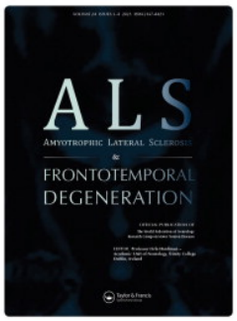

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ALSUntangled #70: caffeine

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BRIEF REPORT

ALSUntangled #70: caffeine

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here, we review caffeine which has plausible mechanisms for slowing ALS progression. However, pre-clinical studies are contradictory, and a large case series showed no relationship between caffeine intake and ALS progression rate. While low doses of caffeine are safe and inexpensive, higher doses can cause serious side effects. At this time, we cannot endorse caffeine as a treatment to slow ALS progression.

Keywords: *Amyotrophic lateral sclerosis (ALS), caffeine, coffee, tea, adenosine*

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ALSUntangled reviews alternative and off-label ALS treatments on behalf of people living with amyotrophic lateral sclerosis (PALS). Here, we review caffeine for, which we have had 710 requests (1).

Overview

Caffeine is a widely consumed stimulant present in coffee, tea, and energy drinks. Some studies have suggested that caffeine consumption might reduce the risk of (2–5) or lessen the severity of (6,7) neurodegenerative diseases. With specific regard to ALS, one Italian study appeared to support the inverse relationship between caffeine intake and disease risk (8), but two large meta-analyses failed to confirm this (9,10). Whether caffeine might slow ALS progression is even less clear and is the subject of this review.

Mechanisms

Caffeine taken orally is rapidly absorbed into the blood and then can cross the blood–brain barrier (5). Once in the central nervous system (CNS), it can influence at least three mechanisms believed to be important in ALS progression: oxidative stress (11), neuroinflammation (12,13), and excitotoxicity (14).

Oxidative stress

Caffeine can directly block lipid peroxidation and decrease reactive oxygen production *in vitro* (15). In rats, intraperitoneal caffeine treatment reduced D-galactose-induced cognitive dysfunction and brain markers of oxidative stress (16). In the $SOD1^{G93A}$ mouse model of ALS, coffee consumption at the equivalent of 5–10 cups per day improved antioxidant protein content in male brains (17); on the other hand, in the brains of female $SOD1^{G93A\ mice}$, the same amount of caffeine supplementation reduced antioxidant enzyme capacity (18). In healthy human male volunteers, oral caffeine at 5 mg/kg per day improved multiple blood markers of oxidative stress (19). We did not find a similar study in human female volunteers.

Neuroinflammation

Caffeine treatment can reduce microglial activation and/or markers of neuroinflammation in animal models of different diseases (16,20–23). We did not find published studies examining caffeine's effect on these in animal models of ALS nor in human trials.

Excitotoxicity

Caffeine has a very similar molecular structure to adenosine, a neuromodulator in the CNS, and it acts as an adenosine receptor antagonist (5). Of the four adenosine receptors in the CNS, A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R, caffeine has the highest affinity for A_1R and $A_{2A}R$ receptors (5). In human brain, A_1R is distributed widely in the cerebral cortices, striatum, thalamus, and cerebellum, while $A_{2A}R$ concentrates within the basal ganglia and thalamus, with low expression in the cortex (24,25). These two receptors play opposing roles in regulating CNS excitotoxicity. A_1R activation reduces CNS excitotoxicity; conversely, $A_{2A}R$ activation increases excitotoxicity (5). In the $SOD1^{G93A}$ mouse model of ALS, decreases in A_1R and increases in $A_{2A}R$ were seen prior to disease onset (26). Selective attenuation of $A_{2A}R$ delays disease onset and enhances motor neuron survival in an ALS animal model (27). Since caffeine antagonizes both A_1R and $A_{2A}R$ receptors, the benefit of attenuating $A_{2A}R$ on excitotoxicity may be canceled by simultaneous A_1R inhibition.

Given that caffeine can reduce markers of oxidative stress in human male, we assign a table of evidence "mechanisms" grade of A (Table 1). We caution that there may be differences in the mechanistic effects of caffeine in male versus female brains. This is an area that requires further study.

Table 1.. Table of evidence for caffeine as an ALS treatment.

