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# Comparison of Baclofen with Acamprosate in Evaluation of Hematological Parameters for The Maintenance of Alcohol Abstinence: A Comparative and Prospective Study

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***Abstract***

- ***Background:*** *Chronic alcohol consumption significantly alters hematological indices through direct bone marrow toxicity, nutritional deficiencies, and splenic sequestration[1]. Both Baclofen (a GABA A receptor agonist) and Acamprosate (a NMDA receptor modulator) are widely used to maintain alcohol abstinence, yet comparative data regarding their long-term impact on hematological recovery during sobriety remain scarce[5].*
- ***Objective:*** *This prospective, open-label, randomized, parallel-group study evaluated and compared the chronological changes in hematological parameters among alcohol-dependent individuals treated with either baclofen or acamprosate over a 24-week abstinence protocol.*
- ***Methods:*** *A total of 180 alcohol-dependent patients successfully undergoing detoxification were randomized into two arms: Group A (n=90) received oral baclofen (30 mg/day in divided doses), and Group B (n=90) received oral Acamprosate (1998 mg/day in divided doses). Complete blood counts (CBC), including hemoglobin (Hb), mean corpuscular volume (MCV), red blood cell (RBC) count, total leukocyte count (TLC), and platelet count, were measured at baseline, week 4, week 12, and week 24. Compliance and abstinence were verified via random urinary ethyl glucuronide testing and self-reports.*
- ***Results:*** *At 24 weeks, both treatment arms demonstrated statistically significant improvements in hematological parameters compared to baseline ($p<0.05$). The mean corpuscular volume (MCV) decreased significantly in both groups, moving from macrocytic baselines to normocytic levels. Group A (Baclofen) exhibited a slightly faster normalization of platelet counts by week 12 compared to Group B (Acamprosate) (p 0.042 ). However, at the endpoint of week 24, there were no statistically significant inter-group differences regarding hemoglobin levels, total leukocyte counts, or absolute neutrophil counts. Relapse rates did not differ significantly between the groups, and hematological recovery strongly correlated with the total duration of verified abstinence rather than the specific pharmacological agent utilized.*
- ***Conclusion:*** *Both baclofen and acamprosate are highly effective in supporting the physiological reversal of alcohol-induced bone marrow suppression and hematotoxicity by facilitating sustained abstinence. The choice between these two agents can be safely guided by their respective metabolic profiles, visceral clearance capacities, and neurological tolerance, as they possess matching therapeutic neutrality concerning bone marrow recovery and peripheral blood cell lines.*

## I. Introduction

**Background**

Chronic alcohol use disorder (AUD) represents a major global health burden, contributing extensively to metabolic, hepatic, neurological, and hematological morbidity. While the neuropsychiatric and gastroenterological consequences of chronic ethanol abuse are widely recognized, its profound suppressive effects on the hematopoietic system are equally critical clinical parameters. Ethanol and its primary toxic metabolite, acetaldehyde, exert direct cytopathic effects on multipotent hematopoietic stem cells within the bone marrow. This leads to impaired cellular maturation, vacuolization of erythroid precursors, and accelerated peripheral destruction of mature blood components. Consequently, individuals suffering from active AUD frequently present with a complex constellation of hematological abnormalities, including macrocytic anemia, leukopenia, thrombocytopenia, and functional immune defects.

Pharmacotherapy plays an indispensable role in maintaining long-term abstinence following acute alcohol withdrawal syndrome management[1]. Among the approved and off-label therapeutic modalities utilized in clinical practice, acamprosate and baclofen stand out as two prominent pharmaceutical interventions operating via distinct neurochemical pathways.

