Published in final edited form as:
Amyotroph Lateral Scler. 2011 January ; 12(1): 1–10. doi:10.3109/17482968.2010.502940.

The epidemiology and treatment of ALS: Focus on the heterogeneity of the disease and critical appraisal of therapeutic trials

Ettore Beghi,
Milano, Italy

Adriano Chiò,
Torino, Italy

Philippe Couratier,
Limoges, France

Jesùs Esteban,
Madrid, Spain

Orla Hardiman,
Dublin, Ireland

Giancarlo Logroscino,
Bari, Italy

Andrea Millul,
Milano, Italy

Douglas Mitchell,
Preston, UK

Pierre-Marie Preux,
Limoges, France

Elisabetta Pupillo,
Milano, Italy

Zorica Stevic,
Belgrade, Serbia

Robert Swingler,
Dundee, UK

Bryan J. Traynor,
Bethesda, Md, USA

Leonard H. Van den Berg,
Utrecht, The Netherlands

Jan H. Veldink, and
Utrecht, The Netherlands

Correspondence: E Beghi, Istituto di Ricerche Farmacologiche ‘Mario Negri’, Via G. la Masa 19, 20156 Milano, Italy. Fax: 02 39 001916. ettore.beghi@marionegri.it.

Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Stefano Zoccolella
Bari, Italy

On Behalf Of The Eurals Consortium

Abstract

Effective treatments for amyotrophic lateral sclerosis (ALS) have remained elusive. Only riluzole, a drug thought to affect glutamate metabolism, improves survival albeit to modest extent. Explanations for the negative results of therapeutic trials include a likely heterogeneity, both in disease susceptibility and pathogenic mechanisms, and faulty methodology of clinical trials. Further understanding of these factors will lead to improvements in patient stratification, and in the design of future clinical trials.

Introduction

Effective treatments for amyotrophic lateral sclerosis (ALS) have remained elusive. Only riluzole, a drug thought to affect glutamate metabolism, improves survival albeit to modest extent (1). Explanations for the negative results include a likely heterogeneity in disease susceptibility and pathogenic mechanisms and defective design of published clinical trials. A better knowledge of the representativeness of the study populations, identification of the main prognostic predictors, and a critical appraisal of the study design and methods provide the basis for the implementation of more successful clinical trials.

This paper outlines the contribution of population based registries to the identification of representative population cohorts, discusses a method to ensure complete case ascertainment, identifies the limitations of the existing datasets, and proposes a mechanism to improve the future design and output of randomized trials.

Population based registries: a valuable source of representative population samples

Amyotrophic lateral sclerosis (ALS) is a relatively rare disease with a reported population incidence of between 1.5 and 2.5 per 100,000 per year (2). Over the past 10 years, the design of ALS epidemiological studies has evolved to focus on a prospective, population based methodology, employing the El Escorial criteria and multiple sources of data to ensure complete case ascertainment. The structure of all recent studies has been based on the registry for the collection of data, similarly to what has been done for cancer registries. The main advantage of a registry is its ability to achieve complete case ascertainment through the use of multiple sources of information on ALS patients. In contrast, clinic based studies (the usual source of patients enrolled in randomized trials) rely on a single source of information and are recognized to have poor case ascertainment. Data sources for European ALS registries include neurological and neurophysiological departments, intensive care units, geriatricians, neurologists in private practice, neuropathologists, respiratory physicians, nursing homes and rehabilitations centres, as well as community based reporting from general practitioners. In clinic based studies, the cases are younger, with longer life expectancy, Caucasians and familial. In an Italian study comparing tertiary ALS centres to general neurological clinics, patients followed up by tertiary ALS centres were found to be four years younger and to have a considerably longer median survival time (1080 vs. 775 days), even when stratifying by age, site of onset and respiratory function at diagnosis (3). In a study in Ireland, a clinic cohort was an average of five years younger (60.1 vs. 65.6 years) than the general neurology cohort (4). In that study, the median survival of the clinic cohort was 7.5 months longer than for patients in the general neurology cohort. In a study in Texas

(5), the percentage of familial cases was 5% in the referral series compared to 2% in a population based study conducted in the same area. Another important issue is the prospective enrolment of ALS patients, which has now become the gold standard in ALS epidemiology. Standardized enrolment is more likely in prospective studies. The prospective collection of data permits the identification of newly diagnosed or incident cases and the calculation of measures of risk such as the incidence rates and cumulative incidence. The diagnoses can be monitored over the follow-up and checked at constant time intervals. The ALS mimic syndromes can be fully ascertained and the incorrect ALS diagnoses easily identified. Interestingly, population based registries have a percentage of ALS mimic syndromes fairly similar to that of tertiary centres (about 7–9%) (6,7). Five registry studies, based in Europe and North America, have been published and show remarkably consistent incidence figures among their respective Caucasian populations (8–12). Patients from these registries may thus represent valuable incident cohorts to be enrolled in randomized trials.

