SVOA Neurology
e-ISSN 2753-9180
ScienceVolks Open Access
Conceptual Paper

Can Lidocaine Preserve Motor Neurons in ALS?

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DOI: https://doi.org/10.58624/SVOANE.2026.07.047

Received: October 14, 2026

Published: November 11, 2026

Citation: Kuyucu M. Can Lidocaine Preserve Motor Neurons in ALS? *SVOA Neurology* 2026, 7:6, 375-384. doi: 10.58624/SVOANE.2026.07.047

Abstract

Background: Altered excitability in amyotrophic lateral sclerosis (ALS) may promote injury or represent protective adaptation. Sodium-channel inhibition therefore cannot be assumed to preserve motor neurons, and available ALS studies do not establish lidocaine-mediated neuroprotection.

Hypothesis: In injured ALS spinal motor neurons with independently confirmed excess persistent sodium current, partial inhibition by lidocaine may reduce ionic and energetic stress while retaining physiological repetitive firing. The critical prediction is a reproducible exposure window in which survival improves without unacceptable functional loss. The comparative research question is whether lidocaine can provide greater joint survival–function benefit than mexiletine, or equally protective inhibition with better functional recovery or a wider exposure margin. These are competing experimental possibilities, not established advantages. Current-directed and activity-matched controls should distinguish reduced sodium loading from general activity suppression. Systemic development additionally requires measured unbound spinal exposure, retained motor-unit output, and acceptable repeated-dose safety.

Conclusions: A focused human motor-neuron experiment should first test engagement, survival, and repetitive firing under measured lidocaine and mexiletine profiles. Independent replication, exposure validation, and motor-unit assessment must precede animal disease-modification studies. Advancement requires confidence bounds supporting worthwhile survival benefit and excluding unacceptable functional loss. Adequately precise failure with verified engagement challenges the tested cellular claim; an inaccessible protective spinal profile rejects systemic development. Equivalent benefit without a meaningful comparative advantage favors mexiletine for further development. The framework defines falsifiable questions rather than evidence supporting lidocaine treatment for ALS.

Keywords: *amyotrophic lateral sclerosis; lidocaine; persistent sodium current; comparative pharmacology; unbound exposure; motor-neuron preservation*

1. Introduction and Biological Rationale

Altered excitability in amyotrophic lateral sclerosis (ALS) can promote injury or compensate for other deficits [1]. The relevant therapeutic question is whether partial inhibition of excess persistent sodium current can preserve vulnerable motor neurons without compromising physiological activity. We propose lidocaine as a comparative experimental probe and distinguish cellular preservation from the separate feasibility of systemic repurposing.

Reported systemic lidocaine use in ALS includes a perioperative case describing short-term analgesia and tolerability [2]. Concurrent treatment limits attribution; the report establishes neither disease modification nor chronic safety. Axonal threshold-tracking studies infer altered conductances and associations with survival [3,4,5], but do not directly quantify spinal somatic persistent current or demonstrate benefit from its inhibition.

Experimental evidence cautions against indiscriminate excitability suppression. Mutant-SOD1 cultures show increased persistent sodium current with conductance-dependent effects on firing [6]. Retigabine improved survival in selected patient-derived SOD1 cultures with potassium-current deficits [7]. Early hyperexcitability in neonatal SOD1-G93A mice occurred in relatively resistant slow-type neurons [8]. Other preparations show hypoexcitability before denervation, activity-dependent protection, or progression toward reduced electrical output [9,10,11]. Hyperexcitability, excess sodium current, and vulnerability are distinct phenotypes.

TDP-43 studies further complicate sodium-specific explanations. Human KCNQ2 mis-splicing impaired potassium-channel function and caused hyperexcitability; the examined mouse systems lacked the same exon-skipping event [12]. A TDP-43 mouse model instead showed reversible spinal hyperexcitability with somatic and axon initial segment remodeling [13]. Cryptic splicing affecting excitability and synaptic genes also impaired human neuronal function, with postmortem validation in frontotemporal dementia tissue [14]. Sodium-current inhibition could compensate for potassium-current loss without correcting the initiating lesion.