- **Acamprosate** (calcium acetylhomotaurinate) is structurally similar to the endogenous neurotransmitter gamma-aminobutyric acid (GABA) and acts primarily as an antagonist at the N-methyl-D-aspartate (NMDA) glutamate receptors. It stabilizes the chronic alcohol-induced disruption of the glutamatergic system, thereby diminishing cravings and reducing the neurotoxic hyper-excitability associated with protracted abstinence.
- **Baclofen**, a specific agonist at the metabotropic receptors, has emerged as a potent off-label alternative for maintaining abstinence. It is highly valued for its safety profile in patients with advanced liver cirrhosis, as it undergoes primary renal excretion rather than extensive hepatic metabolism. Baclofen suppresses central dopamine release in the mesolimbic pathway, muting the reinforcing rewards associated with alcohol cues[6].

**Rationale for the Study**

Sustained sobriety initiates a gradual reversal of ethanol-induced bone marrow toxicity. Peripheral cell counts typically recover in a predictable chronological sequence following the cessation of alcohol intake. However, the potential immunomodulatory and cellular effects of anti-craving medications on this hematological recovery process remain largely uncharacterized.

Emerging pre-clinical evidence suggests that central and peripheral GABA receptors, along with glutamatergic signaling pathways, are functional within the microenvironment of the bone marrow[2]. These pathways influence hematopoiesis, T-lymphocyte activation, and platelet reactivity. For instance, GABAergic signaling via GABA B receptors can modulate cellular proliferation and survival mechanisms in non-neuronal tissues. Conversely, NMDA receptors expressed on erythroid precursors and platelets have been implicated in megakaryocyte differentiation and structural cellular stabilization[3].

Given that baclofen and acamprosate are administered continuously for several months during the critical phase of hematopoietic recovery, it is essential to determine whether either drug accelerates, impedes, or remains neutral toward the normalization of peripheral blood lines. While existing literature extensively documents the psychological efficacy, craving reduction index, and hepatic safety profiles of these compounds, there is a distinct lack of clinical data comparing their direct or indirect impacts on hematological recovery[4]. This prospective clinical trial addresses this gap by monitoring complete blood count parameters in a well-defined cohort of alcohol-dependent patients undergoing long-term abstinence therapy.

## II. Methodology

**Study Design and Setting**

This study was designed as a prospective, randomized, open-label, parallel-group, single-centre clinical trial conducted over a 24-week active treatment period. The trial was hosted within the specialized addiction medicine and clinical hematology outpatient wings of a tertiary care teaching hospital between June 2024 and February 2026. The open-label design was chosen due to distinct differences in dosing frequencies and pill appearance between baclofen and acamprosate, making a double-dummy design logistically unfeasible given the resources available. However, laboratory technicians performing the automated hematological assays were blinded to the treatment allocations to eliminate analytical bias.

**Participant Selection and Ethics**

The study protocol was approved by the Institutional Ethics Committee, Government Medical College, Kadapa (IEC No. 005/GMC/KDP/2025). All participants provided written, informed consent before undergoing any screening or randomization procedures.

**Inclusion Criteria**

- Diagnosed with Alcohol Dependence according to the DSM-5 criteria.
- Aged between 21 and 65 years at the time of screening.
- Successfully completed an inpatient or outpatient alcohol detoxification program within the previous 7 to 14 days.
- Achieved initial clinical sobriety, evidenced by a Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) score of less than 8.
- Expressed a stated therapeutic goal of total alcohol abstinence.

**Exclusion Criteria**

- Presenting with co-existing major psychiatric illnesses (e.g., schizophrenia, bipolar disorder) requiring ongoing antipsychotic or mood-stabilizing medication.
- Known pre-existing primary hematological disorders unrelated to alcohol consumption, such as aplastic anemia, myelodysplastic syndromes, idiopathic thrombocytopenic purpura (ITP), or genetic hemoglobinopathies.

Severe decompensated hepatic impairment (Child-Pugh Class C) or advanced renal failure (estimated Glomerular Filtration Rate [eGFR] (<30 ml/min/1.73 $m^2$).

- Concomitant use of other medications known to cause bone marrow suppression or severe hematotoxicity (e.g., methotrexate, azathioprine, linezolid, or chronic NSAIDs).
- Active pregnancy or lactation.
- Co-dependence on other illicit substances, excluding nicotine or caffeine.

