



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

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ABSTRACT

Background: Although the Clinical Institute Withdrawal Assessment for Alcohol – Revised (CIWA-Ar) is a gold standard tool for the clinical evaluation of alcohol withdrawal syndrome (AWS), a systematic analysis using the total scores of the CIWA-Ar as a means of an objective follow-up of the course and treatment of AWS is missing. The aims of the present study were to systematically evaluate scientific data using the CIWA-Ar, to reveal whether the aggregated CIWA-Ar total scores follow the course of AWS and to compare benzodiazepine (BZD) and non-benzodiazepine (nBZD) therapies in AWS.

Methods: 1054 findings were identified with the keyword “ciwa” from four databases (PubMed, ScienceDirect, Web of Science, Cochrane Registry). Articles using CIWA-Ar in patients treated with AWS were incorporated and two measurement intervals (cumulative mean data of day 1–3 and day 4–9) of the CIWA-Ar total scores were compared. Subgroup analysis based on pharmacotherapy regimen was conducted to compare the effectiveness of BZD and nBZD treatments.

Results: The random effects analysis of 423 patients showed decreased CIWA-Ar scores between the two measurement intervals (BZD: $d = -1.361$; CI: $-1.829 < \delta < -0.893$; nBZD: $d = -0.858$; CI: $-1.073 < \delta < -0.643$). Sampling variances were calculated for the BZD ($v_1 = 0.215$) and the nBZD ($v_2 = 0.106$) groups, which indicated no significant group difference ($z = -1.532$).

Conclusions: Our findings support that the CIWA-Ar follows the course of AWS. Furthermore, nBZD therapy has a similar effectiveness compared to BZD treatment based on the CIWA-Ar total scores.

1. Introduction

Alcohol use disorder (AUD) is a global health problem ranking seventh among the leading causes of death (GBD 2016 Alcohol Collaborators, 2018). Generally, patients with AUD are admitted to hospitals due to the long-term consequences of alcohol use, such as liver insufficiency, polyneuropathy or alcohol withdrawal syndrome (AWS). AWS may occur in the hospital treatment of AUD patients after the rapid reduction or cessation of alcohol consumption (Sachdeva et al., 2015; Saitz, 2005). AWS typically starts within 6–24 hours after the last alcohol intake

(Hall and Zador, 1997) and the characteristic symptoms include insomnia, autonomic symptoms (e.g. sweating or tachycardia), tremors, nausea and/or vomiting, psychomotor agitation, anxiety, seizures and perceptual disturbances (auditory, tactile or visual) (American Psychiatric Association, 2013). The main goals during the treatment of AWS are to reduce the symptoms of withdrawal and to prevent the development of severe consequences such as withdrawal seizures and/or delirium tremens (DT). There is a consensus that the clinical description of AWS divides the first 6–72 hours based on the symptom severity of withdrawal and the possibility of the emergence of severe complications

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such as withdrawal seizure or DT from the complete course of AWS, which may last up to 2 weeks (Haber et al., 2009).

Although AWS is basically a clinical diagnosis, in the last few decades, several psychometric tools were recommended to identify and follow the signs of it (Elefante et al., 2020; Gray et al., 2010; Lindner et al., 2019; Sullivan et al., 1989). Objective measurements for monitoring the course and severity of AWS are necessities, from which the revised version of the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) was the first scale that was developed to monitor and rate the number and severity of symptoms occurring during AWS. Its 10 items reflect on symptom groups of AWS including the leading symptoms of the syndrome. The items of the CIWA-Ar include nausea, vomiting, tremor, paroxysmal sweats, perceptual (tactile, visual or auditory) disturbances, anxiety, agitation, headache and disturbances of orientation and/or consciousness (Sullivan et al., 1989). Clinician-rated scoring is made for each item by a Likert-scale and the maximum attainable score is 67, where the higher score reflects on the more severe AWS (Bakhla et al., 2014; Higgins et al., 2019; Pittman et al., 2007), and the CIWA-Ar scores show a higher internal consistency during the first phase of AWS, during which the more severe symptoms occur (Lázár et al., 2019).

Over the last decades, the CIWA-Ar has been translated into various languages and several reports have revealed its psychometric properties and distinct factor structures in different countries (Davis et al., 2018; Eloma et al., 2018; Lázár et al., 2019; Rappaport et al., 2013). Despite the fact that several modified versions of the CIWA-Ar have been introduced in the scientific literature (Bakhla et al., 2014; Elefante et al., 2020; Gray et al., 2010; Higgins et al., 2019; Lindner et al., 2019; Maldonado et al., 2014; Pittman et al., 2007) and shorter versions of the scale have also been suggested (Elefante et al., 2020; Gray et al., 2010; Lindner et al., 2019; Maldonado et al., 2014), national guidelines such as protocols of the National Institute for Health and Care Excellence (NICE) and the National Institutes of Health (NIH) recommend the CIWA-Ar as the gold standard tool in the management of AWS. Based on these findings, it was proposed that the CIWA-Ar scores could be suitable for clinicians to make a treatment regimen for AWS. Some findings suggested that the CIWA-Ar scores of 0–8, 9–15 and 16 or more indicate mild, moderate, and severe withdrawal syndrome, respectively (Mayo-Smith, 1997; Saitz and O'Malley, 1997). For instance, patients with mild withdrawal symptoms (scores of 8 or less) can be managed without pharmacotherapy.

