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Neuroprotective agents for clinical trials in ALS

A systematic assessment

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Abstract—Background: Riluzole is currently the only Food and Drug Administration–approved treatment for ALS, but its effect on survival is modest. **Objective:** To identify potential neuroprotective agents for testing in phase III clinical trials and to outline which data need to be collected for each drug. **Methods:** The authors identified 113 compounds by inviting input from academic clinicians and researchers and via literature review to identify agents that have been tested in ALS animal models and in patients with ALS. The list was initially narrowed to 24 agents based on an evaluation of scientific rationale, toxicity, and efficacy in previous animal and human studies. These 24 drugs underwent more detailed pharmacologic evaluation. **Results:** Twenty drugs were selected as suitable for further development as treatments for patients with ALS. Talampanel and tamoxifen have completed early phase II trials and have demonstrated preliminary efficacy. Other agents (ceftriaxone, minocycline, ONO-2506, and IGF-1 polypeptide) are already in phase III trials involving large numbers of patients with ALS. Remaining agents (AEOL 10150, arimoclochol, celastrol, coenzyme Q10, copaxone, IGF-1–viral delivery, memantine, NAALADase inhibitors, nimesulide, scriptaid, sodium phenylbutyrate, thalidomide, trehalose) require additional preclinical animal data, human toxicity and pharmacokinetic data including CNS penetration prior to proceeding to large scale phase III human testing. Further development of riluzole analogues should be considered. **Conclusions:** Several potential neuroprotective compounds, representing a wide range of mechanisms, are available and merit further investigation in ALS.

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Riluzole is the only Food and Drug Administration (FDA)–approved drug for ALS, but it has only a modest effect on survival. ALS has a median survival of 3 to 5 years.¹ A number of mechanisms are thought to initiate and propagate the neurodegenerative process in ALS, including oxidative stress, mitochondrial dysfunction, excitotoxicity, apoptosis, inflammation, and glial activation.² These advances in ALS research, together with the application of high throughput drug screening such as the National Institute of Neurologic Disorders and Stroke Neurodegeneration Drug Screening Consortium,³ have yielded a large number of drug candidates that may

be neuroprotective. However, only a small number of drug candidates can be tested at any one time, as resources available to the ALS community are limited both in terms of eligible research participants and funds. A transparent and rational selection process is required to determine which candidate agents should be prioritized for clinical trial development. A systematic approach to drug selection, rather than pursuing the latest “hot” compound, is important both for ALS and for the broader issue of research strategy in neurodegenerative disorders.

We describe the drug identification and review processes and outline attractive neuroprotective candidates for future ALS clinical trials. Priority was given to making the drug selection process explicit, transparent, and reproducible. We also identify data to be collected for each drug prior to proceeding to

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Table 1 Evaluation criteria for potential neuroprotective agents in ALS*

Criteria	Operational definition
Scientific rationale	Consistency of preclinical data; credible mechanism relevant to ALS although mechanism may be unknown in many cases
Safety and tolerability	Safe and tolerable in humans in the dose and route of administration needed for the proposed effect. Further safety data may be required before use in ALS
Efficacy in relevant animal	Efficacy in rodent model of ALS or other relevant models of disease
Indication of benefit in human clinical studies	Evidence from previous trials that is suggestive of a neuroprotective effect or epidemiologic data fulfilling criteria for causal inference

*Developed from criteria for evaluation of neuroprotective agents in Parkinson disease.⁴

phase III efficacy testing enrolling large numbers of patients with ALS.

Methods. Drug selection process. We first identified a wide spectrum of potential therapeutic agents and a broad range of strategies that could potentially slow disease progression and prolong survival in patients with ALS. We incorporated 1) therapies with mechanisms of action relevant to ALS pathogenesis, 2) agents that have already been tested in ALS animal models or clinical trials, and 3) medications approved or under consideration for neurodegenerative diseases other than ALS. Input was obtained from academic scientists, clinicians, and patient groups to capture the broadest range of available compounds. We also searched Medline to identify publications concerning agents that had been tested in ALS animal models (table E-1 on the *Neurology* Web site at www.neurology.org) or in human trials (table E-2).

Selection of drugs for detailed pharmacologic and safety assessment. We identified 113 therapeutic agents as potentially beneficial in patients with ALS (table E-3). Each therapeutic intervention was assessed by the authors (B.J.T., L.B., R.C., F.B., G.O., M.E.C.) according to the following criteria established at the February 2004 meeting: 1) scientific rationale (i.e., an effect on a pathway implicated in ALS), 2) drug safety and tolerability in humans, 3) indication of benefit in human clinical studies, and 4) efficacy of the drug in ALS animal models. The assessment criteria were developed from those previously employed in evaluating neuroprotective agents in Parkinson disease (PD) (table 1).⁴ The inability of ALS animal models to predict beneficial effects in human trials is recognized⁵ and consequently data from SOD1^{G93A} mouse model were only one of several preclinical data points examined in the drug evaluation process. Data from cell-based screening were included where relevant, though an in-depth review of drug discovery techniques is beyond the scope of this article. Both published and unpublished information was considered. To maintain transparency of the process, expand discussion, and further scientific rigor, we circulated the list of 113 therapeutic agents (table E-3) within the ALS research community. Twenty-four drugs judged to be the most promising agents were selected for further analysis. The reasons for not selecting the remaining 89 drugs for detailed review are also listed in table E-3.

Detailed pharmacologic and safety assessment of proposed agents. A clinical pharmacologist (S.F.) with expertise in neurologic drugs performed a detailed pharmacokinetic and safety assessment of the 24 selected drugs (table E-4). The complete pharmacokinetic, tolerability, and preclinical data sets were employed to select neuroprotective candidates for future ALS clinical trials using a scorecard method (table 2). The pharmaceutical company or academic scientist directly responsible for developing that agent was contacted to obtain further data.

TCH346 was excluded from the final list based on negative results of phase III studies that were not available during the initial review.⁶ Vitamin E was excluded based on the results of two negative clinical trials.^{7,8} Adverse side effects and unfavorable pharmacokinetics eliminated NBQX. Nimodipine was eliminated due to insufficient scientific rationale to support its development as an ALS therapy. Through this process we determined that 20 drugs are viable candidates to be explored in ALS clinical trials in the future (figure and table 3).

Annual reassessments of newly published data on existing and novel neuroprotective agents will also be provided on the ALS Association Web site and will be presented at the International ALS/MND Symposium on a yearly basis.

Description of priority agents. AEOL 10150 (Aeolus Science Inc.). Oxidative damage mediated by toxic free radicals has been implicated in the pathogenesis of ALS⁹ and a variety of antioxidants have been tested in patients with ALS (table E-2). AEOL 10150 is a manganoporphyrin antioxidant that catalytically neutralizes superoxide, hydrogen peroxide, and peroxyxynitrite, and inhibits lipid peroxidation.¹⁰ Administration of AEOL 10150 to transgenic mice with the glycine 93 to alanine SOD1 mutation (SOD1^{G93A}) commencing at symptom onset improved the survival interval (the time from symptom onset to death) by 196% (26.5 days).¹¹ The compound has to be administered IV or by subcutaneous injection. A phase I single dose escalating study enrolling 30 patients with ALS is underway to determine pharmacokinetic, optimum dose, and safety properties of this novel drug class.

Arimoclocholol (Cytrx Corporation). Motor neurons have an intrinsically higher threshold for activation of the heat shock protein pathway¹² and agents that upregulate this pathway may be neuroprotective. Arimoclocholol is a hydroxylamine derivative that co-induces heat shock protein (HSP) expression,¹³ a powerful cytoprotective mechanism under acute stress conditions. Treatment with arimoclocholol prolonged the lifespan of SOD1^{G93A} mice by 22% (28 days).¹⁴ The beneficial effect was independent of whether the treatment was started pre-symptomatically or at symptom onset. Arimoclocholol was well tolerated in a phase I study of healthy volunteers (http://www.cytrx.com/prDetail.cfm?pr_id=164&showcspr=1). Safety, optimum dose, and pharmacokinetics of arimoclocholol (including ability to cross blood-brain barrier [BBB]) are unknown for patients with ALS. A multicenter, dose ranging, phase II study of arimoclocholol in ALS has commenced enrollment (n = 80, www.clinicaltrials.gov, NCT00244244).

Ceftriaxone (Roche Laboratories). Glutamate-mediated excitotoxicity arising from repetitive firing or elevation of intracellular calcium by calcium-permeable glutamate receptors is likely to be an important contributor to motor neuronal death in ALS.¹ Glutamate levels are increased in CSF of patients with sporadic ALS¹⁵ and clearance of glutamate from neuromuscular synapses is also diminished in patients with ALS due to loss of the astroglial glutamate transporter EAAT2.¹⁶ Furthermore, spinal motor neurons are relatively reduced in intracellular calcium-binding components,¹⁷ which may account for their selective vulnerability.²

The antiexcitatory and antioxidant properties of cephalosporins were identified by the Neurodegeneration Drug Screening Consortium that screened 1040 FDA-approved drugs for efficacy in in vitro models of neurodegenerative diseases.¹⁸ Cephalosporins increase EAAT2 promoter activ-

Table 2 Scorecard outlining detailed pharmacologic and safety assessment of 24 neuroprotective drugs in patients with ALS

Agent	Mechanism of action	PK	ALS mouse model	Human safety	Benefits in ALS
AEOL 10150	Antioxidant	0	++	0	0
Arimoclomol	HSP inducer	0	+	+	0
Ceftriaxone	Antioxidant and antiglutamate	+	+	+++	0
Celastrol	Antioxidant and anti-inflammatory	0	+	0	0
CoQ10	Antioxidant and mitochondrial factor	+	++	++	0
Copaxone	Immunomodulatory	0	-/+	+++	0
IGF-1	Neurotrophic	0	+ (wobbler)	++	+/-
IGF-1-AAV	Neurotrophic	0	+	0	0
Memantine	Antiglutamate	++	0	+++	0
Minocycline	Antiapoptotic	++	++	+++	0
Naaladase inhibitor	Antiglutamate	0	+	0	0
NBQX	Antiglutamate	0	+	-	0
Nimesulide	Anti-inflammatory and antioxidant	0	-	+++	0
Nimodipine	Ca ²⁺ channel blocker	++	+	+++	-
ONO-2506	Glial modulator and antiglutamate	0	0	0	0
Riluzole	Antiglutamate and Na channel inactivation	+	++	++++	+++
Scriptaid	Antiaggregation	0	0	0	0
Phenylbutyrate	HDAC inhibitor	0	+	+++	0
Talampanel	Antiglutamate	+	+	++	+
Tamoxifen	Protein kinase C inhibitor	+	+ (viral model)	+++	+
TCH346	Antiapoptotic	+	-/+	++	-
Thalidomide	Immunomodulatory and antiangiogenic	+	+	+++	0
Trehalose	Antiaggregation	0	0	+++	0
Vitamin E	Antioxidant	+	+	+++	-

Pharmacokinetics: 0 = data on ability of drug to penetrate CSF are unknown; + = drug known to penetrate CSF; ++ = drug has excellent CSF penetration. ALS mouse model: 0 = effect on ALS mouse model unknown to us; - = one mouse study with negative effect on survival; + = one mouse study with a positive effect on survival; ++ = two mouse studies with positive effects on survival; ½ = two animal studies performed, one showed beneficial effect, the other displayed a negative effect on survival. Human safety: 0 = safety in humans not known; + = one human trial that showed drug was relatively safe; ++ = two human trials that showed drug was relatively safe; +++ = FDA/EMEC approved for chronic use in other disorders; ++++ = FDA/EMEC approved as an ALS drug. Benefits in ALS: 0 = unknown; - = negative trial in well-designed studies; + = positive (or trend) efficacy in phase II trials; +++ = FDA/EMEC approved as an ALS drug.

ity and protect motor neurons from glutamate toxicity in culture.¹⁸ The third generation ceftriaxone was selected for human studies because of its superior CNS penetration and long half-life.¹⁹ SOD1^{G93A} transgenic mice treated with ceftriaxone at symptom onset lived 8% (10 days) longer than control animals.¹⁸ Ceftriaxone is generally well tolerated,²⁰ though experience with long term IV administration (beyond 6 weeks) is limited. A combined phase II and III study will commence enrollment in the near future.

Celastrol (generic). Neuroinflammation occurs in the brainstem and spinal cord of patients with ALS²¹ and SOD1^{G93A} mice suggesting that anti-inflammatory agents may be effective in treating this disease.²² Celastrol is a potent anti-inflammatory and antioxidant triterpene that suppresses TNF α , IL-1 β , and inducible nitric oxide production²³ and induces a heat shock protein response.²⁴ Administration of celastrol from 4 weeks of age improved weight loss, rotorod performance, and survival of SOD1^{G93A} mice.²⁵ Further data concerning the ability of the drug to cross the BBB, toxicity, and safety in patients with ALS

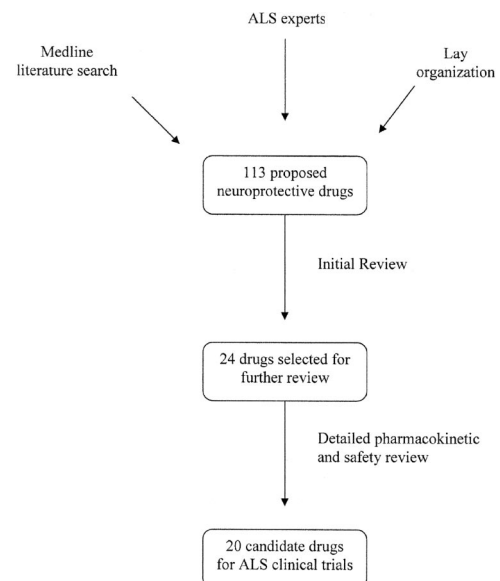


Figure. Drug identification and assessment sequence.

Table 3 Priority list for phase III ALS clinical trials

- A. Suitable for phase III trials in the near future
 1. Talampanel
 2. Tamoxifen
- B. Already in phase III trials involving large number of human subjects
 1. Ceftriaxone
 2. IGF-1 polypeptide
 3. Minocycline
 4. ONO-2506
- C. More data required prior to phase III testing
 1. AEOL 10150†‡§
 2. Arimoclomol*†‡§
 3. Celastrol*†‡§
 4. Coenzyme Q10‡§
 5. Copaxone*§
 6. IGF-1—viral delivery*†‡§
 7. Memantine*†‡§
 8. NAALADase inhibitors*†‡§
 9. Nimesulide*‡§
 10. Scriptaid*†‡§
 11. Sodium phenylbutyrate†‡§
 12. Thalidomide†‡§
 13. Trehalose*‡§
- D. Already Food and Drug Administration approved as ALS therapy
 1. Riluzole and related benzothiazole drugs (see text for further details)

*Transgenic efficacy animal studies.

†Human toxicology.

‡CNS pharmacokinetic studies.

§Dose-ranging studies.

and optimum dose remain to be collected prior to phase III testing.

Coenzyme Q10 (generic). The high metabolic load of motor neurons and the consequent dependence of these cells on oxidative phosphorylation may make them particularly vulnerable to the loss of mitochondrial function.¹ Coenzyme Q10 is an antioxidant and an essential mitochondrial cofactor facilitating electron transfer in the respiratory chain.²⁶ This commonly used nutraceutical is being tested in neurodegenerative conditions in which mitochondrial dysfunction has been implicated including ALS, Huntington disease (HD), and PD. Low dose coenzyme Q10 prolonged median survival of SOD1^{G93A} transgenic mice by only 4.4% (6 days),²⁷ but higher doses are more effective (Flint Beal, personal communication). Doses up to 3,000 mg per day are safe and well tolerated in patients with ALS.²⁸ Coenzyme Q10 is lipophilic and effectively crosses the BBB.²⁹ A phase II study in ALS has commenced enrollment (NCT00243932).

Copaxone/glatiramate (Teva Pharmaceuticals). Previous clinical trials of immunosuppressant therapies failed to slow progression in ALS,³⁰ but immunomodulation may be more effective at preventing neuronal apoptosis.³¹ Cop-

axone evokes a neuroprotective T cell-mediated response and may protect against glutamate toxicity.³¹ Low copy number SOD1^{G93A} ALS mice immunized at 60 days of age followed by oral dosing of copolymer-1 experienced a 24.6% (52 day) increase in lifespan and delayed disease onset,³¹ though these findings have not been replicated in high copy SOD1^{G93A} mice treated with a copaxone derivative.³² Additional preclinical data are required to determine reproducibility and optimum dosing schedule to achieve immunomodulation.

Insulin-like growth factor 1 (IGF-1, Cephalon). Neurotrophic factors selectively regulate survival and differentiation of nerve cells and maintain neuronal structural integrity. Of all neurotrophic factors tested in ALS to date (table E-2), only IGF-1 slowed the rate of functional decline by 26% in a North American phase III trial (n = 266).³³ In contrast, a European IGF-1 trial was negative (n = 183)³⁴ and so a third phase III trial of this neurotrophic factor is currently underway (n = 330, NCT00035815) to conclusively determine efficacy. IGF-1 is well tolerated, though the large size of the IGF-1 polypeptide may prevent BBB penetration. There are no published reports of the effect of IGF-1 on mutant SOD1^{G93A} mouse survival.

IGF-1—viral delivery (Ceregene, Inc.). Adeno-associated virus engineered to contain the gene for IGF-1 (AAV-IGF1) allows targeted delivery of IGF-1 to motor neurons. After IM injection, the gene vector is transported to the neuronal cell body by retrograde axonal transport along motor neurons.³⁵ AAV-IGF-1 prolongs median survival by 30% (37 days) when administered before disease onset.³⁵ Human safety, dose schedule, and pharmacokinetics have not yet been established for this novel gene therapy, though AAV-factor IX vector has proven safe in patients with hemophilia.³⁶ A small phase IIa trial of AAV-IGF-1 is planned for the near future. Expansion of the viral vector production capacity will be required before proceeding to large scale trials.

Memantine (Forest Laboratories, Inc.). The higher expression of calcium-permeable α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors on motor neurons may explain the selective vulnerability of this cell type to glutamate excitotoxicity.³⁷ Memantine (an amino adamantine derivative) is an AMPA receptor antagonist licensed as a neuroprotective agent for Alzheimer disease (AD). The drug exhibits excellent CNS penetration³⁸ and is well tolerated by patients with AD, but there are no published studies of the survival effect of in ALS animal models and additional data to support the rationale for testing in patients with ALS are needed.

Minocycline (generic). The role of apoptosis in motor neuron degeneration is increasingly recognized. In SOD1-mediated ALS, motor neurons probably die through the formation of insoluble mutant SOD1 aggregates that bind to and deplete motor neurons of the antiapoptotic protein Bcl-2 allowing activation of caspases.^{39,40} Although apoptosis is a late event in the degeneration of motor neurons, inhibition of programmed cell death might ameliorate ALS.¹ Minocycline is a second generation tetracycline antibiotic that prevents microglial activation⁴¹ and inhibits caspase activation.⁴² Four SOD1 transgenic mouse studies show enhanced median survival ranging between 6.4% and 16%.⁴¹⁻⁴⁴ Two small phase II studies demonstrated safety and tolerability of minocycline in patients with ALS (n =

19 and 23).⁴⁵ Typical side effects include gastrointestinal upset, vertigo, and cumulative dose-dependant photosensitivity. A phase III efficacy trial of minocycline is currently enrolling 400 patients (NCT00047723). The ability of the drug to penetrate uninflamed meninges should be determined.

N-acetylated alpha-linked acidic dipeptidase (NAALADase, Guilford Inc.). Inhibition of glutamate carboxypeptidase 2 (GCP2) may be neuroprotective by simultaneously decreasing glutamate production and inhibiting glutamate release.⁴⁶ Median survival of SOD1^{G93A} ALS mice was prolonged by 15% (29 days) by administration of the GCP2 inhibitor 2-(3-mecaptopropyl) pentanedioic acid. GCP2 inhibition is attractive as a therapeutic target because the effects only occur during excessive glutamate stimulation avoiding glutamate receptor antagonist side effects.⁴⁶ NAALADase inhibitors have not yet been administered to humans and there are no data on pharmacokinetics and tolerability.

Nimesulide (generic). The enzyme COX-2 is an attractive therapeutic target because of its marked increase in ALS spinal cord stimulating astrocytic glutamate release.^{47,48} Nimesulide is a preferential COX-2 inhibitor with additional antioxidant properties.⁴⁹ Nimesulide administration decreased PG-E2 levels in the spinal cord of SOD1^{G93A} mice and preserved motor skill integrity.⁵⁰ However, the COX-2 inhibitor celecoxib failed to show benefit in a phase II/III trial.⁵¹ Furthermore, safety concerns surrounding long-term administration of this medication class may limit use in patients with ALS.⁵²

ONO-2506 (Ono Pharmaceutical Co. Ltd). Chimeric mice with both normal and mutant SOD1-expressing cells indicate that glia play a role in motor neuron degeneration.⁵³ Possible mechanisms include microglial-mediated neuroinflammation, loss of neurotrophic support,² and diminished clearance of glutamate from neuromuscular synapses by the astrocytic glutamate transporter EAAT2.¹⁶ ONO-2506 is an enantiomeric homologue of valproate that restores normal astrocyte functions after brain damage by preventing reactive astrocytosis, by activating astrocytic GABA_A receptors and suppressing GABA transferase.⁵⁴ This agent has additional ant glutamate⁵⁵ and anti-inflammatory COX-2 inhibitor properties.⁵⁶ Results of a completed phase II trial of 1,200 mg per day oral formulation (cereact) are pending. A phase III trial of the parent compound valproate has commenced enrollment in Europe (n = 173, NCT00136110).

Riluzole (Sanofi-Aventis). Riluzole remains the only FDA-approved drug for ALS based on the 3-month improvement in survival observed in two large clinical trials.^{57,58} Riluzole has a broad range of pharmacologic effects including inhibition of glutamate release, postsynaptic glutamate receptor activation, and voltage-sensitive sodium channels inactivation. It was identified before the SOD1 mouse model became available by studying toxicity of CSF from patients with ALS on neuronal cell cultures.⁵⁹ Subsequently, riluzole was found to have a modest effect on SOD1^{G93A} mouse survival (prolonged median survival by 11%, 14 days).⁶⁰

Riluzole has been included in the final list not to suggest that further trials of this drug are required, but rather to emphasize the surprising lack of effort to build on the modest success of riluzole. Related benzothiazoles have

not been tested in ALS animal models or patients. A collaborative effort between academic scientists and industry may rejuvenate development of this drug class.

Scriptaid (Alexis Biochemicals). Abnormal protein aggregates have been described in neurodegenerative diseases including AD, PD, and HD. Ubiquitin inclusions are present in motor neurons and astrocytes of patients with ALS.⁶¹ It is not known if these aggregates damage or protect motor neurons, though several possible toxic mechanisms have been proposed including aberrant chemistry, loss of normal proteins through sequestration within aggregates, and inhibition of mitochondria, peroxisomes, or proteasomal function overwhelmed with indigestible, misfolded protein.² Agents that decrease aggregation have been hypothesized to be neuroprotective. Scriptaid was identified in a screen for small molecules that disrupt in vitro aggresome formation in cultured COS cells transfected with mutant SOD1-GFP.⁶² Safety, optimum dose, and pharmacokinetic animal and human data remain to be determined for this drug.

Sodium phenylbutyrate (Scandinavian formulas). Sodium phenylbutyrate (NaPB) is FDA-approved for chronic treatment of hyperammonia and has been tested as a treatment of spinomuscular atrophy.⁶³ Its potential benefit in ALS is based on its ability to inhibit histone deacetylase (HDAC) leading to increased gene transcription.⁶⁴ This aromatic short-chain fatty acid extends median survival of SOD1^{G93A} ALS mice by 21.9% (27.5 days).⁶⁴ NaPB has a short half life (45 minutes), though changes in gene expression induced by the drug may be more persistent. CNS distribution of NaPB has been determined by MR spectroscopy.⁶⁵ An open label, dose-escalation study enrolling 40 patients with ALS is underway to determine human safety (NCT00107770).

Talampanel (8-methyl-7H-1,3-dioxolo(2,3)benzodiazepine, IVAX Corporation). Talampanel is a noncompetitive modulator of AMPA glutamate receptors primarily under development as an antiepileptic agent. Talampanel has been shown to prolong SOD1^{G93A} mouse median survival (Jeffrey Rothstein, personal communication). ALSFRS and TQNE scores declined at a slower rate in a 9-month phase II study of talampanel in 60 patients with ALS though the study was not powered to detect efficacy (Robert Pascuzzi, personal communication). The most common side effects were ataxia and sedation. The antiepileptic properties of talampanel indicate that the drug crosses the BBB.

Tamoxifen (Astra Zeneca). Tamoxifen may be neuroprotective in ALS because of its ability to inhibit protein kinase C, which mediates inflammation in spinal cords of patients with ALS.⁶⁶ Tamoxifen extended survival in a virally induced ALS mouse model.⁶⁷ A phase II study of 60 patients with ALS prolonged survival at 10 mg, 20 mg, 30 mg, and 40 mg daily doses (Ben Brooks, personal communication). The drug penetrates the CNS and is generally well tolerated. The effect of the drug on survival of SOD1^{G93A} mice needs to be evaluated and the results of the phase II study should be peer-reviewed. However, if these results are favorable, planning for a phase III study may be expedited.

Thalidomide (Celgene). Angiogenic factors controlling the growth and permeability of blood vessels have been implicated in the pathogenesis of ALS. Mice bearing a deletion of the vascular endothelial cell growth factor

(VEGF) gene develop an ALS-like phenotype⁶⁸ and polymorphisms of the VEGF promoter region increase the risk of ALS.⁶⁹ Coding mutations of a related gene angiogenin have also been linked to the disease.⁷⁰ Thalidomide is a non-barbiturate sedative that was withdrawn from the world market in 1961 on discovery of its teratogenic effects. It has been selectively reintroduced for a variety of conditions including progressive body weight loss related to advanced cancer and AIDS.⁷¹ The drug has anti-angiogenic activity and immunomodulatory properties.⁷¹ Oral thalidomide reduced TNF α , attenuated weight loss, and increased survival in SOD1^{G93A} mice.⁷² Thalidomide crosses the BBB, as indicated by its sedative effects. Peripheral neuropathy has been observed in 8% of patients with HIV and can become irreversible if thalidomide is not discontinued.⁷³ Lenalidomide, a novel 4 amino-glutarimide analogue, shows the same efficacy in animal studies without the neurotoxic and teratogenic effects.^{72,74} An open-label, phase II trial is currently recruiting patients (n = 24, NCT00140452).

Trehalose (Cargill, Inc.). Trehalose is a natural disaccharide used in freeze-dried products to prevent protein denaturation. Trehalose may prevent formation of mutant SOD1 aggregates in ALS by stabilizing mutant proteins.⁷⁵ The agent has a long history of human use and the FDA has issued a "letter of no objection" (GRAS No. GRN 000045). However, there are no data on toxicity in patients with ALS, the ability of the drug to penetrate the CNS is unknown, and its effect in transgenic ALS mouse model remains to be evaluated.

Discussion. We identified and assessed potential compounds for clinical trials in patients with ALS. Academic clinicians and scientists identified 113 compounds, of which 24 were selected for more detailed pharmacokinetic and safety analysis. Twenty were chosen as the most promising agents that should be studied in phase III clinical ALS trials. Two agents on the priority list (talampanel and tamoxifen) show preliminary efficacy in phase II ALS clinical studies. Other agents (ceftriaxone, minocycline, ONO-2506, and IGF-1 polypeptide) are already in phase III trials involving large numbers of patients. Most agents on the final priority list require additional data (preclinical animal data, human toxicity, and pharmacokinetic data [including CNS penetration]) prior to proceeding to large scale human testing (see table 3).

While a detailed attempt was made to make the review process explicit, qualitative judgments had to be prepared about the relative value and weighting of different types of information. The most problematic issues were the evaluation of unpublished data and the authors' biases. Although considerable effort was made to obtain information from investigators developing an agent, not all data were available to the authors. The initial screen was performed by investigators in the field, which may have resulted in bias toward agents studied in their laboratories. To ensure transparency all data relevant to this article were made available to the ALS community throughout the selection process.

Animal drug-screening studies in ALS almost exclusively utilize the mutant SOD1^{G93A} mouse (table E-1), but the ability of this model to predict drug efficacy in humans is ambiguous. Several drugs that prolong survival in animal studies have not shown efficacy in human trials (celebrex,^{51,76} creatine,^{77,78} gabapentin,^{60,79} N-acetylcysteine^{80,81}). This discrepancy may be due to intraspecies differences in pharmacokinetics and the difficulty in establishing dose equivalence to achieve the same biologic activity in humans as observed in mice. It may also be that this mouse model of familial ALS does not predict drug effect in patients with sporadic ALS and that development of alternative models should be prioritized.

Interpretation of animal drug screening studies is complicated by varying experimental designs between laboratories. For example, mouse strain and sex,⁸² as well as environmental factors such as access to exercise, affect survival.⁸³ There is a need to establish consensus guidelines to ensure ALS animal drug studies are conducted in a uniform manner. Experimental design issues that warrant standardization include the type of animal models, number of animals and sex distribution required to reliably detect an effect, as well as the timing and method of drug delivery. The selection of appropriate survival and motor function endpoints is essential. Guidelines on the publication of negative results and the establishment of an online database of ALS animal drug studies should be a priority. Most importantly, guidelines should be established outlining the magnitude and the reproducibility of drug effect in different laboratories and animal models required to proceed to human clinical testing.

The pharmacokinetic profile, the safety/toxicity properties, and the most efficacious dose of the drug in humans must be adequately established prior to phase III studies. There has been a tendency for potentially beneficial candidates to move rapidly to large ALS clinical trials. Although this approach has demonstrated that certain drugs are ineffective, it has been unsuccessful at identifying useful therapies. The ability of a drug to cross the human BBB to reach its target ligand should be determined prior to starting phase II studies. Tolerability of a dose in healthy patients should not be taken as indication that the same dose will be safe in patients with ALS. The frequency of adverse events was significantly higher in patients with ALS receiving topiramate than was seen in patients with epilepsy, possibly related to dehydration and malnutrition in patients with ALS.⁸⁴ Dose-ranging studies are a prerequisite to phase III studies to determine the most effective and safe dosage. Focusing on early clinical safety, dose-finding, and pharmacokinetic testing will increase a drug's early development costs, but will maximize its chance of success in large phase III efficacy studies.

Multiple pathways have been implicated in the pathogenesis of ALS.² A medication or combination

of medications that targets more than one pathogenic pathway may slow disease progression in an additive or synergistic fashion. Such combination therapy has been successful in oncology, though multiple drug interactions and increased incidence of drug side effects should be considered. More detailed animal toxicology studies of combination therapies are required than for therapies given alone. Drug resistance must also be considered when a medication is administered for prolonged periods (months). Upregulation of multidrug resistance proteins has been reported in astrocytes and BBB of patients with neurodegenerative diseases with neuroinflammatory components, such as ALS. These transporters extrude endogenous toxins (such as medications) from CNS from the cells and may nullify a drug's bioactivity.⁸⁵

In this article we evaluated existing drugs for their potential development in ALS in an explicit, systematic, and transparent manner. The selection process is intended to prioritize interventions for phase III trials in patients with ALS and to identify data that need to be collected prior to clinical studies involving large numbers of human subjects. The ALS Association has issued a request for applications building on the final list published in this article.⁸⁶ More candidate drugs will be identified as academic researchers adopt high throughput screening techniques and study candidate neuroprotective drugs in new animal models of ALS. Thus, the need to rationally select agents for clinical testing in patients with ALS will increase and the current approach can be extended to evaluate new therapies as they emerge. New data on both existing and novel neuroprotective agents will be assessed annually and updates made available on the ALS Association Web site and presented at the annual International ALS/MND Symposium.

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