Homeostatic adaptation warrants repeated-exposure testing. β-Adrenergic regulation remained operative in presymptomatic SOD1 mice [15], while 10-day riluzole treatment increased motoneuron excitability and polysynaptic inputs in a separate SOD1-G93A study [16]. Neither tested lidocaine; both caution against extrapolating acute inhibition to sustained treatment.

This narrative hypothesis distinguishes ALS-specific findings, indirect pharmacological evidence, and proposed experiments. The literature assessment is not a systematic review.

2. The Hypothesis and Its Biological Contribution

We hypothesize that partial lidocaine-mediated inhibition of independently confirmed excess persistent sodium current improves survival of injured ALS spinal motor neurons while retaining physiological repetitive firing. Partial inhibition denotes measured reduction toward a matched reference range with residual current. Neither preferential persistent-current inhibition nor a universal block percentage is assumed. The protective window must be defined jointly by exposure, engagement, survival, and function. Motor-unit preservation additionally requires axonal conduction, neuromuscular junction (NMJ) transmission, and muscle output; systemic development requires safely reproducible spinal exposure.

The proposed sequence links excess sodium entry to ionic and energetic stress and injury. Competing explanations include compensatory current upregulation, degeneration-related conductance changes, general reduction in energy demand, and another drug target. Physiological repetitive firing also promotes use-dependent block. Current reduction followed by survival therefore cannot alone establish mechanism or correction of upstream protein or RNA pathology.

The biological prediction is that injurious sodium entry can be reduced while activity required for neuronal maintenance is retained. The methodological contribution is to test this prediction under one measured exposure schedule using joint survival–function outcomes. Rigorous design does not itself establish biological novelty. Cellular validity, comparative value, and systemic feasibility can yield different answers.

Support would require current reduction preceding reduced sodium-associated stress, subsequent preservation with retained firing, and replication of a locked schedule in independent donors. Current-directed interventions should reproduce benefit; activity-matched controls should test general suppression as an alternative. Matching spike counts alone does not match sodium entry or off-target effects. Simultaneous toxin protection establishes prevention; rescue requires treatment after injury emerges.

Phenotype enrichment tests a conditional mechanism rather than defining a clinical subgroup. Report qualification frequency and stability, and compare severity-matched injured preparations without excess current. A prespecified phenotype interaction supports specificity but cannot exclude correlated maturity or subtype differences without mechanistic controls.

3. Evaluation of the Hypothesis

Astrocyte-conditioned-medium experiments support sodium-channel modulation but did not test lidocaine. Mutant-SOD1 astrocyte medium increased persistent current, firing, and calcium transients before motor-neuron loss; simultaneous mexiletine or riluzole prevented death [17].

Tetrodotoxin failed to provide significant rescue and reduced control survival, challenging the assumption that stronger block is protective. Related experiments associated sodium-channel blockade with reduced nitroxidative injury [18] and mitochondrial–reactive oxygen species–c-Abl signaling [19]. These largely overlapping preparations support plausibility, not independent lidocaine validation or rescue of established degeneration.

State- and use-dependent lidocaine block in cardiac and sensory preparations does not establish ALS potency [20,21]. Persistent current also supports function: riluzole abolished sustained repetitive firing in large cultured mouse spinal neurons despite retained responses to brief inputs [22]. A protective window cannot be inferred from preserved isolated spikes.

Reported lidocaine potency varies markedly: nominal 1 μmol/L preferentially reduced persistent current in a small rat CA1 sample [23], while late sensory-current half-inhibition occurred near 58 μmol/L [24]; human sensory NaV1.9 was comparatively insensitive [25]. These observations cannot define ALS potency. Depression of motor-neuron excitability and ventral-root reflexes further motivates functional testing [26].

Microglial NF-κB inhibition prolonged survival in SOD1 mice [27], but does not establish lidocaine benefit. Lidocaine reduced injury in stimulated microglial cells, whereas cytokine experiments used QX314 [28]. Repeated systemic exposure caused glial, synaptic, and cognitive abnormalities in aged mice [29]. Millimolar exposure injured mitochondria in neuronal cell lines [30,31]. These are hazards, not adult ALS toxicity thresholds. Astrocytes require molecular and functional characterization rather than binary A1/A2 labels [32].

