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Ciliary neurotrophic factor (CNTF) for amyotrophic lateral sclerosis or motor neuron disease (Review)

Bongioanni P, Reali C, Sogos V

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[Intervention Review]

Ciliary neurotrophic factor (CNTF) for amyotrophic lateral sclerosis or motor neuron disease

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ABSTRACT

Background

Amyotrophic lateral sclerosis, also known as motor neuron disease, is a fatal neuromuscular disease characterized by progressive muscle weakness resulting in paralysis. It might be treated with ciliary neurotrophic factor. This is an updated review. An updated search was performed in April 2011, but no new studies were found.

Objectives

The objective of this review was to examine the efficacy of ciliary neurotrophic factor in amyotrophic lateral sclerosis.

Search methods

We updated the searches of the Cochrane Neuromuscular Disease Group Specialized Register (19 April 2011), CENTRAL (2011, Issue 2), MEDLINE (January 1966 to April 2011) and EMBASE (January 1980 to April 2011), checked the reference lists of papers identified and contacted the authors of identified studies to get additional unpublished results.

Selection criteria

We considered the following selection criteria:
Types of studies: randomized controlled clinical trials.
Types of participants: adults with a diagnosis of either probable or definite amyotrophic lateral sclerosis according to the El Escorial criteria.
Types of interventions: treatment with ciliary neurotrophic factor for at least six months in a placebo-controlled randomized trial format.
We did not specify outcomes as selection criteria. In the review our outcome measures were as follows.
Primary outcome: survival.
Secondary outcomes: muscle strength, respiratory function, changes in bulbar functions, changes in quality of life, proportion of patients with adverse side effects (such as cough, asthenia, nausea, anorexia, weight loss and increased salivation).

Data collection and analysis

Three review authors independently checked all titles and abstracts from the searches to identify eligible randomized controlled trials. Two review authors independently extracted data and a third checked the data. We obtained some missing data from the investigators. Two authors independently assessed the risk of bias for each included study.

Main results

Two trials with a total population of 1300 amyotrophic lateral sclerosis patients who were randomized to treatment with subcutaneous injections of recombinant human ciliary neurotrophic factor or placebo were examined in this review. The risk of bias was low for one trial but was unclear for the other trial. No new trials were found on updating the search in April 2011. The methodological quality of these trials was considered adequate.

No significant difference was observed between ciliary neurotrophic factor and placebo groups for survival, the primary outcome measure. The risk ratio was 1.07 (95% confidence interval 0.81 to 1.41).

No significant differences between the groups were observed for most of the secondary outcomes. However, a significant increase of the incidence of several adverse events was noted in groups treated with higher doses of ciliary neurotrophic factor.

Authors' conclusions

Ciliary neurotrophic factor treatment had no significant effect on amyotrophic lateral sclerosis progression. At high concentrations, several side effects were observed. A combination of ciliary neurotrophic factor with other neurotrophic factors (as suggested by results on animal models) and more efficient delivery methods should be tested.

PLAIN LANGUAGE SUMMARY

Ciliary neurotrophic factor (CNTF) for amyotrophic lateral sclerosis, also known as motor neuron disease

Amyotrophic lateral sclerosis (ALS) or motor neuron disease (MND) is a fatal neuromuscular disease characterized by progressive muscle weakness that results in paralysis. Ciliary neurotrophic factor (CNTF) has been shown to slow disease progression and improve muscle strength in an animal model of MND, through survival-promoting effects on motor neurons. Ciliary neurotrophic factor treatment did not show any significant effect on the progression of amyotrophic lateral sclerosis and side effects were observed at high concentrations.The review found only two eligible trials with a total of 1300 participants; the risk of bias was low for one trial but was unclear for the other trial; they did not show any significant effect of ciliary neurotrophic factor on progression of ALS or MND in man. On the other hand, several adverse effects were observed after treatment with ciliary neurotrophic factor. An updated search was performed in April 2011, but no new studies were found.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Any CNTF versus placebo for amyotrophic lateral sclerosis or motor neuron disease

Any CNTF versus placebo for amyotrophic lateral sclerosis or motor neuron disease

Patient or population: patients with amyotrophic lateral sclerosis or motor neuron disease
Settings:
Intervention: any CNTF versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Any CNTF				
Deaths Follow-up: 7 to 9 months	**166 per 1000**	**177 per 1000** (134 to 234)	**RR 1.07** (0.81 to 1.41)	1300 (2 studies)	⊕⊕⊕⊕ **high**	Not a significant difference
Muscle strength change from baseline value of isometric muscle strength (combination megascore) Follow-up: 7 to 9 months	The mean muscle strength ranged across control groups from -0.57 to -0.48	The mean muscle strength in the intervention groups was **0.04 lower** (0.1 lower to 0.03 higher)		1300 (2 studies)	⊕⊕⊕⊕ **high**	Not a significant difference
Respiratory function (FVC %) change from baseline measures of forced vital capacity as a percentage of the predicted value (FVC %) Follow-up: 7 to 9 months	The mean respiratory function (FVC %) ranged across control groups from -19.8 to -16.4	The mean respiratory function (FCV %) in the intervention groups was **0.96 higher** (1.65 lower to 3.58 higher)		1300 (2 studies)	⊕⊕⊕⊕ **high**	Not a significant difference
Changes in quality of life (SIP) change in Sickness Impact Profile (SIP) scores (range from 0 = best health to 100 = worst health). Follow-up: 7 to 9 months	The mean changes in quality of life (SIP) in the control group was 6.9	The mean changes in quality of life (SIP) in the intervention groups was **0.74 lower** (2.5 lower to 1.02 higher)		503 (1 study)	⊕⊕⊕⊕ **high**	Not a significant difference
Asthenia Follow-up: 1 to 7 months	**411 per 1000**	**420 per 1000** (333 to 527)	**RR 1.02** (0.81 to 1.28)	570 (1 study)	⊕⊕⊕⊕ **high**	Not a significant difference
Nausea Follow-up: 1 to 7 months	**184 per 1000**	**249 per 1000** (170 to 367)	**RR 1.35** (0.92 to 1.99)	570 (1 study)	⊕⊕⊕⊕ **high**	Not a significant difference

Increased salivation Follow-up: 1 to 7 months	**248 per 1000**	**268 per 1000** (194 to 372)	**RR 1.08** (0.78 to 1.5)	570 (1 study)	⊕⊕⊕⊕ **high**	Not a significant difference

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a fatal neuromuscular disease characterized by progressive muscle weakness that results in paralysis. It occurs in about one to three people per 100,000 population per year; its prevalence is about five to nine per 100,000. ALS targets the motor neurons responsible for transmitting impulses to the voluntary muscles. Without muscle stimulation by electrical impulses the muscles lose strength and atrophy. Upper motor neurons in the brain send impulses to lower motor neurons in the brainstem and spinal cord, which in turn send impulses through nerve processes to the muscles; both types of motor neurons are affected in ALS or MND. Symptoms of upper motor neuron damage include stiffness (spasticity) and repetitive muscle contractions (clonus). Symptoms of lower motor neuron damage include muscle weakness, muscle twitching (fasciculation) and muscle shrinking (atrophy).