**Randomization and Intervention**

A total of 180 eligible participants were assigned in a 1:1 ratio to receive either Baclofen (Group A) or Acamprosate (Group B) using a computer-generated block randomization schedule with variable block sizes.

- **Group A (Baclofen Arm):** Patients were prescribed oral baclofen at an initial dose of three times daily (15 mg per day). This dose was titrated upwards over a 7-day period to a standard maintenance dose of 10 mg three times daily (30 mg/day). Upward or downward adjustments (range: 15 mg to 60 mg per day) were permitted based on clinical tolerance and emergent side effects, such as somnolence or muscular weakness.
- **Group B (Acamprosate Arm):** Patients weighing (<60 Kgs) received oral acamprosate at a standard dose of three times daily (total 1998 mg/day). For participants weighing, the dose was modified to in the morning and 333 mg at noon and night (total 1332 md/day) to account for renal clearance dynamics.

Both groups received standardized bi-weekly brief behavioral compliance enhancement therapy (BBCET) sessions lasting 15 to 20 minutes. These sessions focused on reinforcing medication adherence, developing coping strategies for cravings, and documenting any adverse events.

**Clinical Monitoring and Outcome Assessment**

Patients were evaluated at baseline (Day 0, prior to the first dose of study medication) and subsequently at weeks 4, 12, and 24. At each scheduled follow-up visit, clinical compliance was assessed via pill counts.

Abstinence status was verified through a combination of patient self-reports, collateral histories from designated family members, and objective biochemical verification. The latter involved random, mandatory spot-urine testing for Ethyl Glucuronide (EtG) utilizing an immunoassay kit with a detection threshold cut off of 500 ng/ml.

A positive urine EtG test or a self-acknowledged consumption of more than two standard drinks was classified as a clinical relapse.

Hematological profiles were evaluated at every milestone visit. Venous blood samples (5 ml) were collected via aseptic venipuncture into ethylenediaminetetraacetic acid (EDTA) vacutainer tubes. All samples were analyzed within two hours of collection using a validated, calibrated automated hematology analyzer (Sysmex XN-1000). The primary and secondary hematological endpoints evaluated included:

- **Erythroid Series:** Hemoglobin (Hb, g/dL), Red Blood Cell (RBC) count ($x10^{12}$ ml), Mean Corpuscular Volume (MCV,fL), and Packed Cell Volume (PCV, %).
- **Leukocyte Series:** Total Leukocyte Count (TLC, $x10^9$ ml) and Absolute Neutrophil Count (ANC, ($x10^9$ ml).
- **Thrombocytic Series:** Absolute Platelet Count ( $x10^9$ ml).

**Statistical Analysis**

Statistical analysis was executed using SPSS Version. Continuous demographic data and baseline laboratory variables were expressed as Mean Standard Deviation (SD) or Median with Interquartile Range (IQR) based on normality distributions assessed via the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages.

Inter-group comparisons at individual timelines were performed using the independent-samples t-test or the Mann-Whitney U test. Intra-group changes over the 24-week period were assessed using repeated-measures Analysis of Variance (ANOVA) followed by post-hoc Bonferroni correction.

An Intent-to-Treat (ITT) approach with Last Observation Carried Forward (LOCF) was utilized to handle missing data from dropouts and relapsed patients. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant

**Baseline Demographic and Clinical Characteristics**
Out of the 180 randomized patients, a total of 144 patients completed the full 24-week trial protocol (74 in the Baclofen group, 70 in the Acamprosate group). The remaining 36 patients dropped out due to relapses, non-compliance, or structural loss to follow-up, and their data were processed using ITT methodology.

The baseline demographic data, heavy drinking history, and initial liver function indices did not differ significantly between the two groups, confirming effective randomization (Table 1).

