RESEARCH PAPER

Efficacy and Safety of Telmisartan as Adjunctive Therapy in Alcohol Withdrawal Syndrome: A Randomized, Open-Label Controlled Trial

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Abstract:

Background:

Alcohol withdrawal syndrome (AWS) is a common and potential serious complication of abrupt cessation of chronic alcohol consumption, marked by autonomic hyperactivity, neuropsychiatric symptoms, and the possibility of seizures or delirium. Benzodiazepines remain conventional therapy but are limited by oversedation, respiratory depression, and overuse. Emerging evidence suggests the brain renin-angiotensin system plays a crucial role in addiction biology. Telmisartan, a brain-penetrant angiotensin receptor blocker with partial PPARγ agonism, may affect neuroinflammation and dopaminergic transmission, suggesting its potential efficacy as an adjuvant treatment for AWS.

Methods:

We conducted a prospective, randomized, open label study in people with AWS. Participants were randomly assigned to receive either chlordiazepoxide, telmisartan, or a combination of both for seven days, with standardized supportive care. CIWA-Ar was used to assess withdrawal intensity from baseline to Day 12. Secondary outcomes included short term abstinence, craving value, and biochemical investigation. ANOVA and chi-square test were used, and the analyses were performed in GraphPad Prism version 10.5.

Results:

The combination arm experienced a significantly higher mean reduction in CIWA-Ar scores (about 11 points compared to 9 points with chlordiazepoxide and 7 points with telmisartan; $p<0.01$). Combination therapy resulted in stronger short-term abstinence and lower craving scores at follow-up. Telmisartan containing regimens were more likely to cause hypotension, whereas benzodiazepines caused excessive sedation.

Conclusion:

Adjunctive telmisartan with chlordiazepoxide decreased symptoms and short-term drinking without causing significant safety concerns; larger blinded multicentre trials are required.

Keywords: Alcohol withdrawal syndrome (AWS), Telmisartan, Chlordiazepoxide, CIWA-Ar Scale, Renin-Angiotensin System (RAS), Alcohol Craving, Angiotensin II Type 1 Receptor (AT1R)

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1. Introduction:

Alcohol Withdrawal Syndrome (AWS) is a complex disorder associated with a wide range of clinical manifestations and central nervous system hyperexcitability caused by abrupt cessation of long-term alcohol consumption. The conditions occur due to neuroadaptive alterations in neurotransmitter systems, mainly affecting GABA and glutamate . Clinical manifestations might range from mild symptoms like anxiety and tremors to severe complications, including delirium tremens. In intensive care settings, about half of AWS patients have complicated hospital stays, accompanied by delirium tremens occurring in 50% of cases and a hospital mortality rate of around 16% [1].

Because of their GABAergic effects and clinical effectiveness, benzodiazepines are established as the gold standard, first-line treatment for alcohol withdrawal syndrome. In particular, the most commonly used medications are chlordiazepoxide and diazepam, as demonstrated by decades of clinical research. A comprehensive network meta-analysis of 149 trials, with 10692 participants, found benzodiazepines significantly reduced AWS complications, with fixed schedule diazepam and chlordiazepoxide indicating improved outcomes in preventing seizures and controlling withdrawal symptoms [2]. Early research on autonomic activation during withdrawal found elevated blood pressure and plasma renin activity, but it was not possible to fully associate these changes with the renin-angiotensin-aldosterone system. Numerous studies emphasize how crucial it is to conduct additional research on cutting-edge therapeutic approaches and biomarkers in order to forecast the severity of withdrawal and enhance patient results. The renin angiotensin system (RAS) of the brain plays a crucial role in addiction through two opposing pathways, including the proinflammatory ACE-AngII-AT_1R axis which influences oxidative stress and dopamine accumulation, and the defensive ACE2-Ang(I-VII)-Mas receptor axis that counteracts these effects [3]. Experimental studies using alcohol preferring rats established that chronic alcohol exposure interrupts RAS homeostasis in the ventral tegmental area, with upregulated ACE1 activities and AT_1R expression compared with increased dopamine accumulation in addiction related brain areas. Therapeutic interventions targeting this system show significant potential, like central administration of the AT_1R blocker telmisartan reduced alcohol intake for 24 hours, while ACE1 inhibitors like captopril significantly reduced oxidative stress, alcohol preference, and dopamine accumulation [4]. The therapeutic potential aligns in using brain permeable compounds to reserve RAS balance, associated with existing antihypertensive medications like angiotensin receptor blockers, representing promising candidates for repurposing in addiction treatment. Alcohol use disorder is associated with hepatic dysfunction, electrolyte imbalance, and neuroendocrine changes. Monitoring biochemical markers such as GGT, transaminases, and electrolytes provides objective safety indicators during AWS pharmacotherapy [5].

Telmisartan is a special multipurpose angiotensin receptor antagonist that sets itself apart from other ARBs due to its special capacity to penetrate the blood brain barrier and occupy brain AT_1 receptors, allowing for direct modulation of important CNS cellular components such as neurons, microglia, astrocytes, and oligodendrocytes . Its neuroprotective mechanisms include regulating oligodendrocyte differentiation, inhibiting inflammatory cytokine pathways, and limiting neurotoxic astrocyte conversion through $PPAR\gamma$ mediated NF-kB/p65 degradation [6]. Telmisartan is a paradigm shift toward multimodal therapeutic interventions for cardiovascular, metabolic, and neurological disorders because of its longer half-life, which offers superior cardiovascular management, and its diverse pharmacological actions, which include anti-inflammatory, anticancer, and neuroprotective properties. These qualities establish the notion that telmisartan may complement benzodiazepins, which target acute hyperexcitability; telmisartan could control, telmisartan could control central sympathetic and inflammatory overactivity, as well as potentially minimise relapse by brain RAS regulation [7].

2. Methodology:

2.1. Trial Design:

We conducted a prospective, randomized, open-label, parallel-group clinical trial conducted at a tertiary care hospital in India. The protocol was approved by Institutional Human Ethics Committee Chitkara University (EC/NEW/INST/2025/531/442). Adult patients diagnosed with alcohol withdrawal syndrome requiring pharmacological treatment were recruited after obtaining written informed consent. The median age was 39 years, associated with physiological variability and comorbidities that may influence alcohol withdrawal severity.

