et al., 2020). Therefore, DT is characterized by classic neuropsychiatric symptoms of delirium syndrome and symptoms of severe withdrawal syndrome. However, symptoms can be mainly explained by a severe imbalance in the autonomic nervous system and dopaminergic pathways (Maldonado, 2008; Sarkar et al., 2017; Wilson et al., 2020).

2.3.3. The symptoms and the course of delirium tremens

As a complicated withdrawal syndrome, symptom characteristics are usually described by severe withdrawal syndrome (e.g. tremor, anxiety, paroxysmal sweats, etc.) and symptoms of delirium (e.g. agitation, disorientation, hallucinations, delusions, autonomic hyperactivity).

Severe autonomic hyperactivity can lead to life-threatening complications such as prolonged seizures, respiratory arrest, malignant arrhythmias, and increased risk of nosocomial infections caused by prolonged hospitalization, etc.. Therefore, the recognition of risk factors and possible contributing factors is of critical importance for preventing the most severe eventuality of ADS (Goodson et al., 2014; Maldonado, 2008; Sarkar et al., 2017; Wilson et al., 2020; Wood et al., 2018).

2.3.4. Risk factors of delirium tremens

During the past few decades, several potential predictors of DT have been identified.

Demographic or sociodemographic risk factors include older age. Clinical risk factors include the co-occurrence of somatic disorders (e.g. diabetes mellitus, coronary artery disease, hypertension, or chronic obstructive pulmonary disease), low sodium and potassium levels, SGOT/SGPT higher than two, high blood pressure and pulse, history of SAWS, seizures, and DT (Goodson et al., 2014; Wood et al., 2018). Interestingly, previous reports have suggested that the co-occurrence of psychiatric co-morbidities were also predictors for developing DT during the COVID-19 pandemic (Gajdics et al., 2023).

A meta-analysis of Wood and his colleagues assessing the risk factors of SAWS, DT, and seizures by analyzing 530 studies in a period of 72 years (1946-2018) were revealed that a history of DT and systolic blood pressure higher than 140 mm Hg are associated with an increased likelihood of SAWS (Wood et al., 2018). Moreover, it has been revealed that patients who had three or more seizures during their alcohol cessation attempt had an

increased risk for developing DT. Interestingly, it has been shown that seizures are stronger risks for predicting DT than SAWS (Wood et al., 2018). Additionally, it has also been demonstrated that males had a higher risk for developing SAWS, and in agreement with the COVID-19 study (Gajdics et al., 2023), it has also been shown that co-occurred mental disorders and other comorbid SUDs are a predictor for SAWS (Wood et al., 2018).

2.3.5. The potential role of seasonality in the development of delirium tremens

In recent years, it has been revealed that DT has some sociological risk factors, such as employment status or housing insecurity (Doran et al., 2018). Although it has been previously reported that other environmental factors, such as seasonality, modulate the drinking pattern or frequency of nicotine use (Carpenter, 2003; Cho et al., 2001; Ventura-Cots et al., 2019), there are no data on the interplay between DT and seasonality.

However, the impact of seasonality on the human body has already been investigated from numerous aspects. For instance, it has been shown that temperature and sunshine duration affect vitamin levels, circadian rhythm, and physical activity. It has also been demonstrated that seasonality influences the development of some psychiatric (e.g. seasonal affective disorder) (Denissen et al., 2008; Morales-Muñoz et al., 2017) and somatic (e.g. pancreatitis) disorders (Balcells et al., 2017; Gallerani & Manfredini, 2013).

Studies in the field of addictions have reported that the seasons have an impact on nicotine use and drinking behavior. Cho and his colleagues have revealed that binge drinking is increased during January and July (Cho et al., 2001). This ‘January effect' on alcohol consumption has been confirmed by other authors (Carpenter, 2003; Ventura-Cots et al., 2019). On the other hand, it has also been demonstrated that the incidence of delirium syndrome among geriatric inpatients was higher in winter (Balan et al., 2001). Regarding that several studies have suggested the effect of seasons on the development of various psychiatric and somatic disorders, and there are no available data on the association between seasonality and DT, the role of seasonality should be examined as a potential contributing factor in the incidence of DT.

Overall, despite environmental risk factors, most studies have demonstrated clinical predictors for the development of DT; however, the connection of DT with seizures occurring during AWS has not yet been revealed in detail. Some studies suggest that this type of seizure, alcohol-related seizure (ARS), is dependent on the severity of AWS and is a predictor of DT development (Kim et al., 2015; Maldonado et al., 2014). Other studies have demonstrated that

ARS is a symptom of SAWS and not a ‘classic’ risk factor of DT (Wood et al., 2018). Nevertheless, the clinical characteristics of ARS are still poorly understood.

2.4. ALCOHOL-RELATED SEIZURE

In the past few years, the significance of ARS during withdrawal syndrome and the risk assessment of future episodes of AWS and/or seizures have been demonstrated (Eyer et al., 2011; Jesse et al., 2017; Wood et al., 2018). Furthermore, its role in the development of DT has been highlighted. Therefore, the investigation of the clinical aspects of seizures associated with withdrawal syndrome is substantial.

2.4.1. The basic concept of alcohol-related seizure

According to the definition and concept of the *International League Against Epilepsy* and articles about the severe complications of AWS, seizures occurring during a withdrawal syndrome are provoked seizures (Fisher et al., 2014; Wirrell et al., 2022). Additionally, Victor and Brausch, who first described the term ARS, defined this type of seizure as generalized tonic-clonic seizures (’rum fits’) that occur during alcohol withdrawal (Victor & Brausch, 1967). Although various studies have demonstrated that ARS is closely related to SAWS, all seizures associated with alcohol use, including ADS and DT, are usually defined as ARS (Eyer et al., 2011; Kim et al., 2015; Victor & Brausch, 1967).

2.4.2. Epidemiology and consequences of alcohol-related seizure

Regarding the prevalence of ARS, there is heterogeneity in the literature. Most studies have demonstrated that the prevalence of ARS among alcohol-dependent individuals is approximately 5%–30% (Eyer et al., 2011; Maldonado et al., 2014; Rathlev et al., 2006). Nevertheless, most studies have indicated a relatively high mortality rate (1-3%) due to the development of status epilepticus, traumatic brain injury or Sudden Unexpected Death in Epilepsy (Devinsky et al., 2016; Foster et al., 2019; Long et al., 2017). On the other hand, considering that this type of seizure may be a potential predictor of the development of DT, preventing ARS during AWS is important in reducing the lethal complication of DT (Becker, 1998, 2012; Hillemacher et al., 2012).

2.4.3. Background of alcohol-related seizure

The relationship between ARS and alcohol use was recently investigated (Samokhvalov et al., 2010). Several reports have suggested that there is a complex interplay between alcohol

consumption and seizures (Samokhvalov et al., 2010). Chronic alcohol exposure leads to various mid-term and long-term complications in the CNS, leading to structural and functional changes. It has been demonstrated that patients with ADS have cerebral atrophy, which may precipitate seizures or epilepsy syndrome in the future (Samokhvalov et al., 2010). Furthermore, some studies have suggested that brain lesions caused by head traumas are more prevalent among alcohol-dependent individuals, and thus, patients with ADS are more sensitive to developing seizures (Rathlev et al., 2006; Samokhvalov et al., 2010). Other authors have indicated the significance of the kindling mechanism. Ballenger and Post (1978) proposed the theory of kindling by reporting that repeated withdrawal syndrome leads to a gradual lowering of the epileptogenic threshold (Ballenger & Post, 1978).

During the past few decades, the importance of the kindling mechanism in the development of ARS has been supported by various authors (Becker, 1998; Eyer et al., 2011; Hillemacher et al., 2012; Jarvis & Becker, 1998; Morton et al., 1994; Zhang et al., 2007). Despite all this, it is assumed that neurochemical changes (e.g. glutamatergic hyperexcitation, decreased level of GABA) are the most important regulators of the development of seizure during withdrawal syndrome. Nevertheless, individual vulnerability was demonstrated. Moreover, it has been indicated that the genetic, biological, and molecular background of ARS is different from those of other provoked seizures (Alberto et al., 2023; Fu et al., 2016; Gorwood et al., 2003; Grzywacz et al., 2012; Pestana et al., 2019; Zhou et al., 2022).

2.4.4. Risk factors of alcohol-related seizure

From a clinical point of view, ARS generally occurs once during the first phase of AWS, i.e., 12–48 hours after the abrupt cessation of alcohol intake. However, the literature contradicts the presence of seizures during withdrawal. Some studies have indicated that the occurrence of seizures anticipates the presence of DT, whereas other reports have suggested that seizures are a part or symptom of DT. Interestingly, patients suffering from both ARS and DT may represent a specific genetically determined subgroup of alcohol-dependent individuals (Gorwood et al., 2003; Grzywacz et al., 2012; Pestana et al., 2019).

In summary, withdrawal seizures have a great significance during AWS, and considering their relationship with DT, their prevention is critical regarding the lethal complications of DT. However, the predictors of ARS have not yet been understood in detail.

Some reports have revealed that male sex, older age, and history of ARS are risk factors for developing future episodes of seizures during withdrawal syndrome (Wood et al., 2018).

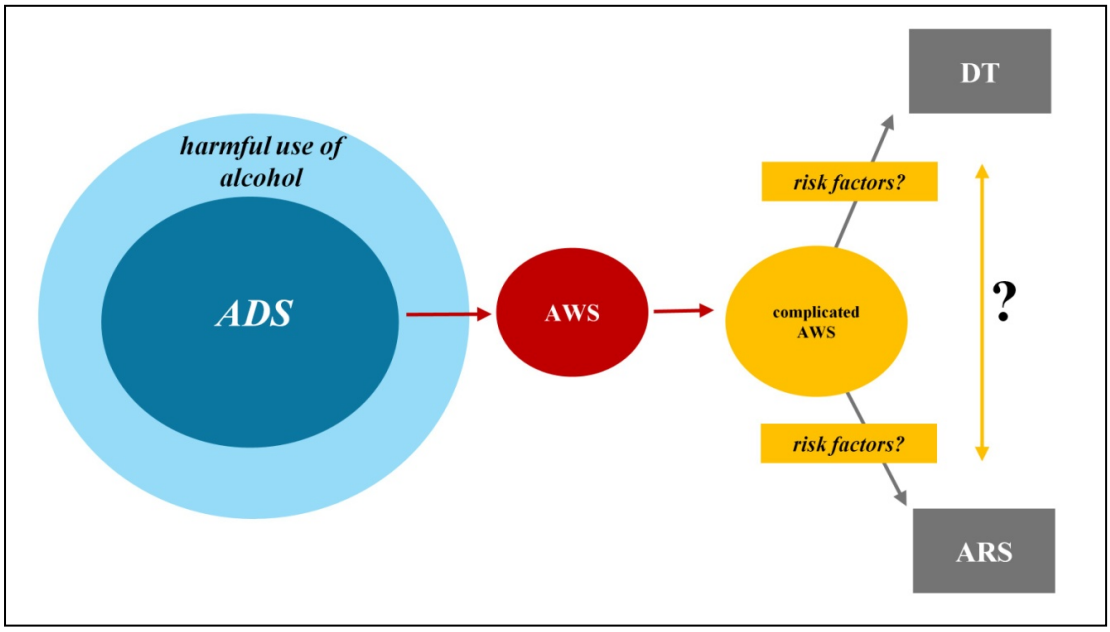
Furthermore, a retrospective cohort study published by Eyer, and his colleagues has demonstrated that patients with ARS showed a significant delay of withdrawal severity measured with a modified version of CIWA-Ar compared with patients without seizures. In addition, this study revealed a higher incidence of reported seizures during withdrawal episodes, a higher number of structural brain lesions, and a higher incidence of an ARS diagnosis on hospitalization in the subgroups of inpatients with seizures (Eyer et al., 2011).

