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Pharmacogenetically Guided Pharmacotherapy for Alcohol Withdrawal Syndrome Complicated by Seizures: A Pilot Randomized Controlled Trial

Valentin Yu. Skryabin *, Svetlana I. Sokolova, Valentina A. Ivanchenko, Alla A. Matskevich, Anton V. Masyakin

Moscow Research and Practical Centre on Addictions, Moscow 109390, Russia
* Correspondence: sardonios@yandex.ru (V.Yu.S.)

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Abstract: Alcohol withdrawal syndrome (AWS) complicated by seizures requires rapid symptom control while avoiding excessive sedation and other dose-related adverse drug reactions. This pilot randomized controlled trial evaluated whether pharmacogenetically guided optimization of pharmacotherapy could improve early clinical dynamics and tolerability in this high-risk inpatient population. Fifty inpatients with alcohol withdrawal state with convulsions (ICD-10 F10.31) were randomized 1:1 to pharmacogenetically guided treatment or control care. Pharmacogenetic testing was performed at admission in all patients; treating physicians in the intervention group received the true PGx report, whereas control physicians received a neutral report of identical format indicating wild-type genotypes and standard dosing. The primary endpoint was the area under the CIWA-Ar curve over 72 hours. Mean AUC CIWA-Ar was lower in the pharmacogenetic group than in controls (790 ± 175 vs 905 ± 185 score-hours; p = 0.032), with consistent non-parametric sensitivity analysis. Repeated-measures modelling showed a significant group-by-time interaction, with adjusted differences at 48 and 72 hours. The pharmacogenetic group also showed shorter time to stabilization, lower rescue medication burden, shorter hospitalization, lower UKU scores, and fewer clinically significant adverse events. These preliminary findings suggest that pharmacogenetically guided prescribing may improve tolerability and early withdrawal dynamics, but require confirmation in larger multicentre studies.

Keywords: *alcohol withdrawal syndrome; withdrawal seizures; pharmacogenetics; CYP2C19; CYP2D6; CIWA-Ar; UKU; personalized medicine.*

1. INTRODUCTION

Alcohol withdrawal syndrome (AWS) remains one of the most clinically important acute complications of alcohol use disorder, with severe forms characterized by autonomic hyperactivity, withdrawal seizures and alcohol withdrawal delirium [1]. Withdrawal-related seizures occur in approximately 3% of patients during alcohol withdrawal and typically appear within the first 48 hours after cessation; their occurrence has been described as both a consequence and an independent risk factor for delirium tremens, with somatic comorbidity and a history of prior alcohol-related seizures further increasing risk [2]. Patients presenting with withdrawal-related seizures therefore represent a particularly vulnerable subgroup who require prompt symptom control and seizure prevention while being exposed to a substantial sedative and anticonvulsant drug burden during the first hours of hospitalization [3].

Current clinical guidance emphasizes structured assessment, dynamic monitoring and symptom-guided pharmacotherapy [3]. The Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) is widely used as a validated 10-item instrument for quantifying withdrawal severity and guiding treatment adjustment [4]. In complicated AWS, however, isolated binary outcomes such as recurrent seizures or progression to delirium may be too infrequent in actively treated inpatient samples to serve as sensitive indicators of early treatment strategy. For this reason, integrated measures of symptom burden over time, such as the area under the CIWA-Ar curve, may better capture clinically meaningful differences during the early treatment window.

Benzodiazepines remain the cornerstone of pharmacological management of moderate to severe AWS, including for the prevention of withdrawal seizures and progression to delirium [3, 5]. Anticonvulsants — most commonly carbamazepine and valproate — are frequently used as adjunctive or alternative agents, particularly in patients with a seizure component or in mild to moderate withdrawal in which benzodiazepine sparing is desirable [6, 7]. In routine inpatient practice, the challenge is not simply to select a drug class, but to individualize starting doses, combinations and subsequent titration in a patient whose metabolic capacity, hepatic status, neurological risk and susceptibility to sedation may vary substantially. Pharmacokinetic variability is therefore clinically relevant, particularly for drugs metabolized by polymorphic cytochrome P450 enzymes and for regimens in which sedative and anticonvulsant effects overlap.