**Table 1: Baseline Demographic and Clinical Status of Study Cohorts**

**TABLE 1**
Baseline Characteristics of Study Participants
**Leukocyte Markers During Follow-up**

| Leukocyte Marker / Timeline | Group A: Baclofen (n=90) | Group B: Acamprosate (n=90) | Inter-group p-value |
|---|---|---|---|
| Total Leukocyte Count ($\times 10^9$/L) | | | |
| Baseline | 4.85 ± 1.22 | 4.91 ± 1.15 | 0.732 |
| Week 4 | 5.42 ± 1.08 | 5.36 ± 1.12 | 0.714 |
| Week 12 | 6.12 ± 0.94 | 6.05 ± 0.99 | 0.623 |
| Week 24 | 6.48 ± 0.81 | 6.52 ± 0.78 | 0.735 |
| Absolute Neutrophil Count ($\times 10^9$/L) | | | |
| Baseline | 2.61 ± 0.74 | 2.68 ± 0.69 | 0.511 |

**Erythroid Parameter Alterations and Recovery Dynamics**
At baseline, mild-to-moderate macrocytic anemia was prevalent across both cohorts, characterized by depressed hemoglobin concentrations and elevated Mean Corpuscular Volume (MCV) levels exceeding 100 fl.
Following the initiation of abstinence and pharmacotherapy, both groups demonstrated a progressive and highly significant increase in overall hemoglobin concentration, paired with a synchronous decline in MCV toward normocytic ranges.

**Table 2: Longitudinal Shifts in Erythroid Parameters**
**TABLE 2**
**Hemoglobin and Mean Corpuscular Volume During Follow-up**

| Parameter / Timeline | Group A: Baclofen (n=90) | Group B: Acamprosate (n=90) | Within-group p-value | Inter-group p-value |
|---|---|---|---|---|
| Hemoglobin (g/dL) | | | | |
| Baseline | 11.8 ± 1.4 | 11.6 ± 1.5 | — | 0.358 |
| Week 4 | 12.4 ± 1.2 | 12.2 ± 1.3 | <0.01 | 0.284 |
| Week 12 | 13.5 ± 1.1 | 13.3 ± 1.1 | <0.001 | 0.221 |
| Week 24 | 14.2 ± 0.9 | 14.1 ± 0.8 | <0.001 | 0.432 |
| Mean Corpuscular Volume (MCV, fL) | | | | |
| Baseline | 104.2 ± 6.3 | 105.1 ± 5.9 | — | 0.325 |
| Week 4 | 101.1 ± 4.8 | 102.3 ± 4.4 | <0.05 | 0.084 |
| Week 12 | 94.6 ± 3.9 | 95.2 ± 3.7 | <0.001 | 0.281 |
| Week 24 | 89.4 ± 3.1 | 89.8 ± 2.8 | <0.001 | 0.369 |

As detailed in Table 2, the decrease in MCV from baseline to week 24 was highly significant within both groups (p value 0.001). This confirms that the macrocytosis directly associated with chronic ethanol exposure resolves steadily during sustained sobriety. There were no statistically significant differences between the baclofen and acamprosate arms at any evaluation point, indicating that neither drug interferes with or alters the physiological lifespan and clearance of macrocytic red blood cells.

**Leukocyte Axis Evaluation**
Mild leukopenia and neutropenia were observed in approximately 18% of the study population at baseline, reflecting the bone marrow suppressive qualities of active ethanol intake[7]. Following detoxification and throughout the maintenance phase, total leukocyte counts (TLC) and absolute neutrophil counts (ANC) stabilized within standard physiological ranges for both groups.
The upward trajectory of white blood cell counts toward ideal baseline homeostatic distributions was linear and parallel between the two treatment arms. Neither baclofen nor acamprosate caused any episodes of drug-induced leukopenia, agranulocytosis, or unexplained neutrophilia during the 24 weeks of continuous therapy.

**Thrombocytic Profiles and Platelet Recovery Kinetics**

Thrombocytopenia (platelet count $150X10^9$ ml ) was a common finding at baseline, affecting 34.4% (n=31) of patients in Group A and 36.6% (n=33) of patients in Group B. This was primarily due to the direct myelosuppressive effects of ethanol on megakaryocytes, combined with subclinical splenic sequestration[8].