Furthermore, in the original version of the CIWA-Ar, the CIWA-A scale had 15 items (Manikant et al., 1992; Shaw et al., 1981), with seizure being one of them. After the validation of the original version, several papers have demonstrated that the seizure item influenced the total score incorrectly and did not reflect the clinical condition. For instance, post-ictal contusion changed the total score. Therefore, this item was dropped from the revised version (Foy et al., 1988; Manikant et al., 1992; Sellers et al., 1983; Shaw et al., 1981; Sullivan et al., 1989).

2.5. SUMMARY: THE CLINICAL SIGNIFICANCE OF COMPLICATED WITHDRAWAL SYNDROME

Individuals with harmful use of alcohol comprise a specific high-risk population for developing alcohol dependence, as shown in Figure 1. This figure shows that patients with ADS have a high risk of developing AWS during the course of their disorder. The occurrence of AWS depends on various ‘internal’ and ‘external’ risk factors. AWS is the most common clinical complication of ADS and may have severe consequences, such as DT and/or ARS. These conditions comprise the complicated withdrawal syndrome. Overall, in Figure 1 the course of these conditions is summarized (Fig. 1.).

Figure 1. The model of the course of alcohol dependence syndrome (ADS) and related research questions.



Abbreviations: ADS, alcohol dependence syndrome; AWS, alcohol withdrawal syndrome; DT, delirium tremens; ARS, alcohol-related seizure

Although several articles during the past few decades have demonstrated the sociodemographic and clinical predictors of DT development (Wood et al., 2018), 'external' or environmental risk factors are still poorly understood. Furthermore, the significance of ARS in the case of the severity of withdrawal symptoms and the development of DT are controversial (Jesse et al., 2017; Kim et al., 2015; Wood et al., 2018). However, some studies have revealed the importance of seizures because of their mortality and its connection with DT (Kim et al., 2015). Nonetheless, the clinical characteristics of this type of seizure remain largely unknown (Fig.1.). Consequently, as Figure 1 illustrates, the primary research questions are: what is the relationship between the occurrence of ARS and DT, and are there any additional "external" or "internal" risk factors for the development of complicated withdrawal syndrome?

In summary, the assessment of the clinical consequences of ADS by focusing on the characterization of complicated withdrawal syndrome leads to a better understanding of the nature and course of the disorder and helps prevent lethal complications by forming new diagnostic and therapeutic algorithms.

3. AIMS

The clinical importance of AWS has been demonstrated in various studies. The complicated form of withdrawal syndrome, which includes ARS and DT, has the potential to develop severe consequences. Therefore, the optimal diagnosis and management of complicated AWS reduces the mortality of patients with ADS. Thus, the characterization of the risk factors for ARS and DT will lead to a comprehensive understanding of AWS. Although several predictors have been previously revealed, external risks of DT, clinical features of ARS, and the connection between ARS and DT, and the severity of AWS in clinical settings have not yet been evaluated in detail.

In the present thesis, three studies were conducted in which complicated AWS was examined by focusing on the characteristics and risk factors of DT and ARS.

In Study 1, the sociodemographic, clinical, and environmental factors of DT were examined in a retrospective study with an emphasis on revealing the role of seasonality. In this retrospective study, medical charts of inpatient admissions with the principal diagnosis of ADS were examined (*Study 1*).

In the case of ARS, a retrospective and follow-up study was conducted (*Study 2 and 3*). Therefore, these studies allowed for a complex investigation of complicated withdrawal syndrome and detailed analysis of ARS in a clinical setting.

In Study 2, in a retrospective study, the sociodemographic and clinical characteristics in connection with and without ARS diagnosis were revealed (*Study 2*). The interplay between ARS and DT was also examined in this study (*Study 2*). In this retrospective study, medical charts of inpatient admissions with the principal diagnosis of AWS were collected.

In Study 3, the relationship between ARS and the severity of withdrawal syndrome was assessed in a follow-up study in which patients with AWS with or without seizures were enrolled (*Study 3*). Furthermore, the severity of AWS was measured using CIWA-Ar. In this follow-up study, patients with the principal diagnosis of AWS were recruited (*Study 3*).

The present thesis addresses three main objectives.

Aim 1: Previous studies have revealed various sociodemographic and clinical predictors of DT development. It has also been demonstrated that the seasons can influence several mental and somatic disorders. Therefore, our first aim was to investigate the clinical characteristics and risk factors of DT and its relationship with seasons in a retrospective study (*Study 1*).

Regarding that DT is the most severe eventuality during the course of ADS, DT was examined among medical charts with a principal diagnosis of ADS, where medical charts with the diagnosis of (1) ADS, (2) ADS and AWS, (3) ADS and DT were separated.

Aim 2: Occasional, provoked seizure occurring during withdrawal syndrome has great clinical significance with regard to the long-term consequences of seizures, mortality rate, and potential connection with DT. However, there is lack of detailed data on the clinical characteristics of this type of seizure. Some studies have demonstrated that kindling is one of the most important mechanisms underlying the development of ARS and complicated AWS. Therefore, our aims were to reveal the clinical features of ARS and its risk factors by focusing on indirect factors of kindling, such as previous episodes of ARS, DT, and AWS, and to determine the relationship between the occurrence of ARS and the development of DT in a retrospective study (*Study 2*). Regarding that the occurrence of ARS is mostly related to withdrawal syndrome, ARS was examined among medical charts with a principal diagnosis of AWS, where medical charts with the diagnosis of AWS with and without ARS were separated.

Aim 3: Some studies have demonstrated that the severity of AWS is affected by the occurrence of ARS. However, some authors have suggested that the severity of AWS may be independent of the presence of seizures. The 'gold standard' objective tool to measure the severity of withdrawal syndrome is the CIWA-Ar. Therefore, the main goal of this study (*Study 3*) was to examine the relationship between the occurrence of ARS and the severity of AWS measured by the CIWA-Ar in a follow-up study with patients hospitalized with the principal diagnosis of AWS.

4. METHODS

In this thesis, three studies are summarized. In Study 1, considering that DT is the most severe consequence of ADS, we examined its clinical characteristics and predictors focusing the role of seasonality. Because ARS is a marked risk factor for the development of DT and plays a pivotal role during AWS, the clinical features and predictors of DT were revealed in Study 2. Furthermore, several reports have suggested that the occurrence of ARS is modulated by the severity of AWS (Maldonado et al., 2014). Therefore, the relationship between the presence of ARS and the severity of AWS was assessed in Study 3.

4.1. Study 1: Clinical characteristics and predictors of delirium tremens: the role of seasonality

4.1.1. Setting

In Study 1, the clinical characteristics, predictors of DT and the role of seasonality in the occurrence of DT were examined in a retrospective database.

Data were collected from 2900 medical charts of 1591 inpatients at the Department of Psychiatry, University of Szeged, Hungary from 2008 to 2015.

The inclusion criteria were medical charts with the principal diagnoses of alcohol dependence syndrome (ADS; F10.20).

Demographic variables (age, sex), seasonality [defined by meteorological seasons: winter (1 December – 28/29 February), spring (1 March – 31 May), summer (1 June – 31 August) and autumn (1 September – 30 November)], year and month of admission, housing situation (recorded permanent address or no record of it), somatic and psychiatric co-morbidities, the occurrence of AWS and DT were collected from the medical charts of inpatient admissions.

Three groups were formed based on ICD-10 diagnoses. Medical charts characterized by the principal diagnosis of ADS without the diagnoses of AWS and/or DT were assigned to the (1) ADS group. Medical charts characterized by the principal diagnosis of AWS without DT, and AWS with DT were classified into the (2) AWS or (3) DT groups.

Every patient received pharmacological treatment (e.g., benzodiazepines and/or antiepileptic drugs) based on the severity of their physiological state.

This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Human Investigation Review Board, University of Szeged (ethical approval numbers: 30/2016-SZTE).

4.1.2. Statistical analysis

All statistical analyses were performed using IBM SPSS 24 (IBM Corp. Released 2016., 2016).

First, we analyzed the differences among the three groups (ADS, AWS, and DT) regarding sociodemographic variables, as these were controlled in the subsequent exploration of potential predictors of AWS and DT. ANOVA was calculated to explore age differences, and chi-square tests were used to analyze the rate of homelessness and the presence of comorbid somatic and psychiatric disorders. Further chi-square tests were conducted to explore the seasonality rates of the three groups as well as the monthly and seasonal breakdowns of the DT. We conducted two multinomial logistic regression analyses to compare the predictive variables for the three groups.

In the first multinomial logistic regression analysis, the dependent variable was the three-group distinction, with the ADS group as the reference group. In the second multinomial logistic regression, the three-group breakdown was also used as the dependent variable, with the AWS group as the reference group. Independent variables (age, sex, homelessness, comorbid somatic disorder, comorbid psychiatric disorder, and seasonality) were the same factors for both multinomial logistic analyses. Sociodemographic and clinical variables were also controlled in the analysis. Statistical significance was considered if $p \leq 0.05$.

4.2. Study 2: Clinical characteristics and predictors of alcohol-related seizure

Previous studies have revealed that ARS is one of the most important predictors of DT. Preventing the development of DT bears critical importance with regard to its lethal consequences. Hence, evaluating the predictors of ARS and its presence with the connection of the development of DT may reduce the consequences of ADS. Therefore, in Study 2, clinical characteristics and predictors of ARS and the interplay between the presence of ARS and the occurrence of DT were examined among medical charts with the diagnosis of AWS in a retrospective database.

4.2.1. Setting

Data were collected from 2851 medical charts of 1630 inpatients at the Department of Psychiatry, University of Szeged, Hungary from 2008 to 2022.

The inclusion criteria were medical charts with principal diagnoses of AWS (F10.30) and/or DT (F10.40).

The ARS variable was defined as the occurrence of diagnoses of occasional, provoked seizures according to the ICD-10. Medical charts with diagnoses of epilepsy syndromes and BZD use disorders were excluded.

The patients hospitalized during this period were treated with the same pharmacological therapy (fixed-schedule doses of BZD).

Demographic variables (age and sex), somatic and psychiatric co-morbidities, levels of electrolytes (sodium, potassium) and liver enzymes (GGT, SGOT, SGPT and SGOT/SGPT quotient) and the history of AWS, DT, and ARS were collected from medical charts of inpatient admissions.

Two groups were formed based on the occurrence of ARS: AWS coursed with (ARS^+) and without ARS (ARS^-).

Demographic variables, laboratory parameters, and the co-occurrence of comorbid disorders were analyzed in both groups. Evaluation of risk factors for the development of ARS was performed. ARS was also identified as a risk factor for DT.

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Human Investigation Review Board of the University of Szeged (ethical approval numbers: 30/2016-SZTE; 82/2022-SZTE).

4.2.2. Statistical analysis

All statistical analyses were performed using IBM SPSS 24 (IBM Corp. Released 2016., 2016).

Chi square tests and independent sample t-tests were used to compare the ratio of the presence of ARS in the total sample and the ratio of demographic variables, laboratory parameters, and comorbid disorders in the ARS^+ and ARS^- subgroups and the DT^+ and DT^- subgroups.

Multinomial logistic regression models were used to determine the variables that explain the appearance of ARS and DT. The dependent variables were the occurrence of ARS and the appearance of DT. The independent variables were those that showed a significant difference between the two groups, and when DT was the dependent variable, ARS was the independent variable.

4.3. Study 3: Assessing the relationship between the presence of alcohol-related seizure and the severity of alcohol withdrawal syndrome

The literature is contradictory regarding the relationship between the presence of ARS and the severity of withdrawal symptoms. Therefore, considering the therapeutic consequences of this question, we examined the course of AWS and its connection with ARS in a follow-up study.

