THE EFFICACY OF CLONIDINE IN THE PHARMACOLOGICAL MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROME: PRELIMINARY RESULTS

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Abstract

Alcohol dependence and harmful use represent the most prevalent addictive disorder worldwide. Alcohol withdrawal syndrome is considered a life-threatening condition by inducing severe physiological imbalances. Pharmacological management of alcohol withdrawal syndrome is very complex and challenging, often involving a long duration in getting remission. Our ongoing study aimed to analyse the efficacy of clonidine (an alpha-2-agonist) for improving alcohol withdrawal syndrome quantified by the mean change of The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) scores. Of 30 patients with alcohol withdrawal syndrome recruited so far, 11 (36.7%) benefited from clonidine treatment. Blood pressure and other physiological signs were periodically monitored. Although at the beginning of the treatment there were no differences between the mean CIWA-Ar scores ($t = 0.352$, $p = 0.599$), after 5 days the difference became significant in favour of those treated with clonidine ($t = 3.147$, $p = 0.004$). Clonidine may provide additional benefit in managing alcohol withdrawal by offering a different mechanism of action for targeting withdrawal symptoms.

Rezumat

Dependența de alcool și consumul dăunător de alcool reprezintă cele mai răspândite tulburări de adicție la nivel mondial. Sindromul de sevraj etanolic este considerat o afecțiune care pune viața în pericol prin inducerea unor dezechilibre fiziologice severe. Managementul farmacologic al sindromului de sevraj la alcool este foarte complex și provocator, implicând adesea o durată lungă de obținere a remisiunii. Studiul nostru în curs a urmărit să analizeze eficacitatea clonidinei (un agonist alfa-2) pentru ameliorarea sindromului de sevraj alcoolic cuantificată prin modificarea mediei scorurilor scalei *The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised* (CIWA-Ar). Din 30 de pacienți cu sindrom de sevraj alcoolic recrutați până în prezent, 11 (36,7%) au beneficiat de tratament cu clonidină. Tensiunea arterială și alte semne fiziologice au fost monitorizate periodic. Deși la începutul tratamentului nu au existat diferențe între scorurile medii CIWA-Ar ($t = 0,352$, $p = 0,599$), după 5 zile diferența a devenit semnificativă în favoarea celor tratați cu clonidină ($t = 3,147$, $p = 0,004$). Clonidina poate oferi beneficii suplimentare în gestionarea sevrăului la alcool, oferind un mecanism diferit de acțiune ce se adresează simptomelor de sevraj.

Keywords: alcohol withdrawal syndrome, clonidine, efficacy

Introduction

According to WHO data, in 2016, 2.3 billion (42%) of people aged 15 or over were current drinkers meaning at least one use of alcohol in the past 12 months. Furthermore, in Romania, the alcohol consumption *per capita* (in liters of pure alcohol) was 12.6 in 2016, representing a downward trend compared to 2010 (15.0 liters of pure alcohol) but remains above

Europe's average of 9.8 liters *per capita*. The prevalence of alcohol use disorders and alcohol dependence in the Romanian population aged 15 and over, for the same year, were 2.8% and 1.3%, respectively. In addition, 11,844 people in Romania died due to alcohol-attributable causes, of these 6,366 died from liver cirrhosis, 802 caused by road traffic injuries, and 4,676 due to cancer [1, 2]. Alcohol

dependence is associated with a higher level of major depression and anxiety disorders, which contributes in a supplementary way to the devastating effect of this type of addiction. Furthermore, several clinical studies have found that in the Romanian population, the presence of depressive and anxiety symptoms is quite widespread, especially during the distinct critical period of life [3-5].

Alcohol withdrawal syndrome (AWS) is a frequent complication of those who met the criteria for alcohol dependence and its intensity may vary from symptoms such as insomnia, tremors, sweating, tachycardia up to more severe complications such as delirium or seizures implying 5 - 15% mortality [6, 7].

Clonidine is the prototypical α_2 -adrenoreceptor agonist, with a higher affinity of 200:1 for α_2 compared to α_1 receptors, respectively. Initially used as a nasal decongestant, it is currently frequently used in the management of hypertension due to its ability to lower systemic blood pressure through central brainstem adrenergic stimulation. Clonidine is rapidly and almost completely absorbed after oral administration [8].