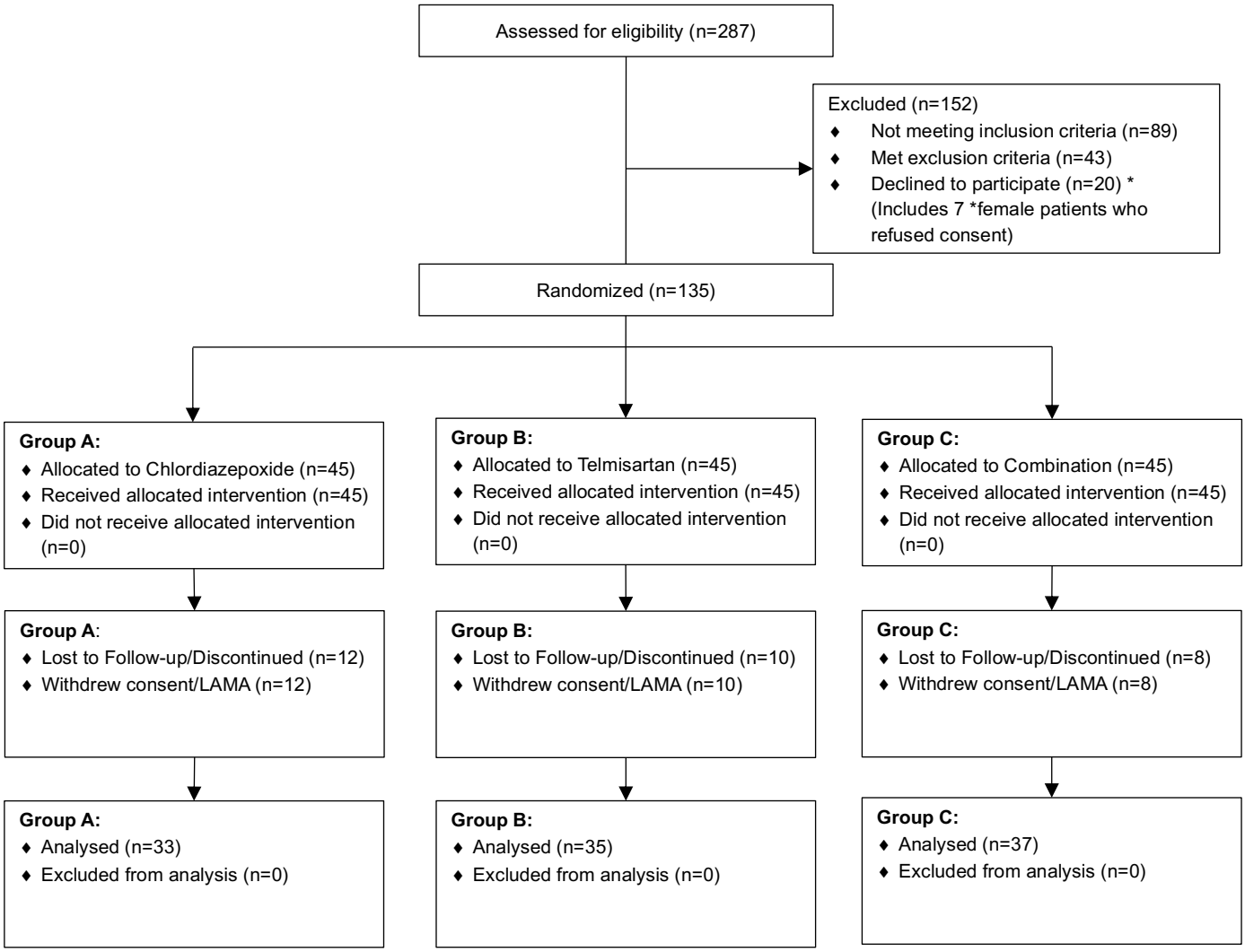
Inclusion Criteria:

- Patients aged between 23 to 55 years.
- Patients meeting DSM-5 criteria for alcohol withdrawal syndrome.
- History of alcohol consumption of a minimum $\geq$ 5 drinks per day in the last 3 months (~90 days).
- Willingness to provide written informed consent.
- Patients presenting with complicated AWS like current use of ARBs/$PPAR_\gamma$ agonists, seizure, delirium, hallucinations, were also eligible.

Exclusion Criteria:

- Patients with significant hepatic or renal failure.
- Patients with hemodynamic instability.

- Patients with severe psychiatric comorbidities (e.g., bipolar disorder, psychosis).
- Pregnant and breastfeeding women.



2.2. Randomization and Interventions:

The investigators implemented a randomization procedure that equally allocated participants to three treatment groups at a ratio of 1:1:1.

- **Group A (Standard Care):** Received Chlordiazepoxide under a symptom, triggered schedule where the patient had to take 25 mg every 4 to 6 hours if the CIWA, Ar score was 8 or above and then the dosage was gradually reduced over a 3 to 5 days period.
- **Group B (Intervention):** Received Telmisartan 40 mg as an oral medication which they took two times each day for a period of seven days.
- **Group C (Adjunctive):** Received both Chlordiazepoxide (symptom, triggered) and Telmisartan (40 mg twice daily). The standard supportive care which included fluids and multivitamins was provided to all groups.

2.3. Study Flow and Attrition:

The participant recruitment process and follow-up procedures took place for a duration of 15 days. From the 287 screened patients 135 patients qualified for the study which assigned them to two groups of 45 participants each. Participants left the study during follow-up because they either withdrew their consent or could not be located. The final analysis included 105 participants (Group A: n=33; Group B: n=35; Group C: n=37).As per study consort below:

2.4. Monitoring and Assessments:

The severity of withdrawal was assessed daily using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. Daily vital measures, including pulse, blood pressure, respiration rate, and body temperature, were recorded. Participants were closely monitored for adverse events (AEs), with an

emphasis on hypotension (systolic BP <90 mmHg or symptomatic decrease and severe drowsiness). Following discharge, participants were observed on days 12 and 15 of admission. Abstinence was determined through self-report and verified by family report. Craving was measured on the 15th day using the obsessive-compulsive drinking scale. Baseline laboratory exams were performed. Biochemical parameters included liver function tests (ALT, AST, GGT, and total bilirubin), renal function tests (Serum creatinine, BUN, and uric acid), serum electrolytes (sodium and potassium), and a complete blood count.