4.3.1. Setting

Patients admitted with a diagnosis of AWS (F.10.30) at the inpatient units of the Department of Psychiatry, University of Szeged, Hungary between 2019 and 2020 were enrolled in this study.

The inclusion criteria were as follows: 1) diagnosis of alcohol dependence syndrome (F.10.20.); 2) diagnosis of AWS (F.10.30.); 3) a minimum of 7 points on the first CIWA-Ar; 4) fixed-schedule regimen with chlordiazepoxide.

The exclusion criteria were as follows: 1) symptoms of delirium tremens; 2) presence of epilepsy syndrome; 3) clinically significant changes in electrolyte levels and liver enzymes; 4) clinically significant somatic and/or neurological disorders; 5) diagnosis of epilepsy syndrome; and 6) BZD use disorder.

The patients hospitalized during this period were treated with the same pharmacological therapy (fixed-schedule doses of BZD).

Following informed consent, each patient who voluntarily enrolled in the study was administered a test pack 6 times every 2 days for 10 days. The study of alcohol consumption habits and withdrawal symptoms was part of the inpatient care. These tests were recorded by a physician experienced in the use of these tests.

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Human Investigation Review Board, University of Szeged (ethical approval number: 28/2018-SZTE).

4.3.2. Measurement methods

At first, a set of demographic questions and the AUDIT were taken in the form of an interview. During the next five visits, the CIWA-Ar was administered. Furthermore, laboratory parameters (sodium levels, SGGT, SGOT/SGPT quotient) and the occurrence of ARS were recorded.

4.3.3. Statistical analysis

All statistical analyses were performed using IBM SPSS 24 (IBM Corp. Released 2016., 2016).

An independent sample t-test was used to compare the mean AUDIT scores between the ARS^{+} and ARS groups. Mixed ANOVA was used to evaluate changes in the CIWA-Ar scores.

5. RESULTS

5.1. Study 1: Clinical characteristics and predictors of delirium tremens: the role of seasonality

5.1.1. Sample characteristics

In the analyses 2900 medical charts of inpatient (N=1591) admissions were included with the relevant ICD-10 diagnoses. In the total sample, 17.3% of the medical charts were characterized with ADS without AWS and DT (ADS group; N = 502), 70.5% of the medical charts with AWS without DT (AWS group; N = 2045) and 12.2% of the medical charts were characterized with DT (DT group; N = 353).

5.1.2. Clinical characteristics of alcohol dependence syndrome, alcohol withdrawal syndrome and delirium tremens

Table 1 compares socio-demographic variables in the case of ADS, AWS, and DT. Co-occurrences of somatic and psychiatric disorders in the three groups were analyzed. As detailed in Table 1, there was a significant difference in the rate of comorbid somatic disorders among the three groups (χ^2 (2) = 120.847; $p < 0.001$); DT had the highest rate (73.08%) of co-occurring somatic diseases. As for co-morbid mental disorders, the three groups also differed significantly (χ^2 (2) = 178.239; $p < 0.001$) with ADS having the highest rate (68.92%) (Table 1.).

Table 1. Characteristics of medical charts in regard of alcohol dependence and its complications (alcohol withdrawal syndrome and delirium tremens).

	ADS (N= 502)	**AWS** (N= 2045)	**DT** (N=353)
Mean Age (SE)	49.73 (0.576)	48.71 (0.238)	55.21 (0.552) *
Male Sex N (%)	386 (76.89)	1619 (79.17)	280 (79.32)
Homelessness N (%)	26 (5.19)	137 (6.7)	19 (5.41)
Seasons			
Spring N (%)	113 (22.5)	495 (24.2)	130 (36.8) *
Summer N (%)	149 (29.7)	513 (25.1)	79 (22.4)
Autumn N (%)	114 (22.7)	518 (25.3)	69 (19.5)
Winter N (%)	126 (25.1)	519 (25.4)	75 (21.2)

Comorbid somatic disorders N (%)	198 (39.44)	877 (42.89)	258 (73.08) *
Comorbid psychiatric disorders N (%)	346 (68.92)	984 (48.14)	80 (22.66) *

*Abbreviations: ADS, alcohol dependence syndrome without alcohol withdrawal state or delirium tremens; AWS, alcohol withdrawal state without delirium tremens; DT, alcohol withdrawal state with delirium; SE, standard error; * = $p < 0.001$.*

5.1.3. Clinical predictors and the role of seasonality in delirium tremens

In the first multinomial logistic regression analysis, the potential predictors of AWS and DT were examined. The ADS group was the reference group in this model (Table 2.). The predictors of ADS and DT were also analyzed in the second multinomial logistic regression, with the reference group being the AWS group (Table 2.).

Based on the results, younger age (OR = 0.990; 95% CI = 0.981–0.999) and lower co-occurrence of psychiatric disorders (OR = 0.419; 95% CI = 0.339–0.518) were identified as significant predictive factors for the AWS group compared to the ADS group (Table 2.).

Our results also revealed that higher age (OR = 1.034; 95% CI = 1.020–1.048), elevated presence of comorbid somatic disorders (OR = 2.963; 95% CI = 2.168–4.049) and lower co-occurrence of psychiatric disorders (OR = 0.142; 95% CI = 0.103–0.196) were significant predictors of the DT group compared to the ADS group (Table 2.).

A significant association was revealed between DT and seasonality: the highest incidence of DT was in spring (36.8%) compared to other seasons (χ^2 (3) = 27.666; $p < 0.001$). In regard to months, the highest incidence of DT was in March (N = 49; 13.9%) (χ^2 (11) = 33.168; $p < 0.001$) (Fig. 2.).

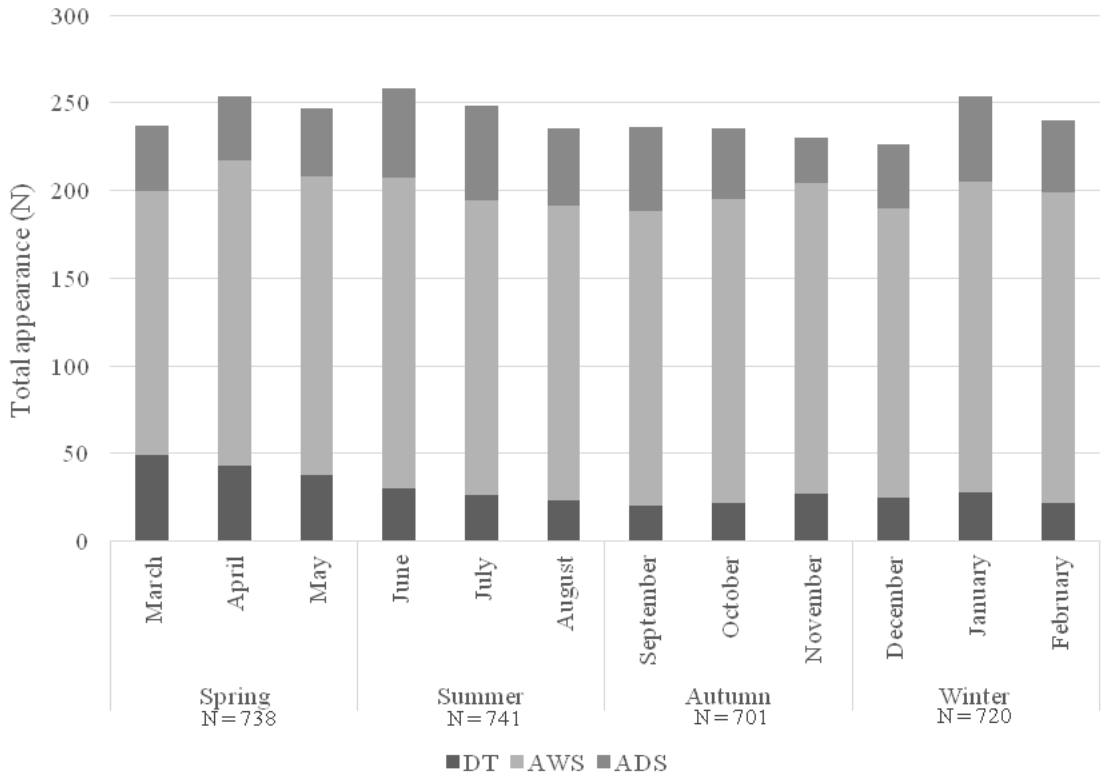
Moreover, spring proved to be a significant predictive variable in the DT group compared with that in the ADS group (with winter as a reference group) when controlling for general socio-demographic and clinical variables. On the basis of these results, the probability of DT was almost two times higher in spring (OR = 1.928; 95% CI = 1.288–2.883); therefore, spring was considered to be a critical period in terms of the emergence of more severe alcohol withdrawal complications (Table 2.).

In the second multinomial logistic regression, considering the DT group, higher age (OR = 1.044; 95% CI = 1.032–1.056), higher presence of comorbid somatic disorders (OR = 2.677;

95% CI = 2.060–3.478) and lower co-occurrence of psychiatric disorders (OR = 0.339; 95% CI = 0.258–0.446) were significant predictive variables compared to the AWS group when controlling for general socio-demographic and clinical variables (Table 2.).

Furthermore, the season of spring (OR = 1.751; CI = 1.263–2.427) was a significant predictive variable in the DT group compared with the AWS group (with the season of winter as a reference group) in the second multinomial regression. These results also underscore the significance of spring in DT (Table 2.).

Figure 2. Number of total medical charts in DT, AWS, and ADS groups in regard of seasonality.



Abbreviations: ADS, alcohol dependence syndrome without alcohol withdrawal state or delirium tremens; AWS, alcohol withdrawal state without delirium tremens; DT, delirium tremens.

Table 2. Multinomial logistic regression of the AWS and DT groups vs. the ADS group as the reference group.

	Model 1			Model 2		
	B (SE)	OR	95%CI	B (SE)	OR	95%CI
	AWS (without DT)			**ADS**		
Age	-0.010 (0.005)	**0.990***	**0.981–0.999**	0.010 (0.005)	**1.010***	**1.001–1.019**
Sex: Males (Ref: Females)	0.073 (0.121)	1.076	0.848–1.365	-0.073 (0.121)	0.929	0.733–1.179
Homelessness	0.023 (0.225)	1.023	0.658–1.591	-0.023 (0.225)	0.978	0.629–1.521
Comorbid somatic disorder	0.102 (0.106)	1.107	0.899–1.363	-0.102 (0.106)	0.903	0.734–1.112
Comorbid psychiatric disorder	-0.870 (0.108)	**0.419*****	**0.339–0.518**	0.870 (0.108)	**2.386*****	**1.932–2.947**
Seasons						
Spring	0.096 (0.146)	1.101	0.827–1.466	-0.096 (0.146)	0.908	0.682–1.209
Summer	-0.139 (0.138)	0.870	0.663–1.141	0 .139	1.150	0.876–1.508
Autumn	0.150 (0.146)	1.161	0.873–1.545	-0.150 (0.146)	0.861	0.647–1.146
Winter		Ref.			Ref.	
DT						
Age	0.033 (0.007)	**1.034***	**1.020–1.048**	0.043 (0.006)	**1.044***	**1.032–1.056**
Sex: Males (Ref: Females)	-0.073 (0.180)	0.929	0.653–1.322	-0.147 (0.151)	0.864	0.643–1.161
Homelessness	-0.210 (0.325)	0.811	0.429–1.533	-0.232 (0.263)	0.793	0.474–1.326
Comorbid somatic disorder	1.086 (0.159)	**2.963*****	**2.168–4.049**	0.985 (0.134)	**2.677*****	**2.060–3.478**

Comorbid psychiatric disorder	-1.950 (0.164)	**0.142*** **	**0.103–0.196**	-1.081 (0.140)	**0.339*** **	**0.258–0.446**
Seasons						
Spring	0.656 (0.205)	**1.928** **	**1.288–2.883**	0.560 (0.167)	**1.751*** **	1.263–2.427
Summer	-0.063 (0.212)	0.939	0.620–1.423	0.077 (0.180)	1.080	0.758–1.538
Autumn	0.110 (0.222)	1.116	0.723–1.724	-0.040 (0.186)	0.961	0.668–1.384
Winter		Ref.			Ref.	