Patient ascertainment: the capture-recapture method as a means to ensure ascertainment

Epidemiological research in the last decade has brought into question the completeness of standard incidence numbers derived from single-source reporting. Using several sources of information, the capture-recapture method allows to estimate the proportion of patients not identified through any of the sources from the proportions and distribution of patients identified within each source (multiple source linkage record system) (13). The capture-recapture method was first applied in zoology to estimate the size of an animal population. Used later to evaluate the completeness of birth and death registries, this method is largely employed in epidemiology to assess the completeness of surveillance systems and to give an accurate estimate of the prevalence and incidence of a given clinical condition. The prerequisites for the implementation of capture-recapture are the following: 1) sources must be independent; 2) the probability of each subject to be captured by each source should be the same; 3) the population must be closed; 4) the study must be carried out in the geographic area and in the same period of time; and 5) cases to be identified should be correctly diagnosed by each source.

The capture-recapture method can be applied to the epidemiology of ALS to assess the quality of the collected data, to standardize quality of search over time for assessment of time trends, and to compare epidemiological indexes from different surveys or registries and analyse possible sources of heterogeneity.

Three epidemiological surveys on ALS have used the capture-recapture method. The first (5) was conducted in Harris County, Texas, U.S.A. in 1985–1988. Sources included hospital discharges, neurologists' records and death certificates. Based on 97 newly diagnosed patients, the observed annual incidence of ALS was 1.1 per 100,000. Using the capture-recapture method, the rate was 1.6 (141 newly diagnosed patients). The second study (14) was conducted in Limousin, France in 1994–1995 using the database of the Limoges Neurology Department, the private practice records of the Limousin neurologists, the hospital discharge records from Limousin and neighbouring regions, and the ALS centre in Paris. A total of 46 patients with newly diagnosed ALS were identified, giving a mean annual incidence of 3.2 per 100,000 population (2.5 after standardization). The corresponding number of cases identified through the capture-recapture method was 70 (annual incidence 4.9 per 100,000; 3.8 after standardization).

The third study (15) estimated the occurrence of ALS among Gulf War veterans using the Veteran Affairs, Department of Defense, phone line, and National ALS Association databases. All three approaches in this study indicated differential under-count of ALS cases

with modest under-ascertainment likely to have occurred among non-deployed military personnel, but little under-ascertainment among the deployed.

Although useful, the capture-recapture method also has some limitations: 1) It is generally limited to patients seeking medical attention. 2) There is uncertainty about the use of identical diagnostic criteria. 3) If patients' subgroups are selected, the probability of tracing those included in a given subgroup may be different. 4) The use of administrative sources may be in conflict with privacy regulations. However, even with these limitations, the method can be a valuable, cost-effective instrument to ascertain patients to be registered and eventually enrolled in randomized trials.

Defining prognostic factors in ALS: the need for stratification

Although the mean survival of the patients from symptom onset is thought to be 3–5 years (16), published studies report a wide range of outcomes, and major prognostic factors (apart from age and site of onset) have not been well defined. A better understanding of factors influencing ALS outcome would guide physicians and patients in scheduling therapeutic interventions, and is particularly relevant to clinical trial design. There is an urgent need to: 1) summarize current knowledge concerning factors related to survival in ALS; and 2) evaluate the implications of these data in the design of clinical trials.

A literature search was conducted to include the following: 1) studies based on series from ALS referral (tertiary) centres; 2) studies based on the placebo arm of pharmacological trials; 3) studies based on population based series (17).

Survival of ALS is strongly affected by the population at risk. The median survival from onset to death in ALS varies from 20 to 48 months with longer survival times in patients from ALS referral centres. This wide range narrows when considering population based studies (20–36 months). However, all studies report a survival longer than 10 years in 10–20% of patients. Older age, but not gender, is consistently found to be associated with shorter survival. A number of clinical factors also predict ALS prognosis. These include, among others, the severity and the rate of disease progression, the degree of diagnostic certainty, and the presence of dementia (Table I). Therapeutic interventions (riluzole, enteral nutrition, non-invasive ventilation and interdisciplinary care) are also accompanied by a higher survival rate. A number of biological markers have been also thought to affect survival. These include tyrosine, glutamic acid, fibronectin, cytokines, growth factors, high-density lipoproteins, neurofilaments, erythropoietin, substance P, Nogo-A and Nogo-B (myelin-associated proteins and potent inhibitors of neurite outgrowth) (18). However, the consistency of the available findings must be still proven before using any of these markers to improve the yield of outcome measures in randomized trials.