Concerning these, clinical management of AWS are centered around the following pharmacotherapeutic treatment regimens: symptom-triggered and fixed-schedule therapies. Symptom-triggered treatment, which is a CIWA-Ar-based regimen, is defined as an approach in which patients are consistently monitored by the CIWA-Ar, and the designation of adequate pharmacotherapy is only used in case symptoms of withdrawal cross a certain threshold of severity. In this treatment regimen, further dosages and the times of reassessments are also based on the score of the structured assessment scale. Whereas a fixed-dose regimen is characterized by giving the patient a previously determined dose of medication in formerly established (i.e., fixed) time intervals based on a schedule. The amount of received doses gradually decrease over time; also, the fixed-dose regimen may be modified according to withdrawal symptom severity, in case the predetermined fixed-dose would prove to be inadequate in controlling withdrawal symptoms (Wong et al., 2020). Previous scientific works have demonstrated that symptom-triggered therapy, which is a CIWA-Ar-based regimen, showed better effectiveness compared to fixed-schedule therapy (Cassidy et al., 2012; Daepfen et al., 2002; Ismail et al., 2019; Jaeger et al., 2001; Reoux and Miller, 2000; Sachdeva et al., 2014).

Benzodiazepines (BZDs) such as diazepam, lorazepam, chlordiazepoxide or oxazepam are predominantly regarded as symptom-triggered therapies and are first choices in the treatment of AWS (Weintraub, 2017). The efficacy of the subclasses of BZDs are similar; however, long-acting drugs such as diazepam and chlordiazepoxide are the more

preferred choices. Additionally, it has been suggested that diazepam is superior in the treatment of AWS (Weintraub, 2017). Despite that BZDs are the drugs of choice in the treatment of AWS, it is important to note that they have a relatively high addictive potential (Weintraub, 2017). For this reason, other agents such as anticonvulsant, adrenergic drugs and barbiturates were approved by the Food and Drug Administration (FDA), which are also used and recommended during the course of AWS.

In summary, the CIWA-Ar is the most commonly used tool to identify and follow the course of withdrawal symptoms. Furthermore, the symptom-triggered therapy of AWS with BZDs using the CIWA-Ar is considered to be the gold standard for the treatment of uncomplicated and complicated (with DT and/or withdrawal seizure) withdrawal syndrome. Based on our literature search, the course of AWS and its treatment options using the CIWA-Ar total score as a means of an objective follow-up of the course and treatment of AWS has not been systematically evaluated yet. Consequently, the aims of the present systematic review-based meta-analysis were 1) to explore and systematically evaluate the empirical data presenting the CIWA-Ar total scores, 2) to assess whether the CIWA-Ar is suitable for following the course of AWS during pharmacotherapeutic treatment, and 3) to compare BZD and FDA-approved nBZD treatments in patients with AWS.

2. Material and methods

2.1. Search strategy and study selection

Three authors (I.K.P., B.A. and I.K.) independently systematically searched four databases (PubMed, ScienceDirect, Web of Science and Cochrane Registry) in order to identify studies published before January 31, 2020, which documented the severity of AWS with the CIWA-Ar in patients treated with AWS. The full-text search was made without filtering, “ciwa” was used as the key search term. Our systematic literature search yielded 1054 articles for possible inclusion in the quantitative meta-analysis. The first author (I.K.P.) listed the previously identified scientific articles for critical revision of a professional researcher team expert in the course and pharmacotherapy of AWS, in clinical psychometrics, and in the methodology of meta-analyses (I.K.P., I.K., B.A. and B.A.L.). During this process, duplicates (N = 209) and grey literature (e.g. conference abstracts, correspondence, editorial letters and RCT registrations) (N = 176) were removed. Non-English articles (N = 58) and publications not connected to AWS (N = 62) were also excluded. Investigations of specific populations were selected out (N = 5), since the comorbid somatic state affects the course and treatment of AWS. In this sense, Kong et al. (2017) and Spies et al. (1995; 1998) have examined alcohol dependent patients with carcinoma, Talbot (2011) have investigated patients developing Wernicke's disease in jail setting and Illig et al. (2001) have explored the unexpected emergence of AWS following aortic surgery. Several articles (N = 70) were excluded because of the use of different versions of the CIWA-Ar (CIWA-A, CIWA-Benzodiazepine or other modified versions). Non-empirical studies (e.g. indexes, author indexes, table of contents, abbreviations, appendixes, reviews, case reports, protocols, guidelines etc.) were also removed (N = 219). Articles not monitoring the course of AWS (e.g. the CIWA-Ar was applied as a screening test and only one assessment point was reported) (N = 71), and the lack of use of the CIWA-Ar total scores (N = 92) were excluded. Additionally, 12 papers fell out due to non-eligibility based on medication. These were the following: patients with AWS were treated with augmented medications (concurrent combination of multiple BZDs and nBZDs) in case of numerous studies (Djokić et al., 2011; Jegham, Cunelle and Matthys, 2018; Love and Zimmerman, 2020), and patients received several BZDs in the study of Jaeger, Lohr and Pankratz (2001). In the study of Karst et al. (2002) patients received nBZD and acupuncture or nBZD and placebo acupuncture. This study was excluded because acupuncture treatment is a non-chemical therapy, and it can only be considered as an alternative therapeutic approach. Additionally, Wilhelm et al. (2011) and