The reference group of Model 1 is alcohol dependence syndrome (without alcohol withdrawal syndrome or delirium tremens). The reference group of Model 2 is alcohol withdrawal syndrome (without delirium tremens).

Abbreviations: ADS, alcohol dependence syndrome without alcohol withdrawal syndrome or delirium tremens; AWS, alcohol withdrawal syndrome without delirium tremens; DT, delirium tremens; B, unstandardized regression coefficient; CI, confidence interval; OR, odds ratio; SE, standard error; Ref., reference group. (: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$).*

5.2. Study 2: Clinical characteristics and predictors of alcohol-related seizure

5.2.1. Sample characteristics

In the analyses, 2851 medical charts of inpatient (N=1630) admissions were included. The sample consisted of 19.6% female and 80.4% male inpatient admissions. The mean age was 50.44 years (SD = 11.311). AWS without DT was the diagnosis of 85.3% (N = 2431) of appearances, and 14.7% (N = 420) were with DT. The occurrence of ARS in the total sample was 9.7% (N = 276). The percentage of complicated forms of AWS was 22.2% (N = 634) and the percentage of diagnoses of ARS and DT together in the total sample was 2.2% (N = 62).

The mean age was 49.21 years (SD = 11.264) in the ARS^+ group and 50.57 years (SD = 11.311) in the ARS^- group. The difference between the two groups had a tendency level of significance ($t(2849) = 1.902$, $p = 0.057$). The percentage of female appearances was 14.9% and 20.1% in the ARS^+ and ARS^- groups, respectively, and this difference was significant ($2 = 4.319$, $p = 0.038$, OR = 0.694). There was also a significant difference between the two groups in the prevalence of DT ($\chi^2 = 14.544$, $p < 0.001$, OR = 1.794; Table 3.)

5.2.2. Characteristics of the ARS$^+$ and ARS$^-$ subgroups

Co-occurrence of somatic and psychiatric co-morbidities, history of AWS, DT, and ARS, and levels of electrolytes and liver enzymes (GGT, SGOT, SGPT, and SGOT/SGPT quotient) were analyzed in the ARS$^+$ and ARS$^-$ subgroups. The percentage of coexisting somatic disorders was significantly higher in the ARS$^+$ group (63.8%) than in the ARS$^-$ group (53.5%) (χ^2= 10.569, p = 0.001, OR = 1.529). However, there was no significant difference in the occurrence of co-existing psychiatric disorders between the ARS$^+$ (40.9%) and ARS$^-$ (45.8%) subgroups (χ^2= 2.398, p = 0.121, OR = 0.820; Table 3).

There was a significant difference in the history of DT (t(299.899) = -3.544, p < 0.001) and the history of ARS (t(278.506) = -7.021, p < 0.001) between the ARS$^+$ (M_{hDT} = 0.22; M_{hARS} = 1,08) and ARS$^-$ (M_{hDT} = 0,09; M_{hARS} = 0,09) groups. Nevertheless, there was no significant difference between the two groups in the history of AWS without DT (t(2849) = -1,681, p = 0,093).

Electrolyte levels were within the normal range in both groups. Elevated GGT, SGOT, and SGPT levels as well as the SGOT/SGPT quotient were determined in the two groups. No significant differences in laboratory parameters were observed between the two groups. Table 3 shows the characteristics of the ARS$^+$ and ARS$^-$ groups.

Table 3. Characteristics of the ARS$^+$ and ARS$^-$ subgroups.

	ARS$^-$ (N = 2575)	**ARS$^+$** (N = 276)
Age (SD)	50.57 (11.311)	49.21 (11.264)
Female	20.1%	14.9% *
Male	79.9%	85.1% *
Prevalence of DT	13.9%	22.5% *
Somatic co-morbidities	53.5%	63.8% *
Psychiatric co-morbidities	45.8%	40.9%
Potassium (mean, SD)	4.04 (0.562)	4.91 (8.994)
GGT (mean, SD)	278.070 (471.253)	308.899 (402.883)
SGOT (mean, SD)	71.18 (77.556)	78.9 (91.679)
SGPT (mean, SD)	55.79 (95.515)	57.37 (56.947)
SGOT/SGPT quotient (mean, SD)	1.467 (0.818)	1.501 (0.865)

*Abbreviations: ARS, alcohol related seizure; SD, standard deviation; AWS, alcohol withdrawal syndrome; DT, delirium tremens; GGT, gamma-glutamyl transferase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; *, p < 0.05.*

5.2.3. Predictors of the development of ARS

A multinomial logistic regression model was created to determine the possible predictors of ARS. The model consisted of variables that showed a significant difference between the ARS^- and ARS^+ groups. Thus, sex, DT, somatic co-morbidity, history of ARS, and history of DT were included in the model, which showed a significant interconnection ($\chi^2 = 186.066$, $p < 0.001$) and had 90.7% certainty. The presence of DT, history of ARS, and somatic co-morbidity played a significant explanatory role in the development of ARS. Table 4 summarizes the results of the regression model.

Table 4. The multinomial logistic regression model of alcohol related seizure.

ARS	B	SE	df	p	OR	95% Confidence	
						Lower	Upper
History of DT	0.05	0.056	1	0.371	1.051	0.942	1.172
History of ARS	0.679	0.073	1	< 0.001	1.973	1.708	2.278
Male	0.365	0.19	1	0.055	1.441	0.992	2.093
Female	0		0		.		
DT^-	-0.608	0.164	1	< 0.001	0.544	0.394	0.751
DT^+	0		0				
Somatic comorbidity$^-$	-0.375	0.143	1	0.009	0.687	0.52	0.909
Somatic comorbidity$^+$	0		0				

Abbreviations: ARS, alcohol related seizure; DT, delirium tremens; B, regression coefficient; SE, standard error; df, degrees of freedom; p, significance; OR, odds ratio.

5.2.4. Relationship between the presence of ARS and DT

A multinomial regression model was used to examine ARS as a predictor of DT. The model was significant (χ^2 = 21.404, p < 0.001) and had 90.3% certainty. According to the model, ARS significantly increases the probability of DT. Table 5 shows the results of the regression model.

Table 5. The multinomial logistic regression model of delirium tremens.

	B	SE	df	p	OR	95% Confidence	
						Lower	Upper
ARS$^-$	-0.74	0.15	1	< 0.001	0.477	0.356	0.641
ARS$^+$	0		0				

Abbreviations: ARS, alcohol related seizure; DT, delirium tremens; B, regression coefficient; SE, standard error; df, degrees of freedom; p, significance; OR, odds ratio.

5.3. Study 3: Assessing the relationship between the presence of alcohol-related seizure and the severity of alcohol withdrawal syndrome

5.3.1. Sample characteristics

The sample consisted of 15 female (32.6%) and 31 male (67.4%) patients (N = 46). The mean age was 44.261 years (SD = 8.928). Two subgroups (ARS+, ARS$^-$) were created based on the presence of seizures during AWS. Patients with ARS had slightly higher scores (M = 30.389, SD = 6.463) on the AUDIT scale compared to the ARS- group (M = 30.143, SD = 5.024); however, the difference was not significant (t(44) = -0.145, p = 0.886). Table 6 shows the sample characteristics.

Table 6. Characteristics of the ARS$^-$ and ARS$^+$ subgroups in the follow-up study.

	ARS$^-$ (N = 28)	**ARS$^+$** (N= 18)
Age (SD)	44.929 (8.886)	43.222 (9.149)
Female	28.6%	38.9%
Male	71.4%	61.1%
AUDIT score (SD)	30.143 (5.024)	30.389 (6.463)

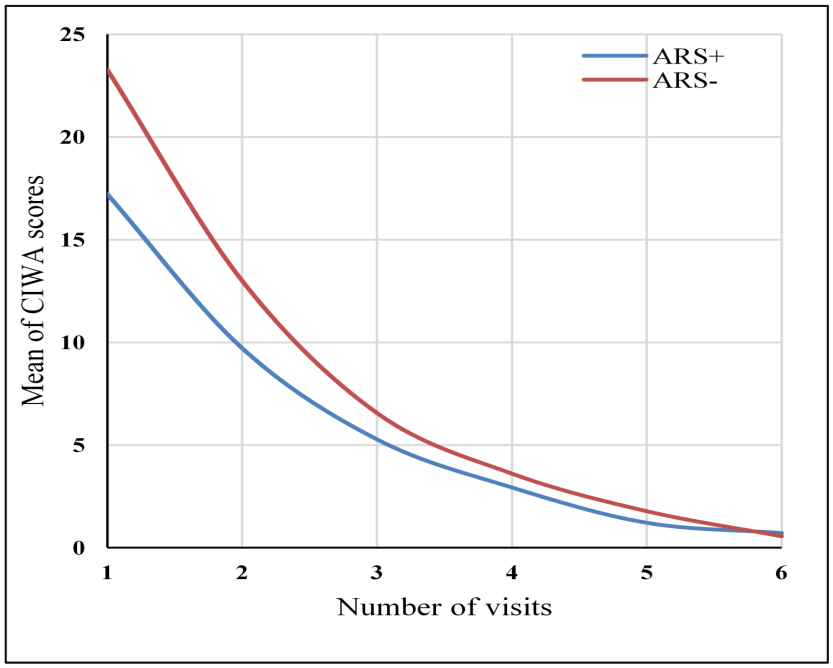
Abbreviations: ARS, alcohol related seizure; SD, standard deviation; AUDIT, Alcohol Use Disorder Identification Test

5.3.2. Changes in the CIWA-Ar scores

Mixed ANOVA and derivation were used to evaluate the difference in changes in CIWA-Ar scores between the ARS^+ and ARS^- groups. In the case of the main effect of CIWA-Ar scores, sphericity was not satisfied ($\chi^2(14) = 216.390$, $p < 0.001$); therefore, the degrees of freedom of the ANOVA were corrected using the Greenhouse– Geisser method ($\varepsilon = 0.347$). The CIWA-Ar scores significantly decreased during the 6 visits ($F(1.736, 76.397) = 193.989$, $MSE = 5819.722$, $p < 0.001$). The Bonferroni post hoc test showed that the scores of all visits differed from each other significantly, except for the 5th and 6th visits' scores ($p = 0.130$). There was no significant difference in the decrease in CIWA-Ar scores between the subgroups ($F(1, 44) = 16.784$, $MSE = 388$, $p = 0.536$).

An index number was created for every patient's six visits to compare the characteristics of the decrease in CIWA-Ar scores between the ARS^+ and ARS^- subgroups. A quadratic curve (CIWA-Ar scores) was fitted to the six points. We calculated the slope of the curve at the six points, and averaged the six obtained values Differences in the CIWA-Ar index numbers between the ARS+ and ARS groups were calculated using the independent sample t-test. There was no significant difference between the two groups ($t(44) = -1.143$, $p = 0.515$); therefore, the decrease in the CIWA-Ar scores during the six visits was not dissimilar (Fig. 3.)

Figure 3. Decrease of CIWA-Ar scores in the ARS^{-} and ARS^{+} subgroups.



Abbreviations: ARS, alcohol related seizure; CIWA, Clinical Institute Withdrawal Assessment of Alcohol, Revised.