The hypothesis that neuronal degeneration is caused by a lack of trophic factors (namely molecules that support cell survival and promote cell differentiation) that are specific to motor neurons is old but it could not be tested until recently (see Sendtner 2000 for review). Ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF) have emerged as prominent motor neuron trophic factors; both show remarkable survival-promoting effects on motor neurons in cell cultures, embryos and adult animals (Arakawa 1990; Kishino 1997; Oppenheim 1992; Sendtner 1992; Sendtner 1997; Yan 1992). In particular, CNTF has been shown to retard disease progression and improve muscle strength in the wobbler mouse model of MND (Mitsumoto 1994b). Subcutaneous injection of CNTF and BDNF on alternate days arrested disease progression in wobbler mice for one month (Mitsumoto 1994a). Glial-derived neurotrophic factor (GDNF) and insulin-like growth factor (IGF-I) have also been reported as having beneficial effects on injured or diseased motor neurons in animal models (Giehl 1997; Hantai 1995). Investigations with neurotrophic factors have rapidly progressed to clinical studies (ACTS Group 1995a; ACTS Group 1995b; ACTS Group 1996; Aebischer 1996; BDNF 1999; Borasio 1998; Lai 1997; Miller 1993; Miller 1996a; Ochs 2000; Penn 1997; Mitchell 2007).

Phase I and II trials indicated that in people with ALS or MND subcutaneous doses of human CNTF up to 5 µg/kg were generally well tolerated (Miller 1996a; Miller 1996b), whereas higher concentrations were not (ACTS Group 1995a; ACTS Group 1995b). Delivery of human CNTF should directly expose motor neurons to the neurotrophic factor, while avoiding side effects related to its peripheral administration. This can be achieved by transplanting immunoprotected xenogeneic cell lines genetically engineered to release human CNTF (Aebischer 1996; Sagot 1995).

The efficacy and safety of cell transplantation was first demonstrated in rodents (Sagot 1995). A device containing baby hamster kidney cells that released CNTF was implanted in the fluid surrounding the spinal cord in 12 patients (Aebischer 1996). According to the protocol the implants were retrieved after three months and replaced by a second capsule. Viable cells and human CNTF secretion were observed in all retrieved implants. No limiting adverse effects were observed in any of the implanted patients. Human CNTF was undetectable before implantation but detectable levels of CNTF were observed in the cerebrospinal fluid up to 20 weeks after transplantation. The biological results demonstrate that neurotrophic factors can be delivered to the central nervous system through transplantation of encapsulated, genetically-modified cells. The small number of patients, however, did not allow the assessment of a potential slowing of the degeneration process. Phase III of this trial has not been published.

No systematic review of this topic is known to exist.

An updated search was performed in February 2009, but no new studies were found.

OBJECTIVES

The objective of this review was to examine the efficacy of CNTF in ALS, also known as MND.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all randomized controlled clinical trials of CNTF treatment for ALS, also known as MND.

Types of participants

We included adults with a diagnosis of either probable or definite ALS or MND according to the El Escorial criteria (Brooks 2000).

Types of interventions

We reviewed trials of treatment with CNTF for at least six months in a placebo-controlled randomized format.

Types of outcome measures

Primary outcomes

The primary outcome measure was survival.

Secondary outcomes

The secondary outcome measures were:

1. muscle strength (isometric myometry) after three months;
2. respiratory function, particularly forced vital capacity as a percentage of predicted (FVC %), after three months;
3. changes in bulbar functions (speech and swallowing) after three months;
4. changes in quality of life (QoL);
5. proportion of patients with adverse side effects, such as cough, asthenia, nausea, anorexia, weight loss and increased salivation.

We used continuous outcome measures for muscle strength, respiratory and bulbar functions.

We included the following outcomes in a 'Summary of findings' table: deaths; muscle strength; respiratory function; changes in quality of life and the adverse effects asthenia, nausea and increased salivation.

Search methods for identification of studies

We searched the Cochrane Neuromuscular Disease Group Specialized Register (19 April 2011) using the following search terms: 'amyotrophic lateral sclerosis' or its synonyms

'Charcot's disease', 'motor neuron disease', 'motor neurone disease', 'motoneuron disease', 'Lou Gehrig's disease' and 'ciliary neurotrophic factor' or 'CNTF' and 'nerve growth factor'. We adapted this strategy to search the following databases: CENTRAL (2011, issue 2), MEDLINE (January 1966 to April 2011), EMBASE (January 1980 to April 2011). We contacted the authors of identified studies to obtain additional unpublished results or clinical trials. We checked the reference lists of the retrieved papers to try to identify further studies.

For search strategies see: Appendix 1 (MEDLINE), Appendix 2 (EMBASE) and Appendix 3 (CENTRAL).

Data collection and analysis

Selection of studies

Three review authors checked all titles and abstracts obtained from the searches to identify potentially relevant studies. Each review author independently examined the full text of these papers to see whether they fitted the inclusion criteria for the review. The review authors discussed and resolved any disagreements about whether to exclude or include studies.

Data extraction and management

Two authors undertook independent data extraction on a specially designed form and the third author checked the extracted data. We tried to obtain missing data by contacting the authors of the trial reports.

Assessment of risk of bias in included studies

We assessed study quality according to the methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We used the Cochrane Collaboration tool for assessing risk of bias. Two authors independently assessed the risk of bias for each included study and assigned a rating for the risk of bias. We resolved any disagreements by discussion. We assessed security of randomisation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting and 'other sources of bias'. We made judgements for each domain and graded them as 'Low risk of bias', 'High risk of bias' or Unclear.

Data synthesis

We performed meta-analysis using Review Manager, the Cochrane statistical software, using a fixed-effect model. We expressed data as risk ratios (RR) with 95% confidence intervals (CI) and risk differences (RD) with 95% CI for dichotomous data, and mean differences (MD) and 95% CI for continuous data. We analyzed all the primary and secondary outcomes, when possible. We tested results for heterogeneity. If heterogeneity had been found, we would have repeated the calculations with a random-effects model and repeated them omitting studies of lower methodological quality, to see whether such omission accounted for the heterogeneity.