2.5. Outcomes:

The primary result was the difference in CIWA-Ar scores between groups on days 0 and 12. Secondary outcomes included time to resolution of withdrawal (CIWA-Ar < 8 without medication), total benzodiazepine dose, 12 and 15 day abstinence rates with percentage maintaining abstinence, craving score on the Obsessive-Compulsive Drinking scale at 15 days, and incidence of adverse events (e.g., hypotension, sedation).

2.6. Statistical Analysis:

Continuous findings were analyzed using ANOVA with appropriate post-hoc testing. Chi-square tests were employed to assess categorical outcomes such as abstinence. A two-sided $p < 0.05$ was considered significant. The analyses followed the intention-to-treat concept. Statistical analysis was carried out with GraphPad Prism version 10.5.

2.7. Data Curation Plan:

For illustrative purposes, we screened patient-level data reflecting the above design. Baseline CIWA-Ar scores were curated from a normal distribution with mean~15, SD~3 across all groups. We assume chlordiazepoxide reduces CIWA by ~10 point by day 7, Telmisartan by ~combination by ~11 points, showing plausible drug effects. Abstinence rates were set by assumption at ~60% at day 15 for chlordiazepoxide; ~50% for Telmisartan, and ~70% for the combination drug. Craving at obsessive compulsive drinking scores were sampled such that mean craving was lowest in combination, moderate in benzodiazepine only, and highest in telmisartan only groups. Adverse events were randomly assigned with hypotension probability in any telmisartan arm (10-15%) vs Chlordiazepoxide alone (2%) and higher sedation in benzodiazepine groups.

3. Result:

3.1. Participants Characteristics:

Out of the 287 patients who were screened, 152 were excluded because they did not match the inclusion criteria (n=89), met the exclusion criteria (n=43), or refused to give consent (n=20). The final study population was made up completely of male patients because seven of the patients who declined consent were female. Demographics and baseline characteristics are mentioned in **"Table 1".** The mean age varied modestly across the groups (Group A: 38.45±8.14 years, Group B: 41.06±9.27 years, Group C: 35.75±7.67 years), with a p-value of 0.040. Rural residency was similar across groups (80%, 76%, 78%), with a p-value of 0.87, and all participants were male. Alcohol related characteristics were balanced, with similar duration of usage (15.8±7.6, 16.3±8.1, and 16.1±7.4 years; p=0.94) and daily consumption (12.4±4.3 vs 11.9±4.8 vs 12.6±4.1 drinks/day; p=0.70). There was no significant difference in the prevalence of concomitant hypertension (32%, 30%, and 28%; p=0.90) or previous AWS episodes (44%, 50%, and 46%; p=0.82). Overall, the three arms showed sufficient comparability based on clinical and demographic features.

Table 1: Baseline Demographics and Clinical Characteristics

Characteristic	Group A (n=33)	Group B (n=35)
Age (years)	38.45 ± 8.14	41.06 ± 9.27
Male, n (%)	33 (100%)	35 (100%)
Rural residence, %	80%	76%
Duration alcohol use, yrs	15.8 ± 7.6	16.3 ± 8.1
Daily consumption, drinks	12.4 ± 4.3	11.9 ± 4.8
Previous AWS episodes, %	44%	50%
Comorbid HTN, %	32%	30%

3.2. Baseline Laboratory Parameters:

Several hepatic and kidney indicators varied between groups, although the majority stayed within clinically anticipated ranges for an AWS population. AST levels varied substantially by group (177 ± 23.9 IU/L in Group A, 151.4 ± 14.4 IU/L in Group B and 189.5 ± 28.3 IU/L in Group C; p= 0.036). The total protein level varied significantly (5.41 ± 0.19 vs 5.68 ± 0.33 vs 5.31 ± 0.20 g/dL; p= 0.018). Serum creatinine levels differed somewhat but significantly (1.89 ± 0.13 vs 1.73 ± 0.10 vs 1.96 ± 0.20 mg/dL; p=0.047) . Phosphorus levels varied significantly between groups (5.41 ± 0.26 vs 4.95 ± 0.13 vs 5.64 ± 0.26 mg/dL; p < 0.001). In contrast, ALT, GGT, albumin, BUN, uric

acid, sodium, potassium, and calcium levels did not differ substantially between groups ($p > 0.05$ for all). Collectively, these findings demonstrate general biochemical comparability with some baseline variability characteristic of patients with persistent alcohol intake.

Table 2: Baseline Laboratory Characteristics

Parameter	Group 1 (Chlordiazepoxide) (n=33)	Group 2 (Telmisartan) (n=35)	Group 3 (Combination) (n=37)	p-value
Liver Function				
AST (IU/L)	177.1 ± 23.9	151.4 ± 14.4	189.5 ± 28.3	0.036
ALT (IU/L)	153.3 ± 26.9	131.5 ± 18.8	166.8 ± 28.5	0.069
GGT (IU/L)	126.1 ± 19.8	102.0 ± 19.9	130.4 ± 20.9	0.058
Albumin (g/dL)	3.69 ± 0.59	4.10 ± 0.59	3.77 ± 0.78	0.568
Total Protein (g/dL)	5.41 ± 0.19	5.68 ± 0.33	5.31 ± 0.20	0.018
Renal Function				
Creatinine (mg/dL)	1.89 ± 0.13	1.73 ± 0.10	1.96 ± 0.20	0.047
BUN (mg/dL)	28.20 ± 1.52	27.25 ± 1.26	28.93 ± 1.83	0.171
Uric Acid (mg/dL)	7.63 ± 0.51	7.30 ± 0.22	7.89 ± 0.75	0.206
Electrolytes				
Sodium (mEq/L)	134.73 ± 1.03	135.00 ± 0.82	134.47 ± 0.99	0.580
Potassium (mEq/L)	5.51 ± 0.20	5.42 ± 0.26	5.63 ± 0.25	0.219
Calcium (mg/dL)	8.17 ± 0.13	8.18 ± 0.13	8.19 ± 0.16	0.927
Phosphorus (mg/dL)	5.41 ± 0.26	4.95 ± 0.13	5.64 ± 0.26	<0.001