6. DISCUSSION

According to a previous report by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), alcohol misuse was the seventh-leading risk factor for premature death and disability globally in 2016 (GBD 2016 Alcohol Collaborators, 2018) . The leading causes of attributable deaths in alcohol use problems are injuries, self-harm, and liver cirrhosis (GBD 2016 Alcohol Collaborators, 2018). However, among patients diagnosed with ADS, the most severe form of alcohol use problems, the major risk of death is the occurrence of complicated withdrawal syndrome in clinical setting (Maldonado et al., 2014; Wood et al., 2018).

Complicated withdrawal includes seizures occurring withdrawal syndrome and DT. During the course of ADS, withdrawal symptoms requiring hospitalization occur in approximately 50% of patients (Maldonado et al., 2014; Schuckit, 2014). Moreover, approximately 10-20% of patients hospitalized with AWS are suffering from complicated form of withdrawal. Furthermore, the mortality rate of DT is about 5% even with optimal treatment (Schuckit, 2014). Therefore, the most important goal of AWS treatment is to prevent the development of complicated or severe withdrawal syndrome.

Although, various ‘external’ (sociological and environmental) and ‘internal’ (demographic and clinical) risk factors have been revealed in the development of ARS and DT, the role of seasonality in DT, the clinical characteristics of ARS, the connection of ARS with DT, and the relationship between the occurrence of ARS and DT have not yet been evaluated in detail.

Accordingly, the main purpose of the studies summarized in the present thesis was to comprehensively examine the complicated AWS with two different methods.

6.1. The clinical characteristics and the role of seasonality in the development of delirium tremens

The most severe form of complicated withdrawal syndrome is DT. In Study 1, the clinical characteristics, predictors and the role of seasonality in the development of DT were demonstrated in a clinical sample.

Previous findings have revealed that sociodemographic risk factors include older age and male sex, whereas the most important clinical predictors are co-occurring somatic disorders and a history of SAWS and ARS (Goodson et al., 2014; Wood et al., 2018). Although novel findings have indicated that the COVID-19 pandemic had an impact on the occurrence of DT among patients with ADS (Gajdics et al., 2023), ‘external’ or environmental risk factors for developing DT remain largely unknown.

Recently, it has been demonstrated that the prevalence of DT is approximately 5%–15%; indeed, the occurrence of complicated withdrawal syndrome is approximately 10%–20% (Maldonado et al., 2014; Wood et al., 2018). Our findings support these observations by demonstrating that approximately 12% of medical charts were characterized with DT and complicated AWS in the total sample.

The results of the present thesis (*Study 1*) suggest that older age and increased occurrence of somatic comorbid disorders play a crucial role in the eventuality of DT among patients with ADS.

It has been indicated that older age may contribute to the development of ADS complications. It is explained by various causes. Older individuals with alcohol use problems may be exposed to alcohol consumption for a longer period; furthermore, a higher prevalence of concomitant somatic and psychiatric comorbidity and worse general condition may be detected (Kraemer et al., 1997).

The co-occurrence of somatic disorders, such as infections, cardiovascular diseases, and liver disorders, has a pivotal impact on the occurrence of DT (Goodson et al., 2014; Kim et al., 2015). Our results showed that somatic comorbidities were detected in approximately 73% of medical charts characterized with DT. Furthermore, we revealed that the chance of DT was 3 times higher in patients with somatic comorbidity. Our findings showed a low occurrence of co-occurred psychiatric disorders among medical charts characterized by the diagnosis of DT. Additionally, the lowest co-occurrence of mental disorders was a significant predictor for the presence of DT.

This result can be explained by the fact that patients who develop DT during their hospitalization may have severe ADS, and their secondary (psychiatric) diagnosis have not been revealed yet. It could be hypothesized that these patients have primary addictions. Nevertheless, previous findings showed that during the COVID-19 pandemic, psychiatric comorbidities increased the likelihood of the development of DT (Gajdics et al., 2023); however, regarding that this is a specific timeframe, findings can be explained by the impact of the pandemic.

Considering the clinical characteristics, our main findings are in accordance with previous findings by demonstrating the importance of somatic co-morbidities and older age in the development of DT.

The main purpose of Study 1 was to explore whether seasonality could be presented as a contributing factor in DT in patients diagnosed with ADS when controlling for general sociodemographic and clinical factors. Environmental factors, such as natural daylight, noise, isolation, sunlight time, or seasonality, may influence the development and development of various somatic and mental disorders.

Decreased natural daylight, isolation, excessive noise, and night-time light exposure are potential risk factors for delirium syndrome among ICU patients (Estrup et al., 2017; Van Rompaey et al., 2009). Furthermore, previous findings have suggested that various types of delirium syndrome, such as dementia-associated delirium or drug-induced delirium, have an elevated occurrence in winter (Balan et al., 2001). However, we lack data on the impact of seasons on the occurrence of DT. Our findings revealed that the highest incidence of DT was in spring, especially in March. Indeed, our results demonstrated that the season of spring is a significant predictor of the emergence of DT.

The impact of seasonality on the development of DT can be explained by various factors. Decreased hours of sunshine and colder weather modulate immunity and vitamin levels, which may increase somatic vulnerability during winter and early spring (Fares, 2013). Therefore, patients with ADS may have a higher risk for the impact of seasons because alcohol-dependent individuals usually suffer from insufficient food intake; consequently, they have deficiencies in vitamins, such as B, C, and D, and minerals, such as magnesium, calcium, or iron (Baj et al., 2020; Grochowski et al., 2019; Hoes, 1979; Hoyumpa, 1986; Marik & Liggett, 2019). Furthermore, the impact of seasonality on the drinking pattern of patients with ADS has been previously suggested. For instance, it has also been proposed that decreased mood and winter weather conditions, which can cause social isolation and stress, lead to an increase in alcohol consumption. In addition, the changing weather in spring can also have an impact on mood, anxiety, and stress, which is related to an increased frequency of drug and alcohol consumption (Klimstra et al., 2011; Ostojić et al., 2012; Witkiewitz et al., 2011). Consequently, these factors may contribute to the development of DT during early spring.

Although recent studies have suggested the importance of winter, the increase in the occurrence of DT in March may also be due to a ‘late winter effect’. Furthermore, in Hungary, the temperature in March is lower than that in other spring months; therefore, the low temperature in March is more similar to that in February. To the best of our knowledge, there are no data on the relationship between the ‘late winter effect' and the development or

occurrence of any psychiatric conditions. Therefore, Study 1 first revealed in the literature the importance of this special form of the impact of seasons on severe medical complications.

In conclusion, regarding previous findings and the results of Study 1, the importance of 'late winter effect' on drinking patterns, the worsening of ADS and the development of DT should be taken into account.

6.2. The clinical characteristics of ARS and its predictors

Seizures associated with alcohol use are important during the care of patients with withdrawal syndrome. Furthermore, alcohol-dependent individuals are usually admitted to emergency units because seizures are an initial symptom of withdrawal syndrome (Kim et al., 2015; Schuckit, 2014). Although DT is the most severe form of complicated AWS, ARS also has lethal complications, and its interplay with the development of DT requires prevention. Therefore, in Study 2, we determined the demographic and clinical characteristics and predictors of ARS in patients with AWS.

Regarding the prevalence of ARS, the data in the literature are heterogeneous. Previous reports have revealed that ARS occurs at approximately 5%–30% among patients with ADS (Eyer et al., 2011; Maldonado et al., 2014; Rathlev et al., 2006; Wood et al., 2018) . Our present data show that approximately 10% of medical charts were characterized with ARS; moreover, in this study, the prevalence of complicated withdrawal syndrome was 20%. Although the results of previous studies are heterogeneous regarding the occurrence of ARS and complicated withdrawal syndrome, our results support the majority of previous findings. Furthermore, we revealed that the concomitance of ARS and DT in AWS was 2.2%.

Differences in demographic and clinical characteristics between patients suffering or not suffering from seizures during their withdrawal episodes remain largely unknown. A meta-analysis published in 2018 revealed that patients with SAWS and DT show differences in clinical characteristics; however, seizure was not examined in detail (Wood et al., 2018). Another study revealed that previous episodes of ARS, occurrence of hospitalization because of ADS, and structural brain lesions are significantly higher in the subgroup of patients diagnosed with seizures during the withdrawal syndrome (Eyer et al., 2011). Interestingly, in this study regarding the laboratory parameters between the two groups (AWS with or without ARS) significant differences have not been determined (Eyer et al., 2011). Our present findings show that most admissions with the diagnosis of seizure were male patients, and the presence of DT, the co-occurrence of somatic co-morbidities, and the history of DT and ARS

were significantly higher among the appearances where ARS occurred. In terms of psychiatric comorbidities and laboratory parameters, significant differences were not observed.

Additionally, in Study 2, predictors of the development of ARS were also revealed. Our findings show that the co-occurrence of somatic disorders, history of ARS, and presence of DT are risk factors for developing seizures during withdrawal syndrome.

Previously, it has been demonstrated that patients with ARS had more detoxification episodes, started to depend on alcohol at an earlier age, and had more severe alcohol dependence measured with SADQ compared with patients without ARS in their history (Pestana et al., 2019). It should be noted, however, that the SADQ mainly reflects the consequences of alcohol use problems such as withdrawal symptoms (Stockwell et al., 1983). Furthermore, it has also been revealed that one-third of patients with a history and presence of ARS developed DT during withdrawal syndrome (Kim et al., 2015). Our findings strongly support these observations by demonstrating that the subgroups of patients with ARS show significant differences in distinct clinical characteristics.

In addition, our results revealed that the occurrence of ARS is a predictor of the development of DT. Moreover, these findings extending our knowledge about the risks of the development of seizures among alcohol-dependent individuals, the demonstrated relationship between ARS and DT should be highlighted.

Philip Gorwood and his colleagues have revealed a genetic link between DT and ARS and have demonstrated that patients suffering from DT and/or ARS comprise a specific subgroup of alcohol-dependent individuals (Gorwood et al., 2003). In addition, it has been demonstrated that patients with AWS with and without ARS have genetic differences (Grzywacz et al., 2012).

In summary, regarding previous and our present results, it could be hypothesized that ARS and DT comprise a genetically and clinically specific subgroup among patients diagnosed with ADS who are at risk for the development of ARS. Moreover, our findings support the key role of the kindling mechanism in the eventuality of withdrawal seizures by showing that a history of ARS and the presence of DT played an explanatory role in the presence of withdrawal seizures during hospitalization with withdrawal syndrome.

6.3. The relationship between the occurrence of alcohol-related seizure and the severity of alcohol withdrawal syndrome

The relationship between seizures occurring during withdrawal syndrome and the severity of withdrawal symptoms has not yet been evaluated in detail. In the original version of CIWA-Ar, CIWA-A included an item for reporting seizures during AWS (Manikant et al., 1992; Shaw et al., 1981). Earlier studies with CIWA-A have suggested that this item is not necessary, and it was dropped from the revised version (Foy et al., 1988; Manikant et al., 1992; Sellers et al., 1983; Shaw et al., 1981; Sullivan et al., 1989). However, during the past few years, the importance of seizures has been suggested (Maldonado et al., 2014). Furthermore, José Maldonado and colleagues reported criticism of the CIWA-Ar regarding the seizure item and they developed a risk assessment scale including the history of ARS and DT items (Maldonado et al., 2014). In addition, patients suffering from seizures during their withdrawal syndrome showed a significant later climax of the severity of withdrawal symptoms measured with a modified version of CIWA-Ar compared with patients without seizures (Eyer et al., 2011).

Therefore, in Study 3, we investigated the relationship among the occurrence of ARS, severity of alcohol dependence, and severity of withdrawal symptoms measured using CIWA-AR among patients during hospitalization with AWS.