Narendran et al. (2018) have not clarified the type and the dosing of the medications. In the study of Nadkarni et al. (2020), patients were treated by home detoxification and the exact type and dosing of pharmacotherapy was also not detailed. The studies of Kumar, Andrade and Murthy (2009); Silpakit et al. (1999), and Ramanujam et al. (2015) were also excluded due to their use of lorazepam or chlordiazepoxide, and since diazepam, as a first-line drug in the treatment of AWS, was in the main focus of the present meta-analysis. In the study of Mason et al. (2006), the patients did not receive any medications, except in cases of the emergence of severe AWS symptoms. Empirical publications were included in case they reported sample size, the means and standard deviations of the CIWA-Ar in patients with clinical diagnosis of AWS and used evidence-based treatments (especially diazepam [BZD] or other FDA-approved medications [nBZD]). Finally, reference lists of studies identified were hand-searched by the first author (I.K.P.) for potential inclusion, and after applying all the exclusion criteria aforementioned, 11 studies met the previously set criteria for inclusion in the present meta-analysis (see Fig. 1).

2.2. Meta-analysis: data extraction

Since articles were excluded due to the lack of available CIWA-Ar means or standard deviations ($N = 92$), when we found an article that was potentially eligible for inclusion for our study but did not include the necessary means and standard deviations for the meta-analysis, we tried to contact the corresponding author two times over two months to ask them to provide these missing data.

Our units of the data analysis were the means and standard deviations of the cumulative CIWA-Ar total scores, which were calculated during the course of AWS in nine days of treatment. The first phase of the AWS was defined as the aggregated means and standard deviations of the CIWA-Ar scores of day 1–3; the second phase was identified as the means and standard deviations of the CIWA-Ar total scores of day 4–9. Thus, 11 studies were incorporated in the meta-regression and the final unit of data analysis was the comparison of the cumulative mean CIWA-Ar total scores of the two phases of the course of AWS.

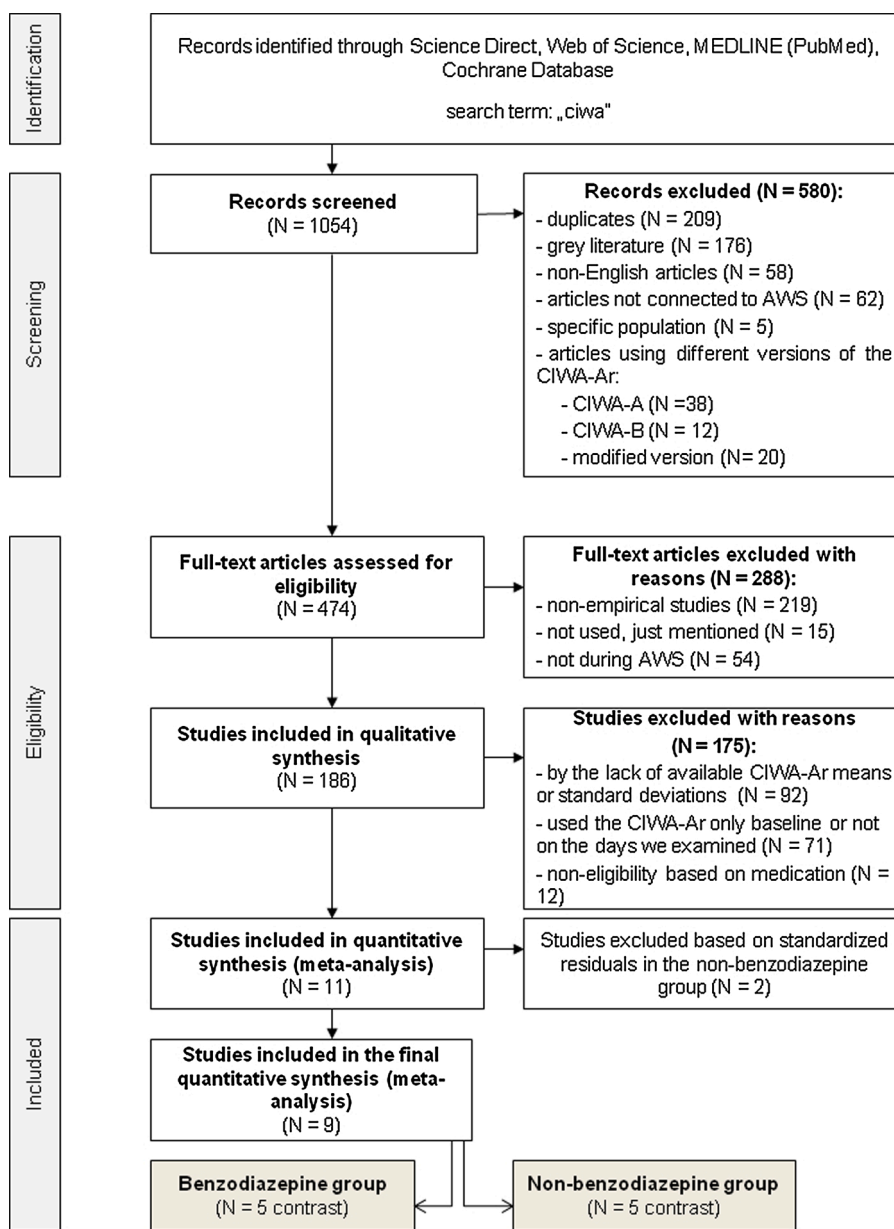


Fig. 1. PRISMA flow diagram.