Pharmacogenetic testing offers one strategy for improving this individualized decision-making and is increasingly endorsed as a tool for psychopharmacological prescribing [8, 9]. Variants affecting CYP2D6, CYP2C19, CYP3A4, CYP3A5 and drug transporters may alter systemic exposure to psychotropic and anticonvulsant medications. CYP2C19 has particular relevance to AWS pharmacotherapy because it is, together with CYP3A4, a principal enzyme in the biotransformation of diazepam; reduced-function CYP2C19 alleles have been linked to higher diazepam exposure and an increased likelihood of dose-related adverse effects, whereas the *CYP2C19*17* increased-function allele has been associated with reduced steady-state diazepam concentrations in patients with AWS [10]. In the context of complicated AWS, the most immediate clinical value of pharmacogenetic testing may lie not in predicting a dramatic improvement in efficacy, but in reducing avoidable dose-related adverse reactions while preserving adequate control of withdrawal symptoms.

Our previous work in acute alcoholic hallucinosis suggested that pharmacogenetically guided prescribing can improve the safety of inpatient psychopharmacotherapy without compromising clinical efficacy [11]. The present pilot module applied the same methodological logic to a different high-risk clinical population: patients with AWS complicated by seizures. Pharmacogenetic testing was performed in all participants, but only the intervention group received clinically actionable interpretation, whereas the control group received a report of identical format containing neutral standard-patient recommendations. This design was intended to reduce the nonspecific behavioural effect of receiving a report and to isolate the added value of individualized interpretation.

The aim of this pilot randomized controlled trial was to evaluate whether pharmacogenetically guided optimization of pharmacotherapy in patients with AWS complicated by seizures is associated with improved early withdrawal dynamics and a more favourable safety profile compared with standard empiric treatment supported by a neutral report.

2. MATERIAL AND METHODS

2.1. Study Design

This module was conducted as part of a prospective randomized controlled clinical programme evaluating the clinical utility of pharmacogenetic testing in a specialized addiction hospital. The present module focused on pharmacogenetically oriented optimization of pharmacotherapy in patients with AWS complicated by seizures. Methodologically, it followed the logic of our previously published study in acute alcoholic hallucinosis [11]: pharmacogenetic testing was performed in all patients, but clinically actionable interpretation was made available only in the intervention group, whereas control physicians received neutral reports that did not disclose real genotype information.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare (protocol No. 6 from June 9, 2025). All participants provided written informed consent before any study procedures.

This was a pilot, hypothesis-generating study. At the planning stage, reliable data were not available for estimating a clinically meaningful between-group difference in AUC CIWA-Ar among patients with AWS complicated by seizures. The target sample size was therefore based on feasibility considerations within a single specialized centre and was set at 50 patients, with 25 patients per group. Accordingly, all findings, particularly those involving secondary endpoints, should be interpreted as preliminary and as requiring confirmation in larger studies.

2.2. Participants

Eligible patients were adults hospitalized with clinically verified AWS complicated by seizures, corresponding to ICD-10 code F10.31 (alcohol withdrawal state with convulsions). Inclusion criteria were: at least one seizure during the current AWS episode before hospitalization or within the first hours after admission but before randomization and initiation of study pharmacotherapy; baseline CIWA-Ar score of at least 10 points; age 18–65 years; and written informed consent.

Exclusion criteria were acute or decompensated severe somatic disease, structural central nervous system lesion or another established non-alcohol-related cause of seizures, severe hepatic insufficiency, pregnancy or lactation, and established alcohol withdrawal delirium or an acute psychotic syndrome at the time of enrolment.

2.3. Randomization, Masking and Pharmacogenetic Intervention

After biological sampling and initiation of pharmacogenetic testing, patients were randomized 1:1 to the pharmacogenetically guided group or the control group using computer-generated block randomization with fixed blocks of four. The randomization sequence was prepared by a staff member not involved in treatment or outcome assessment. Allocation codes were stored in a protected file and were unavailable to treating physicians or to the outcome assessor until completion of recruitment and primary analysis.

In the intervention group, the treating physician received the true pharmacogenetic report containing the patient-specific test results and personalized recommendations for pharmacotherapy optimization. In the control group, the treating physician received a report of identical format; however, this was a mock report for a standard patient, indicating wild-type genotypes for all tested loci and standard dosing recommendations for all drugs. The true report in the control group was provided only after study completion.

Thus, pharmacogenetic testing was performed at the start of hospitalization in 100% of randomized patients, but the clinical use of the information differed by group. This approach was designed to minimize the influence of the mere act of receiving a report on physician behaviour. Patients were unaware of whether their physician received the true or the neutral report, and the investigator responsible for outcome assessment remained blinded to group allocation.