The symptom severity and the characteristics of alcohol dependence was measured using AUDIT. Our results showed that there were no significant differences between the two groups (patients with and without ARS); however, patients with seizures showed slightly higher AUDIT scores. Previous findings have demonstrated that there are no significant differences in the AUDIT scores between the two groups; however, another study using SADQ revealed that patients with seizures had more severe ADS (Pestana et al., 2019). Furthermore, it has been demonstrated that AUDIT alone is not suitable for detecting the risk of AWS (Dolman & Hawkes, 2005). Nevertheless, it is worth highlighting that the SADQ reflects the severity of ADS and withdrawal symptoms, whereas AUDIT is a screening tool for detecting alcohol use problems. Our observations support the finding that there are no significant differences between the groups regarding the AUDIT scores; nevertheless, methodological issues should be addressed.

Considering the severity of AWS, our results revealed that there were no significant differences between patients with seizures or not. Previous findings have shown that the severity of withdrawal symptoms shows a delay among patients suffering from seizures;

however, it has also been revealed that the maximal score measured in a modified CIWA-Ar was similar in the two groups (Eyer et al., 2011).

Our findings suggest that the occurrence of ARS may be independent of the severity of withdrawal symptoms. Overall, it could be hypothesized that regarding the well-defined features of ARS and DT and their relationship with the severity of AWS, complicated withdrawal syndrome is a specific genetic, biological, and clinical form of AWS.

6.4. Limitations

Several limitations need to be considered when interpreting the results of this present thesis.

Overall, the generalisability of these findings is limited because the data collection was from one hospital in Szeged, Hungary and the associated population living in neighbouring areas.

In the view of Study 1, detailed clinical information such as vital signs of patients were not assessed. In addition, regarding the impact of seasonality on the development of DT, our results can only be interpreted in regions within temperate climate zones. Moreover, measured temperature was not detected; therefore, the results can only be explained in this eight-year period.

Regarding Study 2, the major limitation is that only medical charts were examined; hence, our results only reflect clinical data associated with the course of AWS. Furthermore, other clinical information such as drinking pattern or EEG records was unknown due to the retrospective nature of the study.

In the case of Study 3, the small sample size and the short one-year period are the major limitations of our findings. In addition, the severity of AWS was measured using one tool and without vital signs. Moreover, a small number of patients were examined during a relatively short 1-year period.

7. MAIN FINDINGS AND CONCLUSIONS

The main aim of the studies summarized in this thesis was to systematically investigate the clinical characteristics of complicated withdrawal syndrome, including ARS and DT.

In the case of DT, clinical characteristics and seasonality were examined in a retrospective study of medical charts with ADS. Our findings showed that older age and somatic comorbidities are significant predictors of the development of DT. Furthermore, our results suggest a 'late winter effect' in the eventuality of DT. This novel finding demonstrates the new impact of seasonality on the occurrence of medical conditions. These observations may contribute to the prevention of DT by detecting these risk factors during the management of complicated withdrawal.

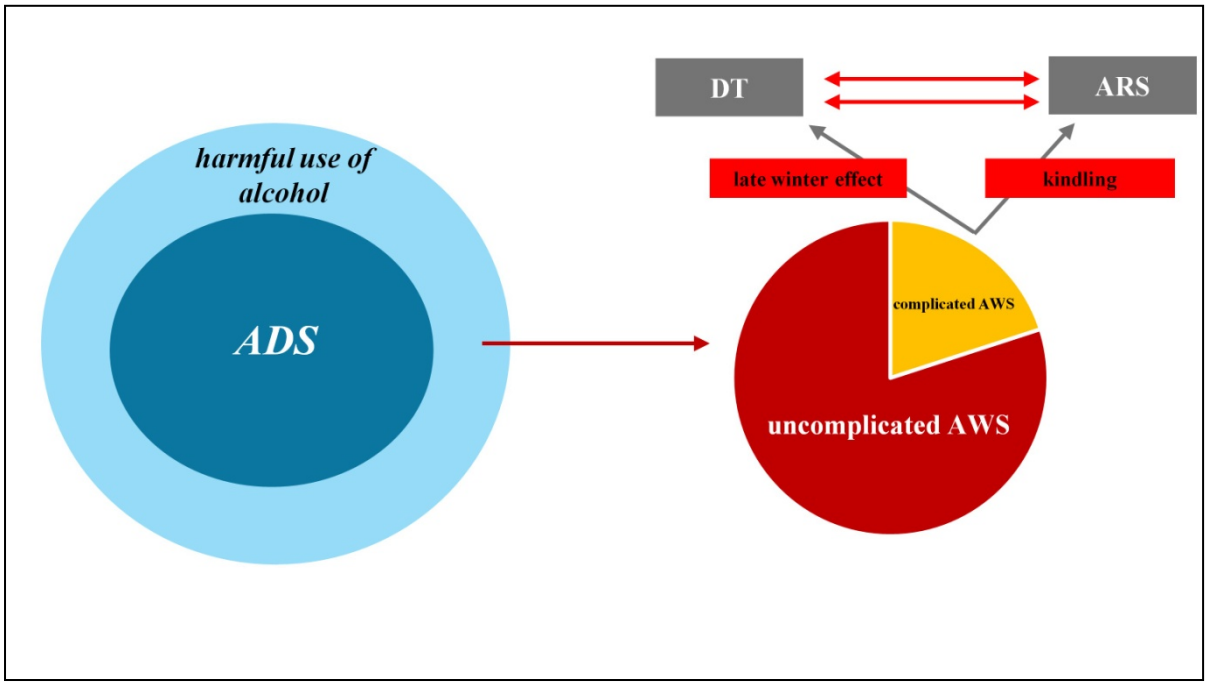
Regarding ARS, in our first study, demographic and clinical differences between medical charts characterized with AWS and ARS and those with AWS without ARS were revealed in a retrospective study. In addition, predictors and the relationship between ARS and DT were determined. Our findings showed that male sex, presence of DT, somatic comorbidities, and history of DT and ARS were significantly higher where seizures occurred. Furthermore, our findings showed that somatic comorbidities, history of ARS, and presence of DT are predictors of ARS, and ARS is a risk factor for developing DT. These observations support and extend previous observations and indirectly suggest the significance of the kindling mechanism. In addition, regarding the revealed connection between ARS and DT, it could be hypothesized that complicated withdrawal syndrome comprises a specific, high-risk subgroup of patients with alcohol dependence.

Finally, the relationship between the occurrence of seizures and the severity of withdrawal symptoms was revealed in a follow-up study. Patients hospitalized with AWS and suffering from seizures did not show differences in CIWA-Ar scores. These findings suggest that ARS may be independent of AWS severity.

In conclusion, the findings of the present thesis suggest that complicated withdrawal syndrome is a complex and severe clinical complication of ADS. Therefore, during the management of ADS, assessing the risk factors related to the development of ARS and DT has substantial significance for preventing lethal complications of alcohol dependence.

The main findings of the present thesis are summarized in Figure 4.

Figure 4. The course of alcohol dependence syndrome and the significance of complicated alcohol withdrawal syndrome.



Abbreviations: ADS, alcohol dependence syndrome; AWS, alcohol withdrawal syndrome; DT, delirium tremens; ARS, alcohol-related seizure

According to the results of the studies, the novel findings of the present thesis are as follows:

1. Our findings revealed that spring, especially March, is a critical season and month in the occurrence of DT in an inpatient sample diagnosed with ADS. These results suggest the importance of 'late winter effect' in the development of DT.

2. Our results determined that there were differences between inpatients diagnosed with AWS concerning the occurrence of ARS. Our findings showed that most admissions with the diagnosis of ARS were male, and the presence of DT, the co-occurrence of somatic co morbidities and the history of DT and ARS were significantly higher among admissions with ARS.

3. Our findings revealed that the co-occurrence of somatic co-morbidities, presence of DT, and history of ARS are risk factors for developing a future episode of ARS. Hence, the kindling hypothesis was indirectly supported.

4. Our results indicate that the occurrence of seizures during withdrawal syndrome is a risk factor for the eventuality of DT.

5. Our findings showed that there were no significant differences in the presence of ARS and severity of withdrawal syndrome between patients diagnosed with AWS.

Although, studies summarized in the present studies revealed novel risk factors for the development of complicated withdrawal syndrome, and highlighted the importance of the classification of the clinical complications of withdrawal syndrome, further research are needed for better understanding the nature of ARS and DT.

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9. REFERENCES

1. Alberto, G. E., Klorig, D. C., Goldstein, A. T., & Godwin, D. W. (2023). Alcohol withdrawal produces changes in excitability, population discharge probability, and seizure threshold. *Alcohol Clin Exp Res (Hoboken)*, *47*(2), 211–218. https://doi.org/10.1111/acer.15004
2. Allen, J. P., Litten, R. Z., Fertig, J. B., & Babor, T. (1997). A review of research on the Alcohol Use Disorders Identification Test (AUDIT). *Alcohol Clin Exp Res*, *21*(4), 613–619. https://www.ncbi.nlm.nih.gov/pubmed/9194913
3. American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. American Psychiatric Association.
4. Baj, J., Flieger, W., Teresiński, G., Buszewicz, G., Sitarz, R., Forma, A., Karakuła, K., & Maciejewski, R. (2020). Magnesium, Calcium, Potassium, Sodium, Phosphorus, Selenium, Zinc, and Chromium Levels in Alcohol Use Disorder: A Review. *J Clin Med*, *9*(6). https://doi.org/10.3390/jcm9061901
5. Balan, S., Leibovitz, A., Freedman, L., Blagman, B., Ruth, M., Ady, S., & Habot, B. (2001). Seasonal variation in the incidence of delirium among the patients of a geriatric hospital. *Arch Gerontol Geriatr*, *33*(3), 287–293. https://doi.org/10.1016/s0167-4943(01)00192-3
6. Balcells, M. E., García, P., Tiznado, C., Villarroel, L., Scioscia, N., Carvajal, C., Zegna-Ratá, F., Hernández, M., Meza, P., González, L. F., Peña, C., & Naves, R. (2017). Association of vitamin D deficiency, season of the year, and latent tuberculosis infection among household contacts. *PLoS One*, *12*(4), e0175400. https://doi.org/10.1371/journal.pone.0175400
7. Ballenger, J. C., & Post, R. M. (1978). Kindling as a model for alcohol withdrawal syndromes. *Br J Psychiatry*, *133*, 1–14. https://doi.org/10.1192/bjp.133.1.1
8. Becker, H. C. (1998). Kindling in alcohol withdrawal. *Alcohol Health Res World*, *22*(1), 25–33. https://www.ncbi.nlm.nih.gov/pubmed/15706729
9. Becker, H. C. (2012). Effects of alcohol dependence and withdrawal on stress responsiveness and alcohol consumption. *Alcohol Res*, *34*(4), 448–458. https://www.ncbi.nlm.nih.gov/pubmed/23584111
10. Brodie, M. S. (2002). Increased ethanol excitation of dopaminergic neurons of the ventral tegmental area after chronic ethanol treatment. *Alcohol Clin Exp Res*, *26*(7), 1024–1030. https://doi.org/10.1097/01.ALC.0000021336.33310.6B

