Letters & Reviews in Neurlogical Sciences

Caffeine and Motor Neuron Disease: Mechanistic Insights and Clinical Implications for Amyotrophic Lateral Sclerosis Treatment- A mechanistic and translational narrative review

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disease (MND), is characterized by progressive degeneration of upper and lower motor neurons through convergent mechanisms of glutamatergic excitotoxicity, oxidative stress, mitochondrial dysfunction and neuro-inflammation. Caffeine, the most widely consumed psychoactive substance worldwide, is a non-selective antagonist of adenosine A1 and A2A receptors and has attracted long-standing interest as a potential modifier of neurodegenerative disease, largely by analogy with its well-established inverse association with Parkinson's disease risk. In ALS, however, the evidence is considerably more heterogeneous. Large pooled cohort analyses (five and eight prospective cohorts, respectively) and a 2024 Mendelian randomization study have produced inconsistent signals, ranging from a modest protective association to no association at all, while a case-control study nested within the European ALS Consortium reported a stronger inverse relationship. At the mechanistic level, caffeine's blockade of A2A receptors is predicted to reduce astrocyte- and microglia-linked excitotoxic glutamate signaling, whereas its concurrent blockade of A1 receptors removes a tonic, adenosine-mediated neuroprotective brake-a duality that plausibly explains the genuinely conflicting preclinical record: chronic caffeine shortened survival in the rapidly progressive $SOD1^{G93A}$ transgenic mouse model, yet reduced reactive oxygen species and preserved motor neurons in the slower-progressing Wobbler mouse model. A 2024 prospective clinical study of 378 ALS patients found no association between habitual caffeine consumption and survival, functional decline (ALSFRS-R) or disease progression, and identified a genotype-dependent cognitive benefit, supporting the overall safety of ordinary dietary caffeine intake during ALS treatment. Independently of its central actions, caffeine and related methylxanthines (notably theophylline) have documented, dose-dependent effects on diaphragmatic contractility and respiratory muscle strength, a property of potential relevance to the respiratory failure that is the leading cause of death in ALS, though this has not been formally tested in ALS patients. This review integrates the epidemiological, mechanistic, preclinical and clinical evidence to propose that ordinary caffeine consumption is neither a validated disease-modifying therapy nor a clinical hazard in ALS/MND, and identifies pharmacogenetics, respiratory-muscle applications and model-specific mechanisms as priority areas for future research.

Key words: Caffeine; amyotrophic lateral sclerosis; motor neuron disease; adenosine A1 receptor; adenosine A2A receptor; excitotoxicity; oxidative stress; SOD1; Wobbler mouse; respiratory muscle; pharmacogenetics; ALSFRS-R.

1. Introduction

Amyotrophic lateral sclerosis (ALS) and the broader category of motor neuron disease (MND) encompass a group of fatal neurodegenerative disorders defined by progressive loss of upper motor neurons in the motor cortex and lower motor neurons in the brainstem and spinal cord, leading to muscle weakness, paralysis and, typically, death from respiratory failure within three to five years of symptom onset [1]. Approved disease-modifying pharmacotherapies: riluzole, edaravone, sodium phenylbutyrate/taurursodiol, and the SOD1-targeted antisense oligonucleotide tofersen - offer only modest benefit, and there remains a pressing need to identify modifiable factors, including diet and widely consumed substances, that might influence disease risk or course [2].

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychoactive compound in the world, present in coffee, tea, cocoa, many soft and energy drinks, and some medications. At physiologically

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relevant doses, its principal pharmacological targets are the adenosine A1 and A2A receptors, both of which it antagonizes without meaningful affinity for other neurotransmitter systems [3]. Because adenosine signaling modulates synaptic glutamate release, astrocytic and microglial activation, and energy metabolism, caffeine has been extensively studied as a candidate neuroprotective or neuromodulatory agent in Parkinson's disease, Alzheimer's disease and, to a lesser extent, ALS [4].

Interest in caffeine and ALS follows directly from the excitotoxicity hypothesis of motor neuron death: Impaired astrocytic glutamate transport and consequent glutamate receptor over-activation are long-established features of ALS pathology, and adenosine A2A receptor blockade was proposed as early as the mid-2000s to protect motor neurons from excitotoxic and mutant-SOD1-induced insult [5,6]. However, unlike Parkinson's disease, where the epidemiological and mechanistic literature converges fairly consistently on a protective association, the ALS literature is markedly more heterogeneous across epidemiological designs, across animal models, and even within a single class of methylxanthine drugs. This review assembles that evidence base systematically: Epidemiology, receptor pharmacology, preclinical models, human clinical data, and the specific question of respiratory muscle support, in order to give a balanced, mechanistically grounded picture of what caffeine can and cannot be expected to do during ALS/MND treatment.

