Clinical consequences of alcohol dependence syndrome: focusing on complicated withdrawal

Ph.D. Thesis

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Research articles related to the thesis

1. Original research articles related to the thesis

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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)
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1. Introduction

According to a previous report by the National Institute on Alcohol Abuse and Alcoholism, alcohol misuse was the seventh-leading risk factor for premature death and disability globally in 2016 (GBD 2016 Alcohol Collaborators, 2018). The prevalence of alcohol dependence syndrome (ADS), one of the most common substance use problem, is 3.7% in Europe and nearly 10% in Hungary, according to a previous report by the World Health Organization (World Health Organization, 2018).

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'); and 2) demographic and 3) clinical or biological ('internal') risk factors.

Patients diagnosed with ADS suffer from the short-, mid-, and long-term consequences of the disorder. The most common clinical complication of ADS is alcohol withdrawal syndrome (AWS). AWS requiring hospitalization occurs in approximately 50% of alcohol-dependent individuals.

AWS can be separated into two subgroups: uncomplicated and complicated withdrawal syndrome. Approximately 20% of patients with AWS develop a complicated form of withdrawal that includes alcohol-related seizures (ARS) and delirium tremens (DT). Although several risk factors for these complications have been identified, environmental risk factors such as seasonality in the development of DT, clinical characteristics of patients who suffer from ARS, predictors of the development of ARS, the relationship between ARS and DT, and the relationship between ARS and the severity of withdrawal syndrome have not been evaluated in detail.

Therefore, the main goals of the three studies summarized in the present thesis were:

1) To investigate the clinical characteristics and risk factors of DT and its connection with seasons in a retrospective study (*Study 1*);

2) 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*);

3) To examine the relationship between the occurrence of ARS and the severity of AWS measured by the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) in a follow-up study with patients hospitalized with the principal diagnosis of AWS (*Study 3*).

2. Background

ADS, one of the most common forms of addictions and substance use disorders, imposes a heavy burden on the health and social system as well as the economy (GBD 2016 Alcohol Collaborators, 2018; Horvat et al., 2018; Paksi et al., 2021; World Health Organization, 2018). ADS is a spectrum disorder where a mild form of it can develop into a severe form because of the occurrence of internal and external risk factors.

Various neurobiological, psychological, and environmental factors play a role in the development and maintenance of ADS. In addition to well-defined psychological features such as increased novelty seeking, reward dependence, and impulsivity (Cloninger et al., 1993; Foulds et al., 2017; Kovács et al., 2017), Nora Volkow and her colleagues identified the main neurobiological abnormalities involved in the modulation of ADS as well as other addictions (Koob & Volkow, 2016). Although these factors are responsible for the core mechanisms of alcohol dependence, chronic alcohol use plays a significant role in the development of ADS clinical complications. The main changes can be summarized as follows: downregulation of g-aminobutyric acid receptors, upregulation of N-methyl-D-aspartate receptors, disturbances in the dopamine, serotonin, and noradrenalin systems, and increased activity of the hypothalamic-pituitary-adrenal axis (Brodie, 2002; Krystal et al., 2003; Kumar et al., 2009; Volkow et al., 2007).

The neural and metabolic side effects of chronic alcohol exposure led to the development of short-, mid- and long-term consequences. The most important short- and medium-term consequence is AWS. Nonetheless, AWS occurs in approximately 50% of alcohol-dependent patients during hospitalization (Maldonado et al., 2014; Schuckit, 2014). AWS is a potentially life-threatening complex neuropsychiatric disorder. Because of the presence of severe clinical complications, two types of AWS can be distinguished: uncomplicated and complicated withdrawal. Between 10% and 20% of hospital admissions for AWS involve a complicated form, including seizures or delirium tremens (DT) (Maldonado et al., 2014; Schuckit, 2014).

Assessment of risk factors for the development of complicated withdrawal syndrome has been the main focus of papers published in the field of withdrawal syndrome over the past few decades (Wood et al., 2018). In the risk assessment, in addition to biomarkers and medical history (Jesse et al., 2017), the significance of questionnaires / rating scales such as the CIWA-Ar (Lázár et al., 2019; Pribék et al., 2021; 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) have been indicated.

DT is the most severe consequence of withdrawal syndrome and occurs in 5%–15% of patients with ADS; its mortality can reach 5% even with optimal therapy (Maldonado et al., 2014; Wood et al., 2018). Although the prevention and treatment of DT is a major public health priority, it is usually overlooked and misdiagnosed. During the past few decades, several potential predictors of DT have been identified, such as older age, co-occurrence of somatic disorders, changes in electrolyte levels, high blood pressure and history of seizures, and DT (Goodson et al., 2014; Wood et al., 2018). It has been previously documented that seasonality and other environmental factors influence drinking patterns, there is no information available regarding the relationship between DT and seasonality (Carpenter, 2003; Cho et al., 2001; Ventura-Cots et al., 2019).