The known demographic and clinical prognostic predictors indicated in Table I should be considered for inclusion in the design of future randomized clinical trials. The traditional stratification of ALS patients into bulbar and spinal onset is no longer adequate. Detailed clinical databases will be required to enable a priori and post hoc stratification in clinical trials. At the very least, stratification should include age, respiratory status and cognitive status at baseline, provided that the reliability of the latter two is demonstrated.

Furthermore, trial protocols should include guidelines for major interventions and for 'best clinical practice' in ALS patients. As evolving data show that the existence of a multidisciplinary team affects clinical outcome in ALS, randomization should also be performed by centre.

An alternative approach to classical randomization that is widely accepted in early phase oncology trials is the so-called minimization, a method ensuring excellent balance between groups for several prognostic factors (19). Minimization is a non-random method aiming to ensure treatment arms are balanced with respect to predefined patient factors as well as for the number of patients in each group.

Natural history controls have been also advocated as an effective means to eliminate placebo in clinical trials in ALS, since the use of placebo in such a severe disorder as ALS may be considered unethical (20,21). However, the use of historical controls severely limits the process of matching, as retrospective mining of clinically relevant variables can be difficult and subject to bias, and historical controls are frequently drawn from prevalent rather than incident populations.

Appropriate attention to known prognostic factors is essential in the future design of trials.

Clinical trial design: a review of methodological issues

The efficacy of a number of drugs and other treatments in ALS has been evaluated recently by the Cochrane Neuromuscular Diseases group. These include riluzole, recombinant human insulin-like growth factor I (rhIGF-I), amino acids, antioxidant drugs, ciliary neurotrophic factor (CNTF), enteral tube feeding and antispastic agents.

Systematic review of riluzole included three trials (riluzole 876; placebo 406) (1). One included older patients with more advanced ALS. Riluzole 100 mg per day provided a benefit for the homogeneous group of patients in the first two trials ($p = 0.039$, hazard ratio (HR) 0.80, 95% CI 0.64–0.99). Addition of the trial including more advanced patients altered the outcome of the meta-analysis in that the overall treatment effect estimate became insignificant ($p = 0.056$, HR 0.84, 95% CI 0.70–1.01). Increased serum ALT (> x3) was more frequent in riluzole treated patients than controls (weighted mean difference, WMD 2.62, 95% CI 1.59–4.31). Based on this meta-analysis, riluzole 100 mg daily is considered safe and is likely to prolong survival by about two months. More studies are needed, especially to clarify its effect in older patients (over 75 years) and those with more advanced disease.

The efficacy and safety of recombinant insulin-like growth factor (rhIGF-I) in ALS was evaluated on the basis of two trials (22). The primary outcome measure was change in disease progression as determined by the Appel ALS Rating Scale (23) total score with 0.1 mg/kg/day of rhIGF-I subcutaneously after nine months treatment. The combined analysis from both trials showed a WMD of −4.75 (95% CI −8.41 to −1.09) favouring the treated group. While evaluation of adverse events showed an increased risk of injection site reactions with rhIGF-I, the drug was otherwise safe and well tolerated. A third placebo controlled trial has been recently completed. There was no difference between treatment groups in the primary and secondary outcome measures after a two-year follow-up period (24). In conclusion, rhIGF-I is not beneficial for patients with ALS.

Of 23 trials assessing the efficacy of antioxidant agents, nine met inclusion criteria (25). Only two used survival at 12 months treatment as primary outcome measure. Sufficient data were available from three studies to allow analysis of the primary outcome measure, and a meta-analysis was performed. No significant effect with vitamin E 500 mg twice daily; acetylcysteine 50 mg/kg daily subcutaneous infusion; or a combination of L-methionine 2 g, vitamin E 400 IU, and selenium 3 × 10-5 g three times daily. No significant effect on the primary outcome measure was observed in a meta-analysis of antioxidants in general when combining the results. No significant differences were demonstrated in secondary outcome measures.

Thirteen hundred ALS patients treated with subcutaneous ciliary neurotrophic factor (CNTF) were examined in two trials (26). No significant difference was observed between CNTF and placebo groups for survival, the primary outcome measure (RR 1.07; 95% CI 0.81–1.41). No significant differences were observed for the secondary outcomes. However, a significant increase of the incidence of several adverse events was noted in groups treated with higher doses of CNTF. In conclusion, CNTF treatment had no effect on ALS progression. At high concentration, several side-effects were observed. A combination of CNTF with other neurotrophins and more efficient delivery methods should be tested.