Several studies have noticed that autonomic hyperactivity in the CNS stands for an important physiological process underlying AWS. It is known that nor-adrenaline synthesis is enhanced in chronic alcohol abusers and during withdrawal [9, 10]. A plethora of studies related to chronic alcohol administration and withdrawal from alcohol use have shown alterations in the central catecholamine levels; therefore, drugs that are able to decrease the autonomic hyperactivity in the brain are considered useful for the management of AWS [11, 12]. Particularly, the α_2 -adrenoceptors subtypes are a specific G protein ($G_{\alpha-i}$ -coupled)-mediated receptor and have an inhibitory auto-receptor effect on noradrenergic neurons simultaneously pre-synaptically and post-synaptically in the brain, brain stem, spinal cord, and peripheral nervous system [13]. According to certain reports that treatment with α_2 adrenoceptor agonists, clonidine [14], lofexidine [15], and dexmedetomidine [16], decreases alcohol dependence/craving and withdrawal signs in both rodents and humans. All α_2 -adrenoceptors agents used clinically are imidazole derivatives and stimulate I1-imidazoline receptors in the brain and brain stem generating a sympatholytic effect [17, 18].

The current study aimed to investigate the efficacy of clonidine as adjunctive medication in the pharmacological treatment of patients having a diagnosis of AWS according to ICD-10 [19].

Materials and Methods

An ongoing study was carried out in 30 inpatients admitted in Timisoara Psychiatric Clinic I for AWS, Romania. Of these, 11 patients were given clonidine and 19 were treated without clonidine in therapeutic schema. All patients benefited from rehydration, B

vitamins and hepato-protective medications. The sampling method was by convenience.

The severity of AWS was measured by using The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar). This scale quantifies 10 symptoms of AWS. Scores of less than 8 to 10 indicate minimal to mild withdrawal. Scores of 11 to 15 indicate moderate withdrawal (marked autonomic arousal); and scores of 15 or more indicate severe withdrawal (impending delirium tremens) [20]. CIWA-Ar was administered twice, at the first day and at the 5th day of continuous hospitalization and treatment.

Inclusion criteria consisted of patients aged 18 or above, meeting diagnostic criteria for alcohol withdrawal syndrome according to ICD-10. Exclusion criteria were represented by the lack of written informed consent, presence of pregnancy, presence of orthostatic hypotension, presence of confusion state at admission. However, 5 subjects have subsequently developed delirium state. The Local Ethics Committee for Scientific Research of the Timisoara County Emergency Hospital approved this study, and all participants were required to provide an informed consent.

Several blood tests were uniformly determined in all patients such as serum potassium concentrations, serum sodium concentrations, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, uric acid, and mean corpuscular volume (MCV).

The following analytes: GGT, ALT, AST, total bilirubin, direct bilirubin, uric acid were performed using Siemens Dimension RXL Max clinical chemistry system by spectrophotometry. Sodium and potassium ions were tested on the same analyser using the indirect ISE method. Regarding MCV we used flow-cytometry method on Siemens Advia 2120 instrument.

Statistical analysis

Statistical analyses were carried out by using STATA version 15 for Windows. Descriptive statistics were conducted dependent on analysis requirements. The Chi-squared test and Fischer Exact test were done to compare the frequencies of categorical variables. To compare the means of continuous data a two-tailed independent t-test was used. A non-parametric rank test (Mann-Whitney U-Test) was done to analyse categorical variables originating from two independent subsamples. Due to the non-normal distribution of CIWA-Ar scores, Spearman's rho correlation coefficients were calculated to establish the relation of these scores to the blood test results values.

Results and Discussion

Demographic data stratified by the presence of clonidine in the pharmacological treatment and family history of self-reported psychopathological conditions

The male gender distribution (n = 28; 93.3%) was consistently more representative compared to the

female gender (n = 2; 6.7%); however, the gender distribution depending on the presence or absence of clonidine in the treatment was not statistically significant different (p = 0.520) (Table I). However, it has to be mentioned that none of the women

treated for AWS benefited from clonidine treatment. None of the other demographic characteristics were statistically significantly different. Hence, we can consider that the two strata were comparable from this perspective (Table I).