Subgroup analysis and investigation of heterogeneity

We predefined subgroups of studies, related to the status of the patients at randomization as follows:

1. age: up to 45 years, and 46 years and older;
2. onset: spinal versus bulbar.

RESULTS

Description of studies

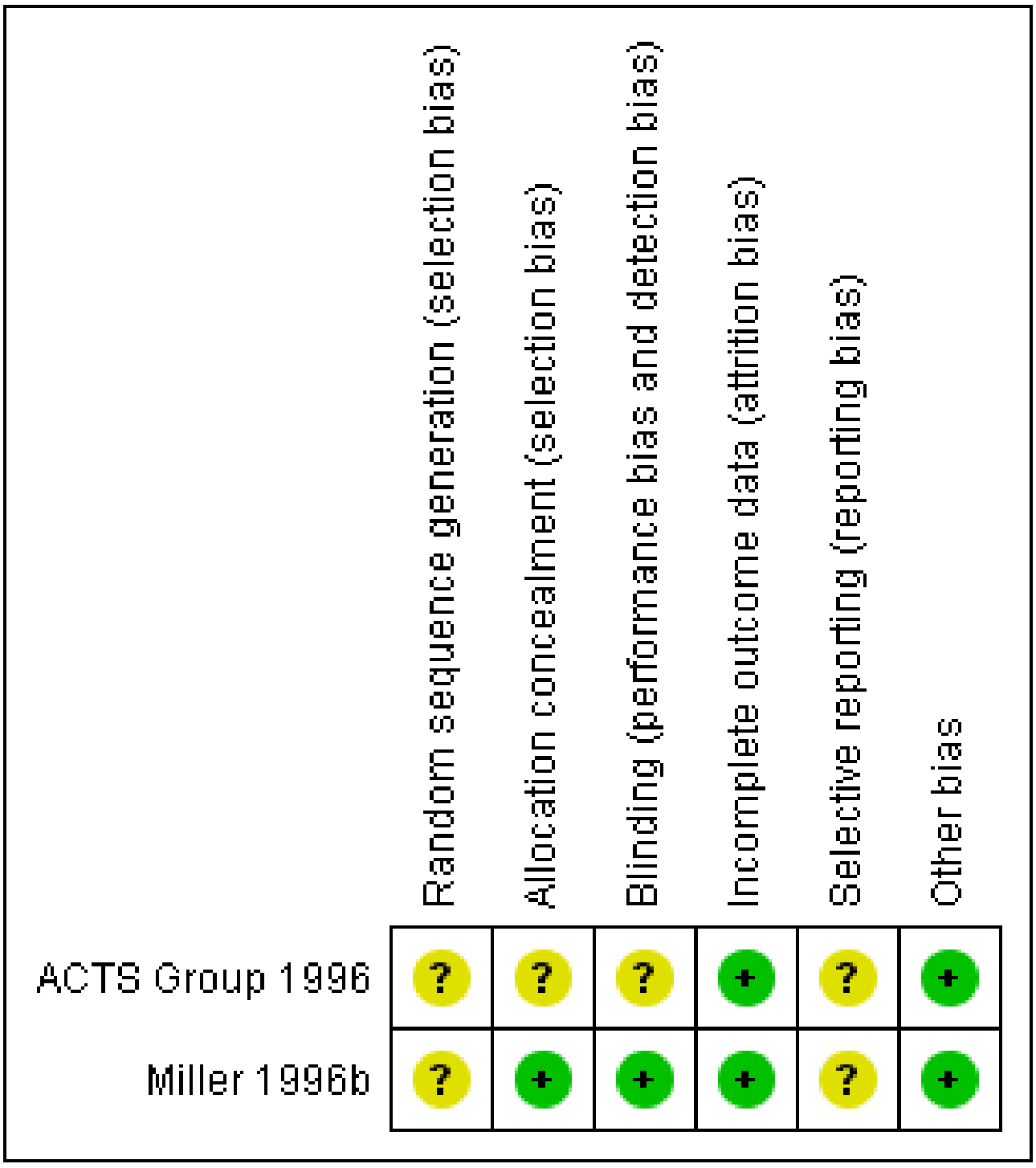
The number of papers retrieved by the current strategies in this review are: MEDLINE 115 (57 new papers); EMBASE 185 (16 new papers); Cochrane Neuromuscular Disease Group Specialized Register 25 (3 new papers) and CENTRAL 13. The searches identified five clinical trials of CNTF treatment for ALS, also known as MND, and no new trials were identified for this update. We excluded three trials, because the treatment period was shorter than six months (ACTS Group 1995a; ACTS Group 1995b; Miller 1996a, see table Characteristics of excluded studies). Only two clinical trials met the selection criteria (ACTS Group 1996; Miller 1996b, see table Characteristics of included studies).

In these two trials, a total population of 1,300 ALS or MND patients was enrolled. In both trials different concentrations of CNTF were used. In the first study (ACTS Group 1996) there were three treatment arms: 15 µg/kg rhCNTF, 30 µg/kg rhCNTF and placebo. In the other trial (Miller 1996b) there were four subgroups: 0.5, 2, and 5 µg/kg/day rhCNTF and placebo. For this reason we had 914 treated patients but only 386 control patients. Both trials compared subcutaneous injections of rhCNTF with placebo. In the first trial (ACTS Group 1996) the study drug was administered three times a week. In the second trial (Miller 1996b) participants received daily injections of CNTF or placebo but at lower concentrations than in the first study (*see* table Characteristics of included studies).

Risk of bias in included studies

Details of risk of bias assessment for each trial are shown in the Characteristics of included studies. Summary results are shown in Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

In both trials participants were randomized to receive CNTF or placebo, but the authors did not provide sufficient information on the method of sequence generation and allocation concealment in the published article. We contacted authors and obtained supplemental information about Miller 1996b trial: a random sequence was generated by the study statistician and allocation to study interventions did not involve any of the personnel on the different sites. Therefore, this trial was judged being at low risk of bias. ACTS Group 1996 did not provide any complementary information and this trial was classified as of 'unclear' risk of bias.

Blinding

Miller 1996b was stated to be double-blind, but no further information on blinding was provided. The corresponding author was contacted and it was established that placebos were made to look like trial medications, and patients and investigators were blind to the assigned treatments. Based on this information blinding was considered adequate.

ACTS Group 1996 did not provide any details on the blinding procedure and this trial was classified as of 'unclear' risk of bias.

Incomplete outcome data

The rate of withdrawals and dropouts was clearly reported in both trials.