Abbreviations: AWS: alcohol withdrawal syndrome; CIWA-A: Clinical Institute Withdrawal Assessment for Alcohol; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol – Revised; CIWA-B: Clinical Institute Withdrawal Assessment for Benzodiazepine; contrast: unit of data analysis.

2.3. Statistical analysis

Analyses were computed using a random-effects model. We also assessed the existence of publication bias, the calculation of effect sizes, the subgroup analysis and moderator analysis. All analyses were conducted with the use of the Comprehensive Meta-Analysis Software 3.0 (Comprehensive Meta-Analysis Software (CMA), 2020). For the calculations, the means and standard deviations of the CIWA-Ar total scores following the course of treatment were collected. In case they were documented, the following demographic (e.g. gender or age) and alcohol-specific data were gathered: duration of alcohol consumption and alcohol dependence, and alcohol consumption in grams. However, these data were reported differently in the articles and many were missing, these collected data could not be analysed as moderator variables in the final analysis.

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

In case of two studies (Chourishi et al., 2010; Girish et al., 2016), nBDZ was compared to lorazepam and chlordiazepoxide, and in the study of Addolorato et al. (1999) BZD was compared to γ -hydroxybutyric acid, thus these studies yielded two comparison pairs for analysis.

Publication bias was estimated based on visual/graphic examination of the funnel plots, and the Begg and Mazumdar's rank correlation test (Begg and Mazumdar, 1994) and Egger's regression (Egger et al., 1997) were calculated to estimate publication bias. Asymmetry was regarded as significant if the p -value was < 0.05 in the Begg and Mazumdar test and the p -value was < 0.1 in the Egger's test. If the standardized residual of a study was greater than 3.29, the study was considered an outlier (Shiffler, 1988). Therefore, two studies (Chourishi et al., 2010; Girish et al., 2016) were excluded based on standardized residuals. Thus, the previously identified 9 studies yielded 10 comparison pairs for the present meta-analysis (Pribék et al., 2020).

Heterogeneity was evaluated with the Q -test and I^2 test to explore whether the results of the studies were consistent. Significant p -value in the Q -test and value over 75 in the I^2 test meant a statistically significant, considerable heterogeneity in the sample. To examine the differences between the BZD and the nBZD groups, sampling variances (v_1 for the BZD and v_2 for the nBZD group) were calculated with the following formula, where d stood for the observed Cohen's d value:

$$v = \frac{1}{n_1} + \frac{1}{n_2} + \frac{d_1}{2(n_1 + n_2)}$$

By this, the results of the two treatment groups were comparable and were contrasted with the standard normal test statistics with the present formula below (Keef and Roberts, 2004):

$$z = \frac{d_1 - d_2}{\sqrt{v_1 - v_2}}$$

If $|z| \geq 1.96$, the differences of the groups were considered statistically significant. Moderator and covariate analysis were calculated to explore the moderating effects of age and the proportion of males on the course of AWS. Significant effect was detected if the p value was < 0.05 .

2.4. Prisma guidelines

This systematic review and meta-analysis are presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) statement, and its reporting is in accordance with the guidelines of meta-analyses in epidemiology described by Stroup and his colleagues (Stroup et al., 2000).

3. Results

3.1. Publication bias and heterogeneity

Based on the results of the visual/graphic examination, symmetric funnel plots were observed in the BZD (Fig. 2) and nBZD subgroups (Fig. 3), while the Egger's test for intercept also indicated symmetry (Intercept = -4.774 , $p = 0.177$). Based on the Begg and Mazumdar test, publication bias was not detected neither in the BZD group (Kendall's tau = -0.5 , $p = 0.221$) nor in the nBZD (Kendall's tau = -0.5 , $p = 0.22$) group.

Significant heterogeneity was expected due to the methodological differences in the studies, thus significant heterogeneity was found in the sample ($Q_w(9) = 32.946$, $p < 0.001$) and the two subgroups also differed in terms of heterogeneity ($Q_w(1) = 9.768$, $p = 0.002$), while the I^2 test indicated a moderate level of heterogeneity in the BZD ($I^2 = 71.333$) and the nBZD groups ($I^2 = 56.639$).

3.2. Comparison of the course of AWS measured with the CIWA-Ar total scores in the BZD and nBZD groups

The nine studies which met the inclusion criteria and yielded 10 comparison pairs are detailed in Table 1.