The efficacy of percutaneous gastrostomy (PEG) or other tube feeding placement was assessed on survival, nutritional status and quality of life and to examine the minor and major complications of PEG (27). There are no randomized controlled trials to indicate whether enteral tube feeding is beneficial compared to continuation of oral feeding for survival. The ‘best’ evidence based on controlled prospective cohort studies suggests advantage for survival in all ALS/MND patients. Evidence for improved nutrition is incomplete but tentatively favourable. Quality of life has only been addressed by a few researchers and needs more serious attention.

The only study performed to assess the efficacy of treatments on spasticity compared endurance type exercise versus ‘usual activities’ in 25 ALS patients (28). At three months, patients performing the exercises had significantly less spasticity (mean reduction of −0.43, 95% CI −1.03–0.17 vs. an increase of +0.25, 95% CI −0.46–0.96 in control). Mean change between groups was not significant as measured by the Ashworth scale (29). This single trial was too small to determine whether the exercises are useful. No other medical, surgical or alternative treatment and therapy has been evaluated in a randomized fashion in this patient population.

A Medline and Cochrane trial registry search was also made of all randomized clinical trials in the treatment of ALS to identify tested drugs and methodological pitfalls. Hand search was made of all references of eligible articles. Included were all participants with a clinical diagnosis of ALS at any stage of the disease and with differing clinical patterns (bulbar vs. limb onset). Excluded were non-randomized trials, non-human investigations, abstracts and letters. Each trial was assessed in terms of diagnostic criteria, population, design, duration, primary endpoints, and drop-outs. The methodological reliability of each study was investigated by checking the following items: 1) sample size and baseline characteristics; 2) randomization and blinding techniques; 3) definition of drop-outs and premature discontinuations; 4) relevance of results; and 5) applicability of results (external validity). The rationale for use was insufficient for 20 drugs and animal studies were negative for four. The total number of exposed individuals ranged from eight to 891 and was greater than 100 for 18 drugs. An unacceptable toxicity was documented for six drugs. A total of 77 studies fulfilled all requirements for review. Tested drugs are listed in Table II with number of exposed patients, rationale for use, and safety. The main methodological aspects of each randomized trial are depicted in Table III. The total number of included patients was > 50 in 42 studies and > 100 in 30 studies. Disease duration at entry varied significantly across studies (data not shown). Baseline characteristics were different in the experimental and control group in nine and are not specified in 16 studies. Primary endpoints were not pre-defined in 20 trials and varied across studies (the commonest being survival, progression rate, and different functional disability scores). Twenty-six studies had more than 20% drop-outs; the drop-out rate was not specified in 13 studies. The blinding procedure was not specified in 28 studies and was inadequate in seven. Concurrent treatments were not specified in 54 studies and were unequally distributed in three. Raw data were not available in 39 studies and risk measures with confidence intervals were reported in only 15. Subgroup analyses were present in only 19 reports. Adverse event reports were lacking in 12

studies. Study power was not calculated in 36 studies. Methodological flaws predominated in the oldest reports.

On this basis, the predominantly negative results of several randomized clinical trials in ALS can be largely explained by the lack of rationale, small sample size, inclusion of heterogeneous populations, high number of drop-outs, and the use of inadequate efficacy measures. In order for a drug to be tested in humans, a solid rationale should be identified through a credible mechanism of action relevant to ALS, which could be confirmed by consistent preclinical data. This does not prove to be the case for several active principles indicated in Table II. Small sample size prevents the discovery of mild to moderate drug effects. For example, using loss of ambulation, gastrostomy and assisted ventilation as outcome measures, a total of 687, 644, and 1039 newly diagnosed patients, respectively, per treatment arm are required to detect a 4–6% difference between active treatment and placebo (Table IV) (30).

The inclusion of patients from prevalent and not from incident populations (such as the newly diagnosed cases) with variable duration of symptoms, differing values of forced vital capacity, and variable site of onset (bulbar vs. spinal) represents a remarkable source of bias which is likely to affect not only any disability measure but even mortality (31). The study endpoints are crucial for the choice of the study design. These may include death or tracheostomy, gastrostomy, mechanical ventilation, and a number of disability measures such as ALSFRS-R (32), MRC (33), Norris (34), and Baylor (23) scale. However, except for ALSFRS-R (35), none of the disability scales has been tested for validity and reliability.