2.4. PharmacotherapyAapproach

All treatment was delivered in accordance with applicable clinical recommendations for AWS [3] and the local inpatient protocol. In routine clinical practice at the participating unit, the baseline benzodiazepine component for patients with AWS complicated by seizures was bromodihydrochlorphenylbenzodiazepine (Phenazepam), a long-acting 1,4-benzodiazepine that is registered in the Russian Federation and a number of other Commonwealth of Independent States countries but is not approved by the United States Food and Drug Administration or the European Medicines Agency. Phenazepam is metabolized primarily through hepatic cytochrome P450 oxidation, with CYP3A4 as the principal enzyme, and is generally considered approximately equipotent to or modestly more potent than diazepam on a milligram basis. For the purposes of this study, cumulative benzodiazepine burden was expressed in diazepam equivalents using the conversion factor 1 mg phenazepam ≈ 10 mg diazepam, consistent with local pharmacopoeia conventions.

Diazepam was not used as a scheduled course; instead, it was administered mainly as a single dose, usually 10 mg or 20 mg (one or two 2 ml ampoules of the 5 mg/ml formulation used locally), in severe withdrawal and/or when a seizure occurred. Because all included patients had a seizure component, combined therapy with a benzodiazepine and an antiepileptic component was used in all cases. Carbamazepine 600 mg/day was the most common antiepileptic component, consistent with international evidence supporting carbamazepine as an effective option for moderate AWS [6, 7]. Treating physicians usually prescribed carbamazepine in the absence of contraindications and selected an alternative strategy when the pharmacogenetic report or clinical factors suggested that a different or more cautious approach would be preferable. Less frequently, valproic acid or a phenobarbital-containing combination preparation was used. Pagluferal — a Russian Federation–registered fixed combination of phenobarbital, bromisoval, caffeine, papaverine and calcium gluconate — was used at the participating unit as an alternative anticonvulsant regimen in selected cases.

Treating physicians in both groups retained clinical discretion regarding medication selection, combinations and dosing within clinical recommendations and local practice. The study therefore compared two management strategies in the same clinical population — empiric pharmacotherapy versus pharmacogenetically guided optimization — rather than the comparative efficacy of individual drugs.

2.5. Pharmacogenetic Testing

Venous blood for genotyping was collected at admission into VACUETTE tubes (Greiner Bio-One, Austria). Genomic DNA was isolated using standard procedures. Genotyping followed the same laboratory protocol as in the acute alcoholic hallucinosis module [11]. Polymorphic variants were determined by real-time polymerase chain reaction on DTprime 5M1 thermal cyclers (DNA-Technology, Russia) using SNP-Screen kits (Syntol, Russia) based on allele-specific fluorescent probes.

The genotyping panel was identical to that used in the alcoholic hallucinosis module and included *CYP2D6*4 (1846G>A, rs3892097)*, *CYP2C19*2 (681G>A, rs4244285)*, *CYP2C19*17 (806C>T, rs12248560)*, *CYP3A4*1B (392G>A, rs2740574)*, *CYP3A5*3 (6986A>G, rs776746)*, and *ABCB1 c.3435C>T (rs1045642)*. Pharmacogenetic data were processed in the local clinical decision support system (CDSS), which generated personalized recommendations in the PDF format.

Genetic variants were interpreted as markers of probable differences in drug metabolism rate and systemic exposure. Reduced-function alleles were considered potential markers of increased risk for dose-related adverse drug reactions, whereas variants associated with increased metabolic activity were interpreted as possible markers of insufficient exposure and inadequate response at standard doses [9, 10]. Final treatment decisions always remained with the treating physician.

2.6. Efficacy Outcomes

The primary endpoint was the area under the CIWA-Ar curve over the first 72 hours of treatment (AUC CIWA-Ar 0–72 h), calculated using the trapezoidal method on the basis of fixed assessments at 0, 6, 12, 24, 48 and 72 hours. This endpoint was selected as an integrated measure of cumulative withdrawal severity during the early observation period and as a measure more sensitive to differences between treatment strategies than rare binary outcomes such as recurrent seizures.