A total of 423 patients were analyzed and classified into two groups based on received pharmacotherapy. Since Addolorato et al. (1999) yielded one comparison pair in the BZD and one in the nBZD group, 5 articles yielding 5 comparison pairs were classified into the BZD group ($N = 127$) and 5 articles resulting in 5 comparison pairs were listed in the nBZD group ($N = 296$). The random effects model showed a decrease between the two measurement intervals, thus indicated the decrease of the CIWA-Ar scores during the course of AWS (BZD: $d = -1.361$; CI: $-1.829 < \delta < -0.893$; nBZD: $d = -0.858$; CI: $-1.073 < \delta < -0.643$) (Fig. 4). For the comparison of the results of the two groups, sampling variances were calculated for the BZD ($v_1 = 0.215$) and the nBZD ($v_2 = 0.106$) group, from which the z -score was computed ($z = -1.532$). This indicates that there is no statistically significant difference between the

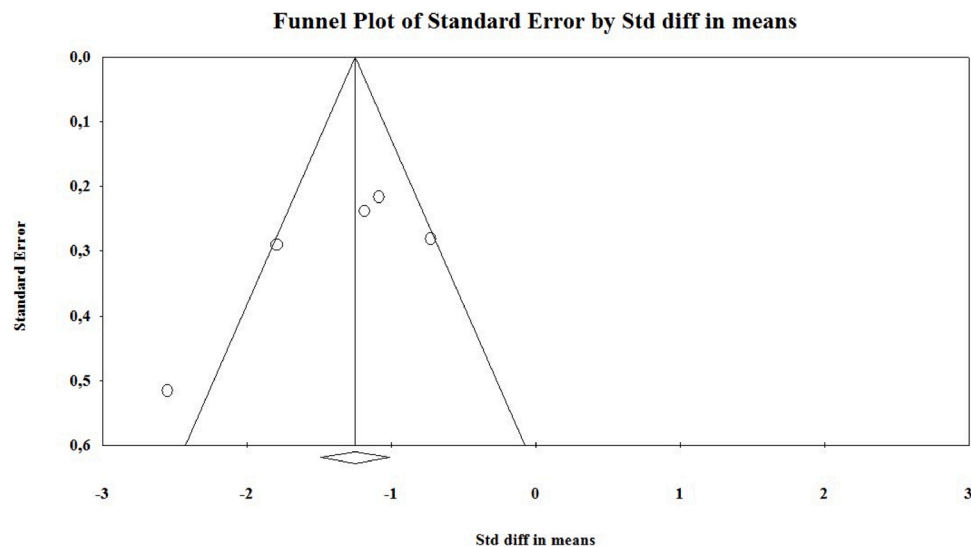


Fig. 2. Funnel plot of standard error by standardized mean differences in the benzodiazepine (BZD) group.

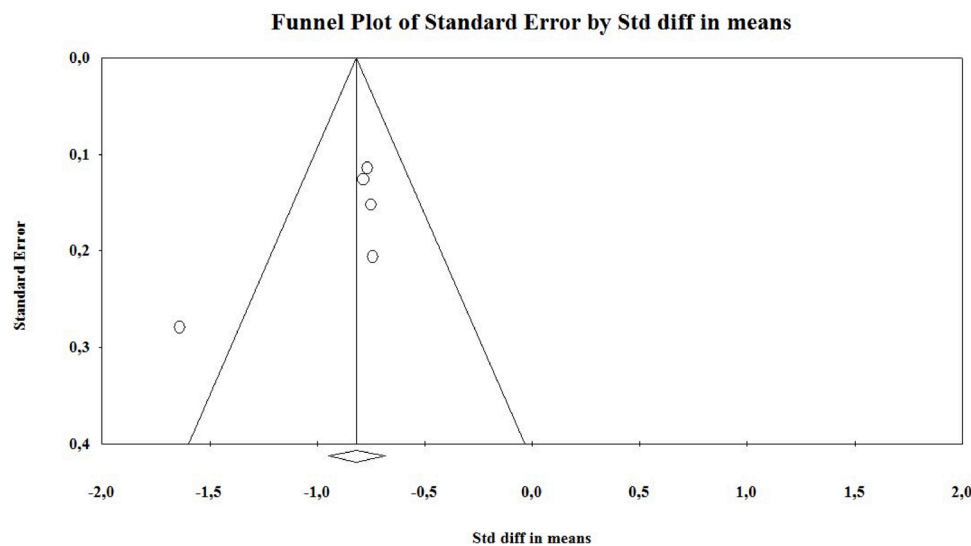


Fig. 3. Funnel plot of standard error by standardized mean differences in the non-benzodiazepine (nBZD) group.

BZD group and the nBZD group. For assessing the role of the proportion of males and age in the samples, moderator analysis was conducted; data regarding the proportion of males were available for 10 comparison pairs and 9 reported ages. No significant effect was detected based on the model, therefore the proportion of males (coefficient: 0.02; $p = 0.48$) and the age (coefficient: 0.10; $p = 0.216$) did not have any moderating effect concerning the change of the total CIWA-Ar score.

4. Discussion

In the present study, a systematic literature search-based meta-analysis was conducted on the effects of different pharmacotherapy-based treatment approaches of AWS evaluated by the change of the total scores of the CIWA-Ar during the course of AWS. This measurement tool was selected, since the major treatment protocols refer to it as a gold standard in the objective follow-up during the course of AWS. A total of 10 comparison pairs in 9 articles were analyzed including 423 patients' data. Our results showed a significant decrease of CIWA-Ar total scores in the course of AWS indicating that this tool appropriately followed the course of AWS (as a means of the ecological validity of this measure). Furthermore, the group receiving BZD treatment did not show a

significant difference from the nBZD group from the perspective of the course of AWS measured by the CIWA-Ar total scores.