11. Carpenter, C. (2003). Seasonal variation in self-reports of recent alcohol consumption: racial and ethnic differences. *J Stud Alcohol*, *64*(3), 415–418. https://doi.org/10.15288/jsa.2003.64.415
12. Cho, Y. I., Johnson, T. P., & Fendrich, M. (2001). Monthly variations in self-reports of alcohol consumption. *J Stud Alcohol*, *62*(2), 268–272. https://doi.org/10.15288/jsa.2001.62.268
13. Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Arch Gen Psychiatry*, *50*(12), 975–990. https://doi.org/10.1001/archpsyc.1993.01820240059008
14. Denissen, J. J. A., Butalid, L., Penke, L., & van Aken, M. A. G. (2008). The effects of weather on daily mood: a multilevel approach. *Emotion*, *8*(5), 662–667. https://doi.org/10.1037/a0013497
15. Devinsky, O., Hesdorffer, D. C., Thurman, D. J., Lhatoo, S., & Richerson, G. (2016). Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurol*, *15*(10), 1075–1088. https://doi.org/10.1016/S1474-4422(16)30158-2
16. Dolman, J. M., & Hawkes, N. D. (2005). Combining the audit questionnaire and biochemical markers to assess alcohol use and risk of alcohol withdrawal in medical inpatients. *Alcohol Alcohol*, *40*(6), 515–519. https://doi.org/10.1093/alcalc/agh189
17. Doran, K. M., Rahai, N., McCormack, R. P., Milian, J., Shelley, D., Rotrosen, J., & Gelberg, L. (2018). Substance use and homelessness among emergency department patients. *Drug Alcohol Depend*, *188*, 328–333. https://doi.org/10.1016/j.drugalcdep.2018.04.021
18. Estrup, S., Kjer, C. K. W., Poulsen, L. M., Gøgenur, I., & Mathiesen, O. (2017). Delirium and effect of circadian light in the intensive care unit: a retrospective cohort study. *Acta Anaesthesiol Scand*, *62*(3), 367–375. https://doi.org/10.1111/aas.13037
19. Eyer, F., Schuster, T., Felgenhauer, N., Pfab, R., Strubel, T., Saugel, B., & Zilker, T. (2011). Risk assessment of moderate to severe alcohol withdrawal--predictors for seizures and delirium tremens in the course of withdrawal. *Alcohol Alcohol*, *46*(4), 427–433. https://doi.org/10.1093/alcalc/agr053
20. Fares, A. (2013). Factors influencing the seasonal patterns of infectious diseases. *Int J Prev Med*, *4*(2), 128–132. https://www.ncbi.nlm.nih.gov/pubmed/23543865
21. First, M., Williams, J., Karg, R., & Spitzer, R. (2016). *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV).*

22. Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel Jr, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475–482. https://doi.org/10.1111/epi.12550
23. Foster, E., Carney, P., Liew, D., Ademi, Z., O'Brien, T., & Kwan, P. (2019). First seizure presentations in adults: beyond assessment and treatment. *J Neurol Neurosurg Psychiatry*, *90*(9), 1039–1045. https://doi.org/10.1136/jnnp-2018-320215
24. Foulds, J., Newton-Howes, G., Guy, N. H., Boden, J. M., & Mulder, R. T. (2017). Dimensional personality traits and alcohol treatment outcome: a systematic review and meta-analysis. *Addiction*, *112*(8), 1345–1357. https://doi.org/10.1111/add.13810
25. Foy, A., March, S., & Drinkwater, V. (1988). Use of an objective clinical scale in the assessment and management of alcohol withdrawal in a large general hospital. *Alcohol Clin Exp Res*, *12*(3), 360–364. https://doi.org/10.1111/j.1530-0277.1988.tb00208.x
26. Fu, X., Guo, Z., Gao, C., Chu, Q., Li, J., Ma, H., & Shu, G. (2016). Long-Term Alcohol-Induced Activation of Mammalian Target of Rapamycin is a Key Risk Factor of Epilepsy. *Med Sci Monit*, *22*, 3975–3980. https://doi.org/10.12659/msm.897018
27. Gajdics, J., Bagi, O., Farkas, F., Andó, B., Pribék, I., & Lázár, B. (2023). The Impact of the COVID-19 Pandemic on the Severity of Alcohol Use Disorder: Significance of Dual Disorders. *International Journal of Environmental Research and Public Health*, *20*(20), 6939. https://doi.org/10.3390/ijerph20206939
28. Gallerani, M., & Manfredini, R. (2013). Seasonal variation in the occurrence of delirium in patients admitted to medical units of a general hospital in Italy. *Acta Neuropsychiatr*, *25*(3), 179–183. https://doi.org/10.1111/j.1601-5215.2012.00677.x
29. GBD 2016 Alcohol Collaborators. (2018). Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)*, *392*(10152), 1015–1035. https://doi.org/10.1016/S0140-6736(18)31310-2
30. Gerevich, J., Bácskai, E., Kó, J., & Rózsa, S. (2005). Reliability and validity of the Hungarian version of the European Addiction Severity Index. *Psychopathology*, *38*(6), 301–309. https://doi.org/10.1159/000088918
31. Gibb, K., Seeley, A., Quinn, T., Siddiqi, N., Shenkin, S., Rockwood, K., & Davis, D. (2020). The consistent burden in published estimates of delirium occurrence in

medical inpatients over four decades: a systematic review and meta-analysis study. *Age Ageing*, *49*(3), 352–360. https://doi.org/10.1093/ageing/afaa040

32. Goodson, C. M., Clark, B. J., & Douglas, I. S. (2014). Predictors of severe alcohol withdrawal syndrome: a systematic review and meta-analysis. *Alcohol Clin Exp Res*, *38*(10), 2664–2677. https://doi.org/10.1111/acer.12529
33. Gorwood, P., Limosin, F., Batel, P., Hamon, M., Adès, J., & Boni, C. (2003). The A9 allele of the dopamine transporter gene is associated with delirium tremens and alcohol-withdrawal seizure. *Biol Psychiatry*, *53*(1), 85–92. https://doi.org/10.1016/s0006-3223(02)01440-3
34. Grochowski, C., Blicharska, E., Baj, J., Mierzwińska, A., Brzozowska, K., Forma, A., & Maciejewski, R. (2019). Serum iron, Magnesium, Copper, and Manganese Levels in Alcoholism: A Systematic Review. *Molecules*, *24*(7). https://doi.org/10.3390/molecules24071361
35. Grzywacz, A., Jasiewicz, A., Małecka, I., Suchanecka, A., Grochans, E., Karakiewicz, B., Samochowiec, A., Bieńkowski, P., & Samochowiec, J. (2012). Influence of DRD2 and ANKK1 polymorphisms on the manifestation of withdrawal syndrome symptoms in alcohol addiction. *Pharmacol Rep*, *64*(5), 1126–1134. https://doi.org/10.1016/s1734-1140(12)70909-x
36. Hall, W., & Zador, D. (1997). The alcohol withdrawal syndrome. *Lancet*, *349*(9069), 1897–1900. https://doi.org/10.1016/S0140-6736(97)04572-8
37. Hammoud, N., & Jimenez-Shahed, J. (2019). Chronic Neurologic Effects of Alcohol. *Clin Liver Dis*, *23*(1), 141–155. https://doi.org/10.1016/j.cld.2018.09.010
38. Heilig, M., MacKillop, J., Martinez, D., Rehm, J., Leggio, L., & Vanderschuren, L. J. M. J. (2021). Addiction as a brain disease revised: why it still matters, and the need for consilience. *Neuropsychopharmacology*, *46*(10), 1715–1723. https://doi.org/10.1038/s41386-020-00950-y
39. Hillemacher, T., Frieling, H., Wilhelm, J., Heberlein, A., Karagülle, D., Bleich, S., Lenz, B., & Kornhuber, J. (2012). Indicators for elevated risk factors for alcohol-withdrawal seizures: an analysis using a random forest algorithm. *J Neural Transm (Vienna)*, *119*(11), 1449–1453. https://doi.org/10.1007/s00702-012-0825-8
40. Hoes, M. J. (1979). The significance of the serum levels of vitamin B-1 and magnesium in delirium tremens and alcoholism. *J Clin Psychiatry*, *40*(11), 476–479. https://www.ncbi.nlm.nih.gov/pubmed/489530

41. Hoyumpa, A. M. (1986). Mechanisms of vitamin deficiencies in alcoholism. *Alcohol Clin Exp Res*, *10*(6), 573–581. https://doi.org/10.1111/j.1530-0277.1986.tb05147.x
42. IBM Corp. Released 2016. (2016). *IBM SPSS Statistics for Windows, Version 24.0.* Armonk, NY:IBM Corp.
43. Jarvis, M. F., & Becker, H. C. (1998). Single and repeated episodes of ethanol withdrawal increase adenosine A1, but not A2A, receptor density in mouse brain. *Brain Res*, *786*(1–2), 80–88. https://doi.org/10.1016/s0006-8993(97)01413-3
44. Jesse, S., Bråthen, G., Ferrara, M., Keindl, M., Ben-Menachem, E., Tanasescu, R., Brodtkorb, E., Hillbom, M., Leone, M. A., & Ludolph, A. C. (2017). Alcohol withdrawal syndrome: mechanisms, manifestations, and management. *Acta Neurologica Scandinavica*, *135*(1), 4–16. https://doi.org/10.1111/ane.12671
45. Kim, D. W., Kim, H. K., Bae, E.-K., Park, S.-H., & Kim, K. K. (2015). Clinical predictors for delirium tremens in patients with alcohol withdrawal seizures. *Am J Emerg Med*, *33*(5), 701–704. https://doi.org/10.1016/j.ajem.2015.02.030
46. Klimstra, T. A., Frijns, T., Keijsers, L., Denissen, J. J. A., Raaijmakers, Q. A. W., van Aken, M. A. G., Koot, H. M., van Lier, P. A. C., & Meeus, W. H. J. (2011). Come rain or come shine: individual differences in how weather affects mood. *Emotion*, *11*(6), 1495–1499. https://doi.org/10.1037/a0024649
47. Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8
48. Kovács, I., Richman, M. J., Janka, Z., Maraz, A., & Andó, B. (2017). Decision making measured by the Iowa Gambling Task in alcohol use disorder and gambling disorder: a systematic review and meta-analysis. *Drug Alcohol Depend*, *181*, 152–161. https://doi.org/10.1016/j.drugalcdep.2017.09.023
49. Kraemer, K. L., Mayo-Smith, M. F., & Calkins, D. R. (1997). Impact of age on the severity, course, and complications of alcohol withdrawal. *Arch Intern Med*, *157*(19), 2234–2241. https://www.ncbi.nlm.nih.gov/pubmed/9343000
50. Krewulak, K. D., Stelfox, H. T., Leigh, J. P., Ely, E. W., & Fiest, K. M. (2018). Incidence and Prevalence of Delirium Subtypes in an Adult ICU: A Systematic Review and Meta-Analysis. *Crit Care Med*, *46*(12), 2029–2035. https://doi.org/10.1097/CCM.0000000000003402
51. Krystal, J. H., Petrakis, I. L., Mason, G., Trevisan, L., & D'Souza, D. C. (2003). N-methyl-D-aspartate glutamate receptors and alcoholism: reward, dependence,

treatment, and vulnerability. *Pharmacol Ther*, *99*(1), 79–94. https://doi.org/10.1016/s0163-7258(03)00054-8