2. Caffeine pharmacology: Absorption, metabolism and CNS targets

Caffeine is rapidly and almost completely absorbed after oral ingestion, reaching peak plasma concentrations within 30–60 minutes, crossing the blood–brain barrier freely because of its small size and lipophilicity, and undergoing hepatic metabolism principally via cytochrome P450 1A2 (CYP1A2) to paraxanthine, theobromine and theophylline [3]. Its elimination half-life in healthy adults is typically 3–7 hours but is significantly prolonged by CYP1A2 genetic variants, hepatic impairment, pregnancy, and certain concomitant medications, all of which are relevant considerations in an ALS population that may have altered hepatic or respiratory physiology.

At the doses obtained from ordinary dietary consumption, caffeine's principal central nervous system targets are the inhibitory A1 receptor (A1R) and the facilitatory A2A receptor (A2AR); its affinity for these receptors exceeds that for any other known receptor or enzyme, including phosphodiesterases, which are inhibited only at supra-dietary concentrations [3,4]. A1R and A2AR are functionally and often physically coupled to dopamine and glutamate receptor systems, and their relative expression differs across brain regions, glial versus neuronal compartments, and disease states — a heterogeneity that helps explain why a single non-selective antagonist such as caffeine can produce different net outcomes in different neurological contexts (Scheme 1).

3. Epidemiological evidence: Coffee, tea and caffeine intake and ALS risk

An early case-control study nested within the European ALS Consortium (EURALS Group), comparing 377 newly diagnosed ALS patients with several types of matched controls, found that ALS patients had a lower lifetime prevalence and lower odds of coffee consumption than neurologic, non-neurologic and general-practice control groups, yielding odds ratios between 0.4 and 0.7 depending on the comparison group-the first substantial epidemiologic evidence for an inverse association between coffee intake and ALS risk [7].

This signal was not replicated in two large prospective pooled analyses. A pooled analysis of five major US cohort studies (over 1,010,000 participants; 1,279 incident ALS cases) found no association between caffeine, coffee or tea intake and ALS risk, with a pooled relative risk of 0.96 (95% CI, 0.81–1.16) for the highest versus lowest quintile of caffeine intake [8]. A subsequent pooled analysis of eight international prospective cohorts (351,565 individuals; 545 ALS deaths) likewise found no statistically significant association between coffee, tea or caffeine intake and ALS mortality [9]. A cross-sectional multicenter study of 241 already-diagnosed ALS patients further found no meaningful relationship between lifetime coffee or tea consumption and the rate of ALS functional decline (log-ΔFS), although a weak correlation with duration (but not intensity) of coffee consumption was noted and interpreted cautiously by the authors [10].

More recently, a two-sample Mendelian randomization study using genetic instruments for coffee consumption from a large genome-wide association dataset found that genetically predicted higher coffee intake was causally associated with a reduced risk of ALS (odds ratio 0.74, 95% CI 0.57–0.96), alongside independent inverse associations for oily fish and fresh fruit intake [11]. Results across designs are compared in Figure 1.

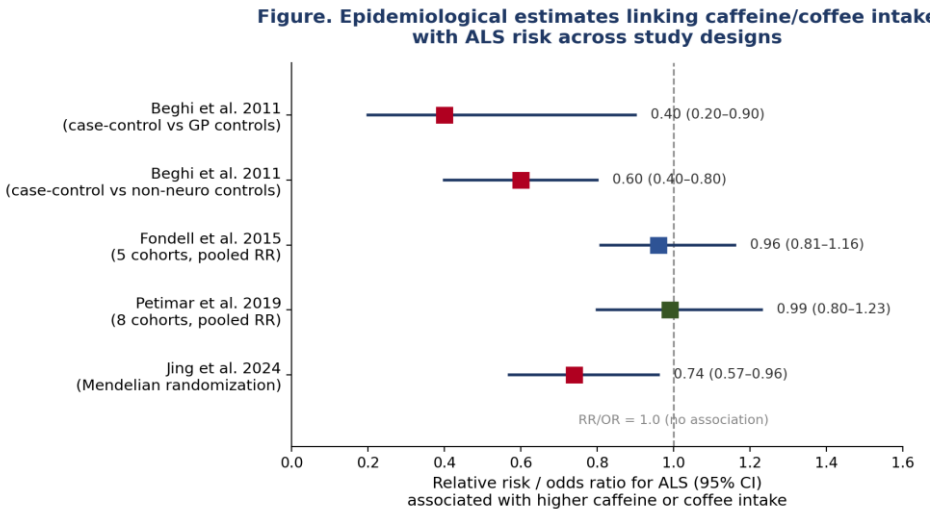


Figure 1. *Forest-plot-style summary of epidemiological estimates linking caffeine or coffee intake with ALS risk, spanning case-control, pooled prospective cohort, and Mendelian randomization designs. Estimates below 1.0 indicate an inverse (potentially protective) association; the dashed line marks no association. Individual study designs, populations and exposure definitions differ substantially and are not directly comparable (Section 3).*