Considering the relatively high morbidity of patients with AWS, the main goal during the treatment of AWS besides reducing the symptoms of withdrawal is to prevent the development of DT. It has been previously demonstrated that complicated or uncomplicated AWS occur in about 50% of AUD patients (de Wit et al., 2010; Lau et al., 2008; Sanibale et al., 2005). Unfortunately, DT, characterized by the fluctuation of consciousness, perceptual abnormalities, agitation and severe autonomic symptoms (Driessen et al., 2005; Jesse et al., 2017; Mirijello et al., 2015), as the most severe complication of treated or untreated withdrawal syndrome, is presented in about 5% of patients hospitalized with AWS (McKeon et al., 2008; Mirijello et al., 2015). Its occurrence during AWS is associated with a worse prognosis, further, it may lead to death in approximately 1–5% of patients (Schuckit et al., 1995).

For monitoring the progress and course of withdrawal, psychometric tools such as the CIWA-Ar have paramount importance during the management of AWS. For instance, it has been evaluated that the CIWA-Ar is a fundamental psychometric tool used by clinicians during symptom-triggered therapy of AWS (Cassidy et al., 2012; Daepfen et al., 2002; Hoffman and Goldfrank, 1989; Ismail et al., 2019; Jaeger et al.,

Table 1
Characteristics of the studies in the benzodiazepine and non-benzodiazepine subgroups included in the quantitative analysis (meta-analysis).

Study	Country	Pharmacological intervention	Dosing of medications	CIWA-Ar mean score, day 1–3 (SD)	CIWA-Ar mean score, day 4–9 (SD)	Sample size N (Male %)	Average age in years (SD)	Average duration of alcohol consumption in years (SD)	Average duration of alcohol dependence in years (SD)	Average alcohol consumption in grams (SD)
BENZODIAZEPINE SUBGROUP										
Addolorato et al. (1999)	Italy	diazepam	0.5–0.75 mg /kg body weight for 6 days, tapering the dose 25% daily until day 10	9.6 (4)	4.93 (3.875)	30 (83.33)	44.3 (10.9)	n/a	15.4 (10.2)	196 (139.7)
Cavus et al. (2012)	Turkey	diazepam	tapering the dose over 7 days (minimum: 30 mg, maximum: 40 mg on day 1)	18.8 (9.9)	1 (0.9)	31 (100)	42.8 (7.9)	17.6 (6.5)	n/a	164.2 (46.2)
Johnston et al. (1991)	United States of America	diazepam	40 mg (10 mg every six hours for 24 h)	7.6 (4.2)	4.9 (2.8)	16 (100)	45.1 (11.2)	25.2 (2.8)	n/a	n/a
Sengul et al. (2009)	Turkey	diazepam and memantine placebo	standard dose of 30 mg/day, tapering the dose daily by 5 mg, discontinued at the end of the sixth day	22.94 (7.47)	6.41 (3.45)	16 (100)	43.6 (7.3)	11.5 (5.7)	n/a	n/a
Sönmez et al. (2016)	Turkey	diazepam	based on the withdrawal symptoms, tapered gradually, cumulative dosage during AWS: M = 318.09 (SD =161.49 mg)	9.79 (5.64)	4.41 (3.62)	34 (100)	45.44 (8.98)	16.32 (8.82)	n/a	n/a
NON-BENZODIAZEPINE SUBGROUP										
Addolorato et al. (1999)	Italy	γ -hydroxybutyric acid (GHB)	50 mg/kg body weight for 10 days	8.83 (3.5)	3.545 (2.86)	30 (86.67)	41.7 (10.4)	n/a	16 (10.2)	214 (124.7)
Heberlein et al. (2010)	Germany	oxcarbazepine	based on the withdrawal symptoms, tapered gradually (minimum 300 mg, maximum: 1200 mg on day 1, M = 770 mg, SD = 244 mg)	15.32 (3.48)	12.87 (2.56)	82 (100)	43.59 (7.84)	8.85 (7.38)	n/a	193.27 (85.59)
Heberlein et al. (2014)	Germany	carbamazepine and clomethiazole	clomethiazole, prometazin in some cases carbamazepine dosage: day 1: M =772.34 mg (SD = 223.31); day 7: M =652.17 mg (SD = 270.59)	15.74 (3.64)	13.30 (2.76)	30 (100)	42.98 (6.91)	9.37 (6.92)	n/a	199.3 (91.61)
Heberlein et al. (2015)	Germany	carbamazepine and clomethiazole	clomethiazole dosage: day 1: M = 8.47 capsules (SD = 4.11) day 7: M = 0.13 capsules (SD = 0.65) carbamazepine dosage: day 1: M =710.97 mg (SD = 299.91) day 7: M =551.877 mg (SD = 340.51)	15.68 (4.22)	12.84 (2.72)	99 (100)	42.9 (9.01)	9.79 (7.67)	n/a	195.43 (81.61)
Heberlein et al. (2017)	Germany	carbamazepine and clomethiazole	clomethiazole dosage: day 1: M = 5.77 capsules (SD = 5.89) day 7: M = 0.08 capsules (SD = 0.52)	15.46 (4.05)	12.79 (2.69)	55 (100)	n/a	n/a	n/a	n/a