Selective reporting

No protocol was available or referenced for either of the included studies.

Other potential sources of bias

Studies appeared free of other sources of bias.

Effects of interventions

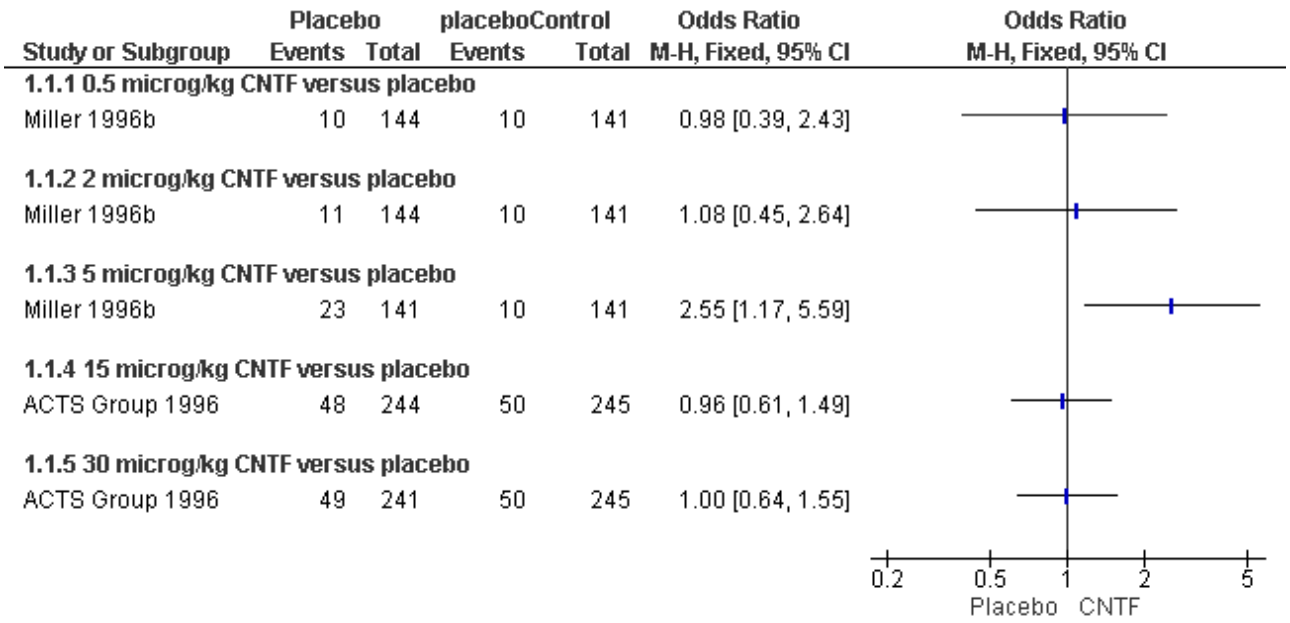
See: **Summary of findings for the main comparison** Any CNTF versus placebo for amyotrophic lateral sclerosis or motor neuron disease

Primary outcome measure: survival during the study period

Our primary outcome measure was survival after six and 12 months, as stated in our protocol. Data on survival were published in both trials but they represented a secondary outcome. Moreover, data were available only at the end of the trial: at seven months (Miller 1996b) and at nine months (ACTS Group 1996). For this reason, we modified the primary outcome and considered death at any time during the entire study. We considered intubation and tracheostomy as a surrogate of death, but in both trials it was not specified if death data included those of tracheostomy or intubation, or both.

Of 914 patients treated with CNTF, 141 died during the study compared with 60 of 386 patients treated with placebo. Differences between CNTF and placebo groups were not significant: RR 1.07 (95% CI 0.81 to 1.41) (see Analysis 1.1; Figure 2 , and Analysis 2.1 for deaths). Only the group of patients treated with CNTF 5 µg/kg/day (Miller 1996b) showed a significantly higher mortality as compared to patients treated with placebo.

Figure 2. Forest plot of comparison: 1 CNTF versus placebo, outcome: 1.1 Deaths.



Secondary outcomes measures

(1) Muscle strength

For one trial (Miller 1996b) data were not available after three months (the time point specified in our protocol) but was available at the end of the study (seven months). In the other study (ACTS Group 1996) data were available after one, two, four, six, eight and nine months of treatment. For this reason, we compared muscle strength at the end of the treatment. Data were expressed as change from baseline value of isometric muscle strength (combination megascore). In both trials no significant differences were observed between treatment and control groups. The MD of both trials was -0.04 (95% CI -0.10 to 0.03) in favour of the placebo group (see Analysis 1.2, and Analysis 2.2).

(2) Respiratory function, particularly forced vital capacity as a percentage of predicted (FVC %)

This outcome was not published after three months (the time point specified in our protocol) for any of the trials. Data were available in one trial (ACTS Group 1996) after one, two, four, six, eight and nine months of treatment and in the other trial (Miller 1996b) at the end of the study (seven months). Consequently,

we compared respiratory function at the end of the study. Data were expressed as change from baseline measures of forced vital capacity as a percentage of the predicted value (FVC %). No significant differences were observed between the CNTF and placebo groups with any CNTF concentration. When the results of the two trials were combined, the MD was 0.96 in favour of the CNTF group (95% CI -1.65 to 3.58) (see Analysis 1.3 and Analysis 2.3).

(3) Changes in bulbar functions (speech and swallowing)

Measures of this outcome were not published in either trial. In one study (ACTS Group 1996) no differences were observed in oro-labio-lingual dexterity between the CNTF and placebo groups, but data were not shown.

(4) Changes in quality of life and functionality

This outcome was published by both trials but different scales were used. In one trial (Miller 1996b) it was measured as change in Sickness Impact Profile (SIP) scores. At the end of the study (seven months) the MD was -0.74 of a grade in favour of the placebo group (95% CI -2.50 to 1.02), which was not significant (see Analysis 2.4 for changes in quality of life). In the other study (ACTS Group 1996) changes in functionality were included in the ALS Functional Rating Scale (ALSFRS) results. Data were reported as slopes of disease outcome measures (30 µg/kg: -0.27, SD ±0.42; 15 µg/kg: -0.22, SD ± 0.37; placebo: 0.22, SD ±0.25). No significant differences were noted at the end of the study between 30 µg/kg and placebo (P = 0.85) or between any CNTF dose (pooled 15 and 30 µg/kg) and placebo (P = 0 .99).