Upon initiating therapy, platelet numbers rose rapidly in both cohorts during the initial four weeks of verified abstinence.

As illustrated above, Group A (Baclofen) exhibited a more pronounced and rapid elevation in mean platelet count at the 12-week checkpoint ($228+44x10^9$ /L ) compared to Group B (Acamprosate, $204=42X10^9$ L). This difference was statistically significant ( p=0.042). However, this variation equilibrated by week 24, where both groups achieved comparable plateau levels (Group A: $254=38x10^9$ L ; Group B: $251=35X10^9$ L; p 0.584 ).

**Table 3:**

| Characteristic Parameter | Group A: Baclofen (n=90) | Group B: Acamprosate (n=90) | P-value |
|---|---|---|---|
| Age (years, Mean ± SD) | 44.2 ± 8.6 | 45.1 ± 7.9 | 0.468 |
| Gender (Male/Female) | 84/6 | 82/8 | 0.572 |
| Mean Weight (kg) | 71.4 ± 9.3 | 72.1 ± 8.8 | 0.598 |
| Duration of Dependent Drinking (years) | 12.4 ± 4.1 | 13.1 ± 3.8 | 0.231 |
| Ethanol Intake (grams/day at baseline) | 142.5 ± 38.6 | 146.2 ± 41.3 | 0.531 |
| Baseline Alanine Aminotransferase (ALT, U/L) | 68.4 ± 24.1 | 65.9 ± 22.3 | 0.473 |

- **Direct Toxicity:** Ethanol suppresses the pluripotency of hematopoietic progenitors, disrupting standard mitotic cycles and inducing premature apoptosis in erythroid and megakaryocytic lineages[9]. This suppression leads to the classic vacuoles seen in early erythroblasts, which resolve only after alcohol clearance.
- **Nutritional Deprivation:** Chronic alcohol consumption impairs folate and vitamin B12 absorption at the jejunal level and compromises hepatic storage capacity[10]. This deficiency halts DNA synthesis during single-lineage development, resulting in ineffective erythropoiesis characterized by abnormally large, structurally fragile macrocytes (elevated MCV).
- **Splenic Sequestration:** Subclinical portal hypertension secondary to alcohol-induced hepatic steatosis or early fibrosis causes mild-to-moderate splenomegaly[11]. This increases the physical entrapment and destruction of viable circulating platelets, compounding the thrombocytopenia caused by direct bone marrow suppression

**Comparative Analysis of Drug Actions on Hematopoiesis**

Our prospective clinical trial demonstrates that both baclofen and acamprosate facilitate a steady, complete recovery of these compromised hematological lines. This recovery is achieved primarily by supporting the maintenance of total alcohol abstinence. Over the 24-week monitoring matrix, the resolution of macrocytosis, recovery of hemoglobin levels, and normalization of leukocyte populations occurred at similar rates in both treatment groups. This indicates that neither drug exerts a negative primary myelosuppressive effect or alters standard physiological hematopoiesis[12].

The single notable variation observed was the accelerated recovery of platelet counts in the baclofen arm at week 12 (p value 0.042). This finding may be due to peripheral physiological mechanisms rather than direct stimulation of megakaryocytopoiesis.

- **Baclofen's Impact:**

GABA B receptors are present on vascular endothelial walls and within splenic tissue matrices. Agonism at these receptor sites has been shown to reduce portal pressure and alleviate transient congestive splenomegaly. By mitigating this splenic entrapment early in the abstinence phase, baclofen may allow a larger fraction of newly synthesized platelets to remain in active circulation[13]. Additionally, baclofen can reduce systemic anxiety and sympathetic tone, lowering circulating catecholamine levels and stabilizing platelet consumption dynamics.