Category	Grade	Explanation
Mechanism	A	Caffeine can reduce markers of oxidative stress in humans
Pre-clinical	C	Conflicting results in cell and animal studies
Cases	F	The only reports available show no benefit
Trials	U	No known trials to date
Risks	B	Caffeine at doses of 400 mg daily or less appears reasonably safe; side effects are rare and generally minor at these doses; doses above 1200 mg should be avoided

Pre-clinical studies

There have been conflicting reports regarding the effects of caffeine in ALS animal models. $SOD1^{G93A}$ALS mice administered caffeine in drinking water from 70 days onward had significantly shorter survival versus untreated $SOD1^{G93A}$ ALS mice (28). In this study, the weight-based dosing was similar to humans drinking 3–4 cups of coffee daily (28). The caffeine-treated mice also exhibited earlier disease onset, reduced motor function, and decreased total weight during the study period. Another group found that caffeine had opposite effects on motor performance in male (17) versus female (18) $SOD1^{G93A}$ ALS mice. While the amount of caffeine administered was similar in both mouse sexes (the equivalent of 5–10 cups of coffee each day), direct comparison is difficult because male mice received coffee (which

contains a variety of different chemicals), whereas females received pure caffeine (17,18).

The wobbler mouse is a distinct model from $SOD1^{G93A}$ and resembles sporadic human ALS at the cellular and phenotypic levels (29). Motor neurons isolated from the wobbler mouse spinal cord cultured in caffeine-containing medium showed significantly increased neurite length versus neurons in caffeine-free medium (30).

Due to the conflicting data in these pre-clinical studies, ALSUntangled assigns a table of evidence "pre-clinical grade" of C (Table 1).

Data in PALS

Cases

A multicenter cross-sectional study examined the effects of caffeine in 241 participants (145 males, 96 females) with confirmed ALS according to the El Escorial diagnostic criteria (31). The study found no correlation between the amount of coffee or tea consumption (cup-years or cups/day) to ALS progression. They further analyzed ALS patients with different progression rates, i.e. slow, intermediate, and fast progressors, and found an equal distribution of coffee or tea consumption status across three groups. Finally, they examined whether the amount of caffeine intake prior to ALS onset might effect the age of ALS onset; they found no evidence to support this idea.

A recently published comparison of caffeinated beverage consumption between patients experiencing "ALS reversals" and those with more typically progressive ALS also failed to find a difference (32).

Based upon these two cohort studies, we assign a table of evidence "cases" grade of F (Table 1).

Trials

We found no clinical trials of caffeine in people PALS. Therefore, we assign a table of evidence "trials" grade of U.

Dosing, risks, and costs

Caffeine is available in a wide variety of products, formulations, and dosages (Table 2, reference (33)). It is not yet clear whether there is any optimal product, formulation, or dose for treating ALS.

Table 2. Amounts of caffeine in different common substances and supplements (from references (33,34)).

Substance	Amount of caffeine (mg)
Coffee (16 ounces)	200–360
Expresso shot (1.5 ounces)	150
Tea (16 ounces)	20–150
Energy drinks (16 ounces)	90–500
Cola (16 ounces)	50–70
Coffee or chocolate ice cream (2/3 cup)	20–50
Pure caffeine supplements (1 teaspoon)	1200–4000

The United States Food and Drug Administration (US FDA) has stated that 400 mg of caffeine (1–2 cups of coffee) daily is generally safe for most people (34) and this is supported by literature reviews (35). Rare patients will experience palpitations, tremor, nervousness, and insomnia with these doses (35). Elderly females with inadequate calcium intake may experience osteoporosis and be at increased risk of hip fracture with these doses (35). Importantly for PALS, caffeine can inhibit riluzole clearance and theoretically cause more riluzole-related side effects (36). Higher doses of caffeine (5–10 cups of coffee per day) are associated with coronary heart disease (35). The US FDA has warned against very high doses of caffeine (>1200 mg in a single dose), which are contained in some over the counter caffeine supplements (34). Severe adverse events such as seizures and cardiac arrhythmia and deaths can occur with such very high doses (34,35,37,38).

Based on this information, we assign caffeine at doses of 400 mg daily or less a table of evidence "risks" grade of B.

Costs

Caffeine is generally inexpensive. Foods and beverages containing caffeine or caffeine supplements can be obtained for a few dollars per day (39).

Conclusions

Caffeine is inexpensive, reasonably safe at doses of under 400 mg daily, and has plausible mechanisms by which it could slow ALS progression. However, data from pre-clinical models are contradictory and a two cohort studies showed no clear relationship between caffeine intake and ALS progression. Based on all this, we cannot endorse caffeine as an ALS treatment.

Declaration of interest

The authors of this paper report no relevant disclosures or conflicts. ALSUntangled is supported by the ALS Association under Grant Number 23-SI-622. Drs. Bedlack and Li receive salary support from this grant.

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