(5) Proportion of participants with adverse side effects

Side effect measures were published for only one trial (Miller 1996b). In the other study (ACTS Group 1996) only data on weight loss were published. A significantly greater incidence of anorexia, asthenia and cough was reported in the CNTF groups but data were not shown. Headache, increased salivation, pain and dyspnea were reported with equal frequency in all treatment groups.

(a) Cough

This adverse event was reported in only one trial (Miller 1996b). A significant increase of incidence of cough was observed in the CNTF-treated group (RR 1.55, 95% CI 1.10 to 2.17) (see Analysis 2.5). In particular, cough was reported in 77/141(55%) patients treated with CNTF 5 µg/kg compared to 31/141 (22%) treated with placebo. The other two doses had no significant effects on this outcome (cough in 22% and 25% of patients).

(b) Asthenia

This adverse event was reported in only one trial (Miller 1996b). No significant differences were observed between treated and placebo groups (RR 1.02, 95% CI 0.81 to 1.28) (see Analysis 2.6). Asthenia was reported in 74/141(53%) patients treated with CNTF 5 µg/kg compared to 58/141 (41%) treated with placebo. The other two doses had no significant effects on this outcome (incidences of 35% and 38%).

(c) Nausea

This adverse event was reported in only one trial (Miller 1996b). No significant differences were observed between treated and placebo groups (RR 1.35, 95% CI 0.92 to 1.99) (see Analysis 2.7). A significant increase in incidence of nausea was observed in patients treated with CNTF 5 µg/kg (49/141, 35%) compared to 26/141 (18%) in the placebo group. The other two doses of CNTF had no significant effects on this outcome (both 20%).

(d) Anorexia

This adverse event was reported in only one trial (Miller 1996b). Significant differences were observed between treated and placebo groups (RR 1.66, 95% CI 1.09 to 2.51) (see Analysis 2.8). An increased incidence of anorexia was reported mostly in patients treated with the 5 µg/kg dose of CNTF (53/141, 38%), compared to 22/141 (16%) in the placebo group. The other two doses had no significant effects on this outcome (17% and 23%).

(e) Weight loss

This outcome was published in both trials but using different scales. Consequently it was not possible to combine results. In one trial (ACTS Group 1996) significant differences in weight loss between groups were observed: patients treated with 30 µg/kg CNTF lost an average of 6.3 ± 0.7% of their body weight, patients treated with 15 µg/kg CNTF lost 7.4 ± 0.6% of their body weight, as compared with 4.5 ± 0.5% for the placebo group (P = 0.0017). The other trial (Miller 1996b) reported a significant difference in the proportion of patients with weight loss, which was greater after treatment with 5 µg/kg CNTF than placebo (RR 2.42, 95% CI 1.29 to 4.54) (see Analysis 1.4).

(f) Increased salivation

This adverse event was reported in only one trial (Miller 1996b). No significant differences were observed between treated and placebo groups (RR 1.08, 95% CI 0.78 to 1.50) (see Analysis 2.9).

Subgroup analysis

Meta-analysis of the effect of CNTF on subgroups was not performed, since no significant effect of this neurotrophic factor on ALS or MND was observed. In addition, no data about interactions between age, bulbar or spinal onset and the effect of treatment were published.

Methodological quality

Data published in the two considered trials were similar, thus no evidence of heterogeneity in the analyses was observed. Moreover, methodological quality was adequate in both trials. For these reasons, and in the absence of a significant effect of CNTF on any outcome measures, sensitivity analysis was not performed.

DISCUSSION

Only two trials of CNTF treatment for ALS, also known as MND, were found that fulfilled the inclusion criteria. They were both multicentre studies, with a large number of participants (730 in ACTS Group 1996, 570 in Miller 1996b). Thus they almost contributed an equal weight to the analysis for this review. The methodological quality of Miller 1996b study was considered adequate, whereas lack of information, despite attempts to contact the author, limited the assessment of the quality of the ACTS Group 1996 study, which was judged unclear. Each study included different CNTF-treated groups (0.5 µg/kg, 2 µg/kg or 5 µg/kg CNTF in Miller 1996b; 15 µg/kg or 30 µg/kg CNTF in ACTS Group 1996); data were examined either separately for each dose or combined. The analysis of these trials revealed a defect in outcome measures in one study (Miller 1996b): outcome data were available for this

trial only at the end of the study (six months of treatment plus one more month) and not after three months, as expected from the protocol. For this reason, we analysed outcome measures at the end of the study for both trials, even though the other study reported the required data. In the absence of any significant effect of CNTF this change should not have influenced the results. Please see Summary of findings for the main comparison for details.

Data showed that subcutaneous administration of CNTF at different concentrations did not alter the progression of ALS or MND compared with placebo. Outcomes published in these two trials were very similar even though CNTF concentrations were different. Administration of CNTF was associated with several adverse events that were more frequent in groups treated with the higher concentrations. Moreover, in the group treated with 5 µg/kg CNTF (Miller 1996b) there was a significant increase in the number of deaths.

It has been demonstrated in different rodent models of ALS or MND that CNTF reduced motor neuron cell death. The two studies examined in this review did not show significant effects of CNTF in any outcome measures we considered. There are some explanations for the lack of effectiveness of CNTF. First of all, CNTF doses may be too low. It has been observed that only doses of 30 µg/kg produced plasma CNTF levels which may potentiate motor neuron survival in vivo. Moreover, patients treated with CNTF developed anti-CNTF antibodies, which may decrease both the negative and positive effects of the neurotrophic factor. The increased incidence of adverse events can be explained, at least in part, by the fact that CNTF is able to activate receptors for interleukin-6 (IL-6), which in turn activate the acute phase response (ACTS Group 1995a).

AUTHORS' CONCLUSIONS

Implications for practice

Ciliary neurotrophic factor when administered subcutaneously had no effect on ALS or MND progression. At high concentrations, several side effects were observed.