Taken together, the epidemiological picture is best summarized as inconsistent rather than uniformly protective or uniformly null: case-control and Mendelian randomization designs have more often suggested a modest inverse association, while large prospective cohort analyses using food-frequency-based caffeine intake have generally found none. Differences in exposure measurement (self-reported dietary recall versus genetic instruments), residual confounding by physical activity or smoking, and the possibility of reverse causation (prodromal ALS altering appetite or beverage preference years before diagnosis) all plausibly contribute to this heterogeneity [7–11].

4. Caffeine and disease progression in diagnosed ALS patients

The epidemiological studies above address caffeine as a risk factor for developing ALS; a separate and clinically more directly relevant question is whether habitual caffeine consumption influences the course of disease once diagnosed i.e., its safety and possible utility as a concomitant exposure during treatment. This question was addressed directly in a 2024 prospective multicenter French study of 378 ALS patients with detailed quantification of habitual caffeine consumption, who were followed with the revised ALS Functional Rating Scale (ALSFRS-R), the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), survival, and riluzole treatment status; 282 patients were additionally genotyped for six single-nucleotide polymorphisms in genes governing caffeine intake and metabolism (CYP1A1, CYP1A2, AHR, POR, XDH and the adenosine A2A receptor gene ADORA2A) [12].

No association was found between caffeine consumption and survival ($p = 0.25$), functional disability (ALSFRS-R; $p = 0.27$), or the rate of disease progression ($p = 0.076$). However, a statistically significant interaction emerged between caffeine intake and CYP1A1 genotype (rs2472297): among patients carrying the C/T or T/T genotype, higher habitual caffeine consumption was associated with better cognitive performance on the ECAS (p-heterogeneity = 0.004) [12]. The authors concluded that regular caffeine consumption at ordinary dietary levels appears safe with respect to ALS progression and survival, and may even confer a genotype-dependent cognitive benefit to date the most direct and best-controlled clinical evidence available on this question.

5. Mechanisms of action: Adenosine receptor antagonism and motor neuron excitotoxicity

The mechanistic rationale for caffeine as an ALS-relevant compound rests on the interconnected biology of adenosine signaling, astrocytic glutamate handling, and excitotoxic motor neuron injury (Scheme 1). Motor neurons in ALS are highly vulnerable to excitotoxicity arising from impaired astrocytic glutamate transport (EAAT2/GLT-1 downregulation), producing excessive extracellular glutamate and pathological Ca^{2+} influx through AMPA and NMDA receptors [13,14].

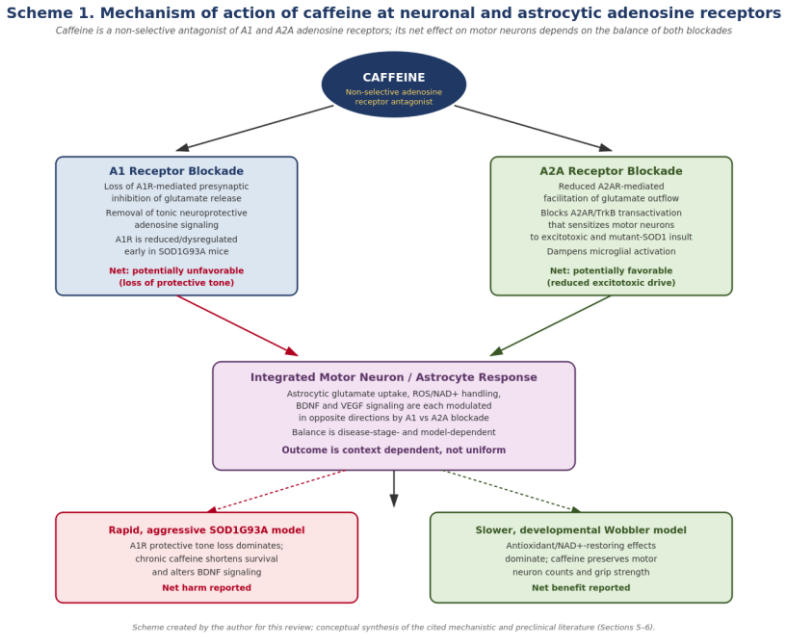
5.1 A2A receptor blockade: A plausible protective mechanism