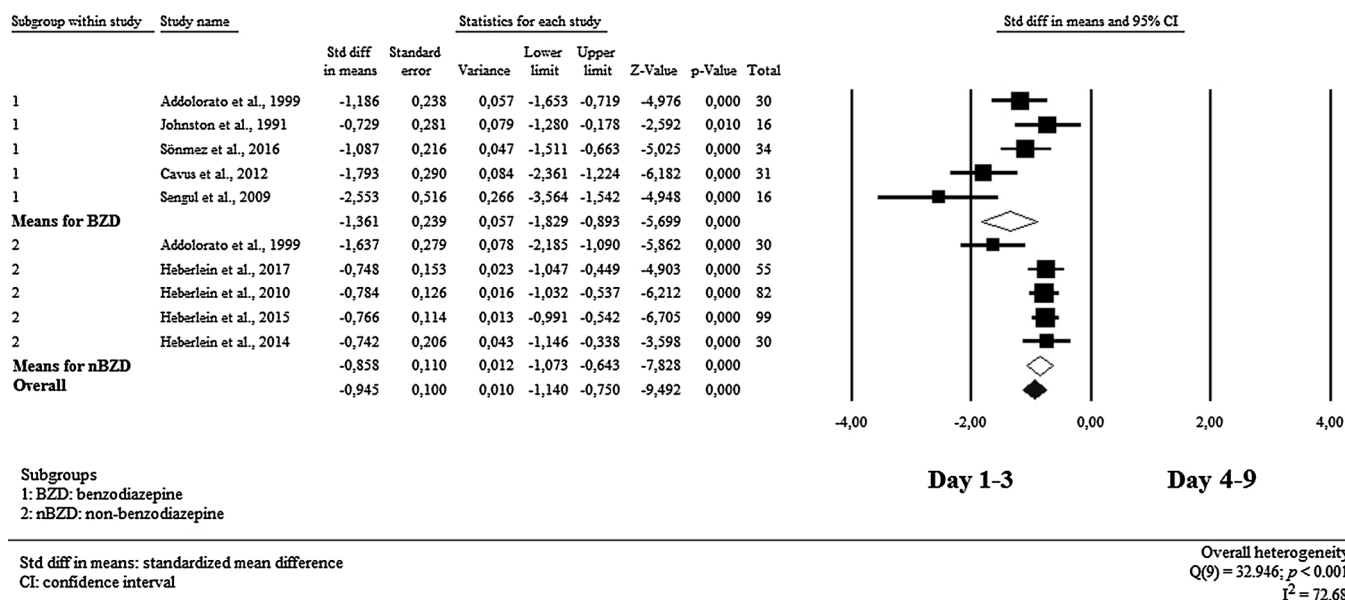


Fig. 4. Forest plot of standardized difference in means for the benzodiazepine (BZD) and the non-benzodiazepine (nBZD) subgroups.

2001; Saitz et al., 1994). Furthermore, the reliability and validity of CIWA-Ar has been previously confirmed in several psychometric analyses revealing the robustness of the measurement tool (Bakhla et al., 2014; Higgins et al., 2019; Lázár et al., 2019; Pittman et al., 2007; Sullivan et al., 1989; Zhuo et al., 2010). However, some research groups formerly suggested shorter versions of the CIWA-Ar and other tools for identifying and following the signs of withdrawal (Elefante et al., 2020; Gray et al., 2010; Lindner et al., 2019; Maldonado et al., 2014), which were excluded from the present analysis, since available literature data indicate that the original CIWA-Ar is the most important and reliable scale in the diagnosis and treatment of AWS.

If AWS is uncomplicated, the symptoms decrease continually as the disease progresses, which is facilitated by the adequate pharmacological approach. BZD is a commonly used pharmacological intervention and is the first choice of drug therapy in the standard treatment of AWS (Daepfen et al., 2002). BZDs, besides their pivotal role in the treatment of all phases of AWS, may have severe side effects such as cardiopulmonary depression, toxicity and addiction. Thus, in the last few decades, several studies have suggested that nBZD agents may be alternative choices during the course of AWS. Although, nBZDs such as carbamazepine or baclofen in general are used in the treatment of mild or moderate AWS (Malcolm et al., 2001), several reports have showed that carbamazepine reduces post-treatment alcohol consumption and prevents the rebound of withdrawal symptoms (Gentry et al., 2002; Malcolm et al., 2001; Stuppaeck et al., 1994). Moreover, some reports suggested that the relapse rate of AUD patients is higher among BZD-treated patients compared to nBZD-treated patients (Maldonado, 2017). Our findings indicating that the decrease of the total scores of the CIWA-Ar is similar between the BZD and nBZD subgroups, which is in agreement with recent works demonstrating that symptoms of AWS were reduced with a similar tendency by using nBZD agents compared to BZD-based therapy (Addolorato et al., 1999; Lucht et al., 2003; Sychla et al., 2017). In addition, some studies have demonstrated that BZD treatment itself might even be a risk factor for the development of DT (Gaudreau et al., 2005; Kudoh et al., 2004; Maldonado, 2008). In addition, our results are consistent with the previous meta-analyses regarding pharmacotherapy, in which BZDs were proved to be more effective than placebo (Mayo-Smith, 1997), but nBZDs showed similar effectiveness compared to BZDs (Amato et al., 2011, 2010; Holbrook et al., 1999). Previous scientific literature also reflected on that general symptoms were similarly reduced (Lucht et al., 2003). Although, it is