Implications for research

Ciliary neurotrophic factor in combination with other neurotrophic factors should be tested, as suggested by results on animal models. More efficient delivery methods, such as implantation of cells genetically engineered to produce CNTF and other neurotrophic factors, should be developed. In addition, future trials should standardize outcome measures, in particular with regard to quality of life scales.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACTS Group 1996

Methods	Double blind, placebo-controlled trial.
Participants	730 patients, with a diagnosis of ALS according to the El Escorial criteria.
Interventions	Subcutaneous injections of 30 or 15 microg/kg, three times a week for 9 months.
Outcomes	Primary: muscle strength. Secondary: pulmonary function (FVC), walking speed, Purdue Pegboard test, oral-labial-lingual dexterity, ALSFRS, S&E, GCIC.
Notes	Multicentre study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization is reported without specification of randomization method
Allocation concealment (selection bias)	Unclear risk	No data are presented on this matter
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial is presented as a double-blind trial, no further data are given

ACTS Group 1996 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors provide an account of all patients lost to follow-up in each group (death or other reasons)
Selective reporting (reporting bias)	Unclear risk	No protocol was available or referenced
Other bias	Low risk	The study appears to be free of other sources of bias

Miller 1996b

Methods	Double blind, placebo-controlled trial
Participants	570 patients, between 21 and 85 years of age, with a diagnosis of ALS according to the El Escorial criteria
Interventions	Daily subcutaneous injections of 0.5, 2, or 5 microg/kg for 6 months
Outcomes	Primary: muscle strength and pulmonary function (FVC) Secondary: arm and leg megascore, quality of life (SIP) and survival
Notes	Multicentre study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method were not specified in the published paper. The author was contacted directly and stated that "A random sequence was generated by the study statistician"
Allocation concealment (selection bias)	Low risk	Contact with author: "No investigator, staff or patient at any site had any access to this information"
Blinding (performance bias and detection bias) All outcomes	Low risk	Unclear in the published paper. The corresponding author has clarified that "Identical appearing placebo was administered in containers which provided no information about drug or placebo. Neither patient nor staff had any clue about which intervention was received until after the results were released to us after locking and analysis of the data"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The rate of withdrawals and dropouts was clearly reported
Selective reporting (reporting bias)	Unclear risk	No protocol was available or referenced
Other bias	Low risk	The study appears to be free of other sources of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTS Group 1995a	Phase I-II trial One-week study
ACTS Group 1995b	Phase I trial Six-week study
Miller 1996a	28-day study

DATA AND ANALYSES

Comparison 1. CNTF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 0.5 microg/kg CNTF versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 2 microg/kg CNTF versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 5 microg/kg CNTF versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 15 microg/kg CNTF versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 30 microg/kg CNTF versus placebo	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Muscle strength	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 0.5 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 2 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 5 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 15 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 30 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

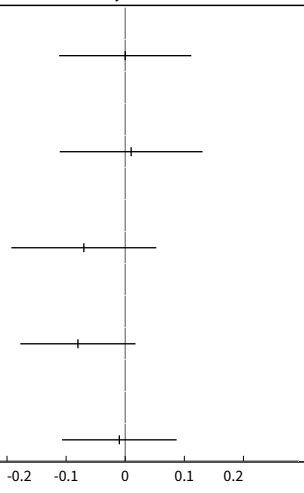
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Respiratory function (FVC %)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 0.5 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 2 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 5 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 15 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 30 microg/kg CNTF versus placebo	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Weight loss	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 0.5 microg/kg CNTF versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 2 microg/kg CNTF versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 5 microg/kg CNTF versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 CNTF versus placebo, Outcome 1 Deaths.

Study or subgroup	Placebo n/N	placeboControl n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.1.1 0.5 microg/kg CNTF versus placebo				
Miller 1996b	10/144	10/141		0.98[0.39,2.43]
1.1.2 2 microg/kg CNTF versus placebo				
Miller 1996b	11/144	10/141		1.08[0.45,2.64]
1.1.3 5 microg/kg CNTF versus placebo				
Miller 1996b	23/141	10/141		2.55[1.17,5.59]
1.1.4 15 microg/kg CNTF versus placebo				
ACTS Group 1996	48/244	50/245		0.96[0.61,1.49]
1.1.5 30 microg/kg CNTF versus placebo				
ACTS Group 1996	49/241	50/245		1[0.64,1.55]
		Placebo	0.2 0.5 1 2 5	CNTF

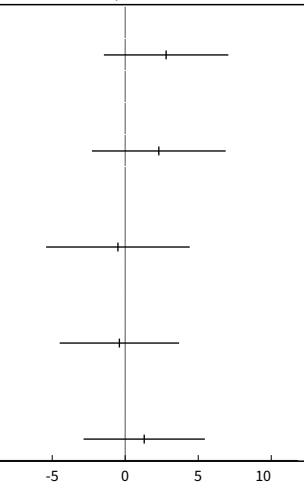
Analysis 1.2. Comparison 1 CNTF versus placebo, Outcome 2 Muscle strength.

Study or subgroup	CNTF N	CNTF Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.2.1 0.5 microg/kg CNTF versus placebo						
Miller 1996b	144	-0.6 (0.5)	141	-0.6 (0.5)		0[-0.11,0.11]
1.2.2 2 microg/kg CNTF versus placebo						
Miller 1996b	144	-0.6 (0.5)	141	-0.6 (0.5)		0.01[-0.11,0.13]
1.2.3 5 microg/kg CNTF versus placebo						
Miller 1996b	141	-0.6 (0.5)	141	-0.6 (0.5)		-0.07[-0.19,0.05]
1.2.4 15 microg/kg CNTF versus placebo						
ACTS Group 1996	244	-0.6 (0.6)	245	-0.5 (0.6)		-0.08[-0.18,0.02]
1.2.5 30 microg/kg CNTF versus placebo						
ACTS Group 1996	241	-0.5 (0.5)	245	-0.5 (0.6)		-0.01[-0.11,0.09]



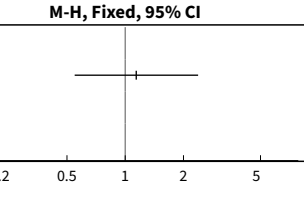
Analysis 1.3. Comparison 1 CNTF versus placebo, Outcome 3 Respiratory function (FVC %).

Study or subgroup	CNTF N	CNTF Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 0.5 microg/kg CNTF versus placebo						
Miller 1996b	144	-13.6 (16)	141	-16.4 (20.4)		2.8[-1.46,7.06]
1.3.2 2 microg/kg CNTF versus placebo						
Miller 1996b	144	-14.1 (19)	141	-16.4 (20.4)		2.3[-2.28,6.88]
1.3.3 5 microg/kg CNTF versus placebo						
Miller 1996b	141	-16.9 (21.7)	141	-16.4 (20.4)		-0.5[-5.42,4.42]
1.3.4 15 microg/kg CNTF versus placebo						
ACTS Group 1996	244	-20.2 (22.6)	245	-19.8 (23.5)		-0.4[-4.49,3.69]
1.3.5 30 microg/kg CNTF versus placebo						
ACTS Group 1996	241	-18.5 (23.2)	245	-19.8 (23.5)		1.3[-2.85,5.45]

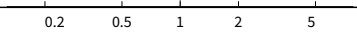


Analysis 1.4. Comparison 1 CNTF versus placebo, Outcome 4 Weight loss.