Motor neurons co-express brain-derived neurotrophic factor (BDNF) receptor TrkB together with adenosine A2A receptors and Src-family kinases in lipid-raft membrane complexes; activation of this complex sensitizes motor neurons to excitotoxic insult and to toxicity from mutant SOD1 (G85R) and mutant p150glued (G59S) proteins linked to familial ALS. Direct pharmacological antagonism of the A2A receptor, or of TrkB kinase activity itself, blocked this sensitization and protected cultured motor neurons from both excitotoxic and mutant-protein-induced death, establishing a specific mechanistic rationale for A2AR blockade as neuroprotective in ALS-relevant paradigms [5]. Because caffeine is an A2AR antagonist at dietary concentrations, this mechanism is often cited as the basis for a hypothesized protective effect of caffeine in ALS [8].

5.2 A1 receptor blockade: A competing, potentially unfavorable mechanism

The A1 receptor plays a largely opposite functional role: A1R activation by endogenous adenosine presynaptically inhibits glutamate release and is considered a tonic, adenosine-mediated neuroprotective mechanism in the CNS [4]. Blocking A1R therefore removes this protective brake. In the $SOD1^{G93A}$ mouse model, cortical and spinal A1R expression is reduced and A2AR expression correspondingly increased even before symptom onset, indicating that the adenosinergic system is already dysregulated early in disease and that the balance of A1R versus A2AR tone may be shifted in a way that alters caffeine's net effect compared with a healthy nervous system [15,16].

Because caffeine antagonizes both receptors simultaneously and non-selectively, its net effect on any given model or patient population depends on which receptor's contribution dominates functionally at that disease stage a balance that, as detailed in Section 6, appears to differ between ALS animal models.



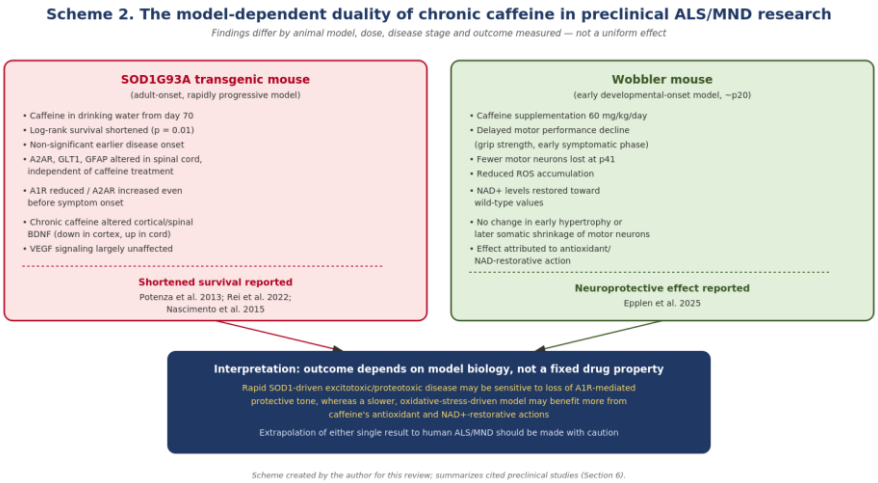
Scheme 1. *Mechanism of action of caffeine at neuronal and astrocytic adenosine receptors. Caffeine's non-selective blockade of A1 and A2A receptors produces opposing predicted effects - loss of A1R-mediated protective tone versus reduction of A2AR-mediated excitotoxic facilitation- whose net balance plausibly explains divergent outcomes across ALS models (Sections 5–6).*

6. Preclinical evidence: A model-dependent, genuinely conflicting record

Unlike the largely convergent preclinical literature on caffeine in Parkinson's disease models, direct testing of chronic caffeine administration in ALS animal models has produced opposite results depending on the model used, providing an instructive case study in how model biology shapes translational conclusions (Scheme 2; Table 2).