Lidocaine injured developing rat motor neurons across concentration–duration conditions [33] and reversibly inhibited sensory-neuron axonal transport, with half-inhibition near 10 μmol/L [34]. Cross-preparation comparisons cannot calculate a therapeutic window, but justify delayed mitochondrial, axonal, and washout assessments.

ALS-related evidence links astrocytes to disrupted motor-neuron autophagy [35] and impaired mitophagy to NMJ denervation [36]. These findings motivate safety endpoints, not lidocaine efficacy claims. Local lidocaine–kainic acid co-administration protected a non-ALS spinal excitotoxicity model [37], without establishing systemic efficacy or rescue after established injury.

4. Comparative Pharmacology and the Pharmacokinetic Rationale

4.1 Why Test Lidocaine?

Mexiletine is the principal comparator because of related pharmacology and ALS cellular evidence. A 60-participant, 12-week trial reduced cramps without a detected progression effect, but could not exclude important differences [38]. A 20-participant, 4-week trial yielded mixed excitability findings [39]. Flecainide did not significantly slow decline on the revised ALS Functional Rating Scale in the 54-participant FANS pilot [40]. Riluzole has randomized survival evidence without establishing sodium-current inhibition as its mediator [41]; ezogabine changed short-term excitability measures [42]. Pharmacodynamic change is not disease modification.

The comparative research question is: can lidocaine provide greater joint survival–function benefit than mexiletine, or equal protection with better functional recovery or a wider useful exposure range? These are unproven possibilities. Compare matched persistent-current engagement and independently optimized schedules under identical functional constraints. Equal nominal concentrations are inadequate. A recovery advantage alone supports experimental utility; systemic development additionally requires protection, feasible delivery, and repeated-dose safety. Equivalent benefit with greater burden favors mexiletine.

Distinguish clearance from channel recovery and delayed injury. In cells, verify defined concentration declines before comparing restoration of sustained firing after engagement-matched inhibition; faster apparatus washout cannot establish superiority. Separately replay each drug's measured in vivo parent–metabolite profile to assess practical recovery and repeated-cycle impairment. Any advantage requires independent donor confirmation.

4.2 Exposure as a Separate Translational Hypothesis

Human studies inform sampling rather than an ALS dose [43,44]. After a surgical bolus, cerebrospinal fluid (CSF) concentrations were approximately 6–8% of plasma from 15 min onward, without significant individual correlation [43]. Subcutaneous administration in 10 neurological patients produced delayed lumbar CSF and monoethylglycinexylidide (MEGX) penetration [45]. Neither acute distribution nor the postoperative consensus limit of 24 h establishes chronic ALS tolerability [46].

The unbound fraction of lidocaine varies with α1-acid glycoprotein concentration [47]. A postoperative model separated total and unbound concentrations but used literature-derived pediatric binding-protein data [48]; parent–metabolite modeling also identified time-dependent postoperative clearance [44]. Direct repeated-dose measurements of binding, physiological covariates, and total/unbound exposure are therefore necessary. Surgical plasma targets cannot define ALS spinal exposure.

The bridge must reproduce the cellular profile preserving survival and function. Pair unbound plasma/CSF measurements, validated spinal extracellular sampling where feasible, and electrophysiological engagement across onset, maintenance, peaks, troughs, and withdrawal. Validate recovery, binding, stability, pH, and sampling injury. Brain residual-blood correction requires spinal validation [49]. CSF and total homogenate cannot substitute for free spinal exposure, itself a surrogate for channel-site exposure. Quantify parent lidocaine, MEGX, and glycinexylidide; reported metabolite GlyT1 inhibition supports testing measured mixtures [50].

Use consistent free-concentration units and matrix-specific assay validation. Where direct sampling is infeasible, model estimates require explicit uncertainty and independent engagement confirmation. Uncertainty spanning engagement and impairment boundaries makes feasibility indeterminate.

Build the bridge bidirectionally: identify protective cellular profiles, measure achievable animal profiles, and replay observed parent–metabolite schedules in cells. Repeated-dose models should estimate distribution, effect delays, accumulation, and recovery, then undergo independent validation. Compare continuous and intermittent schedules using unbound peaks, troughs, cumulative exposure, and time within the useful window. Similar mean exposure can conceal different impairment.