3.3. CIWA-Ar Symptom Resolution Across Treatment Arms

A repeated measures analysis demonstrated a consistent and progressive decline in CIWA-Ar domain scores across all treatment groups from baseline to day 12, indicating effective withdrawal control over time. There were significant improvements in all symptom domains (RM-ANOVA, $p<0.001$). Between group comparisons revealed that the combination therapy arm (chlordiazepoxide with telmisartan) reduced symptom severity more quickly and significantly than the monotherapy groups. These patterns was found in all major withdrawal all major withdrwal groups, including nausea and vomiting, tremors, paroxysmal sweating, anxiety, agitation, sensory abnormality, headache, and orientation. The combination group's CIWA-Ar score reduced from 23.3 ± 1.0 at baseline to 0.7 ± 0.3 by day 12, whereas the chlordiazepoxide and telmisartan groups saw a reduction from 24.87 ± 0.9 to 0.8 ± 0.3 and 27.1 ± 1.2 to 1.0 ± 0.3, respectively. Overall scores showed significant differences among groups ($p<0.001$), indicating that combination therapy is more effective for faster symptom relief. Notably, agitation showed a slight but significant between-group difference ($p=0.002$), although auditory disturbances and orientation domains had lesser between-group effects ($p=0.005$ and $p=0.127$, respectively), reflecting essentially equally recovery trajectories in these specific symptoms. **Table 3** shows that while all regimens effectively reduced withdrawal severity, adjunct telmisartan with chlordiazepoxide was associated with the most accelerated and sustained improvement across CIWA-Ar domains, supporting a potential synergistic effect in controlling multidimensional withdrawal symptoms. **Figure 1** represents repeated measures analysis revealed a consistent and progressive decrease in CIWA-Ar scores across all the treatment groups from baseline to Day 12 , indicating effective withdrawal control over time.

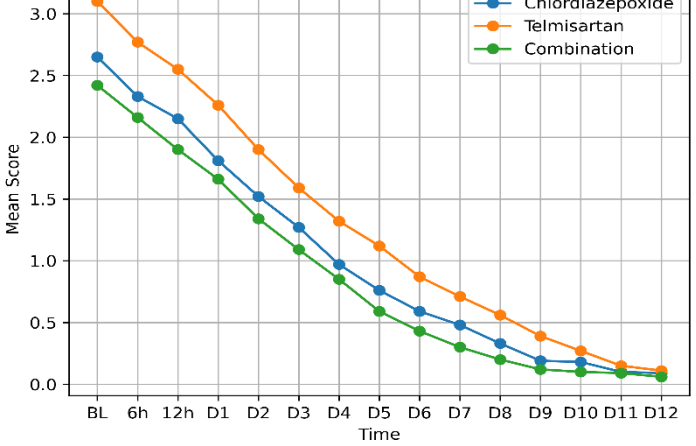
	(mean ± SD)											
Nausea and vomiting	Group A	2.65 ± 0.48	2.33 ± 0.43	2.15 ± 0.41	1.81 ± 0.35	1.52 ± 0.29	1.27 ± 0.29	0.97 ± 0.21	0.76 ± 0.20	0.59 ± 0.18	0.48 ± 0.15	0.33 ± 0.14	0.19 ± 0.12
	Group B	3.10 ± 0.41	2.77 ± 0.39	2.55 ± 0.34	2.26 ± 0.30	1.90 ± 0.30	1.59 ± 0.29	1.32 ± 0.18	1.12 ± 0.20	0.87 ± 0.12	0.71 ± 0.16	0.56 ± 0.16	0.39 ± 0.16
	Group C	2.42 ± 0.40	2.16 ± 0.33	1.90 ± 0.31	1.66 ± 0.29	1.34 ± 0.26	1.09 ± 0.21	0.85 ± 0.18	0.59 ± 0.15	0.43 ± 0.15	0.30 ± 0.13	0.20 ± 0.09	0.12 ± 0.12
Tremors score	Group A	4.79 ± 0.45	4.27 ± 0.40	3.84 ± 0.40	3.35 ± 0.34	2.83 ± 0.29	2.31 ± 0.22	1.87 ± 0.22	1.45 ± 0.17	1.12 ± 0.15	0.79 ± 0.15	0.61 ± 0.11	0.34 ± 0.13
	Group B	5.26 ± 0.43	4.79 ± 0.43	4.32 ± 0.39	3.87 ± 0.34	3.33 ± 0.31	2.81 ± 0.26	2.31 ± 0.21	1.89 ± 0.23	1.55 ± 0.20	1.23 ± 0.16	0.93 ± 0.14	0.69 ± 0.12
	Group C	4.41 ± 0.42	3.91 ± 0.38	3.48 ± 0.34	3.02 ± 0.31	2.49 ± 0.25	1.97 ± 0.20	1.51 ± 0.20	1.11 ± 0.13	0.79 ± 0.14	0.51 ± 0.10	0.38 ± 0.11	0.25 ± 0.10
Paroxysmal sweats	Group A	2.93 ± 0.29	2.62 ± 0.26	2.38 ± 0.26	2.06 ± 0.23	1.75 ± 0.18	1.41 ± 0.22	1.11 ± 0.19	0.91 ± 0.13	0.67 ± 0.12	0.49 ± 0.13	0.34 ± 0.15	0.24 ± 0.11
	Group B	3.11 ± 0.29	2.82 ± 0.30	2.56 ± 0.27	2.31 ± 0.21	2.01 ± 0.21	1.65 ± 0.19	1.39 ± 0.15	1.13 ± 0.17	0.91 ± 0.16	0.73 ± 0.12	0.54 ± 0.15	0.41 ± 0.12
	Group C	2.75 ± 0.34	2.42 ± 0.30	2.17 ± 0.23	1.91 ± 0.23	1.53 ± 0.19	1.22 ± 0.18	0.92 ± 0.17	0.70 ± 0.12	0.51 ± 0.13	0.33 ± 0.12	0.23 ± 0.11	0.13 ± 0.11
Anxiety score	Group A	3.02 ± 0.35	2.69 ± 0.31	2.42 ± 0.29	2.11 ± 0.27	1.78 ± 0.19	1.46 ± 0.19	1.18 ± 0.14	0.90 ± 0.17	0.67 ± 0.17	0.53 ± 0.12	0.39 ± 0.13	0.20 ± 0.13
	Group B	3.26 ± 0.35	2.95 ± 0.32	2.69 ± 0.30	2.39 ± 0.28	2.01 ± 0.23	1.72 ± 0.19	1.43 ± 0.17	1.17 ± 0.17	0.93 ± 0.16	0.74 ± 0.17	0.58 ± 0.16	0.40 ± 0.15
	Group C	2.81 ± 0.28	2.53 ± 0.23	2.21 ± 0.25	1.89 ± 0.26	1.59 ± 0.22	1.24 ± 0.17	0.95 ± 0.18	0.69 ± 0.15	0.51 ± 0.10	0.35 ± 0.10	0.26 ± 0.13	0.13 ± 0.10
Agitation score	Group A	2.51 ± 0.33	2.18 ± 0.29	1.99 ± 0.33	1.76 ± 0.23	1.49 ± 0.20	1.22 ± 0.21	0.96 ± 0.17	0.74 ± 0.14	0.59 ± 0.14	0.41 ± 0.13	0.29 ± 0.13	0.20 ± 0.13
	Group B	2.62 ± 0.35	2.36 ± 0.32	2.15 ± 0.32	1.90 ± 0.27	1.65 ± 0.27	1.39 ± 0.24	1.16 ± 0.21	0.94 ± 0.17	0.76 ± 0.16	0.58 ± 0.13	0.43 ± 0.12	0.32 ± 0.13
	Group C	2.35 ± 0.26	2.08 ± 0.25	1.82 ± 0.20	1.57 ± 0.21	1.28 ± 0.19	1.02 ± 0.18	0.79 ± 0.15	0.56 ± 0.15	0.40 ± 0.11	0.29 ± 0.12	0.23 ± 0.15	0.12 ± 0.09
Tactile disturbance	Group A	2.52 ± 0.34	2.23 ± 0.33	2.03 ± 0.28	1.79 ± 0.23	1.48 ± 0.22	1.19 ± 0.19	0.98 ± 0.21	0.74 ± 0.13	0.58 ± 0.14	0.42 ± 0.12	0.33 ± 0.11	0.19 ± 0.08
	Group B	2.70 ± 0.31	2.51 ± 0.29	2.26 ± 0.34	2.03 ± 0.26	1.74 ± 0.22	1.45 ± 0.21	1.17 ± 0.17	1.02 ± 0.18	0.78 ± 0.14	0.63 ± 0.13	0.53 ± 0.10	0.37 ± 0.13
	Group C	2.33 ± 0.31	2.09 ± 0.27	1.83 ± 0.23	1.61 ± 0.21	1.34 ± 0.15	1.04 ± 0.17	0.78 ± 0.13	0.60 ± 0.15	0.40 ± 0.13	0.28 ± 0.15	0.20 ± 0.13	0.10 ± 0.10
Auditory disturbance	Group A	1.43 ± 0.31	1.29 ± 0.26	1.13 ± 0.26	1.01 ± 0.24	0.87 ± 0.21	0.67 ± 0.19	0.55 ± 0.17	0.42 ± 0.14	0.36 ± 0.12	0.22 ± 0.12	0.18 ± 0.11	0.11 ± 0.09
	Group B	1.55 ± 0.35	1.44 ± 0.35	1.28 ± 0.29	1.13 ± 0.25	1.01 ± 0.22	0.84 ± 0.24	0.69 ± 0.20	0.55 ± 0.15	0.48 ± 0.15	0.34 ± 0.13	0.32 ± 0.13	0.20 ± 0.11
	Group C	1.37 ± 0.28	1.22 ± 0.26	1.08 ± 0.24	0.91 ± 0.21	0.73 ± 0.19	0.60 ± 0.14	0.46 ± 0.13	0.33 ± 0.13	0.25 ± 0.11	0.16 ± 0.11	0.13 ± 0.11	0.07 ± 0.07
Visual disturbance	Group	1.40 ±	1.28 ±	1.10 ±	0.99 ±	0.81 ±	0.69 ±	0.53 ±	0.43 ±	0.34 ±	0.27 ±	0.17 ±	0.16 ±