In the SOD1^{G93A} transgenic mouse, the most widely used ALS model, chronic caffeine administered via drinking water from day 70 until death significantly shortened overall survival (log-rank test, $p = 0.01$) and produced a non-significant trend toward earlier disease onset, without materially changing body weight or motor performance trajectories; expression of A2AR, the glial glutamate transporter GLT1, and the astrocyte marker GFAP were altered in the spinal cord of ALS mice but were not further changed by caffeine treatment itself [15]. A related study in the same model found that A1R expression was reduced and A2AR expression increased in cortex and spinal cord even at the pre-symptomatic stage, and that chronic caffeine treatment normalized cortical A1R levels toward control values while significantly altering BDNF levels decreased in cortex, increased in spinal cord leading the authors to propose that caffeine's negative influence on survival in this model may act through interference with BDNF signaling rather than through the VEGF pathway, which was largely unaffected by treatment [16]. A parallel electrophysiological study in the same strain found that presymptomatic and symptomatic SOD1^{G93A} mice differ in the balance of A1R- and A2AR-mediated tonic modulation of neuromuscular transmission, providing a physiological correlate for the receptor expression changes described above [17].

In marked contrast, chronic caffeine supplementation (60 mg/kg/day via drinking water) in the Wobbler mouse, a non-transgenic model with early, developmental-onset motor neuron degeneration beginning around postnatal day 20, delayed the decline in motor performance on grip-strength testing during the early symptomatic phase, significantly preserved motor neuron counts at postnatal day 41, reduced reactive oxygen species accumulation, and restored NAD^+ levels toward wild-type values, without affecting the early motor neuron hypertrophy or later somatic shrinkage characteristic of this model [18]. The authors of this 2025 study explicitly noted that the differing receptor-antagonism balance and differing disease kinetics between the SOD1^{G93A} and Wobbler models may explain why the same chronic caffeine exposure paradigm produced opposite survival/neuroprotection signals.



Scheme 2. *The model-dependent duality of chronic caffeine in preclinical ALS/MND research. The rapidly progressive, adult-onset SOD1^{G93A} model and the slower, developmental-onset Wobbler model have yielded opposite survival and neuroprotection outcomes with chronic caffeine exposure, most plausibly reflecting differences in which arm of adenosine receptor signaling (A1 versus A2A) dominates at each model's dominant pathogenic mechanism and disease tempo (Section 6).*

This divergence carries an important translational caveat: neither animal model recapitulates human ALS in its entirety, both models differ substantially from each other in genetic driver, onset kinetics and primary pathogenic mechanism, and neither result should be extrapolated directly to patients

without corroborating clinical data which, as described in Section 4, has so far shown no net harm or benefit on survival or progression in humans at ordinary dietary caffeine exposures [12].

7. Caffeine, oxidative stress and NAD^+ metabolism

A distinct, receptor-independent mechanism implicated in caffeine's neuroprotective signal in the Wobbler model is restoration of NAD^+ metabolism and reduction of reactive oxygen species (ROS) accumulation, both of which are recognized features of ALS motor neuron pathology arising from mitochondrial dysfunction and impaired antioxidant defense [18]. NAD^+ is a cofactor central to mitochondrial oxidative phosphorylation, sirtuin-mediated protein deacetylation, and PARP-dependent DNA repair, all of which are implicated in motor neuron survival pathways. Whether the antioxidant/NAD^+-restorative action of caffeine observed in the Wobbler model is receptor-mediated (via adenosine receptor signaling effects on mitochondrial function) or reflects a separate, direct biochemical action remains to be clarified [18].

8. Caffeine and neurotrophic signaling: BDNF and VEGF

Beyond direct receptor pharmacology, chronic caffeine treatment modulates neurotrophic signaling pathways implicated in ALS. In $SOD1^{G93A}$ mice, chronic caffeine altered BDNF levels in a region-specific and directionally opposite manner (decreased in cortex, increased in spinal cord), a pattern the study authors suggested could help explain caffeine's negative influence on survival in this model, since BDNF/TrkB signaling has itself been shown to sensitize motor neurons to excitotoxic insult when co-activated with A2A receptors [5,16]. Vascular endothelial growth factor (VEGF) signaling, in contrast, showed only modest, largely disease-stage-specific alterations in $SOD1^{G93A}$ mice and was not substantially modified by chronic caffeine treatment, suggesting that VEGF is not a major mediator of caffeine's effects in this model [16]. These findings illustrate that caffeine's net impact on motor neuron survival cannot be reduced to adenosine receptor occupancy alone, but reflects downstream modulation of an interconnected neurotrophic signaling network whose baseline state is itself altered by ALS-causing mutations.