Secondary efficacy endpoints were time to clinical stabilization, defined as the interval from treatment initiation to the first CIWA-Ar value ≤8 confirmed at the next assessment 24 hours later; unplanned treatment correction, defined as additional non-planned sedative dosing and/or a change in pharmacotherapy due to insufficient AWS symptom control; cumulative dose of medications used for unplanned correction expressed in diazepam equivalents; progression to alcohol withdrawal delirium; and length of hospitalization.

The decision to perform unplanned treatment correction was made by the treating physician on the basis of the clinical picture, current CIWA-Ar values and applicable clinical recommendations. The outcome assessor remained blinded to group allocation. A pre-specified sensitivity analysis used a stricter definition of stabilization that required no subsequent unplanned treatment correction after first reaching CIWA-Ar ≤8.

2.7. Safety Outcomes

Safety was assessed using the UKU Side Effect Rating Scale [12]. Clinically significant adverse events were also recorded, including excessive sedation, marked dizziness, ataxia, impaired coordination, hypotension, laboratory abnormalities, and adverse reactions requiring a change in therapy.

Sedation was assessed using the Ramsay Sedation Scale (RSS) every 6 hours during the first 24 hours and every 12 hours thereafter until 72 hours. RSS ≥5 was considered clinically significant excessive sedation because, at this level, sedation could interfere with neurological examination, oral intake and dynamic clinical assessment; we acknowledge that the RSS was originally developed for the intensive care setting and that the threshold used here was a study-specific operational choice. Laboratory monitoring included alanine aminotransferase, aspartate aminotransferase, sodium, and complete blood count at admission and on days 3 and 7.

To improve transparency, the actual pharmacotherapy delivered in both groups was additionally analysed, including the frequency of individual medications and medication classes, frequency of combination therapy, and cumulative benzodiazepine burden in diazepam equivalents. In the intervention group, adherence to pharmacogenetic recommendations was classified prospectively as full (initial therapy and dosing fully consistent with the report), partial (selected recommendations followed but the regimen modified for clinical reasons), or absent (complete departure from the report).

2.8. Statistical Analysis

Analyses were conducted according to the intention-to-treat principle, including all randomized patients regardless of adherence to the assigned treatment strategy. Distributional assumptions for quantitative variables were assessed using the Shapiro–Wilk test. Quantitative data are presented as mean ± standard deviation or as median [Q1, Q3], depending on distribution. Categorical data are presented as counts and proportions.

For the primary endpoint, between-group comparison was based on AUC CIWA-Ar 0–72 h using Student's t test, with a pre-specified non-parametric sensitivity analysis using the Mann–Whitney test. Secondary quantitative endpoints were analysed using Student's t test or the Mann–Whitney test, as appropriate. For 2 × 2 categorical comparisons, Fisher's exact test was used with calculation of odds ratios and 95% confidence intervals. Hardy–Weinberg equilibrium was assessed for each genetic marker using the chi-square test, with the exact test substituted for *CYP3A5*3* because of the high minor allele frequency and low expected counts in some genotype cells.

CIWA-Ar change over time was analysed using a mixed model for repeated measures including values at 6, 12, 24, 48 and 72 hours after treatment initiation. The baseline CIWA-Ar score was used as a covariate and was not included among the repeated dependent measurements. Fixed effects included group, time and group-by-time interaction; baseline CIWA-Ar, age and duration of the last drinking episode were entered as covariates. Several covariance structures were pre-specified, including unstructured, compound symmetry, Toeplitz and first-order autoregressive structures; the final model used the first-order autoregressive structure selected by the lowest Akaike information criterion. Parameters were estimated using restricted maximum likelihood, and degrees of freedom were calculated using the Kenward–Roger correction.

The proportion of missing post-baseline CIWA-Ar observations was quantified. The primary analysis assumed that missingness depended on observed data. A pattern-mixture sensitivity analysis was also performed to examine the robustness of the findings under alternative missing-data assumptions.

Time to clinical stabilization was analysed using Kaplan–Meier curves and the log-rank test. The Benjamini–Hochberg correction for multiple comparisons [15] was applied separately within three pre-specified families of tests: secondary efficacy endpoints, safety endpoints, and additional comparisons of CIWA-Ar at individual time points.

3. RESULTS

3.1. Baseline Characteristics

Fifty patients were randomized: 25 to pharmacogenetically guided optimization and 25 to the control group. The groups did not differ significantly in age, sex, baseline CIWA-Ar severity, duration of alcohol misuse or duration of the last drinking episode (**Table 1**).