	Group B	2.76 ± 0.31	2.49 ± 0.31	2.26 ± 0.29	1.99 ± 0.24	1.77 ± 0.24	1.47 ± 0.22	1.20 ± 0.17	1.00 ± 0.15	0.79 ± 0.14	0.66 ± 0.13	0.51 ± 0.15	0.39 ± 0.12
	Group C	2.36 ± 0.33	2.06 ± 0.32	1.83 ± 0.26	1.55 ± 0.25	1.29 ± 0.21	1.02 ± 0.18	0.78 ± 0.15	0.59 ± 0.16	0.45 ± 0.12	0.30 ± 0.12	0.19 ± 0.14	0.14 ± 0.12
Orientation and clouding	Group A	1.04 ± 0.29	0.93 ± 0.25	0.84 ± 0.23	0.75 ± 0.22	0.66 ± 0.19	0.52 ± 0.19	0.41 ± 0.13	0.32 ± 0.14	0.22 ± 0.09	0.20 ± 0.10	0.12 ± 0.08	0.11 ± 0.09
	Group B	1.09 ± 0.32	0.98 ± 0.28	0.92 ± 0.27	0.80 ± 0.24	0.69 ± 0.19	0.57 ± 0.18	0.49 ± 0.17	0.40 ± 0.16	0.31 ± 0.13	0.25 ± 0.16	0.22 ± 0.13	0.15 ± 0.12
	Group C	0.95 ± 0.27	0.84 ± 0.29	0.71 ± 0.25	0.61 ± 0.23	0.53 ± 0.20	0.41 ± 0.16	0.33 ± 0.14	0.23 ± 0.15	0.17 ± 0.12	0.12 ± 0.10	0.08 ± 0.09	0.07 ± 0.08
Total CIWA-Ar score	Group A	24.7 ± 0.9	22.0 ± 1.0	19.8 ± 0.9	17.3 ± 0.7	14.6 ± 0.7	11.9 ± 0.7	9.5 ± 0.6	7.4 ± 0.5	5.6 ± 0.4	4.2 ± 0.4	3.0 ± 0.4	2.0 ± 0.4
	Group B	27.1 ± 1.2	24.6 ± 1.1	22.3 ± 1.0	19.8 ± 0.8	17.1 ± 0.8	14.3 ± 0.6	11.9 ± 0.7	9.9 ± 0.5	7.9 ± 0.5	6.3 ± 0.5	4.9 ± 0.5	3.5 ± 0.5
	Group C	23.3 ± 1.0	20.7 ± 1.0	18.2 ± 0.9	15.8 ± 0.8	13.0 ± 0.7	10.3 ± 0.6	7.9 ± 0.5	5.8 ± 0.5	4.2 ± 0.4	2.8 ± 0.4	2.0 ± 0.4	1.2 ± 0.4