Table I

Demographic characteristics of the studied group depending on the clonidine treatment administration

Sociodemographic data	Without clonidine (n = 19)	With clonidine (n = 11)	Statistical significance
Average current age (SD)	51.05 (7.856)	53.55 (10.172)	p = 0.459
Gender – male, n (%)	17 (89.5%)	11 (100.0%)	p = 0.520
Educational level, mean ranks	13.97	18.14	p = 0.158
Residency - Urban area, n (%)	3 (27.3%)	9 (47.4%)	p = 0.279
Professional status - Employed or Student, n (%)	7 (63.6%)	9 (47.4%)	p = 0.389
Marital status – with intimate partner, n (%)	6 (54.5%)	7 (36.8%)	p = 0.346

Note: The confidence interval (CI) is 95%; The listed percentages are reported to either strata considered separately.

The correlations of AWS severity with different biologic indexes of blood tests

The severity of baseline AWS measured by CIWA-Ar total score was significantly positively correlated with the level of gamma-glutamyl transferase (GGT)

($r_s = 0.453$, $p = 0.012$) (Figure 1) and alanine transaminase (ALT) ($r_s = 0.450$, $p = 0.012$) (Figure 2) and inversely correlated with the level of potassium ($r_s = -0.429$, $p = 0.018$) (Figure 3).

Figure 1.

Correlation between CIWA-Ar score at baseline and GGT levels

Figure 2.

Correlation between CIWA-Ar score at baseline and ALT levels

Figure 3.

Correlation between CIWA-Ar score at baseline and K⁺ levels

At the 5th day of hospitalization, we found that GGT remained strongly and constantly correlated ($r_s = 0.654$, $p < 0.001$) with the severity of AWS measured by

the same scale while AST was revealed as a new blood marker positively correlated with the severity of AWS ($r_s = 0.384$, $p = 0.036$) (Figures 4 and 5).

Figure 4.

Correlation between CIWA-Ar score at day 5 and GGT levels

Figure 5.

Correlation between CIWA-Ar score at day 5 and AST levels

The frequency, doses and efficacy of psychotropics used in managing AWS symptoms

Most of the enrolled patients have also benefited from treatment with benzodiazepines (86.7%), followed by trazodone and tianeptine (66.7%), anticonvulsants (63.3%) and antipsychotics (43.3%) (Table II). It is worth mentioning that trazodone was administered

in a dosage that exerts a hypnotic and anxiolytic effect only and not as an antidepressant, acting as an antagonist of histaminergic H1 and α 1-adrenergic receptors at this dose [21]. The association of different psychotropic classes did not differ between those treated with clonidine and those without clonidine ($p > 0.05$) (Table II).

Table II

Psychotropic medications used in the pharmacological treatment stratified by the presence or absence clonidine during the studied period

Associated psychotropics, n (%)	With clonidine (n = 11)	Without clonidine (n=19)	Statistical significance
Benzodiazepines and hypnotics, 26 (86.7 %)	11 (100.0%)	15 (78.9%)	$p = 0.268$
Antidepressants, 20 (66.7 %)	9 (81.8%)	11 (57.9%)	$p = 0.180$
Antipsychotics, 13 (43.3 %)	5 (45.5%)	8 (42.1%)	$p = 0.858$
Anticonvulsants, 19 (63.3 %)	8 (72.7%)	11 (57.9%)	$p = 0.417$

Note: The confidence interval (CI) is 95%; The listed percentages are reported to either strata considered separately.

Regarding the efficacy of other psychotropic drugs, other than clonidine, in ameliorating symptomatology of AWS, it is noteworthy that although these have generally induced a decrease in global CIWA-Ar scores at 5 days, there was no statistically significant difference

according to each class of medication (Table III). However, without reaching statistical significance it seems that trazodone, an antidepressant, tended to decrease CIWA-Ar scores at 5 days more than other psychotropics [22].