Another form of complicated withdrawal syndrome is the ARS, which is a special, occasional, and provoked seizure. The importance of ARS during withdrawal syndrome and the evaluation of the likelihood of further episodes of AWS and/or seizures have been recently demonstrated (Eyer et al., 2011; Kim et al., 2015). In addition, its role in the development of DT has been highlighted. Therefore, the clinical aspects of seizures associated with withdrawal syndrome should be investigated.

During the past few decades, the importance of the kindling mechanism in the development of ARS has been suggested by various authors (Becker, 1998; Eyer et al., 2011; Hillemacher et al., 2012; Kim et al., 2015). It has also been demonstrated that ARS has a distinct genetic, biological, and molecular background from other provoked seizures (Gorwood et al., 2003; Grzywacz et al., 2012; Pestana et al., 2019). The literature contradicts the relationship between the occurrence of seizures and the development of DT. 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, it has been suggested that patients who have both DT and ARS may be part of a specific genetically defined subgroup of patients with alcohol dependence (Gorwood et al., 2003; Grzywacz et al., 2012; Pestana et al., 2019). Nevertheless, it has been revealed that male sex, older age, and history of ARS are risk factors for developing future episodes of seizures during withdrawal syndrome (Eyer et al., 2011; Wood et al., 2018).

Previous studies have shown that patients with ARS show a significantly later climax of withdrawal severity measured using a modified version of CIWA-Ar than patients without seizures. Moreover, the initial maximal scores of the groups were similar (Eyer et al., 2011).

In conclusion, preventing complicated withdrawal syndrome is substantial during the treatment of patients diagnosed with ADS. Therefore, risk assessment of ARS and DT is of critical importance. Although previous findings have revealed various factors underlying the development of complicated withdrawal syndrome, the role of seasonality in DT, clinical characteristics and predictors of ARS, relationship between ARS and DT, occurrence of ARS, and severity of withdrawal symptoms remain largely unknown.

3. Aims

The complicated form of withdrawal syndrome, which includes ARS and DT, may lead to severe consequences. Therefore, the optimal diagnosis and management of complicated AWS reduces the mortality rate 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, the external risks of DT, clinical features of ARS, the connection between ARS and DT, and the severity of AWS in clinical settings have not yet been evaluated in detail.

Therefore the studies summarized in 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 connection 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 ADS, ADS and AWS, 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 relationship 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*). ARS occurrence was assessed where the principal diagnosis was AWS, therefore the diagnosis of AWS with and without AES 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

The three studies were performed in line with the principles of the Declaration of Helsinki, and approved by the Human Investigation Review Board, University of Szeged (ethical approval numbers: 30/2016-SZTE [*Study 1 and 2*]; 82/2022-SZTE [*Study 2*]; 28/2018-SZTE [*Study 3*]). All statistical analyses were performed in the three studies using IBM SPSS 24 (IBM Corp. Released 2016., 2016).

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

In Study 1, the clinical characteristics and predictors of DT were examined in a retrospective database. 2900 medical charts of 1591 inpatients with the principal diagnosis of ADS between 2008 and 2015 from the Department of Psychiatry, University of Szeged, Hungary were analyzed. Demographic variables (age, sex), seasonality, year and month of admission, housing situation, somatic and psychiatric co-morbidities and the occurrence of AWS and DT, were collected. Three groups were formed on the basis of the ICD-10 diagnoses of the patients. Medical charts with ADS and without the diagnoses of AWS and/or DT were assigned to the (1) ADS group. Medical charts with AWS and without DT, and AWS with DT were classified into the (2) AWS or (3) DT groups. First, we analyzed the differences among the three groups (ADS, AWS and DT) regarding sociodemographic variables, and these were controlled in the subsequent exploration of potential predictors of AWS and DT. One-way ANOVA was calculated to explore age differences, chi-square tests were used to analyze the rate of homelessness and the presence of comorbid somatic and psychiatric disorders. Chi-

square tests were conducted to explore the seasonality rates of the three groups and the monthly and seasonal breakdowns of DT. Two multinomial logistic regression analyses were conducted 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 dependent variable was also the three-group breakdown, but with the AWS group as the reference group. The independent variables were the same factors for both multinomial logistic analyses (age, sex, homelessness, comorbid somatic disorder, comorbid psychiatric disorder and seasonality). These sociodemographic and clinical variables were also controlled in the analyses. Statistical significance was considered if $p < 0.05$.