Table 1. Baseline characteristics of the study population.

Variable	PGx-guided group (n = 25)	Control group (n = 25)	*p*-value
Age, years (M ± SE)	45.8 ± 7.2	46.6 ± 7.5	*0.71*
Male sex, n (%)	21 (84%)	22 (88%)	*> 0.999*
Baseline CIWA-Ar score, points (M ± SE)	20.3 ± 3.1	20.8 ± 3.3	*0.58*
Duration of alcohol misuse, years (M ± SE)	13.9 ± 5.8	14.2 ± 6.0	*0.86*
Duration of last drinking episode, days (Me [Q1, Q3])	9 [7, 12]	10 [7, 13]	*0.64*

3.2. Actual Pharmacotherapy

The structure of prescribed pharmacotherapy reflected routine practice in a specialized addiction hospital. In all patients, the benzodiazepine component was a phenazepam-containing regimen, and all patients received combined therapy with a benzodiazepine and an antiepileptic drug. Carbamazepine 600 mg/day remained the most frequent antiepileptic component in both groups, although it was not used in every case because alternative therapy was selected in some patients for clinical or pharmacogenetic reasons. No between-group differences in the actual treatment structure reached statistical significance, and this conclusion was unchanged after Benjamini–Hochberg correction (**Table 2**).

Table 2. Actual pharmacotherapy delivered during the study.

Variable	PGx-guided group (n = 25)	Control group (n = 25)	*p*-value
Phenazepam-containing regimen, n (%)	25 (100%)	25 (100%)	—
Combined benzodiazepine + antiepileptic therapy, n (%)	25 (100%)	25 (100%)	—
Carbamazepine 600 mg/day, n (%)	20 (80%)	23 (92%)	0.41
Valproic acid, n (%)	3 (12%)	1 (4%)	0.61
Pagluferal, n (%)	2 (8%)	1 (4%)	>0.999
Diazepam 10 mg single dose, n (%)	4 (16%)	5 (20%)	>0.999
Diazepam 20 mg single dose, n (%)	2 (8%)	3 (12%)	>0.999
Cumulative benzodiazepine burden, mg diazepam equivalents (Me [Q1, Q3])	25 [20, 35]	30 [20, 40]	0.18

3.3. Genotype Distribution and Adherence to Pharmacogenetic Recommendations

For most markers, Hardy–Weinberg equilibrium was assessed using the chi-square test; for *CYP3A5*3*, the exact test was used because of the high minor allele frequency and low expected counts in some genotype cells. No substantial deviations from Hardy–Weinberg equilibrium were detected (**Table 3**).

In the intervention group, full adherence of prescribed therapy to pharmacogenetic recommendations was observed in 22 of 25 patients (88%), partial adherence in 2 patients (8%), and no adherence in 1 patient (4%). The most common practical implementation of the report was not radical replacement of the entire regimen, but avoidance of routine carbamazepine use in favour of an alternative antiepileptic strategy or more cautious titration.

Table 3. Distribution of pharmacogenetic markers by group.

Group	Genetic Marker	Variant	rsID	Genotype AA, %	Genotype AB, %	Genotype BB, %	HWE χ^2	HWE *p*-value
PGx-guided	*CYP2D6*4*	1846G>A	rs3892097	20	5	0	0.31	*0.58*
PGx-guided	*CYP2C19*2*	681G>A	rs4244285	23	2	0	0.04	*0.83*
PGx-guided	*CYP2C19*17*	806C>T	rs12248560	17	7	1	0.07	*0.79*
PGx-guided	*CYP3A4*1B*	392G>A	rs2740574	21	4	0	0.19	*0.66*
PGx-guided	*CYP3A5*3*	6986A>G	rs776746	0	4	21	0.19	*0.66*
PGx-guided	*ABCB1 c.3435C>T*	3435C>T	rs1045642	8	14	3	0.69	*0.40*
Control	*CYP2D6*4*	1846G>A	rs3892097	22	4	0	0.18	*0.67*
Control	*CYP2C19*2*	681G>A	rs4244285	22	3	0	0.10	*0.75*
Control	*CYP2C19*17*	806C>T	rs12248560	15	8	2	0.38	*0.54*
Control	*CYP3A4*1B*	392G>A	rs2740574	24	1	0	0.01	*0.92*
Control	*CYP3A5*3*	6986A>G	rs776746	0	4	21		*0.67*
Control	*ABCB1 c.3435C>T*	3435C>T	rs1045642	11	10	4	0.43	*0.51*