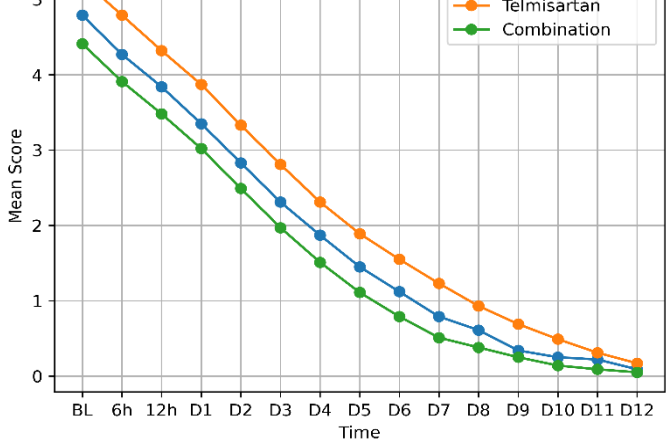
Abbreviations: SD: Standard deviation; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-Revised scale; RM-ANOVA: Repeated measures analysis of variance.

p (Within group): One-way RM-ANOVA (paired t-test, Baseline vs Day 12 within each group).

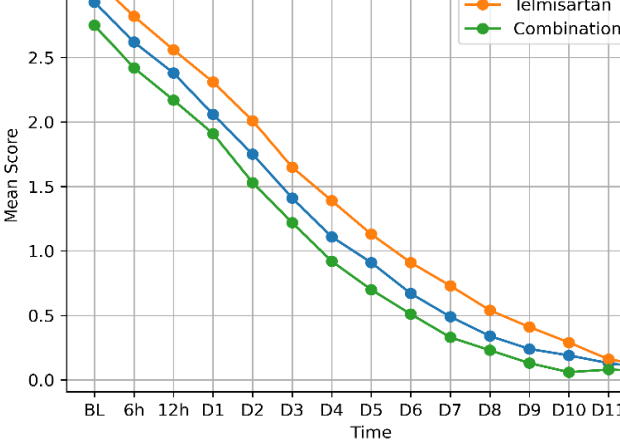
p (Between group): Two-way RM-ANOVA (ANOVA comparing groups at Baseline).



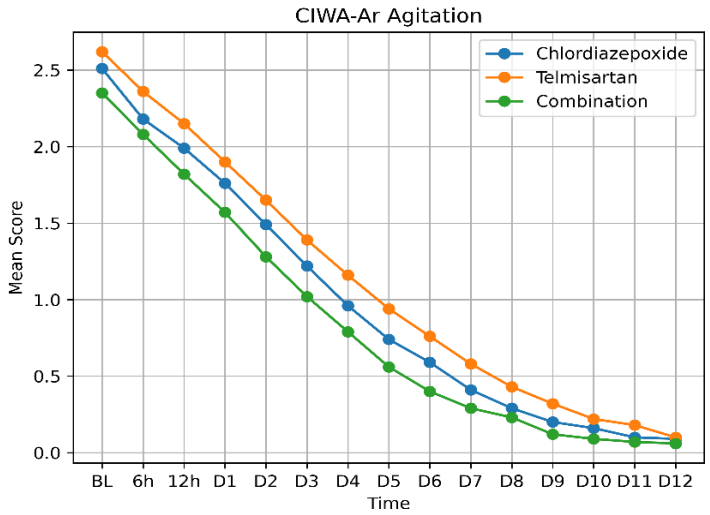
E. CIWA-Ar score for agitation



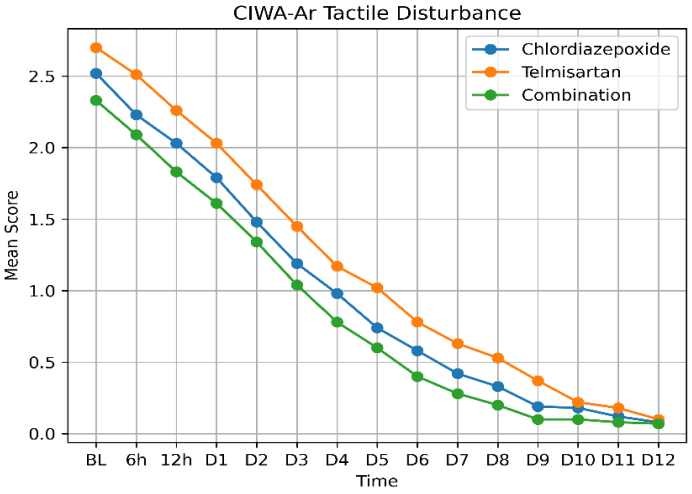
F. CIWA-Ar score for tactile disturbance



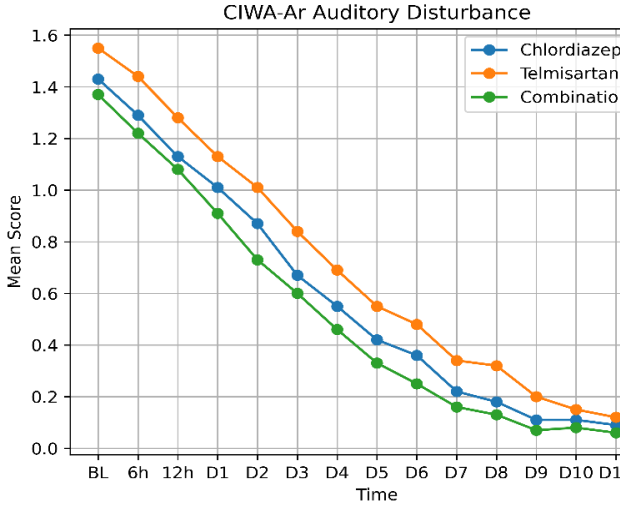
G. CIWA-Ar score for auditory disturbance