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

In Study 2, clinical characteristics and predictors of ARS and the interplay between the presence of ARS and the occurrence of DT were examined in a retrospective database. 2851 medical charts of 1630 inpatient admissions with the principal diagnosis of AWS and/or DT between 2008 and 2023 from the Department of Psychiatry, University of Szeged, Hungary were analyzed. The ARS variable was defined as the occurrence of ICD-10-related diagnoses of occasional, provoked seizures. Medical charts with diagnoses of epilepsy syndromes and benzodiazepine use disorders were excluded. Demographic variables (age and sex), somatic and psychiatric co-morbidities, levels of electrolytes and liver enzymes and the history of AWS, DT, and ARS were collected from medical charts. 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. The evaluation of risk factors for the development of ARS was performed. ARS as a risk factor for DT was also assessed. 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. Multinomial logistic regression models were used to determine the variables that explain the appearance of ARS and DT in the case of ARS. The dependent variables were the occurrence of ARS and 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.

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

In Study 3, the relationship between the presence of alcohol-related seizure and the severity of alcohol withdrawal syndrome was examined in a follow-up study. Patients admitted with a diagnosis of AWS at the inpatient units of the Department of Psychiatry, University of Szeged, Hungary between 2019 and 2020 were enrolled in this study. Patients with the diagnosis of ADS and AWS, minimum of 7 points on the first CIWA-Ar and with fixed-schedule regimen with chlordiazepoxide were included. Patients with the symptoms of DT, clinically significant changes in electrolyte levels and liver enzymes, clinically significant somatic and/or neurological disorders, and the diagnosis of epilepsy syndrome and benzodiazepine use disorder were excluded. Two groups formed based on the occurrence of ARS: ARS^- and ARS^+. 28 (ARS^-) and 18 (ARS^+) patients were enrolled in this study. Alcohol Use Disorders Identification Test (AUDIT), and CIWA-Ar in every 2 days for 10 days were recorded. Demographic variables and laboratory parameters were also documented. 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

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

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

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). Based on the results, the mean age was significantly higher in the DT group (M = 55.21; SE = 0.552) than in the ADS (M = 49.73; SE = 0.576) ($p < 0.001$) and AWS (M =48.71; SE = 0.238) ($p < 0.001$) groups. 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%). 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; $p < 0.001$). In the first multinomial logistic regression, our results 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), lower co-occurrence of psychiatric disorders (OR = 0.142;

95% CI = 0.103–0.196), and the season of spring were significant predictors of the DT group compared to the ADS group. In the second multinomial logistic regression, regarding 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), lower co-occurrence of psychiatric disorders (OR = 0.339; 95% CI = 0.258–0.446) and season of spring (OR = 1.751; CI = 1.263–2.427) were significant predictive variables compared to the AWS group when controlling for general socio-demographic and clinical variables. These findings revealed that older age, higher presence of somatic co-morbidities, lower occurrence of psychiatric co-morbidities and the season of spring are significant risk factors for the development of DT.

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

In the total sample, 85.3% (N = 2431) of medical charts characterized with AWS without DT, and 14.7% (N = 420) were characterized 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 percentage of co-existing 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). 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. There was no significant difference in the laboratory parameters between the two groups. In the first multinomial logistic regression, our results revealed that the presence of DT, history of ARS, and somatic co-morbidity played a significant explanatory role in the development of ARS. In the second model, our results showed that ARS significantly increases the probability of DT. In Study 2, our findings indicated that the presence of DT, the history of ARS and somatic comorbidities were a significant risk factor for the development of ARS. Moreover, our result showed that the presence of ARS is a predictor for the development of DT.

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

The sample consisted of 15 female (32.6%) and 31 male (67.4%) patients (N = 46). 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 5^{th} and 6^{th} 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). Moreover, to compare the characteristics of the decrease in CIWA-Ar scores between the ARS^+ and ARS^- subgroups an index number was created for every patient's six visits. A quadratic curve was fitted to the six points (CIWA-Ar scores). The difference between the ARS^+ and ARS^- groups regarding these CIWA-Ar index numbers was calculated using the independent samples t-test. There was no significant difference between both groups (t(44) = -1.143, p = 0.515); therefore, the decrease in the CIWA-Ar scores during the six visits was not similar. These findings suggest that the occurrence of ARS may be independent from the severity of alcohol withdrawal syndrome.

6. Discussion

AWS is a life-threatening neuropsychiatric disorder which occurs in the half of the alcohol-dependent patients. The most important goal of AWS treatment is to prevent the development of complicated form of withdrawal syndrome. Previously, various 'external' (sociological and environmental) and 'internal' (demographic and clinical) risk factors have been revealed in the development of ARS and DT. However, the role of seasonality in DT, the clinical characteristics of ARS, the relationship between 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.