Note: *[1] HWE = Hardy–Weinberg equilibrium. For CYP3A5*3, an exact test was used; for other markers, the chi-square test was used.*

3.4. CIWA-Ar Dynamics

Both groups showed a progressive reduction in AWS symptoms over time. Baseline CIWA-Ar scores were comparable and were used as a covariate in the longitudinal model. In the pharmacogenetic group, mean CIWA-Ar scores were 17.5 ± 3.2, 14.7 ± 3.0, 11.8 ± 2.8, 8.1 ± 2.5 and 5.9 ± 2.1 at 6, 12, 24, 48 and 72 hours, respectively. In the control group, the corresponding values were 18.0 ± 3.4, 15.6 ± 3.2, 13.4 ± 3.0, 10.1 ± 2.8 and 7.8 ± 2.5.

The proportion of missing post-baseline CIWA-Ar values was 3.2%. The mixed model for repeated measures, adjusted for baseline CIWA-Ar, age and duration of the last drinking episode, showed a statistically significant group-by-time interaction: F(4, 176) = 2.64; p-value = 0.036 using the Kenward–Roger correction. Post-hoc comparisons with Benjamini–Hochberg correction indicated significant between-group differences at 48 hours (raw p = 0.021; adjusted p = 0.041) and 72 hours (raw p-value = 0.009; adjusted p-value = 0.028). The direction of the effect was preserved in the pattern-mixture sensitivity analysis.

3.5. Primary and secondary endpoints

The primary endpoint, AUC CIWA-Ar 0–72 h, was 790 ± 175 score-hours in the pharmacogenetic group and 905 ± 185 score-hours in the control group. The Shapiro–Wilk test did not indicate a significant departure from normality for this endpoint (W = 0.97; p-value = 0.29). The between-group difference was statistically significant (p-value = 0.032), and the non-parametric Mann–Whitney sensitivity analysis preserved both the direction and the significance of the effect (p = 0.041).

Median time to clinical stabilization was 50 [42, 61] hours in the pharmacogenetic group and 63 [52, 75] hours in the control group; the unadjusted log-rank p value was 0.018 and the Benjamini–Hochberg adjusted p value was 0.036. A sensitivity analysis using the stricter stabilization definition preserved the direction of the difference.

The cumulative dose of medications used for unplanned treatment correction was lower in the pharmacogenetic group: 10 [0, 20] mg diazepam equivalents versus 20 [10, 30] mg in the control group (raw p-value = 0.019; adjusted p-value = 0.038). Median length of hospitalization was 7 [6, 8] days versus 8 [7, 10] days, respectively (raw p-value = 0.027; adjusted p-value = 0.041).

Unplanned treatment correction was required in 5 of 25 patients (20%) in the pharmacogenetic group and 10 of 25 patients (40%) in the control group (OR 0.38; 95% CI 0.11–1.33; p-value = 0.22). Progression to alcohol withdrawal delirium occurred in 1 patient (4%) in the pharmacogenetic group and 3 patients (12%) in the control group (p-value = 0.61).

A subgroup analysis among patients who received carbamazepine in both groups (pharmacogenetic group, n = 20; control group, n = 23) preserved the direction of the primary endpoint effect: AUC CIWA-Ar 0–72 h was 785 ± 170 versus 892 ± 182 score-hours, respectively (p-value = 0.048). This finding suggests that the observed advantage was not explained solely by switching some patients in the intervention group away from carbamazepine but may also reflect broader individualization of therapeutic strategy.

The five intervention-group patients in whom an alternative regimen was selected instead of carbamazepine received valproic acid in three cases and Pagluferal in two cases. In these patients, the decision to depart from the routine regimen was based on the combination of clinical factors and pharmacogenetic profile.

3.6. Safety

The total UKU score on day 3 was 5 [3, 7] in the pharmacogenetic group and 8 [6, 11] in the control group (raw p-value = 0.009; adjusted p-value = 0.021). On day 5, the corresponding values were 3 [2, 5] and 6 [4, 8] (raw p-value = 0.014; adjusted p-value = 0.028).

At least one clinically significant adverse event was recorded in 6 of 25 patients (24%) in the pharmacogenetic group and 14 of 25 patients (56%) in the control group (OR 0.25; 95% CI 0.07–0.88; raw p-value = 0.021; adjusted p-value = 0.041). Given the pilot design and moderate sample size, this finding should be interpreted as a signal of better tolerability requiring confirmation in larger samples.