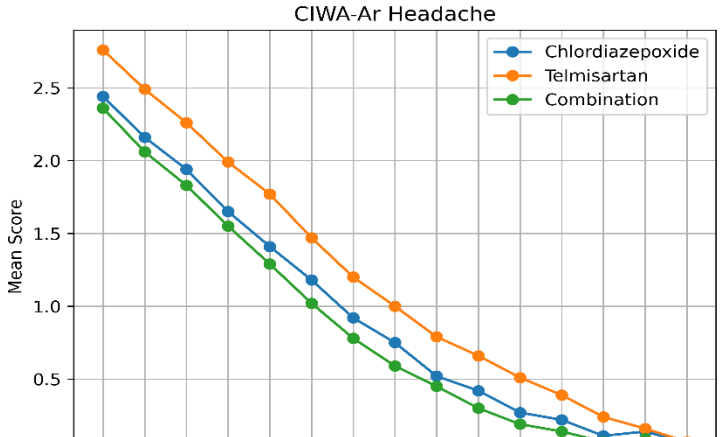


I. CIWA-Ar score for headche



J. CIWA-Ar score for orientation and clouding





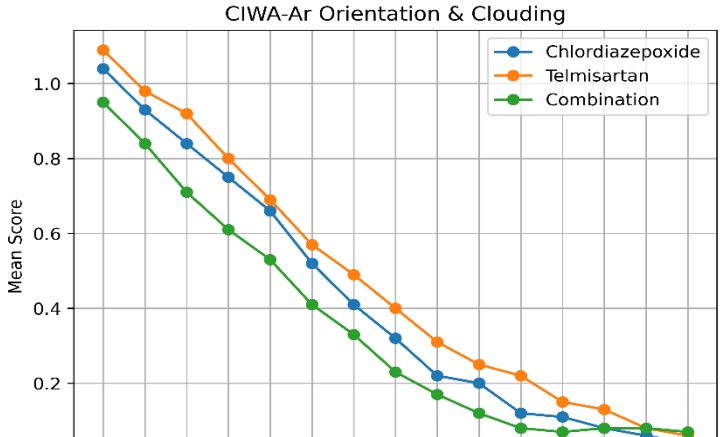


Figure 1: Trajectory of CIWA-Ar scores across treatment arms during alcohol withdrawal. Mean CIWA-Ar scores (± SD) from baseline to Day 12 in patients receiving chlordiazepoxide alone (Group A), telmisartan alone (Group B) or combination therapy (Group C). All groups showed significant symptom reduction over time (RM-ANOVA p<0.001). Combination therapy demonstrated the most rapid and sustained decline in withdrawal severity compared to monotherapy arms

3.4. Differential Modulation of Alcohol Craving: Obsessive Compulsive Drinking Scale Outcomes

At follow-up, all treatment arms showed substantial reduction in Obsessive-Compulsive Drinking Scale (OCDS) rating from Day 7 to Day 15 ($p<0.001$), indicating a decrease in alcohol-related cravings over time. However, significant between-group differences were found, supporting combination therapy. The overall OCDS score decreased from 17.6 ± 0.8 to 8.5 ± 0.3 in the chlordiazepoxide group and from 17.9 ± 0.7 to 8.4 ± 0.4 in the telmisartan group, indicating similar efficacy between both monotherapies. The combination group experienced a significantly higher reduction, from 12.6 ± 0.6 to 5.2 ± 0.4 ($p<0.001$ across groups). A similar pattern emerged across subscales. The obsessive domain reduced to 3.6 ± 0.3 in both monotherapy arms against 2.2 ± 0.3 with combination therapy. The compulsive domain decreased to 4.9 ± 0.3 and 4.8 ± 0.3 in Group A and B, respectively, compared to 3.0 ± 0.3 in the combination arm. Comparison between groups were statistically significant ($p<0.001$). **Table 4** shows that whereas telmisartan and chlordiazepoxide monotherapy induce equal craving reductions, supplementary usage produces higher improvements across both obsessive and compulsive drinking dimensions, demonstrating a potential additive effect on seeking control in AWS. **Figure 2** represents follow-up, treatment arms showed substantial reduction in OCDS ratings from Day 7 to Day 15, indicating decreased alcohol-related cravings over time.

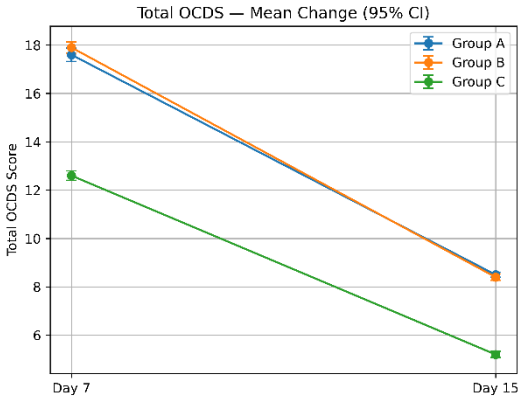
Table 4: Obsessive Compulsive Drinking Scale Outcomes

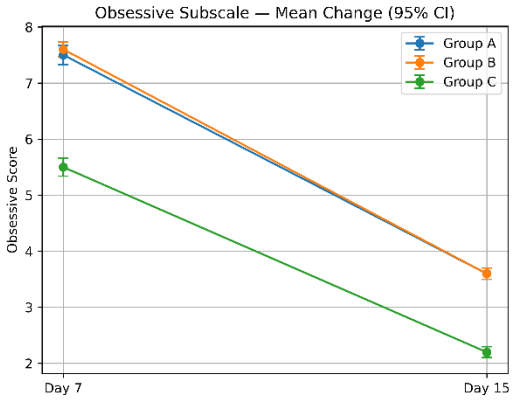
Day 7 and Day 15 | n=105 | Group A ≈ Group B (equal efficacy), Group C (best)

Subscale/Item	Group (mean ± SD)	Day 7	Day 15	p (Within)	p (Between)
Total OCDS score (0-56)	Group A	17.6 ± 0.8	8.5 ± 0.3	<0.001	<0.001
	Group B	17.9 ± 0.7	8.4 ± 0.4	<0.001	
	Group C	12.6 ± 0.6	5.2 ± 0.4	<0.001	
Obsessive subscale (0-24)	Group A	7.5 ± 0.5	3.6 ± 0.3	<0.001	<0.001
	Group B	7.6 ± 0.4	3.6 ± 0.3	<0.001	
	Group C	5.5 ± 0.5	2.2 ± 0.3	<0.001	
Compulsive subscale (0-32)	Group A	10.1 ± 0.5	4.9 ± 0.3	<0.001	<0.001
	Group B	10.2 ± 0.5	4.8 ± 0.3	<0.001	
	Group C	7.2 ± 0.4	3.0 ± 0.3	<0.001	

KEY FINDING: Group B (Telmisartan) shows EQUAL efficacy to Group A (Chlordiazepoxide-standard) at both timepoints ($p > 0.05$). Group C (Combination) superior to both ($p < 0.001$).