This is an exposure-validation strategy, not evidence that a protective concentration is attainable. Any comparative advantage must survive realistic profiles and delivery burden. Neither bath potency nor acute surgical concentrations justify an ALS regimen.

5. Empirical Tests and Decision Criteria

5.1 A Discriminating Cellular Experiment

The first decisive experiment is a randomized, blinded comparison of vehicle, lidocaine, mexiletine, and benchmark riluzole in qualified patient-derived spinal motor neurons. Randomize within donor and differentiation blocks; donors provide biological replication. Document sex, genotype, maturation, and baseline injury. Initial SOD1 preparations should be followed by sporadic ALS donors, available isogenic controls, and unrelated healthy controls. Confirmation requires new donors, independent batches, locked schedules, and a prespecified analysis.

Qualification must precede treatment and establish identity, maturity, ongoing injury, and reproducibly increased persistent current. Record absolute current, capacitance-normalized density, voltage dependence, cell size, leak, and voltage-control quality; characterize subtype. Matched sister cultures permit qualification without selecting recorded survivors. Independent calibration must define eligibility, with injured current-negative preparations as specificity controls. Report all qualification failures.

Begin after measurable injury and excess current emerge. A limited concentration–duration map should measure free medium exposure, persistent/transient currents, sustained repetitive firing, longitudinal survival, and recovery. Control holding potential, pulse history, temperature, and recording quality. Physiological demand testing must extend beyond isolated spikes. The question is whether any locked profile improves joint survival–function over vehicle and how it compares with mexiletine. Broader systemic studies follow only after confirmation.

Account for binding, adsorption, and stability in medium. Validate minimally disruptive longitudinal activity against endpoint electrophysiology; use parallel cells for destructive current measurements. Demonstrate assay responsiveness with an independently validated protective control. Promising schedules then require sodium, calcium, energetic, mitochondrial, and axonal assessments. Simultaneous toxin exposure remains a separate prevention arm.

5.2 Preservation Requires Survival and Function

The primary cellular estimand is the between-group difference in survival probability at a fixed time among pretreatment-identified neurons. Longitudinal tracking and orthogonal death measures should avoid metabolic-assay artifacts. A key joint endpoint is the probability of remaining alive and meeting validated firing criteria. Survivor-only functional analysis introduces selection bias. Death fails the joint endpoint; missing recordings require sensitivity analyses, including conservative failure assumptions. Compartmentalized motor-neuron–muscle preparations must subsequently verify conduction, NMJ transmission, and contraction.

Before confirmation, calibrate minimum worthwhile survival gain, maximum acceptable functional loss, joint-outcome threshold, comparative margin, and safety rules. Specify firing metric, time point, confidence level, and donor sample size. Numerical margins require independent reproducibility and biological calibration, not favorable treatment responses. Donor-based power and hierarchical analyses should address clustering, batches, heterogeneity, and missingness. Prespecified sequential testing should control multiplicity across survival, functional retention, joint benefit, and comparative claims.

5.3 Mechanistic Attribution and Decision Rules

Advancement requires the lower confidence bound for survival gain to exceed its minimum worthwhile margin, and the functional-change lower bound to remain above the negative acceptable-loss margin. The joint endpoint must pass its threshold with engagement and no safety stopping event. Independent donors must replicate benefit. Current-directed and activity-matched interventions test attribution; current restoration may test necessity, but genetic off-target effects and acute dynamic-clamp limitations remain. Temporal stress-marker changes support causality without proving it.

With verified engagement, responsive assays, and adequate duration, an upper confidence bound below the minimum worthwhile gain rejects the tested cellular claim; an interval spanning the margin is indeterminate. Unacceptable functional loss or a predefined safety event rejects the regimen despite improved survival. Protection without intended current change suggests another mechanism. Cellular benefit without safe spinal exposure rejects systemic development. Washout distinguishes reversible impairment from persistent injury. Report failed schedules; post hoc analyses of responder subgroups remain exploratory. Table 1 summarizes the decisions.