Excessive sedation (RSS ≥5) occurred in 2 patients (8%) in the pharmacogenetic group and 8 patients (32%) in the control group (p = 0.074). Ataxia, marked dizziness or impaired coordination occurred in 3 (12%) and 8 (32%) patients, respectively (p = 0.17). ALT and/or AST elevation greater than two times the upper limit of normal was recorded in 1 patient (4%) in the pharmacogenetic group and 3 patients (12%) in the control group (p-value = 0.61). Hyponatraemia below 135 mmol/L occurred in 0 and 2 patients (8%), respectively (p-value = 0.49). No life-threatening adverse reactions or deaths were recorded.

3.7. Sensitivity Analysis

A per-protocol sensitivity analysis including only intervention-group patients with full adherence to pharmacogenetic recommendations preserved the direction of the main effects, with lower AUC CIWA-Ar, lower UKU scores and fewer clinically significant adverse events compared with the control group. Because the module was pilot and hypothesis-generating, these findings should be viewed as supporting the robustness of the observed signal rather than as definitive evidence of clinical superiority.

4. DISCUSSION

This pilot randomized trial evaluated the clinical relevance of pharmacogenetically guided pharmacotherapy optimization in patients with AWS complicated by seizures in a real-world inpatient addiction setting. The central methodological point is that the study did not compare individual medications. Rather, it compared two strategies for treating the same high-risk clinical population: standard empiric pharmacotherapy and pharmacotherapy optimized using pharmacogenetic information. This framing is clinically important because everyday inpatient decisions involve selecting and titrating the most appropriate regimen for a particular patient rather than identifying a universally superior drug.

The findings suggest that a pharmacogenetically guided approach may be associated with a more favourable early clinical course. The intervention group had a lower cumulative CIWA-Ar burden over the first 72 hours, faster achievement of clinical stabilization, lower rescue medication burden and shorter hospitalization. Because this was a pilot study, these efficacy findings should be considered hypothesis-generating; nevertheless, the direction of effects was coherent across the primary endpoint, the longitudinal CIWA-Ar dynamics and several clinically meaningful secondary outcomes.

The distinction between statistical and clinical significance requires careful interpretation. Absolute between-group differences in CIWA-Ar scores at individual time points were moderate and became most evident by 48 hours, when mean values approached the transition from moderate to milder withdrawal. The clinical meaning of the effect is therefore unlikely to be a sudden transformation of the withdrawal course; rather, it may reflect a more rapid movement into a safer clinical range, with less need for additional sedative correction. This is particularly relevant for patients with AWS complicated by seizures, in whom the goal is not only to prevent recurrent seizures but also to reduce overall withdrawal severity rapidly while avoiding excessive medication burden.

The selection of AUC CIWA-Ar 0–72 h as the primary endpoint deserves explicit comment. Recurrent withdrawal seizures were deliberately not used as the primary outcome. Under active inpatient treatment with combined benzodiazepine and antiepileptic therapy, recurrent seizures are uncommon, and a sample of 50 patients would be markedly underpowered to detect between-group differences in this binary outcome. Although recurrent seizures are arguably the most clinically dramatic event in this population, an integrated measure of cumulative withdrawal severity is more sensitive to differences in early treatment strategy and aligns with the symptom-driven monitoring approach recommended in current guidelines [3, 13]. AUC CIWA-Ar therefore provides a more granular and statistically tractable signal of treatment-strategy effects than rare hard outcomes alone.

Importantly, the observed differences cannot be explained by a gross imbalance in actual pharmacotherapy. Both groups were treated within the same clinical recommendations and local protocol. Phenazepam was used as the core benzodiazepine component, diazepam was administered mainly as single-dose rescue treatment in severe withdrawal and/or seizure situations, and all patients received combined benzodiazepine and antiepileptic therapy. Carbamazepine remained the most common antiepileptic drug in both groups. The pharmacogenetic intervention therefore primarily influenced the selection among clinically acceptable options and the caution of titration, rather than whether active treatment was given at all.

