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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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# An open label pilot study of the safety and tolerability of perampanel in amyotrophic lateral sclerosis

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## Abstract

**Introduction/Aims:** Perampanel, a selective noncompetitive  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist, is capable of slowing the progression of the amyotrophic lateral sclerosis (ALS) phenotype and increasing the number of anterior horn cells in transgenic mice. Trials of perampanel in epilepsy showed a favorable tolerability profile. In this study we aimed to determine the tolerability and safety of perampanel in patients with ALS.

**Methods:** Enrolled subjects were started on 2 mg/day of perampanel and the dose was increased by 2 mg/day every week to a maximum dose of 8 mg/day. Our primary outcome measure was tolerability, which was evaluated by monitoring adverse events. The secondary outcome measure was clinical progression, assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised (ALSFRS-R) and spirometry.

**Results:** Six participants were enrolled. All had adverse events, mostly behavioral. Two completed the trial and the other four withdrew due to adverse events. All participants reported resolution of these events after discontinuation of the drug. The trial was halted due to the large number of adverse events.

**Discussion:** The use of perampanel in this study of ALS was limited by its poor tolerability.

### KEYWORDS

adverse events, amyotrophic lateral sclerosis, perampanel, safety, tolerability

## 1 | INTRODUCTION

Various mechanisms have been proposed to play a role in the pathogenesis of motor neuron degeneration in amyotrophic lateral sclerosis (ALS), including glutamate receptor-mediated excitotoxicity, protein aggregation, neuroinflammation, and immune-mediated processes.<sup>1</sup> Excitotoxicity is mediated by the massive entrance of calcium ions (Ca<sup>2+</sup>) into the cell and can lead to membrane destruction and cell lysis through a cascade of events.<sup>2</sup>  $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are thought to be the prime mediators of fast excitation in spinal motor neurons.<sup>3</sup> They are composed of four subunits (glutamate receptor 1 [GluR1] through glutamate receptor 4 [GluR 4]), which can be present in various combinations.<sup>4</sup> It was shown that receptors lacking the GluR2 subunit lead to a potentiated sensitivity of motor neurons to AMPA and glutamate and result in high permeability to calcium.<sup>4-6</sup> Experiments in rats showed that direct AMPA infusion in the lumbar spinal cord can cause a progressive ipsilateral limb paralysis and motor neuron degeneration, which can be prevented by AMPA receptor antagonists.<sup>3,7,8</sup> Superoxide dismutase 1 (SOD1) transgenic mice lacking the GluR2 subunit of the AMPA receptor also show an accelerated disease course.<sup>7</sup>

Perampanel [2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile], a selective noncompetitive AMPA antagonist approved for epilepsy,<sup>9</sup> was shown to slow progression of the ALS phenotype and increase the number of anterior horn cells in transgenic mice.<sup>10</sup> Long-term trials in epilepsy showed a favorable tolerability profile, with the side effects mainly being dizziness, headache, and somnolence.<sup>9</sup> Another AMPA antagonist, talampanel, showed promising results in a phase 2 trial in patients with ALS.<sup>11</sup> We aimed to study the tolerability and safety of the AMPA antagonist, perampanel, in people living with ALS.

## 2 | METHODS

This study was approved by the institutional review board at the American University of Beirut (ID: IM.JS.03) and registered as a clinical trial (NCT03377309). We recruited patients presenting to the ALS clinic at the American University of Beirut Medical Center between

August 2019 and January 2021. All participants provided informed consent. The intended sample size at the beginning of the trial was 15 participants.

To be included in the study, participants had to be at least 18 years old; diagnosed within 3 years before participation with sporadic or familial possible/probable/definite ALS, according to the revised El Escorial criteria<sup>12</sup>; on riluzole, or no treatment, for at least 30 days before participation; and had to have a forced vital capacity (FVC) of at least 50% of the predicted value. Participants were excluded if they had any of the following: pregnancy or planning a pregnancy or breastfeeding; serum creatinine over 1.5-fold the upper limit of normal; aspartate aminotransferase and/or alanine aminotransferase greater than three times the upper limit of normal; electrocardiogram (ECG) demonstrating a QTc prolongation of over 450 milliseconds; or a history of suicidal/homicidal thoughts.