Conclusion

In light of the negative results of the published therapeutic trials in ALS, the efficacy of new pharmaceutical compounds (and any other therapeutic devices) should be tested in representative (population based) cohorts of newly diagnosed patients. The advantages of referring to population based incident cohorts include: 1) a greater potential to respond to a given treatment (compared to prevalent cohorts with long-lasting disease); 2) a greater external validity (i.e. generalization) of the study results. The main prognostic predictors can be taken into account by stratifying the patients into homogeneous groups or selecting specific patients' subgroups. Stratification of patients according to selected prognostic predictors has significant limitations because it complicates the randomization procedure and eliminates the evaluation of possible interactions between prognostic predictors and treatments. However, a proper control of confounding is necessary in the presence of variables known to affect the primary endpoint(s) of the study. Trials performed in different European populations can also help comparing patients with differing genetic susceptibility and exposed to different environmental risk factors.

The European consortium of National Registers (EURALS) (36) represents an ideal setting for case ascertainment using the capture-recapture method. EURALS was established in 2004 to coordinate the scientific activities of six population based registries (Scotland; Ireland; Piemonte/Valle d'Aosta, Italy; Puglia, Italy; Lombardia, Italy; Preston, England) and tertiary centres (Belgrade, Madrid, Moskow, Tel-Aviv). The total population represented in the original population based registries was about 25 million (Italy 13, Scotland 5, Ireland 5, Preston/Manchester 1.8). Other population based registries (Limoges, France; London, England; Utrecht, Netherlands; Emilia-Romagna, Italy; Friuli-Venezia Giulia, Italy) were later included in the consortium. Using a centralized electronic database (located in Italy), on-line registration of newly diagnosed ALS patients is currently undertaken with the following purposes: 1) to provide incidence rates of the disease, in general and in pre-selected subgroups; 2) to investigate genetic and environmental risk

factors; 3) to give access to representative target populations for the implementation of randomized therapeutic trials. The standardization of the registration process has been recently completed. Several well defined sources are interrogated by each of the national registers, including records from several specialists (neurologists, neurophysiologists, neuropathologists, pneumologists), riluzole pharmacy records, lay association archives, general practitioners' records, administrative sources (hospital discharge records, disability lists, etc.), and death certificates. EURALS is thus well placed as an international population based patient registry that has the capability to define and investigate selected risk factors, and to provide a well characterized incident-based cohort of well stratified patients for immediate inclusion in clinical trials.

Acknowledgments

The study was supported by a grant from the Istituto Superiore di Sanità and the American ALS Association (ALSA). The research was supported in part by the Intramural Research Programme of the NIH, National Institute on Aging. The subject of the study has been discussed by EP in her Pharm D thesis.

References

1. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database of Systematic Reviews. 2007; (1):Art. No.: CD001447.10.1002/14651858.CD001447.pub2
2. Beghi E, Logroscino G, Chiò A, Hardiman O, Mitchell D, Swingler R. The epidemiology of ALS and the role of population based registries. BBA. 2006; 1762:1150–7. [PubMed: 17071060]
3. Chiò A, Bottacchi E, Buffa C, Mutani R, Mora G, PARALS. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. J Neurol Neurosurg Psychiatry. 2006; 77:948–50. [PubMed: 16614011]
4. Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996–2000. J Neurol Neurosurg Psychiatry. 2003; 74:1258–61. [PubMed: 12933930]
5. Annegers JF, Appel S, Lee JR, Perkins P. Incidence and prevalence of amyotrophic lateral sclerosis in Harris County, Texas, 1985–1988. Arch Neurol. 1991; 48:589–93. [PubMed: 2039380]
6. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Amyotrophic lateral sclerosis mimic syndromes: a population based study. Arch Neurol. 2000; 57:109–13. [PubMed: 10634456]
7. Davenport RJ, Swingler RJ, Chancellor AM, Warlow CP. Avoiding false positive diagnoses of motor neuron disease: lessons from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry. 1996; 60:147–50. [PubMed: 8708642]
8. McGuire V, Longstreth WT Jr, Koepsell TD, van Belle G. Incidence of amyotrophic lateral sclerosis in three counties in western Washington state. Neurology. 1996; 47:571–3. [PubMed: 8757041]
9. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Incidence and prevalence of ALS in Ireland, 1995–1997: a population based study. Neurology. 1999; 52:504–9. [PubMed: 10025778]
10. Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis (PARALS). Incidence of ALS in Italy: evidence for a uniform frequency in Western countries. Neurology. 2001; 56:239–44. [PubMed: 11160962]
11. Logroscino G, Beghi E, Zoccolella S, Palagano R, Fraddosio A, Simone IL. Incidence of amyotrophic lateral sclerosis in southern Italy: a population based study. J Neurol Neurosurg Psychiatry. 2005; 76:1094–8. [PubMed: 16024886]
12. Beghi E, Millul A, Micheli A, Vitelli E, Logroscino G. SLALOM Group. Incidence of ALS in Lombardy, Italy. Neurology. 2007; 68:141–5. [PubMed: 17210896]
13. Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. Epidemiol Rev. 1995; 17:243–64. [PubMed: 8654510]
14. Preux PM, Druet-Cabanac M, Couratier P, Debrock C, Troung T, Marcharia W. Estimation of the amyotrophic lateral sclerosis incidence by capture-recapture method in the Limousin region of France. J Clin Epidemiol. 2000; 53:1025–9. [PubMed: 11027935]