A. Total OCDs score **B. Obsessive subscale score** **C**





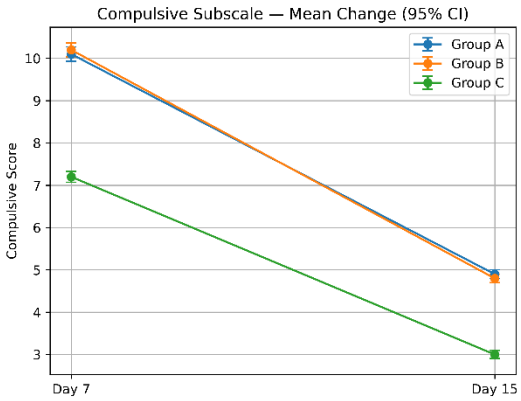
C. Compulsive subscale score

Figure 2: Changes in alcohol craving measured by the Obsessive-Compulsive Drinking Scale (OCDS). Mean OCDS total subscale (± SD) from Day 7 to Day 15 among treatment groups. All groups demonstrated significant craving reduction over time (p<0.001). the combination therapy group showed the greatest improvement in total, obsessive and compulsive drinking scores compared with monotherapies.

3.5. Comparable safety profile across treatment arms

Adverse events were usually few and moderate in all groups, with no statistically significant differences between them. The most prevalent recorded incident was sedation or drowsiness, which occurred in 18% of patients receiving chlordiazepoxide, 8% with telmisartan and 16% with combined medication (p=0.31). Neurological issues as dizziness and headaches were rare and consistent across groups (p<0.05). Vascular events demonstrated a numerically larger incidence of symptomatic hypotension in telmisartan-exposed groups (12% with telmisartan alone and 10% with combination medication) than in chlordiazepoxide (4%), while this difference was not statistically significant (p=0.29).

Table 5: Adverse events



Adverse Event	Group 1 (Chlordiazepoxide)	Group 2 (Telmisartan)	Group 3 (Combination)	p-value
Nervous System				

- Sedation/Drowsiness	9 (18%)	4 (8%)	8 (16%)	0.31
- Dizziness	2 (4%)	6 (12%)	5 (10%)	0.29
- Headache	5 (10%)	6 (12%)	4 (8%)	0.79
Vascular				
- Symptomatic Hypotension	2 (4%)	6 (12%)	5 (10%)	0.29
Gastrointestinal				
- Nausea	4 (8%)	5 (10%)	3 (6%)	0.75
- Diarrhea	3 (6%)	2 (4%)	3 (6%)	0.86
Laboratory				
- Hyperkalemia (K+ >5.5)	0 (0%)	2 (4%)	1 (2%)	0.36

4. Discussion:

This exploratory randomized experiment sought to determine whether telmisartan modulation of the brain-renin-angiotensin system could improve standard benzodiazepine therapy in alcohol withdrawal syndrome (AWS). The combination of telmisartan and chlordiazepoxide resulted in a higher reduction in CIWA-Ar scores, fewer cravings and a numerical increase in short-term abstinence when compared to either medicine alone. While all groups recovered with supportive care, the long-term advantage of combination therapy implies that it has benefits beyond symptomatic sedation. These data supports a larger neurological explanation of AWS, which encompass neuroinflammation, oxidative stress and dopaminergic dysregulation, in addition to GABA-glutamate imbalance. Chronic alcohol intake may promote a shift in central RAS activity to the ACE/AngII/AT1P axis, hence increasing pro-inflammatory and stress-related signaling in reward pathways. Telmisartan, a brain-penetrant AT1R blocker with mild PPAR$^{\gamma}$ agonist activity, can help reduce neuroinflammation and oxidative stress[8, 9]. According to this perspective, benzodiazepines primarily treat acute hyperexcitability, but telmisartan may impact upstream neuroimmune and early relapse. This hypothesis is supported by the observed reduction in craving and improved abstinence in the combination arm, which also suggests possible effects after the detoxification period. The safety data were broadly consistent with known pharmacology. Mild hypotension was more likely in telmisartan-containing arms, but benzodiazepines were linked with more severe sedation. Important, no clinically significant hepatic or renal impairment was observed, which is an important consideration in the alcohol dependent group. Several limitations restrict interpretation. The dataset was used for planning and illustrative reasons and the sample size after attrition was small. The open label design allows for expectancy and observer bias, which is particularly relevant for symptom based outcome judgements. The study's focus on uncomplicated AWS restricts generalizability to severe or complicated withdrawal. However, our study's findings offer a clinically relevant hypothesis: Ras regulation may supplement benzodiazepines in AWS. Future double-blind, suitably powered trails incorporating biomarker profiling and objective alcohol consumption outcomes are required. If confirmed, repurposing RAS modifying medicines such as telmisartan could be a viable method to integrate neuronal targeting into AWS treatment and early relapse prevention.

5. Conclusion

In this randomized, open-label trail, adjunctive telmisartan plus symptom-triggered chlordiazepoxide resulted in greater reductions in withdrawal severity, higher short-term abstinence and lower craving scores than either therapy alone, with no clinically significant deterioration in hepatic, real or electrolyte parameters. These findings corroborate the biological reasoning that manipulating the brain's renin-angiotensin system through AT1R blockade and partial PPAR$^{\gamma}$ agonism may supplement GABAergic techniques by attenuating neuroinflammation and sympathetic overactivity during alcohol withdrawal. However, these findings should be interpreted with caution due to the partially structured dataset, open-label design, and small sample size, which limit generalizability and introduce potential bias; importantly, telmisartan monotherapy cannot replace benzodiazepines in AWS, particularly in severe withdrawal.

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Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability

The datasets generated during and/or analysed during the current study will be available from the corresponding author on reasonable request