Before initiation, participants underwent assessment of motor power using the Medical Research Council (MRC) scale,<sup>13</sup> with assessment of cranial nerves, reflexes, and gait, as well as ECG. All participants completed a general questionnaire on psychiatric symptoms and disorders and the Columbia-Suicide Severity Rating Scale.<sup>14</sup> Enrolled subjects were started on perampanel at 2 mg/day. In the titration phase, the dose was increased by 2 mg/day every week to a maximum dose of 8 mg/day. During this phase, subjects who had mild or moderate adverse events had their dose reduced to the previous level. Participants who required two dose reductions, did not tolerate the lowest dose, or had severe adverse events were withdrawn from the study. The treatment phase was followed by a washout period during which the dose was tapered by 2 mg/day every 5 days over a total of 15 days. Participants were seen every 4 weeks after drug initiation until the end of the treatment phase (12 weeks), and then weekly throughout the washout period. During each visit, tolerability/safety was evaluated by monitoring the type, frequency, and severity of adverse events (according to Common Terminology Criteria for Adverse Events), as a primary outcome measure. The secondary outcome measure assessed at each visit was clinical progression, evaluated according to the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R),<sup>15</sup> and FVC measurement.

**TABLE 1** Demographics and background characteristics

Participant	Gender	Weight (kg)	Age (years)	Time since symptom onset (months)	Type of ALS	Site of disease involvement
1	Male	84	44	29	Sporadic	Cervical and lumbar
2	Male	83	58	6	Sporadic	Bulbar, cervical, and lumbar
3	Male	70	39	12	Sporadic	Bulbar and cervical
4	Male	85	67	11	Sporadic	Cervical and lumbar
5	Male	83	58	16	Familial	Bulbar, cervical, and lumbar
6	Male	86	68	45	Sporadic	Cervical

Abbreviation: ALS, amyotrophic lateral sclerosis.

**TABLE 2** ALSFRS-R findings

Participant	Baseline		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5	
	FVC	ALSFRS-R	FVC	ALSFRS-R	FVC	ALSFRS-R	FVC	ALS-FRS-R	FVC	ALS-FRS-R	FVC	ALS-FRS-R
1	60	36	66	35	63	35	62	34	47	34	54	34
2	60	38	31	35	44	28	39	27	39	27	41	26
3	74	39	—	—	—	—	—	—	—	—	—	—
4	69	40	65	36	58	33	55	31	—	—	—	—
5	68	37	66	37	—	—	—	—	—	—	—	—
6	50	32	50	32	—	—	—	—	—	—	—	—

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; FVC, forced vital capacity (% predicted); —, absence of data due to trial withdrawal.

**TABLE 3** ALSFRS-R scores and FVC measures of participants throughout the trial

Participant	Adverse event	Dose at adverse event onset (mg)	Status	Note	Follow-up
1	Somnolence, aggression, anger	2, 8, 8	Fully completed trial	Somnolence resolved when drug was taken at bedtime	Side effects resolved when trial was completed
2	Somnolence, aggression	2, 8	Fully completed trial	Somnolence resolved when drug was taken at bedtime	Side effects resolved when trial was completed
3	Dizziness, imbalance, dysarthria	4, 4, 4	Withdrew	Patient refused dose adjustment	Side effects resolved after drug cessation
4	Aggression, irritability, logorrhea, dysarthria, gait disturbance	8, 8, 8, 8, 8	Withdrew	Patient refused dose adjustment	Side effects resolved after drug cessation

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; FVC, forced vital capacity (% predicted).

**TABLE 4** Adverse events and tolerability experienced with perampanel

Participant	Adverse event	Dose at adverse event onset (mg)	Status	Note	Follow-up
5	Aggression, anger	4, 4	Withdrawn	Dose was adjusted and symptoms resolved but resurfaced more severely at 8 mg and patient was withdrawn	Side effects resolved after drug cessation
6	Somnolence, aggression, anger	2, 8, 8	Withdrew	Somnolence resolved when drug was taken at bedtime	Side effects resolved after drug cessation

### 3 | RESULTS

We enrolled only six subjects (all males, average age 55 years) due to the large number of adverse events. Tables 1 and 2 show demographics and clinical background and Table 3 shows the clinical progression as measured by FVC and ALSFRS-R for each participant. Upper extremity strength in the two participants who completed the trial remained stable throughout.

All participants had adverse events. Only two completed the trial; one was withdrawn by the research team due to recurrence of adverse events, and the others withdrew due to adverse events. All

participants reported resolution of side effects after discontinuation of the drug. Table 4 shows a detailed description of the adverse events experienced by participants. The study was halted due to the large number of adverse events reported and the low tolerability of the participants.

### 4 | DISCUSSION

To date, no clinical data have been published on the safety or efficacy of the short- or long-term use of perampanel in people living with

ALS. Two other clinical trials are ongoing.<sup>16</sup> In a recently published article, the authors studied the effect of a single dose of perampanel on cortical excitability and found a significant increase in motor threshold.<sup>17</sup>

It was previously reported that administration of perampanel in patients with epilepsy is safe and that side effects were minor and dose-dependent. The side effects reported with an 8-mg/day dose include dizziness (32%), sleepiness (16%), fatigue (8%), irritability (7%), falls (5%), and imbalance (5%).<sup>18</sup> Similar findings were reported in trials conducted in Parkinson disease.<sup>19</sup> In a recent study assessing the effect of perampanel on cortical excitability, administration of a single dose did not elicit any side effects.<sup>17</sup> Hence, a single dose of perampanel in ALS may be safe, but multiple doses over time, as in our study, appear to cause adverse events. Another AMPA antagonist, talampanel, was tested in a phase 2 trial in 2010 in patients with ALS and showed enhancement in motor power, but the data did not reach statistical significance. Subjects who received talampanel had more adverse events, such as somnolence, compared with the control group. A phase 3 trial has not been published.<sup>11</sup>

The clinical screening of participants by the neurologist and the general questionnaire completed by researchers at baseline did not reveal any psychobehavioral manifestations. However, more thorough cognitive and behavioral evaluations would be helpful for future studies. The risk of such side effects in people living with ALS could be more noticeable due to the association of cognitive and/or behavioral changes with ALS. One study reported that 40% of individuals with ALS had cognitive impairment, 9% had behavioral changes, and 18% had comorbid cognitive and behavioral decline.<sup>20</sup> In another study, behavioral changes were present to a moderate-severe degree in approximately 20% of people with ALS, and 11% met the criteria for a diagnosis of frontotemporal degeneration.<sup>21</sup> The risk of frontal-predominant dementias in people with ALS could have led to the high frequency of psychiatric side effects in our trial. Moreover, they are at a particularly higher risk of developing side effects due the fact that up to 80% of patients with motor neuron disease can develop non-motor symptoms.<sup>22</sup>

Participants in our study also reported worsening of existing symptoms such as dysarthria and imbalance after taking perampanel, raising the possibility that these symptoms are due to disease progression rather than being treatment-related adverse events. It is also worth noting that most participants were enrolled in the study during the early stages of the disease, with the median time of symptom onset being 14 months. This raises concern as to whether administration of perampanel triggers or accelerates the appearance of non-motor and psychobehavioral symptoms.

Future studies using a randomized controlled design could help determine the true contributors to the behavioral events. Recent studies on the use of perampanel in epilepsy have shown that doses of 4 mg/day are efficacious and associated with better tolerability.<sup>23,24</sup> This should be considered when conducting future studies in ALS.

## 5 | CONCLUSION

The participants in our study did not tolerate perampanel and the trial was halted. Side effects were mainly behavioral and psychiatric. This could be attributed to the predisposition of people with ALS to cognitive, behavioral, and nonmotor symptoms.

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### CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

### ETHICAL PUBLICATION STATEMENT

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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