9. Caffeine as a respiratory-muscle-supporting agent: Relevance to ALS respiratory failure

Respiratory failure secondary to diaphragmatic and other respiratory muscle weakness is the leading cause of death in ALS, and pharmacological strategies that support respiratory muscle strength are of direct clinical interest independent of any disease-modifying effect. Caffeine and the related methylxanthine theophylline have long-documented, dose-dependent stimulatory effects on respiratory muscle contractility that are mechanistically distinct from their CNS adenosine-receptor actions and instead involve phosphodiesterase inhibition (raising intracellular cyclic AMP), increased calcium availability in muscle, and adenosine-receptor-mediated effects at the neuromuscular level [19].

In healthy volunteers, a single oral 600 mg dose of caffeine increased trans diaphragmatic pressure at all levels of diaphragmatic electromyographic activity, with a larger effect than an equivalent dose of theophylline, indicating a direct increase in diaphragmatic contractility rather than a change in lung volume or thoracoabdominal configuration [19]. Oral theophylline has similarly been shown to augment hypercapnic and hypoxic ventilatory responses and respiratory muscle strength in normal subjects [20], and, in a retrospective cohort of patients with prolonged mechanical ventilation, a population with ventilator-induced diaphragmatic dysfunction analogous in some respects to the respiratory muscle weakness of advanced ALS, theophylline therapy was associated with improved respiratory muscle strength measures [21].

These findings raise a biologically plausible, but as yet clinically untested, hypothesis: that caffeine or related methylxanthines could offer symptomatic respiratory muscle support in ALS patients with emerging respiratory insufficiency, analogous to their established use in neonatal apnea and ventilator weaning. No controlled trial has evaluated caffeine specifically for this indication in ALS, and any such use would need to be weighed against caffeine's stimulant, cardiovascular and sleep-disrupting effects,

particularly in patients with compromised cardiopulmonary reserve; this remains an area for future targeted clinical investigation rather than a basis for current practice recommendations.

10. Pharmacogenetic modifiers of caffeine's effects in ALS

A recurring theme across both the preclinical and clinical literature is that caffeine's net effect is not fixed but is modulated by the genetic and physiological context in which it acts. In the 2024 prospective clinical study described in Section 4, genotyping of six single-nucleotide polymorphisms governing caffeine intake and metabolism (CYP1A1, CYP1A2, AHR, POR, XDH, ADORA2A) revealed that the cognitive benefit associated with higher caffeine consumption was confined to patients carrying specific CYP1A1 genotypes (C/T and T/T at rs2472297), a gene involved in xenobiotic and caffeine-related metabolism [12]. This gene–environment interaction suggests that inter-individual variability in caffeine metabolism and adenosine receptor expression, rather than caffeine exposure alone, may determine whether a given patient experiences a net cognitive, motor, or null effect — a pharmacogenetic framework consistent with the model-dependent duality already evident at the preclinical level (Section 6) and pointing toward genotype-stratified analysis as a priority for future caffeine-ALS research.

Table 1. Summary of epidemiological studies of caffeine/coffee/tea intake and ALS risk or progression

Study (design)	Population	Key exposure metric	Key finding
Beghi et al. 2011 [7] (case-control, EURALS)	377 ALS cases; multiple matched control groups (Italy)	Ever/current coffee consumption, duration	Lower coffee exposure in ALS patients; OR 0.4–0.7 vs. controls
Fondell et al. 2015 [8] (pooled prospective cohorts, n = 5)	>1,010,000 participants; 1,279 ALS cases (USA)	Caffeine, coffee, tea intake (FFQ)	No association; pooled RR 0.96 (95% CI 0.81–1.16) highest vs. lowest quintile
Petimar et al. 2019 [9] (pooled prospective cohorts, n = 8)	351,565 participants; 545 ALS deaths (multinational)	Caffeine, coffee, tea intake (FFQ)	No association with ALS mortality (pooled RR ≈ 0.99–1.04)
Cucovici et al. 2021 [10] (cross-sectional, multicenter)	241 diagnosed ALS patients (Italy, Moldova, Romania)	Lifetime coffee/tea consumption, duration, cup-years	No association with rate of disease progression (log-ΔFS)
Jing et al. 2024 [11] (two-sample Mendelian randomization)	GWAS summary data; dietary exposures incl. coffee intake	Genetically predicted coffee intake	Coffee intake causally associated with reduced ALS risk (OR 0.74, 95% CI 0.57–0.96)
Huin et al. 2024 [12] (prospective multicenter clinical cohort)	378 diagnosed ALS patients; 282 genotyped (France)	Habitual caffeine consumption + 6 metabolism/receptor SNPs	No association with survival, ALSFRS-R or progression; genotype-dependent cognitive benefit (ECAS)

FFQ, food-frequency questionnaire; OR, odds ratio; RR, relative risk; ALSFRS-R, ALS Functional Rating Scale-Revised; ECAS, Edinburgh Cognitive and Behavioural ALS Screen; ΔFS, rate of functional decline.