Table 1. Discriminating tests and decision criteria

Question	Discriminating test	Decision
Cellular window	Verified current engagement and calibrated repetitive firing under a measured free-exposure profile.	Proceed to survival testing only if function is retained; functional block rejects the schedule.
Independent preservation	Locked profile in new donors; survival, functional retention, and joint endpoint with prespecified confidence bounds.	Advance only if all confirmatory gates pass; precise failure rejects the claim, imprecision is indeterminate.
Mechanism and comparator	Matched engagement and optimized profiles; verified withdrawal kinetics, joint benefit, and repeated-cycle recovery.	Confirm an independent survival–function or protection-plus-recovery advantage; equal benefit without practical advantage favors mexiletine.
Exposure bridge	Measured unbound spinal parent–metabolite profiles, direct engagement, cellular replay, and repeated-dose safety.	Unsafe or inaccessible exposure stops systemic development despite cellular benefit.
Disease modification	Powered survival experiment with all randomized animals, concordant function and pathology, and independent replication.	Advance only with replicated preservation and acceptable safety; physiological change alone is insufficient.

5.4 Testing Systemic Feasibility Before Disease Modification

Before efficacy testing, qualify the intended animal model's current phenotype and function. Compare disease-model and wild-type animals of both sexes during repeated dosing. Validate formulation, delivery, absorption, and parent–metabolite profiles. Intravenous dosing may provide a reference; sustained subcutaneous delivery requires validation. Pair exposure, engagement, and safety where feasible, using matched cohorts for terminal measurements. Monitor rhythm, respiration, conduction, motor output, arousal, weight, and delayed injury. Group-average engagement cannot override serious individual safety events.

Only replicated cellular protection and feasible exposure justify long-term experiments under ALS design guidance [51] and ARRIVE reporting standards [52]. Use concealed allocation, blinding, sex-balanced cohorts, and prespecified exclusions. Begin at a defined symptomatic milestone while the phenotype persists. Power one primary endpoint, preferably survival to uniform humane criteria, and analyze all randomized animals, including suspected toxicity deaths. Require supporting motor/respiratory function, NMJ integrity, and neuron counts. Measure analgesia/arousal without automatic adjustment for post-treatment variables. Verify function during exposure and after justified washout. Replicate in a distinct qualified model; human preparations remain necessary for species-specific splicing [12]. A factorial riluzole comparison should assess added benefit and impairment before clinical development.

6. Implications and Translational Limitations

Protection without comparative advantage may justify an experimental probe but not preferred repurposing. A wider cellular window with inaccessible spinal exposure stops systemic development. Precise failure of both agents challenges the tested modulation schedule in the qualified domain, not all sodium-channel interventions. Alternative-target protection requires a different mechanistic hypothesis.

The framework concerns spinal lower motor neurons, not established benefit throughout multisystem ALS. Patient-derived preparations incompletely reproduce aging and mature motor units. Phenotype prevalence and clinical relevance remain unknown; peripheral/cortical excitability is not a validated selection marker. Chronic delivery, interactions, metabolites, and limited respiratory reserve remain unresolved. Translation requires a safe exposure bridge and accessible engagement strategy consistent with ALS trial guidance [53].

7. Conclusions

Can lidocaine preserve qualified ALS motor neurons while retaining activity, and offer measurable value over mexiletine under fair exposure comparisons? A focused human motor-neuron experiment should precede broader development. Joint survival–function benefit, mechanistic discrimination, independent replication, motor-unit validation, and safe spinal exposure are sequential requirements. Equal protection without comparative value favors mexiletine; precise failure with engagement challenges the tested claim. Existing evidence does not justify lidocaine treatment for ALS.

Declarations

Funding: No external funding was received for this article.

Competing Interests: The author declares no conflicts of interest.

Ethics approval: Not applicable. No new human or animal experiments are reported.

Consent for publication: Not applicable.

Data availability: No new datasets were generated or analyzed.

Author contributions: Mutlu Kuyucu conceived the hypothesis, developed the experimental framework, and contributed to literature interpretation and manuscript revision. The author is responsible for the final content and submission approval.

Acknowledgments: None.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process:

During preparation of this manuscript, the author used ChatGPT (OpenAI) for drafting, translation, language editing, structural revision, and assistance with literature assessment. The author is responsible for the scientific interpretation, accuracy of references and declarations, and final approval of the submitted manuscript. No new experimental data are reported.

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