Study or subgroup	CNTF n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.4.1 0.5 microg/kg CNTF versus placebo				
Miller 1996b	14/144	12/141		1.14[0.55,2.38]
1.4.2 2 microg/kg CNTF versus placebo				



Study or subgroup	CNTF n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Miller 1996b	15/144	12/144		1.25[0.61,2.58]
1.4.3 5 microg/kg CNTF versus placebo				
Miller 1996b	29/141	12/141		2.42[1.29,4.54]



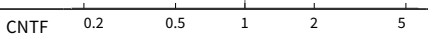
Placebo CNTF

Comparison 2. Any CNTF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.81, 1.41]
2 Muscle strength	2	1300	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.10, 0.03]
3 Respiratory function (FVC %)	2	1300	Mean Difference (IV, Fixed, 95% CI)	0.96 [-1.65, 3.58]
4 Changes in quality of life (SIP)	1	503	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-2.50, 1.02]
5 Cough	1	570	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.10, 2.17]
6 Asthenia	1	570	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.28]
7 Nausea	1	570	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.92, 1.99]
8 Anorexia	1	570	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.09, 2.51]
9 Increased salivation	1	570	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.78, 1.50]

Analysis 2.1. Comparison 2 Any CNTF versus placebo, Outcome 1 Deaths.

Study or subgroup	CNTF n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTS Group 1996	97/485	50/245		81.53%	0.98[0.72,1.33]
Miller 1996b	44/429	10/141		18.47%	1.45[0.75,2.8]
Total (95% CI)	**914**	**386**		**100%**	**1.07[0.81,1.41]**
Total events: 141 (CNTF), 60 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.11, df=1(P=0.29); I^2=10.23%					
Test for overall effect: Z=0.45(P=0.65)					



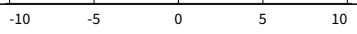
CNTF Placebo

Analysis 2.2. Comparison 2 Any CNTF versus placebo, Outcome 2 Muscle strength.

Study or subgroup	CNTF N	CNTF Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
ACTS Group 1996	485	-0.5 (0.6)	245	-0.5 (0.6)		56.88%	-0.05[-0.13,0.03]
Miller 1996b	429	-0.6 (0.5)	141	-0.6 (0.5)		43.12%	-0.02[-0.12,0.08]
Total ***	**914**		**386**			**100%**	**-0.04[-0.1,0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%							
Test for overall effect: Z=1.14(P=0.25)							

Analysis 2.3. Comparison 2 Any CNTF versus placebo, Outcome 3 Respiratory function (FVC %).

Study or subgroup	CNTF N	CNTF Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
ACTS Group 1996	485	-19.3 (23)	245	-19.8 (23.5)		53.19%	0.45[-3.13,4.03]
Miller 1996b	429	-14.8 (19)	141	-16.4 (20.4)		46.81%	1.55[-2.27,5.37]
Total ***	**914**		**386**			**100%**	**0.96[-1.65,3.58]**
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%							
Test for overall effect: Z=0.72(P=0.47)							

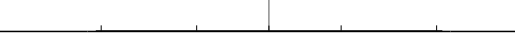


Analysis 2.4. Comparison 2 Any CNTF versus placebo, Outcome 4 Changes in quality of life (SIP).

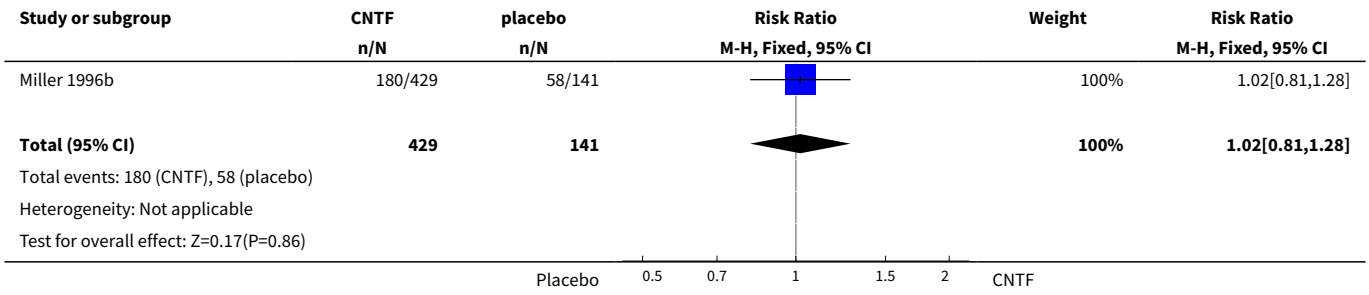
Study or subgroup	CNTF N	CNTF Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Miller 1996b	382	6.2 (8.4)	121	6.9 (8.7)		100%	-0.74[-2.5,1.02]
Total ***	**382**		**121**			**100%**	**-0.74[-2.5,1.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.82(P=0.41)							

Analysis 2.5. Comparison 2 Any CNTF versus placebo, Outcome 5 Cough.

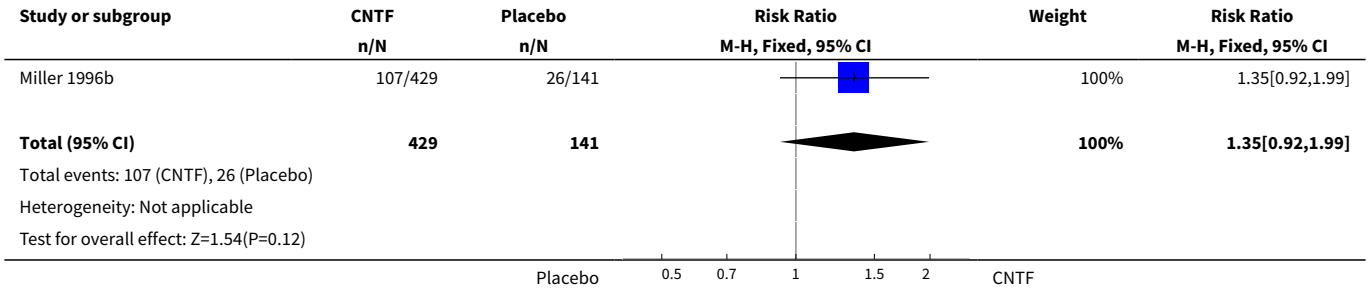
Study or subgroup	CNTF n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Miller 1996b	146/429	31/141		100%	1.55[1.1,2.17]
Total (95% CI)	**429**	**141**		**100%**	**1.55[1.1,2.17]**
Total events: 146 (CNTF), 31 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.54(P=0.01)					