Table 2. Summary of preclinical (animal model) studies of chronic caffeine in ALS models

Model	Regimen	Key findings	Net direction
SOD1^{G93A} mouse [15]	Caffeine in drinking water, day 70 to death	Shortened survival ($p = 0.01$); non-significant earlier onset; no change in A2AR/GLT1/GFAP expression	Harm
SOD1^{G93A} mouse [16]	Chronic caffeine treatment	Normalized cortical A1R; altered BDNF (↓ cortex, ↑ cord); VEGF largely unaffected	Harm / mixed
SOD1^{G93A} mouse [17]	Electrophysiology, no caffeine treatment	Pre-symptomatic vs. symptomatic mice differ in A1R/A2AR tonic modulation of neuromuscular transmission	Mechanistic (context)
Wobbler mouse [18]	Caffeine 60 mg/kg/day via drinking water	Delayed grip-strength decline; preserved motor neuron counts at p41; ↓ ROS; restored NAD^+	Benefit

Table 3. Typical caffeine content of common beverages and practical dosing context

Beverage (typical serving)	Approx. caffeine content	Relevant note for ALS/MND patients
Decaffeinated coffee (240 mL)	~3 mg	Negligible adenosine-receptor activity; other bioactive compounds (chlorogenic acid) still present
Green tea (240 mL)	~28 mg	Lower dose; co-contains L-theanine and polyphenols
Cola soft drink (355 mL)	~34 mg	Often combined with high sugar content; relevant to nutritional planning
Black tea (240 mL)	~47 mg	Moderate dose; tannins may affect iron absorption with frequent use
Espresso (30 mL shot)	~63 mg	High concentration per volume; easy to underestimate cumulative intake
Energy drink (250 mL)	~80 mg	Often combined with taurine and high sugar; caution with cardiac comorbidity
Brewed coffee (240 mL)	~95 mg	Most common source of dietary caffeine in the studies reviewed here

Values are approximate and vary with preparation method, bean/leaf type, and brewing time; individual product labels should be consulted for precise content.

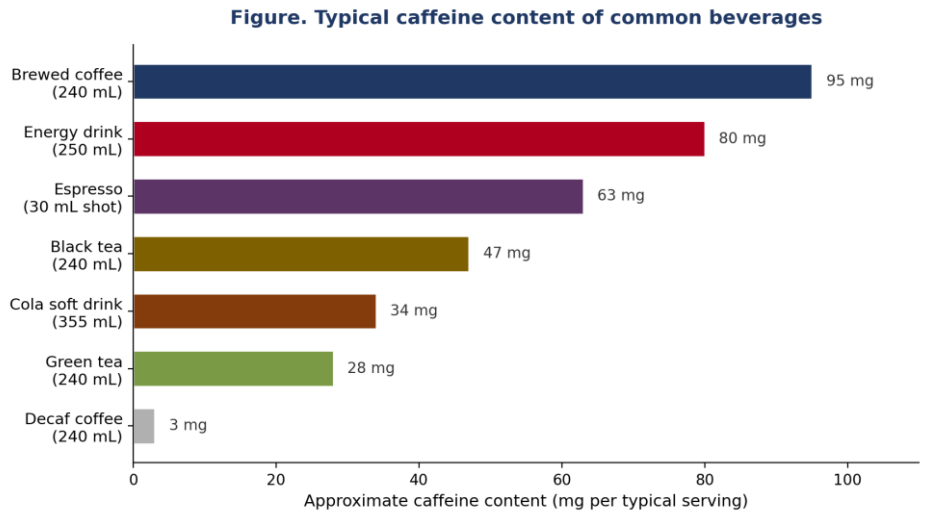


Figure 2. *Typical caffeine content of common beverages, ordered from lowest to highest per typical serving, for practical reference when discussing dietary caffeine exposure with ALS/MND patients (Table 3).*

11. Safety considerations and practical recommendations during ALS/MND treatment

Based on the totality of evidence reviewed here, several practical points can be drawn for clinicians and patients:

- Ordinary dietary caffeine consumption has not been shown to accelerate ALS progression, worsen functional decline, or shorten survival in the best-controlled human clinical data available to date, and there is no clinical basis for advising patients to discontinue habitual coffee or tea consumption on disease-course grounds [12].
- Caffeine should not be regarded as a validated disease-modifying therapy for ALS: epidemiological associations are inconsistent, and the strongest preclinical signal in the standard SOD1^{G93A} model points toward harm, not benefit, with chronic high-dose exposure [15,16].
- Potential drug interactions merit routine consideration: caffeine and riluzole are both metabolized in part via hepatic pathways, and concomitant use of other CYP1A2 substrates or inhibitors could alter caffeine's own pharmacokinetics; no formal interaction study between caffeine and ALS-specific therapies (riluzole, edaravone, sodium phenylbutyrate/taurursodiol) has been published.
- Respiratory-muscle-supporting effects of caffeine/methylxanthines are pharmacologically plausible and supported by data in other patient populations, but remain untested in ALS specifically; any use for this purpose should currently be considered investigational rather than standard care [19–21].
- Caffeine's stimulant, cardiovascular, and sleep-disrupting properties, together with common ALS comorbidities (dysphagia affecting safe fluid/caffeine intake, anxiety, insomnia, autonomic changes), warrant individualized, symptom-guided moderation rather than either blanket restriction or blanket encouragement.
- Genotype-dependent effects (e.g., CYP1A1 variants and cognitive outcomes) suggest that, as pharmacogenetic testing becomes more accessible, individualized guidance may eventually be possible, but this is not yet ready for routine clinical application [12].

12. Limitations and future research directions

Several limitations qualify the current evidence base. First, all human epidemiological studies are observational and subject to reverse causation, recall bias (particularly in case-control designs), and residual confounding by correlated lifestyle factors (smoking, physical activity, diet quality); Mendelian randomization mitigates but does not eliminate these concerns, and different MR studies of the same

exposure have reached different conclusions [8–11]. Second, preclinical studies to date have used only two rodent models (SOD1^{G93A} and Wobbler), leaving the generalizability of either result to TDP-43-, FUS- or C9ORF72-associated ALS, which together account for a substantial share of genetic and sporadic disease, entirely untested. Third, the single available prospective human clinical study, while well designed, is a single cohort with a specific European population and a moderate sample size for genotype-stratified subgroup analysis; independent replication is needed [12]. Fourth, no controlled trial has evaluated caffeine or methylxanthines specifically for respiratory muscle support in ALS, despite plausible mechanistic and cross-disease rationale [19–21].

Priority directions for future research include: replication of the caffeine–CYP1A1–cognition interaction in independent ALS cohorts; mechanistic studies directly comparing A1R and A2AR expression and functional balance across ALS genetic subtypes and disease stages, to test whether the SOD1^{G93A}/Wobbler divergence extends to TDP-43 and C9ORF72 models; a dedicated, adequately powered trial of caffeine or a selective A2AR antagonist for respiratory muscle support in ALS patients with early respiratory involvement; and pharmacokinetic/pharmacodynamic studies of caffeine–riluzole and caffeine–edaravone co-administration.

13. Conclusions

Caffeine occupies a genuinely ambiguous position in ALS/MND research, in clear contrast to its more consistently protective epidemiological and mechanistic profile in Parkinson's disease. Mechanistically, its simultaneous, non-selective blockade of adenosine A1 and A2A receptors sets up a biological tug-of-war between loss of a tonic neuroprotective brake (A1R) and reduction of excitotoxic facilitation (A2AR), and the direction in which this balance resolves appears to depend on the specific disease model, genetic driver, and stage examined, shortening survival in the standard SOD1^{G93A} mouse while proving neuroprotective, *via* antioxidant and NAD^+-restorative actions, in the Wobbler mouse. Epidemiological studies in humans are similarly inconsistent, ranging from a modest inverse association in case-control and Mendelian randomization designs to no association in large prospective cohorts, while the best available direct clinical evidence, a prospective, genotyped cohort of 378 diagnosed ALS patients found no effect of habitual caffeine consumption on survival or disease progression, alongside a genotype-dependent cognitive benefit. Independently of these central mechanisms, caffeine's well-established capacity to enhance diaphragmatic and respiratory muscle contractility offers a biologically plausible, but currently untested, avenue for symptomatic respiratory support in ALS. On the currently available evidence, ordinary dietary caffeine consumption should be regarded as safe to continue during ALS/MND treatment, but not as a validated disease-modifying intervention; future research should prioritize genotype-stratified clinical studies, cross-model mechanistic comparisons, and a dedicated evaluation of methylxanthines for respiratory muscle support.

Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological disorders.

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Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a literature review and is not a treatment recommendation for an individual patient. The treatment, generally, should be taken only for a clinically justified indication and with appropriate medical monitoring by an expert neurologist.

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