- **Acamprosate's Impact:** Acamprosate stabilizes central NMDA-mediated glutamatergic pathways. While NMDA receptors are functionally present on the surface membranes of mature platelets and involved in thrombus stabilization, acamprosate's impact remains largely localized to the central nervous system. It does not appear to alter peripheral platelet survival or accelerate their release from bone marrow niches, leading to a standard, unassisted chronological recovery curve.

By week 24, platelet levels in both groups converged, indicating that the initial differences in recovery rates do not influence long-term hematological outcomes. The normalization of these parameters is ultimately driven by sustained abstinence from ethanol, which allows the hematopoietic stem cell niche to fully regenerate[14].

**Safety and Clinical Utility Considerations**

From a clinical safety perspective, the lack of toxic hematological deviations in either group is highly reassuring. Anti-craving medications are often prescribed to patients who already have mild bone marrow suppression due to chronic alcohol use. The absolute stability of the leukocyte and neutrophil lines observed in this study confirms that neither baclofen nor acamprosate carries a risk of idiosyncratic agranulocytosis or secondary immune suppression[15].

Consequently, the choice between baclofen and acamprosate can be guided by other clinical factors, such as the patient's hepatic and renal function, compliance potential, and side-effect profile:

- **Baclofen Clinical Profile:**
  - **Metabolism:** Undergoes minimal hepatic clearance (<15 percent); excreted largely unchanged by the kidneys.
  - **Clinical Utility:** The preferred option for patients with advanced alcohol-related liver disease, steatohepatitis, or compensated cirrhosis.
  - **Dosing:** Requires a three-times-daily schedule; relies on careful upward titration to manage initial side effects like somnolence or dizziness.
- **Acamprosate Clinical Profile:**
  - **Metabolism:** Excreted entirely unchanged via renal pathways; possesses no hepatic clearance signature.
  - **Clinical Utility:** Highly safe for patients with severe liver dysfunction, provided renal function is preserved (Contraindicated if CrCl <30 ml/min).
  - **Dosing:** Involves a high pill burden (666mg three times daily), which can present compliance challenges for some patients[16].

Our findings show that both medications are neutral regarding hematological recovery. This allows clinicians to focus on these metabolic and logistical factors when tailoring treatment for alcohol dependence.

**Limitations and Future Directions**

While this study provides valuable comparative insights, several limitations should be noted:

- **Open-Label Design:** The open-label structure may introduce subtle behavioral or reporting biases among participants, though this risk was mitigated by using objective urinary EtG testing and blinded laboratory technicians.
- **Nutritional Status:** Nutritional variables, such as baseline serum folate and vitamin B12 levels, were not systematically measured or standardized. Although participants received general nutritional advice, variations in dietary recovery could have influenced the rate of hemoglobin and MCV normalization.
- **Sample Size and Scope:** The single-center setting and 24-week duration limit the ability to detect rare, long-term hematological side effects.

Future multi-center trials with larger cohorts and longer follow-up periods are needed to confirm these findings[17]. Additionally, evaluating bone marrow aspirates or tracking specific cytokine and hematopoietic growth factor profiles (such as erythropoietin and thrombopoietin) would help clarify the molecular mechanisms underlying the accelerated platelet recovery observed with baclofen.

## III. Conclusion

This 24-week prospective randomized study demonstrates that baclofen and acamprosate are both hematologically safe and effective options for patients recovering from alcohol dependence. Both medications support the steady normalization of hemoglobin, red blood cell volume, leukocyte profiles, and platelet counts by facilitating sustained abstinence and removing the myelosuppressive effects of ethanol[18].

The slightly faster recovery of platelet counts observed in the baclofen group around week 12 suggests potential peripheral benefits, such as reduced splenic sequestration[19], though both groups achieved equal homeostatic stability by week 24. Ultimately, both agents demonstrate an excellent safety profile concerning hematopoiesis. This allows clinicians to choose between them based on hepatic safety, renal tolerance, dosing convenience, and individual patient compliance profiles without concern for adverse hematological effects[20].

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