Table III

The differences in the average CIWA-Ar scale total scores at 5th day of hospitalization depending on the presence or absence of different psychotropic medications in treatment schema

Associated psychotropics (mean doses)	Absent	Present	Significance
Benzodiazepines and hypnotics (16.35 mg equivalent doses of diazepam/24 h)	15.25 (14.523)	9.96 (6.296)	$p = 0.207$
Trazodone (54.54 mg/24 h)	12.26 (9.024)	7.91 (3.506)	$p = 0.073$
Tianeptine (33.33 mg/24 h)	11.00 (7.894)	8.50 (6.856)	$p = 0.555$
Antipsychotics (198.08 mg equivalent doses of chlorpromazine/24 h)	11.35 (9.354)	9.77 (5.019)	$p = 0.586$
Carbamazepine (515.62 mg/24 h)	11.64 (8.898)	9.81 (6.666)	$p = 0.526$
Gabapentin (600.00 mg/24 h)	9.73 (6.096)	16.75 (14.385)	$p = 0.403$
Benzodiazepines and hypnotics (16.35 mg equivalent doses of diazepam/24 h)	15.25 (14.523)	9.96 (6.296)	$p = 0.207$

Note: The confidence interval (CI) is 95%; The listed percentages are reported to either strata considered separately

The efficacy of clonidine in managing AWS symptoms at day 5 as measured by CIWA-Ar scale

The clonidine treatment was administered under strict blood pressure and heart rate monitoring to 11 (36.7%) of the 30 total subjects. At baseline, the difference in CIWA-Ar scores between those with and without clonidine treatment was not statistically significant. However, the difference reached statistical significance after 5 days of clonidine treatment ($p = 0.01$) (Figure 6).

Regarding the family history of probable psychopathological conditions in first-degree relatives of the subjects, 18 (60%) declared that at least one family member had had alcohol use disorders, 1 (3%) self-reported at least one family member suffering from a mood or anxiety-related disorders and 11 (37%) self-reported no positive psychopathologic condition in their family history. These results are in line with other reports from the literature [23]. We consider that educational and sociocultural factors increase

the risk for alcohol use disorders in individuals that are genetically predisposed.

Figure 6.

CIWA-Ar scores dynamics at baseline and day 5 stratified by clonidine use (Clo 1 – clonidine at baseline; Clo 5 – clonidine at day 5; Y – yes; N – no)

At baseline, the correlation with GGT and ALT is suggestive of the fact that the severity of AWS is correlated to the degree of liver function impairment. On the other hand, increased catecholamine activity in AWS activates the sodium–potassium ATPase pump causing hypokalaemia. Hence, the AWS severity correlated with autonomous nervous system activity could be reflected in the potassium blood levels. Similar data was previously reported by others [24, 25]. Somehow expectedly, at the 5th day of continuous AWS symptoms, the elevated blood level of AST has become significantly positively correlated with the severity of clinical status. Probably, its increasing tendency stems from skeletal muscles that might be a biological marker of the progressive intensity of tremulous as a specific symptom of AWS. The role of AST in predicting the severity of AWS was also evidenced by another study [26].

Concerning the psychotropics used in the treatment of AWS patients, this was in line with our institutional therapeutic protocols, mostly overlapping with pharmacological strategies existing in other current national guidelines [27, 28]. However, although without reaching statistical significance, there are two results worth mentioning. First, the largest difference between CIWA-Ar mean scores at day 5 was due to the presence of trazodone in the treatment schema. Trazodone efficacy could be explained through the added sympatholytic effect by the antagonism on the α_1 -adrenergic receptor, confirmed by another previous report [29]. Secondly, gabapentin was associated with an increased CIWA-Ar score at day 5 in our study. An increased dose of gabapentin could contribute to altering the mental state, especially in vulnerable patients. This result is also supported by another research [30].

Finally, in our study, clonidine was the only medication from the therapeutic schema that was associated with a significantly lower CIWA-Ar mean score after 5

days. The efficacy of clonidine in the treatment of AWS was also confirmed by numerous previous studies, leading to its common use in medical practice [31–33]. It is worthwhile mentioning that one study revealed the fact that clonidine is effective not only in managing of AWS symptoms, but also in sustaining alcohol abstinence for extended periods [34].

Conclusions

The biological markers analysed in the present study might have a predictive value for the severity of AWS. Furthermore, hydro electrolytic rebalancing along with liver function support should represent key therapeutic objectives in the therapeutic management of AWS.

The efficacy of trazodone in alleviating AWS symptoms is worth considering by further larger studies, especially due to its increased tolerability and safety in alcoholic patients.

Clonidine represents a valuable therapeutic resource for the remission of autonomous nervous system related symptoms of AWS, having a rapid onset of the therapeutic effect. Therefore, clonidine use should be included in the therapeutic protocols of AWS in eligible patients.

Conflict of interest

The authors declare no conflict of interest.

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