In Study 1, the clinical characteristics and predictors of DT were revealed in a retrospective clinical database. Our results revealed that approximately 12% of medical charts were characterized with DT in the total sample. Furthermore, our findings showed that older age, increased occurrence of somatic co-morbidities and lowest co-occurrence of mental disorders were significant predictor for the development of DT. Previous reports have documented 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). Furthermore, recently, the role of older age and co-occurred somatic disorders in the development of DT has been suggested (Goodson et al., 2014; Kim et al., 2015). Our results with a robust, eight years data confirmed these observations. The role of age in the development of ADS complications were investigated recently. This finding can be explained by the causes that older patients may be exposed to alcohol for a longer period, may have more somatic and psychiatric co-morbidities and have a worse general condition (Kraemer et

al., 1997). The role of co-occurred somatic disorders in the eventuality of DT has also been proposed. It has been revealed that infections, cardiovascular disorders and liver disorders have a pivotal impact on the occurrence of DT (Goodson et al., 2014). Although, psychiatric co-morbidities could be a risk factor for the development of DT (Gajdics et al., 2023), it could be hypothesized that these patients who developed DT during their hospitalization may have severe ADS, and their secondary mental disorders have not been revealed.

The results of Study 1 also revealed that seasons especially spring is a contributing factor in the development of DT. Previously, it has been demonstrated that winter modulates the immunity and vitamin levels (Fares, 2013) and the drinking pattern (Klimstra et al., 2011; Ostojić et al., 2012; Witkiewitz et al., 2011). Our observations showed that March is the critical months in the development of DT. 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 Study 2, the clinical characteristics and predictors of ARS, and its connection with DT were revealed. Our results showed that approximately 10% of medical charts were characterized with ARS; and the prevalence of complicated withdrawal syndrome was 20%. These findings support previous observations. Our results also revealed that the presence of DT, the co-occurrence of somatic co-morbidities, the history of DT and ARS were significantly higher among medical charts characterized with ARS compared to the medical charts without seizures. Furthermore, our findings indicated that the co-occurrence of somatic comorbidities, history of ARS, and presence of DT are risk factors for developing seizures during withdrawal syndrome. Recent findings have revealed that previous episodes of ARS, incidence of hospitalization because of ADS, and structural brain lesions are significantly higher in the subgroup of patients diagnosed with ARS (Eyer et al., 2011). The results of Study 2 confirmed and extended these observations, furthermore, indirectly suggest the significance of kindling mechanism. In addition, our results showed that the occurrence of ARS is a risk factor for the development of DT. Previously, some authors demonstrated that patients with DT and/or ARS may comprise a specific subgroup of alcohol-dependent individuals by revealing genetic differences between patients suffering from un- and complicated withdrawal syndromes (Gorwood et al., 2003; Grzywacz et al., 2012; Pestana et al., 2019). Our results support this hypothesis by showing a strong link between ARS and DT.

In Study 3, the relationship between the occurrence of ARS and the severity of withdrawal symptoms measured using CIWA-Ar was revealed. Recently, it has been suggested that seizure is not a core symptom of AWS (Foy et al., 1988; Manikant et al., 1992; Sellers et al., 1983; Shaw et al., 1981; Sullivan et al., 1989). Interestingly, the original version of CIWA-Ar, the CIWA-A contained the seizure item, but later some authors found that this item negatively influences the psychometric properties (Foy et al., 1988; Manikant et al., 1992; Sellers et al., 1983; Shaw et al., 1981; Sullivan et al., 1989). However, regarding the role of the kindling mechanism, it has been suggested that during the assessment of withdrawal syndrome, seizure plays a substantial role (Kim et al., 2015). Our results revealed that there were no significant differences in the maximal score and the decrease in the CIWA-Ar scores between patients suffering from seizure or not. Therefore, our findings confirm previous findings and hypotheses that the occurrence of ARS may be independent of the severity of withdrawal. Thus, it could be suggested that patients with ARS comprise a specific subpopulation of individuals with ADS.

In conclusion, the studies summarized in the present thesis support previous observations and reveal novel risk factors for complicated withdrawal syndrome. Overall, our main findings indicated that the presence of ARS, and the 'late winter effect' are the risk factors of development of DT. Furthermore, the presence of DT, co-occurring somatic disorders, and history of ARS are predictors for the development of ARS. Finally, the occurrence of ARS may be independent of the severity of withdrawal symptoms.

7. Summary of the results and conclusions

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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