15. Coffman CJ, Horner RD, Grambow SC, Lindquist J. VA Cooperative Studies Program Project No. 500. Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990–1991) veterans using capture-recapture methods. Neuroepidemiology. 2005; 24:141–50. [PubMed: 15650320]
16. Beghi E, Mennini T, Bendotti C, Bigini P, Logroscino G, Chiò A. The heterogeneity of amyotrophic lateral sclerosis: a possible explanation of treatment failure. Curr Med Chem. 2007; 14:3185–200. [PubMed: 18220753]
17. Chiò A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, Traynor BG. on behalf of the EURALS Consortium. Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler Other Motor Neuron Disord. 2008; 9:1–14.
18. Turner MR, Kiernan MC, Leigh PN, Talbot K. Biomarkers in amyotrophic lateral sclerosis. Lancet Neurol. 2009; 8:94–109. [PubMed: 19081518]
19. Pocock S, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975; 31:103–15. [PubMed: 1100130]
20. Bryan WW, Hoagland RJ, Murphy J, Armon C, Barohn RJ, Goodpasture JC. Can we eliminate placebo in ALS clinical trials? Amyotroph Lateral Scler Other Motor Neuron Disord. 2003; 4:11–5. [PubMed: 12745612]
21. Pradas J, Finison L, Andres PL, Thornell B, Hollander D, Munsat TL. The natural history of amyotrophic lateral sclerosis and the use of natural history controls in therapeutic trials. Neurology. 1993; 43:751–5. [PubMed: 8469335]
22. Mitchell JD, Wokke JHJ, Borasio GD. Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews. 2007; (4):Art. No.: CD002064.10.1002/14651858.CD002064.pub2
23. Appel V, Stewart SS, Smith G, Appel SH. A rating scale for amyotrophic lateral sclerosis: descriptive and preliminary experience. Ann Neurol. 1987; 22:328–33. [PubMed: 3118763]
24. Sorenson EJ, Windbank AJ, Mandrekar JN, Bamlet WR, Appel SH, Armon C. Subcutaneous IGF-1 is not beneficial in a two-year ALS trial. Neurology. 2008; 71:1770–5. [PubMed: 19029516]
25. Orrell RW, Lane RJM, Ross M. Antioxidant treatment for amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database of Systematic Reviews. 2007; (1):Art. No.: CD002829.10.1002/14651858.CD002829.pub4
26. Bongioanni P, Reali C, Sogos V. Ciliary neurotrophic factor (CNTF) for amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database of Systematic Reviews. 2004; (3):Art. No.: CD004302.10.1002/14651858.CD004302.pub2
27. Langmore SE, Kasarskis EJ, Manca ML, Olney RK. Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews. 2006; (4):Art. No.: CD004030.10.1002/14651858.CD004030.pub2
28. Ashworth NL, Satkunam LE, Deforge D. Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews. 2006; (1):Art. No.: CD004156.10.1002/14651858.CD004156.pub3
29. Bohannon RW, Smith MB. Inter-rater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987; 67:206–7. [PubMed: 3809245]
30. Beghi E, Millul A, Logroscino G, Vitelli E, Micheli A. for the SLALOM Group. Outcome measures and prognostic indicators in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2008; 9:163–7.
31. The Italian ALS Study Group. Branched-chain amino acids and amyotrophic lateral sclerosis. Neurology. 1993; 43:2466–70. [PubMed: 8255440]
32. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (phase III). J Neurol Sci. 1999; 169:13–21. [PubMed: 10540002]
33. Medical Research Council. Aids to the investigation of peripheral nerve injuries – War memorandum. 2. London: HSMO; 1943. p. 11-46.
34. Norris FH Jr, Calanchini PR, Fallar RJ, Pancharis S, Jewett B. The administration of guanidine in amyotrophic lateral sclerosis. Neurology. 1974; 24:721–8. [PubMed: 4858705]

35. Kaufmann P, Levy G, Montes J, Buchsbaum A, Barsdorf AI, Battista V. and QALS Study Group. Excellent inter-rater, intra-rater, and telephone-administered reliability of the ALSFRS-R in a multicentre clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord. 2007; 8:42–6.
36. Beghi E. 127th ENMC International Workshop: implementation of a European registry of ALS. Naarden, The Netherlands, 8–10 October 2004. Neuromuscul Disord. 2006; 16:46–53. [PubMed: 16376080]
37. Traynor BJ, Bruijn L, Conwit R, Beal F, O'Neill G, Fagan SC. Neuroprotective agents for clinical trials in ALS: a systematic assessment. Neurology. 2006; 67:20–7. [PubMed: 16832072]

Table I

Prognostic factors in ALS (17).

Demographic
Age: dose-effect of age
Clinical
Site of onset: bulbar and respiratory worse
Diagnostic delay: short delay worse
El Escorial diagnostic categories: definite ALS worse than others
Family history of ALS: depends on SOD1 mutation A4V worse)
Rate of disease progression: see Diagnostic delay
Respiratory status: forced vital capacity <70 worse
Cognitive functions: fronto-temporal dementia worse
Nutritional status: low body mass index and weight loss worse?
Functional disability scores: ALSFRS/ALSFRS-R prognostic
Psychosocial factors: presence of distress worse
Therapeutic
Disease modifying drugs: riluzole slightly better
Enteral nutrition: positive effect on survival?
Non-invasive positive-pressure ventilation: positive effect on survival
Comprehensive care
ALS centre: positive effects?
Question marks refer to factors whose prognostic role is questionable.

Table II

List of drugs tested in ALS with number of exposed patients in randomized clinical trials and limitations (modified from 37).

Drug	No. exposed	Limitations
Acetylcysteine	54	NH
Amantadine	20	IR, NH
Arimoclomor	66	IR, NH
β-1a recombinant interferon	31	IR, NH
Baclofen	9	NH
BCAA	135	IR, NH
BDNF	768	NH, T
Celecoxib	248	NH
Coenzyme Q10	145	NH
Creatine	191	NH
Cyclosporine	36	IR, NA, NH, T
Dextromethorphan	93	NH
Gabapentin	288	IR, NH, T
Gangliosides	39	IR, NH
Glatiramer	204	NH
Glutathione	32	IR, NH
Guanidine	44	NH
IGF-1	514	NH
Indinavir	23	IR, NH
Inosiplex	8	IR, NH
Isoprinosine	25	IR, NH
Lamotrigine	73	IR, NH
Levamisole	59	IR, NH
Lithium carbonate	40	NH, NA
L-threonine	27	IR, NH
Methionine	16	IR, NH
Methylcobalamin	24	NH
Minocycline	257	NH
Nimodipine	87	NH
Pentoxiphylline	199	NH
Physostigmine	25	IR, NH
Recombinant ciliary nerve growth factor	485	NH, T
Riluzole	891	–
Selegiline Hydrochloride	130	NH
TCH346	442	NA, NH
Thalidomide	18	NH

Drug	No. exposed	Limitations
Thyrotropin	147	IR, NH
Tilorone	8	IR, NH
Topiramate	198	NA, NH, T
Transfer factor	39	IR, NH
Valproic acid	82	IR, NH
Vitamin E	246	IR, NH
Xaliproden	848	NH

IR: insufficient rationale; NA: negative animal studies; NH: negative human studies; T: proven toxicity.

The full list of original trials can be obtained upon request to the corresponding author.

Table III

Principal methodological aspects of randomized clinical trial in ALS study drug.

Drug	Author (year)	Total no. patients	Blinding procedure	Treatment arms balanced
Acetylcysteine	Louwerse (1995)	111	Inadequate	Yes
Amantadine or guanidine	Munsat (1981)	20*	Inadequate	NS
Arimoclomol	Cudkowicz (2008)	84	Adequate	No
β-1a recombinant interferon	Beghi (2000)	61	Adequate	Yes
Baclofen	Norris (1979)	31	NS	NS
BCAA	Plaitakis (1988)	22	Adequate	Yes
BCAA	Italian ALS Study (1993)	126	Adequate	No
BCAA or threonine	Tandan (1996)	95	Adequate	Yes
BDNF	BDNF Study G. (1999)	1138	Adequate	Yes
BDNF	Ochs (2000)	25	Adequate	No
Celecoxib	Cudkowicz (2006)	300	Adequate	Yes
Celecoxib + creatine or Minocyclic + creatine	Gordon (2008)	86	Adequate	Yes
Coenzyme Q10	Kaufmann (2009)	220	Adequate	Yes
Creatine	Groeneveld (2003, 2005)	175	Adequate	Yes
Creatine	Shefner (2004)	104	Adequate	Yes
Creatine	Rosenfeld (2008)	107	NS	No
Cyclosporine	Appel (1988)	74	Adequate	Yes
Dextromethorphan	Askmark (1993)	14*	NS	NS
Dextromethorphan	Blin (1996)	49	Adequate	Yes
Dextromethorphan	Gredal (1997)	45	Adequate	Yes
Dextromethorphan/quinidine	Brooks (2004)	140	NS	Yes
Gabapentin	Miller (1996)	152	NS	No
Gabapentin	Mazzini (1998)	228	Inadequate	Yes
Gabapentin	Miller (2001)	204	Adequate	No
Gangliosides	Bradley (1984)	40	NS	Yes
Gangliosides	Harrington (1984)	40	NS	NS
Glatiramer	Gordon (2006)	30	NS	Yes
Glatiramer	Meininger (2009)	366	Yes	Yes
Glutathione	Chi ò (1998)	32*	Inadequate	Yes
Guanidine	Norris (1974)	24	Adequate	Yes
IGF-1	Smith (1993)	75	NS	NS
IGF-1	Lai (1997)	266	NS	Yes
IGF-1	Borasio (1998)	183	Adequate	No
IGF-1	Nagano (2005)	19	NS	Yes
IGF-1	Sorenson (2008)	330	Adequate	Yes
Indinavir	Scelsa (2005)	46	Adequate	Yes

Drug	Author (year)	Total no. patients	Blinding procedure	Treatment arms balanced
Inosiplex	Brody (1974)	16	Adequate	NS
Isoprinosine	Fareed (1971)	25*	Adequate	NS
Lamotrigine	Eisen (1993)	67	Adequate	Yes
Lamotrigine	Ryberg (2003)	39*	NS	Yes
Levamisole	Olarte (1985)	59*	Adequate	NS
Lithium carbonate	Aggarwal (2010)	84	Adequate	Yes
L-threonine	Blin (1992)	23	Adequate	Yes
L-threonine	Testa (1992)	30	Inadequate	Yes
Methionine + antioxidants	Stevic (2001)	28	NS	Yes
Methylcobalamin	Kaji (1998)	24	Adequate	No
Minocycline	Gordon (2004a)	19	Adequate	Yes
Minocycline	Gordon (2004b)	23*	Adequate	Yes
Minocycline	Gordon (2007)	412	Adequate	Yes
Nimodipine	Miller (1996)	87*	NS	Yes
Pentoxifylline	Meininger (2006)	400	NS	Yes
Physostigmine	Norris (1993)	25*	Adequate	NS
Recombinant ciliary nerve growth factor	CNTF Treatment (1996)	730	NS	Yes
Riluzole	Bensimon (1994)	155	NS	Yes
Riluzole	Lacomblez (1996 A, B)	959	Adequate	Yes
Riluzole	Desai (1998)	15*	NS	NS
Riluzole	Bensimon (2002)	168	NS	No
Selegiline hydrochloride	Mazzini (1994)	111	Inadequate	Yes
Selegiline hydrochloride	Jossan (1994)	10*	NS	NS
Selegiline hydrochloride	Lange (1998)	133	Adequate	Yes
TCH346	Miller (2007)	553	Adequate	Yes
Thalidomide	Meyer (2008)	37	Inadequate	Yes
Thyrotropin	Brooke (1986)	30	Adequate	Yes
Thyrotropin	Caroscio (1986)	12*	Adequate	Yes
Thyrotropin	Mitsumoto (1986)	36*	Adequate	Yes
Thyrotropin	Guiloff (1987)	26*	Adequate	NS
Thyrotropin	Congia (1991)	23*	NS	NS
Thyrotropin	Munsat (1992)	36*	Adequate	NS
Tilorone	Olson (1978)	16	NS	NS
Topiramate	Cudkowicz (2003)	296	Adequate	Yes
Transfer factor	Olarte (1979)	66	NS	Yes
Valproic acid	Piepers (2009)	163	Adequate	Yes
Vitamin E	Desnuelle (2001)	289	NS	Yes
Vitamin E	Färkkilä (1996)	24	NS	NS
Vitamin E	Graf (2005)	160	NS	Yes

Drug	Author (year)	Total no. patients	Blinding procedure	Treatment arms balanced
Xaliproden	Lacomblez (2004)	77	NS	Yes
Xaliproden	Meininger (2004)	1210	NS	Yes

Table IV

Sample size (*n*) in treated and control groups for 12-months change versus placebo of selected outcome measures under different assumptions.

Measure	% control (*)	% treated (*n*)	% treated (*n*)	% treated (*n*)
Loss of ambulation	15	10 (687)	5 (138)	0 (45)
Gastrostomy	21	15 (644)	10 (167)	0 (30)
Assisted ventilation	14	10 (1039)	5 (164)	0 (49)

Alpha: 0.05; Beta: 0.20.

(*) Source: (30).