important to note that from the studies included in the present meta-analysis, only Addolorato et al. (1999) addressed the issue of side effects. However, developing adverse effects were not consistent in the literature in the cases of BZD and nBZD treatments. For example, some articles suggest that the adverse effects were less common with nBZDs than with BZDs (Addolorato et al., 1999; Sychla et al., 2017). On the other hand, a meta-analysis (Holbrook et al., 1999) showed no significant differences between BZDs and nBZDs regarding adverse effects.

Additionally, several limitations of the present findings should be taken into account. From a clinical point of view, the course of AWS takes 5–10 days (McKeon et al., 2008; Mirijello et al., 2015); however, in this study, only two measurement intervals were identified and could statistically be compared, using the aggregated means of CIWA-Ar total scores. These two measurement intervals (day 1–3 and day 4–9) were contrasted, since empirical studies using the total scores of CIWA-Ar generally lacked the comprehensive reporting of the daily data of the means and standard deviations of the CIWA-Ar total scores. This methodological diversity presented in the publications lead to the relatively smaller sample size and comparable units of data.

Based on the results, the CIWA-Ar follows the course of withdrawal, but the total score includes several factors (e.g. delirious, autonomic and non-specific factors) (Bakhla et al., 2014), so it can be assumed that these factors are not equally sensitive to the therapy. Moreover, the medications may have caused changes in the patient's conditions, but it was not conceivably explored due to the two measurement intervals utilized in the present analyses. It is important to note that in the present meta-analysis, only articles written in English language were incorporated. Several strategies exist for handling non-English studies besides omitting them, but in the present systematic review-based meta-analysis, papers written in different languages than English were automatically excluded, which may cause language bias (Grégoire et al., 1995). On the notion of the potential presence of bias, it should also be noted that the studies incorporated in the present analyses were mostly conducted in the European region (especially in Germany and Turkey), and they predominantly examined men (Addolorato et al., 1999), which could potentially cause geographical and gender bias (Holdcroft, 2007).

Another limitation is the significant heterogeneity observed in the sample, which may be reasoned with several factors. Firstly, different medications and dosing were in the nBZD subgroup (for a detailed list of medications and dosages, see Table 1). For instance, the standard dosage of diazepam was 30 mg/day in the study of Sengul and his colleagues

(Sengul et al., 2009), but in the study of Johnston et al. (1991), 40 mg/day of diazepam was given to the patients. Furthermore, the time during which patients actually received these medications also altered in the studies, for example diazepam was tapered over 6 (Sengul et al., 2009) or 7 (Cavus et al., 2012) days, respectively. Other alcohol-related factors, such as the duration of problematic alcohol consumption and alcohol dependence or the consumed amount of alcohol in grams could also serve as moderating variables in the severity and course of AWS (Pristach et al., 1983; Schuckit et al., 1995). Despite the gathering of alcohol-specific data in the present study, they could not be incorporated in the moderator or covariate analysis due to insufficient data available. Therefore, future empirical research should elucidate and report these variables in order to take into account their possible confounding effects. Based on the DSM-5 criteria, the most significant symptoms of AWS are monitored by the CIWA-Ar. However, other symptoms can occur during the course of AWS, which can be measured by other instruments as well. CIWA-Ar is an abbreviated version of the Clinical Institute Withdrawal Scale - Alcohol (CIWA-A), and the original instrument includes additional symptoms, such as vital signs, seizures and quality of contact (Shaw et al., 1981). Other measurement scales, e. g. the Alcohol Withdrawal Symptom Checklist (AWSC) further monitors the symptoms of sleep disturbance, poor appetite, depression, asthenia, craving, muscle cramps, nervousness and irritation (Pittman et al., 2007). Since CIWA-Ar has not operationalized the previously listed symptoms, this represents a potential limitation regarding the interpretation of the BZD and nBZD group differences described in the present meta-analysis.

On this notion, there is a great need of further empirical and also meta-analytical data to address the potential effects of alcohol-specific variables on the course and treatment of AWS. More empirical research would be vital to further explore the role of the CIWA-Ar in the different symptom-based treatment regimens of AWS, with the incorporation of such additional data (e.g. alcohol-related factors) that might be important in gaining a more detailed picture of the clinical management of AWS.

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Contributors

B.A.L. and B.A. designed and B.A.L., I.K.P., I.K. and B.A. conceptualized the study. I.K.P., I.K., and B.A. conducted literature search and I.K.P. and I.K. analysed the data. I.K.P., B.A.L., I.K., B.A. wrote the draft version of the manuscript. B.K.K., C.S.S.K., M.J.R. and Z.J. contributed to providing edits and feedbacks to the manuscript. All authors contributed and approved the final version of the article.

Declaration of Competing Interest

No conflict declared.

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