The safety findings may be the most clinically important aspect of the study. The pharmacogenetic group had lower UKU scores on days 3 and 5 and fewer clinically significant adverse events. This pattern is consistent with the pharmacokinetic rationale of the intervention. If the treating physician receives early information about genetically influenced metabolism and likely drug exposure, the initial regimen can be selected and titrated more cautiously, excessive drug accumulation can be avoided, and alternative strategies can be chosen when appropriate [9, 10]. In this framework, pharmacogenetic testing functions primarily as a tool for reducing preventable treatment-related harm while maintaining adequate symptom control.

From a practical perspective, the safety profile may be the principal clinical argument for implementing pharmacogenetic testing in a specialized addiction hospital. Patients with AWS complicated by seizures are at high baseline risk: they often require intensive medication adjustment within the first hours of hospitalization and their clinical state can change rapidly. In this context, even a moderate reduction in adverse drug reactions has independent value because it

lowers the probability of forced regimen changes, simplifies clinical observation and supports more rapid clinical stabilization.

The present results extend our previous work in acute alcoholic hallucinosis [11]. In that earlier module, pharmacogenetic guidance primarily improved tolerability without producing a clear efficacy advantage. In the present AWS-with-seizures module, signals were observed not only for safety but also for the primary integrated measure of withdrawal severity and time to stabilization. This difference may reflect the distinctive clinical dynamics of AWS, where changes in sedative and anticonvulsant exposure can influence both symptom control and adverse effects during a short and intensive early treatment period.

Another strength of the study is the high adherence to pharmacogenetic recommendations in the intervention group. This supports the conclusion that the intervention was implemented in actual clinical practice and was not merely a laboratory procedure. At the same time, the intention-to-treat analysis preserves pragmatic relevance, because in real inpatient care the final decision remains with the physician and may change as the patient's condition evolves.

5. LIMITATIONS

Several limitations should be considered. First, the sample size was modest and the study was explicitly pilot and hypothesis-generating. This limits statistical power, particularly for rare outcomes such as progression to delirium, recurrent seizures, severe adverse reactions and individual adverse event categories. Secondary endpoints should therefore be interpreted cautiously.

Second, although the study used randomization, matched report formats and blinded outcome assessment, the influence of physician clinical judgement cannot be completely eliminated. This is particularly relevant to unplanned treatment correction, which is inherently more dependent on clinician decision-making than AUC CIWA-Ar or laboratory parameters. The identical report format in both groups and assessor blinding reduce but do not remove this source of potential bias.

Third, the genotyping panel was pharmacokinetically focused and did not cover all potentially relevant genetic mechanisms. Pharmacodynamic markers and broader genetic predictors of treatment response were not included. This focus was intentional, because the study was designed as a practical model of medication-metabolism-guided optimization suitable for routine inpatient care; future studies could evaluate whether broader panels add incremental clinical value.

Fourth, the study did not include a formal economic evaluation. The cost-effectiveness of pharmacogenetic testing in specialized addiction hospitals therefore remains to be determined.

Fifth, the single-centre design and the specific local pharmacotherapy practice — in particular the use of phenazepam as the baseline benzodiazepine — limit direct generalizability to settings in which diazepam, lorazepam, chlordiazepoxide or oxazepam are routinely used as first-line agents, and to settings with different anticonvulsant practices, monitoring intensity and decision-support availability. The pharmacokinetic logic of the intervention should nevertheless extend to other CYP2C19/CYP3A4 substrates commonly used in AWS, including diazepam itself [10].

6. FUTURE DIRECTIONS

Further research should test these findings in larger multicentre trials with adequate power for both efficacy and safety endpoints. Future studies should also examine whether the clinical benefit of pharmacogenetic guidance is driven primarily by titration within the same drug strategy or by switching to alternative regimens in genetically vulnerable patients. Combining pharmacogenetic testing with therapeutic drug monitoring may further improve the precision of individualized treatment in complicated AWS.

7. CONCLUSION

In this pilot randomized controlled trial, pharmacogenetically guided pharmacotherapy optimization in patients with AWS complicated by seizures was associated with lower cumulative withdrawal severity during the first 72 hours, faster clinical stabilization, lower rescue medication burden and a more favourable safety profile. Even in the absence of significant differences in rare hard outcomes, the reduction in overall withdrawal burden and clinically significant adverse events suggests that pharmacogenetic testing may be a promising tool for safer individualized management of complicated AWS. These findings require confirmation in larger multicentre studies.

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Data Availability Statement: The data that support the findings of this study are available on reasonable request from the corresponding author.

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