52. Kumar, S., Porcu, P., Werner, D. F., Matthews, D. B., Diaz-Granados, J. L., Helfand, R. S., & Morrow, A. L. (2009). The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology (Berl)*, *205*(4), 529–564. https://doi.org/10.1007/s00213-009-1562-z
53. Lázár, B. A., Pribék, I. K., Kovács, C., Demeter, I., Kálmán, J., Szemelyácz, J., Kelemen, G., Janka, Z., Demetrovics, Z., & Andó, B. (2019). The first step towards a unified approach: validation of the Hungarian version of the Clinical Institute Withdrawal Assessment of Alcohol, Revised in Hungarian general hospital settings. *Orvosi Hetilap*, *160*(30). https://doi.org/10.1556/650.2019.31424
54. Lee, S., Smith, G. W., Vale, W., Lee, K. F., & Rivier, C. (2001). Mice that lack corticotropin-releasing factor (CRF) receptors type 1 show a blunted ACTH response to acute alcohol despite up-regulated constitutive hypothalamic CRF gene expression. *Alcohol Clin Exp Res*, *25*(3), 427–433. https://www.ncbi.nlm.nih.gov/pubmed/11290855
55. Long, D., Long, B., & Koyfman, A. (2017). The emergency medicine management of severe alcohol withdrawal. *Am J Emerg Med*, *35*(7), 1005–1011. https://doi.org/10.1016/j.ajem.2017.02.002
56. Maldonado, J. R. (2008). Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin*, *24*(4), 789–856, ix. https://doi.org/10.1016/j.ccc.2008.06.004
57. Maldonado, J. R. (2017). Novel Algorithms for the Prophylaxis and Management of Alcohol Withdrawal Syndromes-Beyond Benzodiazepines. *Crit Care Clin*, *33*(3), 559–599. https://doi.org/10.1016/j.ccc.2017.03.012
58. Maldonado, J. R., Sher, Y., Ashouri, J. F., Hills-Evans, K., Swendsen, H., Lolak, S., & Miller, A. C. (2014). The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol*, *48*(4), 375–390. https://doi.org/10.1016/j.alcohol.2014.01.004
59. Manikant, S., Tripathi, B. M., & Chavan, B. S. (1992). Utility of ciwa - a in alcohol withdrawal assessment. *Indian J Psychiatry*, *34*(4), 347–350. https://www.ncbi.nlm.nih.gov/pubmed/21776143

60. Marik, P. E., & Liggett, A. (2019). Adding an orange to the banana bag: vitamin C deficiency is common in alcohol use disorders. *Crit Care*, *23*(1), 165. https://doi.org/10.1186/s13054-019-2435-4
61. McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argeriou, M. (1992). The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*, *9*(3), 199–213. https://doi.org/10.1016/0740-5472(92)90062-s
62. Morales-Muñoz, I., Koskinen, S., & Partonen, T. (2017). Seasonal affective disorder and alcohol abuse disorder in a population-based study. *Psychiatry Res*, *253*, 91–98. https://doi.org/10.1016/j.psychres.2017.03.029
63. Morton, W. A., Laird, L. K., Crane, D. F., Partovi, N., & Frye, L. H. (1994). A prediction model for identifying alcohol withdrawal seizures. *Am J Drug Alcohol Abuse*, *20*(1), 75–86. https://doi.org/10.3109/00952999409084058
64. NICE. (2011). *National Institute for Health and Clinical Excellence Alcohol-use disorders: Diagnosis, assessment and management of harmful drinking and alcohol dependence.*
65. Ostojić, J. N., Mladenović, D., Ninković, M., Vučević, D., Bondžić, K., Ješić-Vukićević, R., & Radosavljević, T. (2012). The effects of cold-induced stress on liver oxidative injury during binge drinking. *Hum Exp Toxicol*, *31*(4), 387–396. https://doi.org/10.1177/0960327111433899
66. Pestana, P. C., Novais, F., Ismail, F., & Pombo, S. (2019). Are Patients With Alcohol-Related Seizures a Specific Subgroup? *Prim Care Companion CNS Disord*, *21*(6). https://doi.org/10.4088/PCC.19m02501
67. Pribék, I. K., Kovács, I., Kádár, B. K., Kovács, C. S., Richman, M. J., Janka, Z., Andó, B., & Lázár, B. A. (2021). Evaluation of the course and treatment of Alcohol Withdrawal Syndrome with the Clinical Institute Withdrawal Assessment for Alcohol - Revised: A systematic review-based meta-analysis. *Drug Alcohol Depend*, *220*, 108536. https://doi.org/10.1016/j.drugalcdep.2021.108536
68. Rácz, J., Pogány, C., & Máthé-Árvay, N. (2002). Az EuropASI (Addikció Súlyossági Index) magyar nyelvű változatának reliabilitás- és validitásvizsgálata. *Magyar Pszichológiai Szemle*, *57*(4), 587–603. https://doi.org/10.1556/mpszle.57.2002.4.4
69. Rathlev, N. K., Ulrich, A. S., Delanty, N., & D'Onofrio, G. (2006). Alcohol-related seizures. *J Emerg Med*, *31*(2), 157–163. https://doi.org/10.1016/j.jemermed.2005.09.012

70. Samokhvalov, A. V, Irving, H., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis. *Epilepsia*, *51*(7), 1177–1184. https://doi.org/10.1111/j.1528-1167.2009.02426.x
71. Sarkar, S., Choudhury, S., Ezhumalai, G., & Konthoujam, J. (2017). Risk factors for the development of delirium in alcohol dependence syndrome: Clinical and neurobiological implications. *Indian J Psychiatry*, *59*(3), 300–305. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_67_17
72. Schuckit, M. A. (2014). Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med*, *371*(22), 2109–2113. https://doi.org/10.1056/NEJMra1407298
73. Schuckit, M. A., Tipp, J. E., Reich, T., Hesselbrock, V. M., & Bucholz, K. K. (1995). The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects. *Addiction*, *90*(10), 1335–1347. https://doi.org/10.1046/j.1360-0443.1995.901013355.x
74. Sellers, E. M., Naranjo, C. A., Harrison, M., Devenyi, P., Roach, C., & Sykora, K. (1983). Diazepam loading: simplified treatment of alcohol withdrawal. *Clin Pharmacol Ther*, *34*(6), 822–826. https://doi.org/10.1038/clpt.1983.256
75. Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V, Keane, K. A., Tesoro, E. P., & Elswick, R. K. (2002). The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*, *166*(10), 1338–1344. https://doi.org/10.1164/rccm.2107138
76. Shaw, J. M., Kolesar, G. S., Sellers, E. M., Kaplan, H. L., & Sandor, P. (1981). Development of optimal treatment tactics for alcohol withdrawal. I. Assessment and effectiveness of supportive care. *J Clin Psychopharmacol*, *1*(6), 382–389. https://doi.org/10.1097/00004714-198111000-00006
77. Stockwell, T., Hodgson, R., Edwards, G., Taylor, C., & Rankin, H. (1979). The development of a questionnaire to measure severity of alcohol dependence. *Br J Addict Alcohol Other Drugs*, *74*(1), 79–87. https://doi.org/10.1111/j.1360-0443.1979.tb02415.x
78. Stockwell, T., Murphy, D., & Hodgson, R. (1983). The severity of alcohol dependence questionnaire: its use, reliability and validity. *Br J Addict*, *78*(2), 145–155. https://doi.org/10.1111/j.1360-0443.1983.tb05502.x
79. Suchyta, M. R., Beck, C. J., Key, C. W., Jephson, A., & Hopkins, R. O. (2008). Substance dependence and psychiatric disorders are related to outcomes in a mixed

ICU population. *Intensive Care Med*, *34*(12), 2264–2267. https://doi.org/10.1007/s00134-008-1263-9

80. Sullivan, J. T., Sykora, K., Schneiderman, J., Naranjo, C. A., & Sellers, E. M. (1989). Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction*, *84*(11), 1353–1357.
81. Sutton, T. (1813). Tracts on Delirium Tremens, on Peritonitis, and on Some Other Internal Inflammatory Affections, and on the Gout. *Edinburgh Medical and Surgical Journal*, *9*(35), 352–358.
82. Tiwari, A. M., Zirpe, K. G., Khan, A. Z., Gurav, S. K., Deshmukh, A. M., Suryawanshi, P. B., Kapse, U. S., Wankhede, P. P., Bamne, S. N., Bhoyar, A. P., Malhotra, R. V., Sontakke, S. M., & Borade, P. B. (2023). Incidence, Subtypes, Risk factors, and Outcome of Delirium: A Prospective Observational Study from Indian Intensive Care Unit. *Indian J Crit Care Med*, *27*(2), 111–118. https://doi.org/10.5005/jp-journals-10071-24407
83. Van Rompaey, B., Elseviers, M. M., Schuurmans, M. J., Shortridge-Baggett, L. M., Truijen, S., & Bossaert, L. (2009). Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit Care*, *13*(3), R77. https://doi.org/10.1186/cc7892
84. Ventura-Cots, M., Watts, A. E., Cruz-Lemini, M., Shah, N. D., Ndugga, N., McCann, P., Barritt 4th, A. S., Jain, A., Ravi, S., Fernandez-Carrillo, C., Abraldes, J. G., Altamirano, J., & Bataller, R. (2019). Colder Weather and Fewer Sunlight Hours Increase Alcohol Consumption and Alcoholic Cirrhosis Worldwide. *Hepatology*, *69*(5), 1916–1930. https://doi.org/10.1002/hep.30315
85. Victor, M., & Brausch, C. (1967). The role of abstinence in the genesis of alcoholic epilepsy. *Epilepsia*, *8*(1), 1–20. https://doi.org/10.1111/j.1528-1157.1967.tb03815.x
86. Volkow, N. D., Torrens, M., Poznyak, V., Sáenz, E., Busse, A., Kashino, W., Krupchanka, D., Kestel, D., Campello, G., & Gerra, G. (2020). Managing dual disorders: a statement by the Informal Scientific Network, UN Commission on Narcotic Drugs. *World Psychiatry*, *19*(3), 396–397. https://doi.org/10.1002/wps.20796
87. Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Logan, J., Jayne, M., Ma, Y., Pradhan, K., & Wong, C. (2007). Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. *J Neurosci*, *27*(46), 12700–12706. https://doi.org/10.1523/JNEUROSCI.3371-07.2007

88. Wilson, J. E., Mart, M. F., Cunningham, C., Shehabi, Y., Girard, T. D., MacLullich, A. M. J., Slooter, A. J. C., & Ely, E. W. (2020). Delirium. *Nat Rev Dis Primers*, *6*(1), 90. https://doi.org/10.1038/s41572-020-00223-4
89. Wirrell, E., Tinuper, P., Perucca, E., & Moshé, S. L. (2022). Introduction to the epilepsy syndrome papers. *Epilepsia*, *63*(6), 1330–1332. https://doi.org/10.1111/epi.17262
90. Witkiewitz, K., Bowen, S., & Donovan, D. M. (2011). Moderating effects of a craving intervention on the relation between negative mood and heavy drinking following treatment for alcohol dependence. *J Consult Clin Psychol*, *79*(1), 54–63. https://doi.org/10.1037/a0022282
91. Wood, E., Albarqouni, L., Tkachuk, S., Green, C. J., Ahamad, K., Nolan, S., McLean, M., & Klimas, J. (2018). Will This Hospitalized Patient Develop Severe Alcohol Withdrawal Syndrome?: The Rational Clinical Examination Systematic Review. *JAMA*, *320*(8), 825–833. https://doi.org/10.1001/jama.2018.10574
92. World Health Organization. (2016). *International statistical classification of diseases and related health problems (10th ed.).*
93. World Health Organization. (2018). *Global Status Report on Alcohol and Health*.
94. World Health Organization. (2019). *International statistical classification of diseases and related health problems (11th ed.).*
95. Zhang, Z., Morse, A. C., Koob, G. F., & Schulteis, G. (2007). Dose- and time-dependent expression of anxiety-like behavior in the elevated plus-maze during withdrawal from acute and repeated intermittent ethanol intoxication in rats. *Alcohol Clin Exp Res*, *31*(11), 1811–1819. https://doi.org/10.1111/j.1530-0277.2007.00483.x
96. Zhou, Z., Metten, P., Yuan, Q., Sun, H., Hodgkinson, C. A., Shen, P.-H., Marietta, C., Crabbe, J. C., & Goldman, D. (2022). Genetic and genomic signatures in ethanol withdrawal seizure-prone and seizure-resistant mice implicate genes involved in epilepsy and neuronal excitability. *Mol Psychiatry*, *27*(11), 4611–4623. https://doi.org/10.1038/s41380-022-01799-x