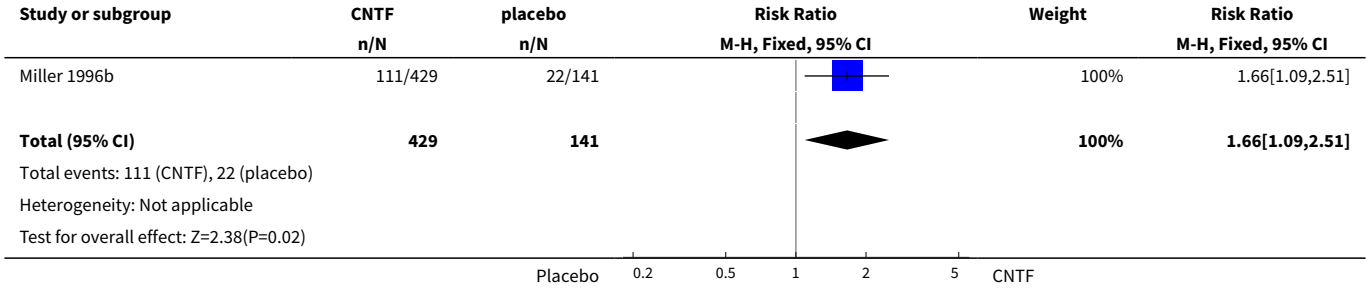
Analysis 2.6. Comparison 2 Any CNTF versus placebo, Outcome 6 Asthenia.



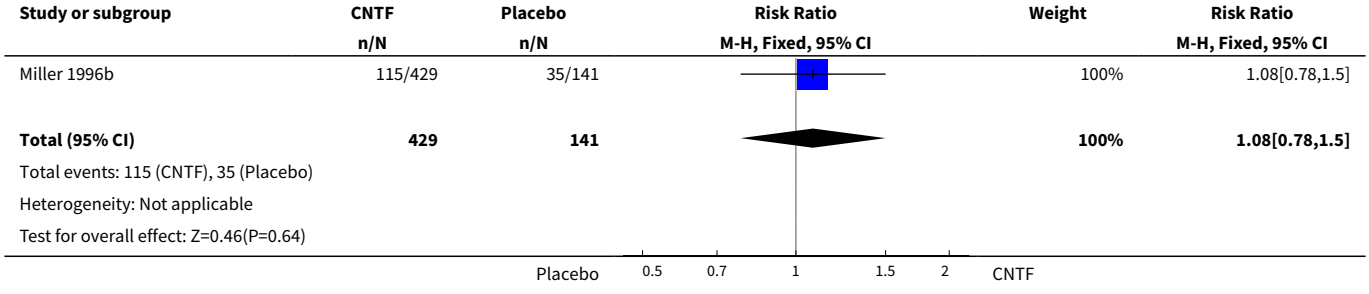
Analysis 2.7. Comparison 2 Any CNTF versus placebo, Outcome 7 Nausea.



Analysis 2.8. Comparison 2 Any CNTF versus placebo, Outcome 8 Anorexia.



Analysis 2.9. Comparison 2 Any CNTF versus placebo, Outcome 9 Increased salivation.



APPENDICES

Appendix 1. MEDLINE OvidSP search strategy

randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.)
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 exp Motor Neuron Disease/
13 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp.
14 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp.
15 charcot disease.tw.
16 Amyotrophic Lateral Sclerosis.mp.
17 or/12-16
18 Ciliary Neurotrophic Factor/
19 ciliary$ neurotrophic$ factor$.mp.
20 cntf$.mp.
21 nerve growth factor/
22 (nerve$ growth$ factor$ or ngf).mp.
23 or/18-22
24 11 and 17 and 23
25 remove duplicates from 24

Appendix 2. EMBASE OvidSP search strategy

crossover-procedure/
2 double-blind procedure/
3 randomized controlled trial/
4 single-blind procedure/
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
6 clinical trial/
7 or/1-6
8 exp animals/
9 exp humans/
10 8 not (8 and 9)
11 7 not 10
12 limit 11 to embase
13 motor neuron disease/ or amyotrophic lateral sclerosis/
14 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease$1).mp.
15 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp.
16 charcot disease.tw.
17 amyotrophic lateral sclerosis.tw.
18 or/13-17
19 Ciliary Neurotrophic Factor/
20 cntf$.mp.
21 ciliar$ neurotrophic$ factor$.mp.
22 nerve growth factor/
23 (nerve$ growth$ factor$ or ngf).mp.
24 or/19-23
25 12 and 18 and 24
26 remove duplicates from 25

Appendix 3. CENTRAL search strategy

1MeSH descriptor Motor Neuron Disease explode all trees
#2(moto* neuron* disease* or moto?neuron* disease)
#3"Amyotrophic Lateral Sclerosis"
#4("Lou Gehrig*" and (disease* or syndrome*))
#5(#1 OR #2 OR #3 OR #4)
#6"ciliary neurotrophic factor*"
#7cntf*
#8"nerve growth factor*"
#9(#6 OR #7 OR #8)
#10(#5 AND #9)

WHAT'S NEW

Date	Event	Description
28 June 2011	New search has been performed	The searches were updated in April 2011; no new studies were found. A 'Summary of findings' table was added

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 3, 2004

Date	Event	Description
18 March 2009	New search has been performed	The searches were updated in February 2009; no new studies were found. Risk of bias table has been completed.
5 May 2008	Amended	Converted to new review format.
30 April 2007	New search has been performed	The searches were updated in August 2006; no new studies were found.
25 April 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the protocol

Paolo Bongioanni and Fulvia Gremo prepared the first draft of the protocol. Valeria Sogos and Camilla Reali commented on the draft and agreed the final text.

For the review

Paolo Bongioanni, Valeria Sogos and Camilla Reali independently identified potentially relevant studies and assessed their methodological quality; Valeria Sogos and Camilla Reali extracted data and Paolo Bongioanni checked them; all review authors independently analysed patient data and wrote the first drafts of the review. After a consensus meeting, review authors wrote the final version of review together.

Valeria Sogos and Paolo Bongioanni updated the review.
Fulvia Gremo could not take part in the review work, because she died unexpectedly.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- University of Cagliari, Italy.

External sources

- NeuroCare Onlus, Italy.

NOTES

Relevant research on this intervention in ALS is slow to emerge. The next planned update of this review will be 2015, four years after the current date of search.

INDEX TERMS

Medical Subject Headings (MeSH)

Amyotrophic Lateral Sclerosis [*drug therapy]; Ciliary Neurotrophic Factor [*therapeutic use]; Disease Progression; Motor Neuron Disease [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans