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[Intervention Review]

Drug treatment for myotonia

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Editorial group: Cochrane Neuromuscular Disease Group.
Publication status and date: Edited (no change to conclusions), published in Issue 6, 2011.
Review content assessed as up-to-date: 29 July 2009.

Citation: Trip J, Drost GG, van Engelen BGM, Faber CG. Drug treatment for myotonia. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004762. DOI: 10.1002/14651858.CD004762.pub2.

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ABSTRACT

Background
Abnormal delayed relaxation of skeletal muscles, known as myotonia, can cause disability in myotonic disorders. Sodium channel blockers, tricyclic antidepressive drugs, benzodiazepines, calcium-antagonists, taurine and prednisone may be of use in reducing myotonia.

Objectives
To consider the evidence from randomised controlled trials on the efficacy and tolerability of drug treatment in myotonia.

Search methods
In July 2009 we updated the searches of the Cochrane Neuromuscular Disease Group Trials Specialized Register, The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2009), MEDLINE (from January 1966) and EMBASE (from January 1980). We hand searched the grey literature and contacted disease experts and anti-myotonic drug manufacturers.

Selection criteria
We considered all (including quasi) randomised trials of participants with myotonia treated with any drug treatment versus no therapy, placebo or any other active drug treatment.

Primary outcome: reduction of clinical myotonia.

Secondary outcomes:
(1) clinical relaxation time; (2) electromyographic relaxation time; (3) stair test; (4) presence of percussion myotonia; and (5) adverse events.

Data collection and analysis
Two review authors extracted the data independently onto standardised extraction forms. Meta-analysis was not possible.
Main results

No new trials were found for this update. Ten double-blind or single-blind crossover studies involved a total of 143 participants of whom 113 had myotonic dystrophy type 1 and 30 had myotonia congenita. The studies were of poor quality and did not provide adequate data. Two small crossover studies without a washout period demonstrated a significant effect of imipramine and taurine in myotonic dystrophy. One small crossover study with a washout period demonstrated a significant effect of clomipramine in myotonic dystrophy. Meta-analysis was not possible.

Authors’ conclusions

Due to insufficient good quality data and lack of randomised studies, it is impossible to determine whether drug treatment is safe and effective in the treatment of myotonia. Larger, well-designed randomised controlled trials are needed to assess the efficacy and tolerability of drug treatment for myotonia.

Plain Language Summary

Drug treatment for myotonia (delayed muscle relaxation after contraction) in muscle diseases such as myotonic dystrophy and myotonia congenita

Myotonia is an abnormal delay in the relaxation of muscles after contraction. It is a key symptom in a number of muscle diseases called myotonic disorders. It can be mild or severe, interfering with daily activities such as walking, climbing stairs or opening and closing the eyelids. It can be worse after periods of rest or triggered by cold or fatigue. People with mild myotonia can manage their disease without medication but in severe cases treatment is usually necessary. Drugs that have been used to treat myotonia include sodium channel blockers such as procainamide, phenytoin and mexiletine, tricyclic antidepressant drugs such as clomipramine or imipramine, benzodiazepines, calcium antagonists, taurine and prednisone. This review describes ten randomised controlled trials which tested the effectiveness of twelve different drug treatments. The review was updated in July 2009 and no new trials were found. The ten trials included a total of 143 participants of which 113 had myotonic dystrophy and 30 had myotonia congenita. The trials were generally small and of poor quality. Meta-analysis was not possible due to a lack of appropriate trials and data. Two small studies suggested that clomipramine and imipramine might have a short-term beneficial effect on the myotonia in myotonic dystrophy and one small study suggested that taurine might have a long-term beneficial effect in myotonic dystrophy. Minor side effects such as dry mouth and dizziness were reported with clomipramine and imipramine, but not with taurine. It was not possible to determine whether drug treatment is safe and effective for myotonia in people with a myotonic disorder based on the evidence from the ten trials included in this review. Larger, well-designed randomised controlled trials are needed.

Background

Myotonia is a clinical phenomenon, which refers to a delayed muscle relaxation after voluntary or evoked muscle contraction (Logigian 2005). It is a cardinal feature of myotonic disorders including myotonic dystrophy and the non-dystrophic myotonias. Myotonia may be present in every skeletal muscle. Clinical examination reveals action myotonia and percussion myotonia, or both. Action myotonia and percussion myotonia are best tested in the hand muscles: following a forceful grip, the ability to relax the grip is delayed (action myotonia or grip myotonia); or mechanical stimulation, for example a blow with the percussion hammer on the thenar muscles will also contract the muscle for a few seconds (percussion myotonia). Furthermore, an acute muscle contraction may give a transient decline in muscle force (transient paresis) (Drost 2001; Ricker 1978). Repeated contraction and relaxation may improve myotonia as well as muscle force, which is called the ‘warming-up’ phenomenon. However, in a condition called paramyotonia, the myotonia worsens after repetitive contractions (paradoxical myotonia).

A number of conditions are associated with delayed relaxation of muscles in a way that resembles myotonia but they do not have the characteristic electrophysiological features of true myotonia (pseudomyotonia) (Harper 2001). Because such pseudomyotonia may have a different physiological basis from true myotonia, we excluded these conditions from our review. These conditions include
McArdle's disease (glycogenosis type V), Hoffman's disease (myotonia in hypothyroidism), Brody's disease (sarcoplasmic reticulum-Ca\(^{2+}\)-ATPase deficiency), neuromyotonia, neuroleptic malignant syndromes and tetanus. Schwartz-Jampel syndrome (chondrodystrophia myotonia) was also excluded because myotonic activity in this disease persists during general anaesthesia, which does not happen in true myotonia (Fowler 1974). True myotonia syndromes included in this review are discussed below.

**Myotonic dystrophy**

Myotonic dystrophy type 1 is an autosomal-dominant disorder in which myotonia is accompanied by a characteristic pattern of muscle weakness and by the involvement of several organs (Cürschmann 1912; Harper 2004; Steinert 1910). This condition is caused by an expanded CTG (cytosine-thymine-guanine) trinucleotide repeat in the DMPK-gene on chromosome 19q (Brook 1992; Harley 1992). The inheritance is characterised by anticipation, that is the earlier and more severe onset of the disease in successive generations (Howeler 1989). The prevalence of myotonic dystrophy type 1 varies from 2 to 12 per 100,000 (Emery 1991).

Myotonia is clinically detectable in almost every symptomatic patient. Recently, myotonic dystrophy type 2 was described, which differs from type 1 in its predominant proximal muscle weakness. It was, therefore, originally named proximal myotonic myopathy (PROMM) (Moxley 1996; Ricker 1999). Myotonic dystrophy type 2 is caused by an increased CCTG repeat in the ZNF9 gene on chromosome 3. We have included people with clinical myotonia due to both types of myotonic dystrophy.

**Non-dystrophic myotonias**

Clinically non-dystrophic myotonias have myotonia with or without periodic paralysis (Rüdel 1999). Recently the molecular basis of these disorders has been discovered, but it is difficult to make a diagnosis on the basis of the clinical picture because no obvious genotype-phenotype correlation exists (Koty 1996; Papponen 1999; Plassart-Schiess 1998). Over the past decade, a combination of electrophysiologic and molecular biological studies have led to a reclassification of this group of diseases (Drozd 2001; Ptácek 1998; Rüdel 1997; Rüdel 1999). They are now classified as chloride or sodium channel diseases.

**Chloride channel disorders**

There are two forms of chloride channel disorders: autosomal-recessive myotonia congenita (Becker's disease) (Becker 1970; Becker 1977) and autosomal-dominant myotonia congenita (Thomsen's disease) (Thomsen 1876). Both diseases are characterised by clinical myotonia. Autosomal-recessive myotonia congenita also shows transient paresis (Drozd 2001; Ricker 1978). The disorders are caused by a mutation in the skeletal muscle chloride channel gene (CLCN1) on chromosome 7q (Fontaine 1997; George 1993; Koch 1992). The prevalence of chloride channel diseases varies in different studies between 2 to 7.3 per 100,000 (Baumann 1998; Becker 1977; Rüdel 1994). We included all patients with dominant and recessive myotonia congenita in our review.

**Sodium channel disorders**

Sodium channel disorders are all autosomal-dominantly inherited or sporadic and are divided into paramyotonia congenita, potassium-aggravated myotonia (myotonia fluctuans, myotonia permanens and acetazolamide responsive myotonia congenita) and hyperkalaemic periodic paralysis (hyper PP) (Lehmann-Horn 1994; Lennox 1992; Leche 1993; Ricker 1990; Ricker 1994). The sodium channelopathies are caused by a mutation in the sodium channel gene (SCN4A) on chromosome 17q encoding for SkM1, the alpha-subunit of the sodium channel (Fontaine 1999; Fontaine 1997). The exact prevalence of sodium channel diseases is not known although the prevalence of paramyotonia congenita has been estimated at 1 per 356,000 (Becker 1970). Hyper PP can occur with myotonia or paramyotonia and sometimes without either. We excluded Hyper PP without (para)myotonia and included all other sodium channel disorders in our review.

The pathophysiological mechanisms in the several myotonic disorders are different. Recent publications suggest that the expanded CTG-repeat in myotonic dystrophy triggers aberrant splicing of chloride channel mRNA (Charlet-B 2002; Mankodi 2002) but it is also possible that the myocytes in myotonic dystrophy display an abnormal Na\(^+\) channel activity (Bernareggi 2005). Thus, the exact pathophysiologic mechanism leading to myotonia in myotonic dystrophy is unknown. It could be assumed that there is an overlap with the non-dystrophic channelopathies.

The chloride channel myotonias are caused by a permanent reduction of the resting chloride conductance of the muscle fiber membranes (Franke 1993; Lipicky 1979). Normal chloride conductance is necessary for a fast repolarisation of the muscle fiber membranes, otherwise these tend to stay depolarised causing myotonia (Jurkat-Rott 2001) or become hyperdepolarised causing a loss of excitability of the muscle fiber membrane and thereby a transient paresis.

Sodium channel myotonias are caused by a long-lasting depolarisation of the muscle fiber membrane due to an inactivation defect of the sodium channels (Lehmann-Horn 1987a; Lehmann-Horn 1987b). These can initiate successive action potentials, which is the basis for myotonia (Jurkat-Rott 2001).

Many people with mild myotonia can manage their disease without medication. Severe myotonia can interfere with daily activities and in these individuals treatment is often necessary. No treatment for the cause of myotonia is available so treatment is merely symptomatic. In general drugs that block the sodium channels, inde-
DEPENDENT of the disease process involved, can diminish myotonia. These agents reduce the excitability of the cell membrane of the skeletal muscle and include local anaesthetics, cardiac agents, such as anti-arrhythmic drugs, and anti-epileptics.

The first treatment for myotonia was published by Wolf in 1936 who treated four people with myotonia congenita with quinine, an anti-arrhythmic drug (Wolf 1936). The literature also suggests that procainamide, tocainide and phenytoin have favourable effects (Dengler 1979; Kwiecinski 1992; Leyburn 1960; Munsat 1967; Rüdel 1980; Streib 1986). However, procainamide and tocainide could have serious long-term side effects. Expert opinion suggests that mexiletine is the agent of first choice (Rüdel 1994). However the published evidence basis for this opinion is unclear. There are some case reports (Ceccarelli 1992; Leheup 1986; Pouget 1983), one study with a heterogeneous population (Kwiecinski 1992) and an electrophysiological evaluation (Rossi 1985) on the use of mexiletine in people with myotonia in the literature. Acetazolamide is a carbonic anhydrase inhibitor traditionally thought of as a diuretic, but it has been described as useful for myotonia in some sodium channelopathies (Griggs 1978; Prácek 1994).

A crucial aspect to this review is how to quantify myotonia because it can be difficult to standardize this as highlighted by a report of an experimental protocol to quantify myotonia using quantitative muscle assessment (Sanone 2000). The problems include the variability of the myotonia between people and within a given patient at different times of the day, and how to take account of the warm up phenomenon all of which exacerbate the usual problem of inter rater variability. Possible solutions might be the use of specific devices with a computerized protocol (Logigian 2004; Logigian 2005). One of the most used parameters of myotonia is the relaxation time after maximum voluntary contraction (MVC) as measured by stopwatch, special technical equipment or computerized protocols. A related measure is the electromyographic variant, the electromyographic (EMG) relaxation time after MVC. Another used parameter is to record the presence or absence of percussion myotonia. These parameters measure the impairment, but not the functional effect of myotonia. The stair test (time needed to climb ten stairs) is possibly the best available method for measuring approximate functional benefit.

No systematic reviews of drug treatment for myotonia are known. Two non-systematic reviews of therapy for the myotonic disorders have been published (Meola 2000; Meola 2004). This systematic review aims to provide the evidence on which to base treatment.

**OBJECTIVES**

To consider the evidence from randomised controlled trials on the efficacy and tolerability of drug treatment in people with clinical myotonia due to a myotonic disorder.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included all randomised and quasi-randomised (alternate or other systematic treatment allocation) trials of any drug treatment in people with clinical myotonia due to one of the myotonic disorders described below.

**Types of participants**

Participants of all ages with clinical myotonia caused by myotonic disorders such as myotonic dystrophy and the non-dystrophic myotonias were included. It is now possible to diagnose the myotonic disorders by DNA-analysis. This was not possible at the time when the included studies were performed so DNA-analysis was not an inclusion criterion in our review.

We excluded people with McArdle’s disease (glycogenosis type V), Hoffman’s disease (myotonia in hypothyroidism), Brody’s disease (sarcoplasmic reticulum-Ca2+ATPase deficiency), neuromyotonic diseases, neuroleptic malignant syndromes, tetanus and Schwartz-Jampel syndrome. For trials or treatment groups including people with myotonic dystrophy and non-dystrophic myotonias we described the different diseases and the degree of myotonia separately, if this was possible.

**Types of interventions**

We included any drug treatment (given either singly or in combination) versus no therapy, placebo or another active drug treatment. The list of potential drugs included quinine, procainamide, tocainide, phenytoin, mexiletine and acetazolamide but this list was not exclusive.

**Types of outcome measures**

**Primary outcomes**

As there is no consensus regarding the best measure of myotonia leading to disparate outcome measures in each of the randomised trials, we devised a measure using a categorisation of the changes in clinical myotonia after drug treatment for each trial based on the conclusion of the original authors as follows:

1. improvement of myotonia with no residual clinical myotonia;
2. improvement of myotonia but still clinically detectable;
3. no change of myotonia;
4. worsening of myotonia.
Secondary outcomes

1. Relaxation time: the time taken to fully open the hand after a maximum voluntary contraction (MVC) (hand-grip myotonia). This might be determined manually by stopwatch or by computerized protocols. When using a computerized hand-grip myometer the decline in maximum voluntary contraction from 90 to 5%, during relaxation is frequently used to measure the relaxation time. However some researchers have used 50%, 75% or 100% decline from peak MVC as the relaxation time. We included all such protocols.

2. Electromyographic (EMG) relaxation time: the phenomenon of myotonia can be recorded with an electromyographic needle electrode and are seen as positive waves, so called myotonic discharges or after-discharges. After MVC these myotonic or afterdischarges wax and wane and finally stop. The duration of these after-discharges is also called EMG relaxation time. For example after-discharges can be recorded from the opponens pollicis muscle.

3. Stair test: time needed to climb ten stairs

4. Presence of percussion myotonia: percussion myotonia is myotonia occurring after a mechanical stimulus; for example tested using percussion of the thenar muscles of the hand with a reflex hammer.

5. The occurrence of one or more adverse events during treatment with the different agents. We specified the adverse events.

For all outcome measures we used a minimum treatment duration of one week and maximum treatment duration of twelve weeks and where necessary planned to adjust for different follow-up periods.

Search methods for identification of studies

See: Cochrane Neuromuscular Disease Group search strategy.

Electronic searches

The Cochrane Neuromuscular Disease Group Trials Specialized Register was searched using: 'myotonia', 'myotonic dystrophy', 'non-dystrophic myotonias', 'myotonia congenita', 'Morbus Thomsen', 'Morbus Becker', 'potassium-aggravated myotonia', 'myotonia fluctuans', 'myotonia permanens', 'paramyotonia congenita', 'hyperkalaemic periodic paralyses', 'relaxation' AND 'muscle' and 'treatment' OR 'therapy' as the primary search items (July 2009). We adapted this strategy to search The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2009), MEDLINE (January 1966 to July 2009) and EMBASE (January 1980 to July 2009). See Appendix 1, Appendix 2 and Appendix 3 for MEDLINE, EMBASE and CENTRAL strategies. Following the initial publication of this review in January 2006, searches were updated in December 2007 and again in July 2009.

Searching other resources

Grey literature such as neuromuscular text books (Myology) and abstracts from international neuromuscular congresses (WMS/ AAN) were handsearched and we checked the reference lists of the identified literature and reviews concerning myotonia. We also contacted authors, disease experts and manufacturers of anti-myotonic drugs.

Data collection and analysis

Selecting trials for inclusion

Two review authors (JT and CGF) independently reviewed the titles and abstracts from the electronic search to identify relevant trials for full review. The full text of all potentially relevant studies was obtained for assessment. The review authors decided which trials fitted the inclusion criteria and graded their methodological quality. Disagreement was resolved by discussion. Review authors were not blinded to trial authors’ names, institutions and the journals of publication.

Assessment of methodological quality

Two review authors (JT and CGF) independently assessed randomised trials for methodological quality with respect to the following items: allocation concealment, patient blinding, observer blinding, explicit diagnostic inclusion and exclusion criteria and explicit outcome measures. These items were assessed according to the Cochrane approach: A - adequate, B - unclear, C - inadequate, D - not done. Disagreement was resolved by discussion.

Data extraction

Data extraction on participants, methods, intervention, outcomes and adverse events was performed independently by two review authors (JT and CGF) using a data extraction form. We attempted to obtain missing data from the trial authors if this was necessary. For the primary outcome we had created a special scoring system: (1) no residual clinical myotonia; (2) improvement of myotonia but still clinically detectable; (3) no change; (4) worsening of myotonia; and data were transformed from the original studies by two review authors (JT and CGF) with any disagreement being resolved by discussion.

Analysis

For statistical analysis of the primary outcome we dichotomised the variable scoring systems to define two groups:

(1) no residual myotonia or an improvement
(2) no change or worsened.
Risk ratios (RRs) with 95% confidence intervals (CI) were to be calculated from the dichotomised data for each study if this was possible. Where possible the numbers needed to treat (NNNT) and the numbers needed to harm (NNH) would also have been calculated. If all necessary data could be deduced from the published results, the primary outcome for crossover studies were analysed using the McNemar’s test (Armitage 1987; Breslow 1980), calculating the odds ratios. If there had been continuous data in the secondary outcomes we would have calculated the mean difference (MD) with 95% CI or presented the original statistical analysis of the study. If there had been more than one trial with the same agent in the same disease group we would have calculated a weighted treatment effect across those trials using a fixed-effect model with the Cochrane statistical package, Review Manager (RevMan). We interpreted a P value less than or equal to 0.05 as statistically significant. If chi-squared analysis showed heterogeneity of the study results (P < 0.1), sensitivity analyses would have been carried out to explore plausible causes. If heterogeneity could still not be explained, we would have reported the results using a random-effects model. We would have analysed myotonic dystrophy and the non-dystrophic myotonias as subgroups if possible, however, we did not analyse them as a total group. We also discussed adverse events and cost benefits drawing upon non-randomised data (Dukes 2000).

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.

See Tables: Characteristics of included studies and Characteristics of excluded studies.

The original search revealed nine trials that compared active drug treatment with placebo for the treatment of myotonia, in a total of 103 participants with myotonic dystrophy type 1 and 30 participants with myotonia congenita (Antonini 1990; Durelli 1983; Kratz 1986; Gascon 1989; Grant 1987; Kwiecinski 1992; Lewis 1966; Leyburn 1960; Munsat 1967). One trial was found that compared two different drug treatments for the treatment of myotonia, in 10 participants with myotonic dystrophy type 1 (Finlay 1982). On the basis of the title or the abstract a further 34 studies initially appeared to be eligible. However, by reading the full text of all potentially relevant studies 17 were non-randomised or uncontrolled studies (Backman 1990; Birnberger 1975; Brumback 1983; Durelli 1982; Griggs 1977; Griggs 1978; Guilleminault 1984; Mielke 1985; Milner-Brown 1990; Müller 1980; Orndahl 1986; Ricker 1980; Rüdel 1980; Samaha 1964; Sechi 1983; Sugino 1998; Matsumura 2004), ten were case studies (Alfonsi 2007; Benstead 1987; Cook 1984; Garai 1954; Geschwind 1955; Hughes 1991; Jackson 1994; Karli 1974; Pendefunda 1974; Streib 1987) and a further seven did not have measures of myotonia as outcome measures (Griggs 1989; Orndahl 1994; Péronisson-Benier 2008; Schneider-Gold 2003; Vlachopapadopoulou 1995; Walter 2002; Tarnopolsky 2004).

Another study (Martens 2005) is awaiting assessment because at the time of writing this review the trial results were not available in sufficient detail. We were informed about this study by contacting one of the disease experts in this field and read the abstract. When this trial is published in full, it will be included in the next update to the review.

When we repeated the searches in July 2009, 8 new references were obtained form the NMD Register, 28 from CENTRAL, 171 from MEDLINE, and 108 from EMBASE but none were new RCTs eligible for inclusion.

**Trial design**

Eight included trials were placebo-controlled, randomised, double-blind, crossover studies. The other two were placebo-controlled, randomised, single-blind, crossover studies (Grant 1987; Kwiecinski 1992). All included trials were performed in a single centre and a total of 143 participants received treatment (active drug or placebo) over two weeks to six months. In Antonini 1990 the treatment period was separated by a 30-day period washout interval. The other nine trials had no washout interval between the treatment periods. The trial of Kwiecinski 1992 started as a crossover study. Afterwards randomisation for three different study drugs took place. Remarkably the sum of the number of participants in the different treatment groups in the randomised part of the study exceeded the total number of included participants. An attempt to clarify this with the author was unsuccessful. We assume the second part of the study was not randomised until we receive evidence to the contrary.

**Participants**

The trials did not provide baseline characteristics of the individual participants or of the two separated groups. Five trials did not give the baseline characteristics at all (Durelli 1983; Kratz 1986; Lewis 1966; Leyburn 1960; Munsat 1967), the other trials gave the characteristics of the entire study population. Five trials included people with myotonic dystrophy only and five trials (Kwiecinski 1992; Kratz 1986; Lewis 1966; Leyburn 1960; Munsat 1967) included participants with myotonic dystrophy as well as myotonia congenita. Five trials did not define explicit inclusion criteria (Finlay 1982; Kratz 1986; Gascon 1989; Lewis 1966; Leyburn 1960). Only Antonini 1990 defined explicit exclusion criteria. In this trial cardiac, ophthalmologic or urologic diseases were excluded. Since cardiac and ophthalmologic symptoms are features of myotonic dystrophy, this trial probably included a selected group of patients.
Interventions
The regimens of treatment varied between studies (see Characteristics of included studies). Most studies used drugs that block sodium channels (procainamide, disopyramide, phenytoin, quinine, tocaainide and mexiletine) by which myotonia is diminished by reducing the level of depolarisation. Other drugs used were clomipramine, imipramine, taurine, nifedipine, diazepam and prednisone. It is hypothesised that the tricyclics (imipramine and clomipramine) act on the sympathetic nerve terminals to increase levels of norepinephrine, which exerts an inhibitory influence on skeletal muscle membranes by ß2-adrenoreceptor stimulation (Bowman 1981; Gascon 1989). Taurine, an amino-acid, may affect cellular hyperexcitability by increasing membrane conductance of potassium and chloride (Durelli 1982; Durelli 1983). All these types of drugs seem to act as membrane-stabilisers.

Outcome measures
The outcome measures used differed between trials. The most frequently used outcome measure was the clinical relaxation time in seconds. It was measured after three seconds (Antonini 1990), two to three seconds (Gascon 1989), five seconds (Lewis 1966) and three minutes (Finlay 1982) of maximum voluntary contraction (MVC). Others (Grant 1987; Kritz 1986; Kwiecinski 1992) did not specify the length of maximum voluntary contraction. The EMG relaxation time (after-discharge) in seconds after MVC was also used (Durelli 1983; Kritz 1986; Kwiecinski 1992). Additional ways of measuring relaxation time were used such as the use of EEG surface electrodes (Lewis 1966) or an ergographic device (Munsat 1967). Two trials used a mean score of three relaxation times (Gascon 1989; Lewis 1966) and one used a mean score of five relaxation times after MVC (Grant 1987). Another trial used a mean score of six measurements consisting of three clinical relaxation times and three EMG relaxation times (Leyburn 1960). Other outcome measurements were occurrence of percussion myotonia (Durelli 1983), percussion myotonia in seconds (Gascon 1989), lid myotonia in seconds after firm closure (Kwicinski 1992), occurrence of myotonic discharge induced by electrical stimulation of the median nerve (Durelli 1983), potassium chloride (KCl) loading test in mmol/litre for occurrence of myotonia (Durelli 1983), time to climb ten stairs (stair test) (Kwicinski 1992) and subjective responses (Finlay 1982; Kwicinski 1992). The methodological quality assessment took into account allocation concealment, patient blinding, observer blinding, explicit inclusion and exclusion criteria and explicit outcome measures. We graded these items as: A: adequate, B: unclear, C: inadequate, D: not done. If the information was not available the item was graded as unclear. The scores of each trial are included in Additional Table 1.

In all ten trials participants were randomised for crossover studies to either active treatment or placebo (or another active drug treatment). The allocation concealment was considered adequate in the study Leyburn 1960; a statistician randomised trial participants. For Lewis 1966 the allocation concealment was inadequate; the procedure was described as ‘arbitrary by secretary’. The other allocation concealments were unclear, because the method of randomisation was not explained.

Patient blinding was intended in at least nine trials. In only three trials the blinding was considered adequate (Durelli 1983; Kwiecinski 1992; Munsat 1967). In six trials the blinding was unclear because it was not described (Antonini 1990; Gascon 1989; Grant 1987; Kritz 1986; Lewis 1966; Leyburn 1960) and in Finlay 1982 the patient blinding was inadequate because participants could recognise the side effects having used the medication previously in a clinical setting. Observer blinding was also intended in at least nine trials. Four trials were considered adequate for observer blinding (Durelli 1983; Finlay 1982; Gascon 1989; Lewis 1966). In one trial the observer could recognize the origin of the medication by the kind of adverse events (Munsat 1967). Another single trial did not have observer blinding (Kwicinski 1992) and the study of Grant 1987 was designed as a randomised single-blind crossover study but it was unclear if the participants or the observers were blinded. The other two studies were unclear. None of the trials recorded effectiveness of blinding. We also graded the inclusion and exclusion criteria. This item is discussed under participants in the Description of studies section.

As expected there was no uniform outcome measurement. The explicit outcome measurements were considered adequate in eight trials. We considered the outcome measure of Leyburn 1960 as inadequate only because it was the mean value of six measurements in which three were EMG relaxation times and three were clinical relaxation times. It is difficult to give an explanation of the meaning of these values. Moreover, some studies took the mean of three to five relaxation times. It is likely that these times are shortened by the warming-up phenomenon.

Analysis
All trials were analysed on a per protocol basis instead of an intention-to-treat basis (withdrawals were not included in the analysis).

Risk of bias in included studies
See Additional Table 1.

Effects of interventions
A total of ten single centre trials were included, in which 143 participants with myotonia were randomised in a single-blind or double-blind crossover study with a treatment period ranging from two weeks to six months. Twelve different drugs were used in those ten trials. Participants could be divided into 113 people with myotonic dystrophy type 1 and 30 people with myotonia congenita.
Three studies were performed in the 1960s, six in the 1980s and one in the 1990s. In general the trials were small, with the participant numbers ranging from nine to thirty, and the methodological quality was poor. All ten included randomised crossover trials were based on a per-protocol analysis which could result in an attrition bias. The data for an intention-to-treat analysis were not available. The data analysis of Finlay 1982 was inadequate. The study only presented descriptive results. The individual continuous data were not stated and no statistical analysis was performed. The data of Kratz 1986 were incomplete because we only have the information in the abstract (descriptive results). Attempts to contact the authors were unsuccessful. Lewis 1960 had a large placebo effect. Research into the placebo tablets identified that they contained 0.5 mg quinine sulphate per tablet. This substance could be an effective treatment for myotonia, resulting in performance bias. For these reasons we were unable to use the data from these three trials.

Six studies (Durelli 1983, testing taurine; Gascon 1989, testing imipramine; Grant 1987, testing nifedipine; Kwiecinski 1992, testing disopyramide, lenytoin, mexiletine and tocaande; Leyburn 1960, testing quinine, predesnion and procainamide; Munsat 1967, testing diphenylhydantoin and procainamide) were of crossover design without washout intervals. Data were inappropriately presented in the form of combined results of both active treatment arms and both placebo arms. Since a washout interval was not incorporated, there is a strong possibility of a carry-over effect. Data from the first arms were not presented and four studies did not present data individually (Grant 1987; Kwiecinski 1992; Leyburn 1960; Munsat 1967). From these four studies three included both participants with myotonic dystrophy as well as myotonia congenita, without defining subgroups. For these reasons we were unable to use data from those four trials. We tried to contact the authors of the trials but have not yet been successful in obtaining the raw data. Two single studies (Durelli 1982; Gascon 1989) gave data for some of our specified outcomes and in spite of a possible carry over effect we will present these data. For one study (Antonini 1990) we can provide the results for the treatment of myotonia without any restrictions. Because most trials included different diseases in the same trial without giving the individual data and used different drug treatments, meta-analysis was not possible.

Thus it is only possible to present the data of three studies for the treatment of myotonia in myotonic dystrophy (Antonini 1990; Durelli 1983; Gascon 1989). We could not present potentially valuable data for the treatment of myotonia in myotonia congenita. For the Durelli 1983 study with a treatment period of six months it is only possible to present the data for our secondary outcome measure, the EMG relaxation time. The EMG relaxation time after treatment with taurine was lower (average 0.58 seconds; SD 0.24) than both the baseline (average 1.33 seconds; SD 0.71) and after placebo (average 1.02 seconds; SD 0.36) \( (P < 0.01; \text{Student's t test}) \). Taurine had no side effects.

Gascon 1989 measured both left and right-hand relaxation times after imipramine and placebo. Our primary outcome with the McNemar test was significant for the right hand with an infinity odds ratio (95% CIs from binomial distribution 0.92 to infinity) \( (P = 0.025) \) and also significant for the left hand with an infinity odds ratio (95% CIs from binomial distribution 0.66 to infinity) \( (P = 0.046) \). The relaxation time was measured as a secondary outcome. Repeated measures of analysis of variance (ANOVA) of these data revealed significant improvement of myotonia as measured by right grip \( (F(2.20) = 11.14, P < 0.001) \) and left grip \( (F(2.20) = 6.65, P < 0.01) \). The most important side effects of imipramine were dry mouth (8 out of 12 participants; 67%), dizziness (4 out of 12; 33%), increased sweating (4 out of 12; 33%), constipation (4 out of 12; 33%), tremor (3 out of 12; 25%), blurred vision (3 out of 12, 23%) and diarrhoea (3 out of 12, 23%).

The trial of Antonini 1990 used clomipramine and had two washout intervals of thirty days so the risk of carry-over effect was reduced. They stated that there were no differences between people receiving clomipramine in the first or second treatment period. The primary outcome of improvement of myotonia with the McNemar test was not significant and showed an odds ratio of 3.00 (95% CIs 0.25 to 157.49) \( (P = 0.32) \). The analysis of a secondary outcome with a paired t-test (crossover study) demonstrated that the mean relaxation time after clomipramine (average 15.85 seconds, SD 9.44) was significantly shorter \( (P = 0.02) \) than after placebo (average 22.54 seconds, SD 16.47). The study had no electromyographic relaxation time, stair test or presence of percussion myotonia as outcomes. Minor side effects were drowsiness (6 out of 15 participants; 40%), dry mouth (2 out of 15; 13%), tiredness (2 out of 15; 13%), hyperhydrosis (1 out of 15; 7%) and dizziness (1 out of 15; 7%).

In conclusion, it was only possible to calculate our primary outcome for two studies (Antonini 1990; Gascon 1989). This outcome was only significant for treatment with imipramine for myotonia in myotonic dystrophy (Gascon 1989). Our secondary outcome measure of relaxation time could be calculated in the same two studies. Both imipramine and clomipramine showed a significant result in relieving myotonia in myotonic dystrophy. We could only provide data for the EMG relaxation time from the Durelli 1983 study with the treatment of taurine for myotonia in myotonic dystrophy. This result was also significant. Meta-analysis was not possible.

The side effects of the other active drug treatments taken from the included trials were:

- Mexiletine: 20% (6 of 30) epigastric distress sometimes prevented by taking the drug with food, 3% (2/30) rash, esophageal burning and nasal congestion.
- Tocainide: 6% (1 of 18) lymphadenopathy and 11% (2 of 18) dizziness, anxiety and tremor.
- Dipyridamole: 10% (3 of 30) skin rash, somnolence and mild ataxia.
- Disopyramide: 32% (7 of 22) dry mouth and blurred vision while taking high doses.
Nifedipine: 20% (2 of 10) headache and lethargy while taking 3 doses of 20 mg and 10% (1 of 10) light T wave flattening or T wave inversion on the ECG.

Procainamide: 39% (15 of 39) gastro-intestinal complaints.

Quinine: 45% (9 of 20) mild and tolerable tinnitus, 30% (6 of 20) some degree of deafness and 5% (1 of 20) dull head without tinnitus.

Prednisone: no side effects in three weeks. This is of course of little value in judging safety of steroid therapy as a long-term measure. Diazepam: 64% (7 of 11) sedation and 27% (3 of 11) of dizziness. The tested drug treatments in this review varied in costs from EUR 2.29 per month (phenytoin) to EUR 23.67 per month (quinine) (Loenen 2005).

DISCUSSION

Despite the fact that different drug treatments have been used to reduce symptoms of myotonia since 1936, very few good randomised crossover trials have been performed to study the effect of these treatments. Overall, the methodological quality of the studies considered was poor. Most methods reported in original papers were not described in sufficient detail. Only one crossover trial had a washout interval and reported data from each treatment period. Clomipramine, studied in this small trial, demonstrated a significant effect on the relaxation time in participants with myotonic dystrophy. For more reliable results it is necessary to perform studies with a larger cohort. The other crossover trials did not have a washout interval and did not report data from each (or at least the first) treatment period separately. Four studies included participants with myotonic dystrophy as well as myotonia congenita without defining subgroups. For these reasons it was not possible to estimate the treatment effect of four studies. Two other small studies indicated, despite a carry-over effect, a short-term effect of imipramine and a long-term effect of taurine on myotonia in myotonic dystrophy. In spite of the evidence (admittedly limited) for these three drugs reducing myotonia, they are probably not used very often in medical practice. Expert opinion on the base of clinical experience still favours mexiletine, particularly in myotonia congenita. This is despite the lack of randomised controlled trials with mexiletine although one is awaiting assessment (Martens 2005). In conclusion, better randomised crossover studies with a proper washout interval and clearly presented data from both arms and with clear separation of the different diseases associated with myotonia are necessary for further determination of an effective and safe treatment for myotonia.

The adverse events from randomised data are given in the results. Non-randomised data suggest serious side effects for tocainide and procainamide such as agranulocytosis and pancytopenia (Gelfand 1994; Nelson 1984; Shields 1988; Soft 1987; Wang 1969). These serious side effects are a contraindication for their use in myotonia. Other side effects of tocainide are diplopia, dizziness, nausea, tremor and anxiety (Mielke 1985; Ricker 1980; Rüdel 1980). For procainamide more than 50% of the participants had gastro-intestinal side effects and 33% complained of insomnia (Geschwind 1955). Three participants with myotonic dystrophy and treated with phenytoin or carbamazepine had cardiac side effects (ventricular tachycardia and atrioventricular block grade 1) (Durelli 1985). Reported side effects of acetazolamide were paraesthesias, anorexia, weight loss, renal failure, renal calculi, osteoporosis, and haematological and hepatic dysfunction (Griggs 1977; Griggs 1978). In a non-randomised study of amitriptyline for myotonia six from the eight participants complained of a dry mouth and two had drowsiness. One participant had supraventricular tachycardia due to an adrenergic effect (Milner-Brown 1990). Verapamil for myotonia was tested in a non-randomised study in five people. One participant complained of dizziness with a first-degree heart block, another had transient nausea (Cook 1984).

The lack of appropriate trials and data is not the only difficulty in determining the treatment effect in myotonia. Difficulty also exists in the clinical assessment of myotonia. Although many outcome measures have been developed, until now no validated scale has been used with unanimous consent. Sansone 2000 wrote an experimental protocol but also reported some unsolved problems. One of the main problems is the inter- and intra-variability of myotonia under the same conditions and the inter rater variability. Furthermore, myotonia can be dependent on temperature, physical effort, rest, food intake, pregnancy, phenotype and genotype. Therefore, it is difficult to standardize outcome measures for myotonia. A technique to overcome some of these problems in measuring relaxation times, is the use of computerized protocols in which a computer program places cursors along the relaxation phase and calculates the relaxation times between these points (Loggian 2004; Loggian 2005).

Another problem in determining the treatment effect of myotonia is the intriguing warming-up phenomenon (diminishing of myotonia after repetitive contractions). In chloride channelopathies this is probably the result of an improvement of both myotonia and transient paresis (Drost 2001) and in myotonic dystrophy and sodium channel myotonias it is only the improvement of myotonia. The exact pathophysiological mechanism of the warming-up phenomenon is unknown but the phenomenon could influence the degree of myotonia, especially when measuring repeated maximum voluntary contractions. The length and frequency of maximum voluntary contractions differed between studies which could influence the outcome measures. Furthermore paramyotonia can occur, which is a worsening of myotonia after repetitive contractions (paradoxical myotonia). Myotonia is thus a symptom in different diseases. We excluded the diseases with no true myotonia (see background and type of participants) but when these are excluded there are still three groups left: (1) myotonic dystrophy...
type I (and probably type II), (2) non-dystrophic chloride channel myotonias, and (3) non-dystrophic sodium channel myotonias. In general myotonia is a mild symptom in myotonic dystrophy and a much more serious symptom in myotonia congenita and the sodium channelopathies.

Paradoxically in our review only 30 people with myotonia congenita were studied and the majority had myotonic dystrophy perhaps reflecting the higher prevalence of myotonic dystrophy. However most people with myotonic dystrophy do not seek treatment for their myotonia because it often is a relatively mild symptom compared to the other symptoms they suffer. They also may have an avoidant personality with “avoidance” of medical treatment as part of their disease. All studies which included participants with myotonia congenita included people with myotonic dystrophy as well. This causes a mixture of different diseases with different pathophysilogies, but the outcome measures were not analysed for the two disorders separately. For all the reasons mentioned above it would seem appropriate to perform different RCTs for the different kinds of myotonic diseases. It is also unlikely that a single method of assessment is appropriate for each separate disease.

Finally, there is the lack of functional outcome measures. The most used functional outcome measure is the stair test (see last part of background), but only one study used this test. We recommend this test as a secondary outcome measure in future RCTs. Another possible functional test for future studies could be the chair test (time needed to stand up from a chair, walk around the chair and sit down again).

In conclusion, the best evidence for the treatment of myotonia in myotonic dystrophy is from single small studies of clomipramine, imipramine and taurine. We could not present separate data for the treatment of myotonia in myotonia congenita. However, a beneficial effect from drug treatment for myotonia cannot be excluded and its use in certain people with severe myotonia might be appropriate (for example in those in whom there is a clear impact on daily activities). Taurine did not have any side effects in nine people for six months. Clomipramine and imipramine have some side effects but seem to be safe treatments. Based on three single small randomised trials and clinical observations (subjective responses of the patients and expert opinion) some drugs have a potential effect in decreasing myotonia. To prove this hypothesis, properly designed, double-blind, randomised controlled (multi-centre) trials have to be performed for the different types of myotonic disorders. In the case of crossover trials, a washout interval is recommended. Moreover, intention-to-treat analysis and appropriate analysis and presentation of the results are required.

AUTHORS’ CONCLUSIONS

Implications for practice
There is a lack of high quality randomised evidence to determine whether any drug treatment is safe and effective in the treatment of myotonia.

Implications for research
The clinical efficacy of drug treatment for myotonia has not yet been properly evaluated. Larger, well designed RCTs are needed to assess the efficacy and tolerability of drug treatment for myotonia.

ACKNOWLEDGEMENTS
We are grateful to FA Kessels and E van Raak for a critical look at the review and statistical advice, and to the Princess Beatrix Foundation for financial support (MAR04-0118). Editorial support from the Cochrane Neuromuscular Disease Group was funded by the TREAT NMD European Union Grant 036825.

REFERENCES

References to studies included in this review

Antonini 1990 [published data only]

Durelli 1983 [published data only]

Finlay 1982 [published data only]

Gascon 1989 [published data only]

Grant 1987 [published data only]

Drug treatment for myotonia (Review)
Kratz 1986 (published data only)

Kwiecinski 1992 (published data only)

Lewis 1966 (published data only)

Leyburn 1960 (published data only)

Munsat 1967 (published data only)

References to studies excluded from this review

Alfonsi 2007 (published data only)

Backman 1990 (published data only)

Benstead 1987 (published data only)

Birnberger 1975 (published data only)

Brumback 1983 (published data only)

Cook 1984 (published data only)

Durelli 1982 (published data only)

Garai 1954 (published data only)

Geschwind 1955 (published data only)

Griggs 1977 (published data only)

Griggs 1978 (published data only)

Griggs 1989 (published data only)

Guilleminault 1984 (published data only)

Hughes 1991 (published data only)

Jackson 1994 (published data only)

Karli 1974 (published data only)

Matsumura 2004 (published data only)

Miele 1985 (published data only)

Milner-Brown 1990 (published data only)

Müller 1980 (published data only)
Drug treatment for myotonia (Review)

References

Orndahl 1994 [published data only]

Orndahl 1994 [published data only]

Pendefunda 1974 [published data only]

Penisson-Besnier 2008 [published data only]

Ricker 1980 [published data only]

Rüdel R 1980 [published data only]

Samaha 1964 [published data only]

Schneider-Gold 2003 [published data only]

Sechi 1983 [published data only]

Streib 1987 [published data only]

Sugino 1998 [published data only]

Tarnopolsky 2004 [published data only]

Vlachopapadopoulou 1995 [published data only]

Walter 2002 [published data only]

References to studies awaiting assessment

Martens 2005 [published data only]

Additional references

Armitage 1987

Baumann 1998

Becker 1970

Becker 1977

Bernareggi 2005

Bowman 1981

Breslow 1980
Drug treatment for myotonia (Review)

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Brook 1992

Ceccarelli 1992

Cürschmann 1912

Dengler 1979

Drost 2001

Dukes 2000

Durelli 1985

Emery 1991

Fontaine 1997

Fontaine 1997

Fowler 1974

Franke 1991

Gelfand 1994

George 1993

Harley 1992

Harper 2001

Harper 2004

Howeler 1989

Jurkat-Rott 2001

Koch 1992

Koty 1996

Leheup 1986
Leheup B, Himon F, Morali A, Brichet F, Vidalilhet M. Value of mexiletine in the treatment of Thomsen-Becker myotonia [Intérêt de la mexiletine dans le traitement de
Drug treatment for myotonia (Review)

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Meola 2004

Moxley 1996

Nelson 1984

Papponen 1999

Plas Bart-Schiess 1998

Pouget 1983

Ptácek 1994

Ptácek 1998

Ricker 1978

Ricker 1990
Rossi 1985

Rüdel 1994

Rüdel 1997

Rüdel 1999

Sansone 2000

Shields 1988

Soff 1987

Steinert 1910

Streib 1986

Thomsen 1876

Wang 1969

Wolf 1936

* Indicates the major publication for the study
## Characteristics of included studies  
*ordered by study ID*

### Antonini 1990

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, double-blind crossover study. Method of randomisation not stated. Single centre Italy. Treatment periods of 33 days. Total duration 166 days. Results presented as combined data from both active treatment arms and both placebo arms. Two washout periods of 30 days. Results first arms stated</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>17 patients with 2 withdrawals. 17 patients with myotonic dystrophy. 8 patients were male, 9 female. Mean age 29 (SD not stated) Inclusion criteria: Established clinical EMG-criteria. Exclusion criteria: Subjects with cardiac, ophthalmologic, or urologic diseases were excluded</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Clomipramine 75 mg/day. Comparison treatment placebo.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Grip myotonia by relaxation time in seconds; time necessary to completely open the fist after three seconds of maximum voluntary contraction performed by maintaining a constant pressure in a rolled sphygmomanometer cuff</td>
</tr>
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</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
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### Durelli 1983

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, double-blind crossover study. Method of randomisation not stated. Single centre Italy. Treatment periods of 6 months. Total duration of 1 year. Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arms not stated</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>9 patients without withdrawals. 9 patients with myotonic dystrophy. Number of males and females not stated. Mean age not stated. Inclusion criteria: Established clinical EMG-criteria. Exclusion criteria: None stated.</td>
</tr>
</tbody>
</table>
**Durelli 1983**  
(Continued)

| Interventions | Taurine 100-150 mg/kg.  
|               | Comparison treatment placebo.  

| Outcomes | EMG relaxation time after maximum voluntary contraction.  
|          | Occurrence of percussion myotonia.  
|          | Occurrence of myotonic discharges by electrical stimulation of median nerve.  
|          | KCl loading test in mmol/litre necessary for occurrence of myotonia  

| Notes |  

**Risk of bias**

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<tr>
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<td>Unclear risk</td>
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</table>

**Finlay 1982**

| Methods | Randomised, double-blind crossover study.  
|         | Method of randomisation not stated.  
|         | Single centre United Kingdom.  
|         | Treatment periods of 14 days. Total duration 28 days.  
|         | Results presented as descriptive, individually data for the four treatment arms. No washout period. Descriptive data first arms stated  

| Participants | 10 patients with 2 withdrawals.  
|             | 10 patients with myotonic dystrophy.  
|             | 7 patients were male, 3 female.  
|             | Mean age not stated. Range from 31-59 years.  
|             | Inclusion criteria: none stated.  
|             | Exclusion criteria: none stated.  

| Interventions | Procainamide 250 mg 4x/day first week and 500 mg 4x/day second week versus disopyramide 100 mg 3x/day first week and 200 mg 3x/day second week.  
|               | Comparison between both treatments.  

| Outcomes | Grip myotonia by measuring relaxation time in seconds necessary to completely open the fist after three minutes of maximum voluntary contraction.  
|          | Grip strength by using a RAF Gripometer.  
|          | Subjective comments.  

| Notes | Individually continuous data not stated.  
|      | No statistical analysis.  
|      | Patients could recognize their original medicine by kind of adverse events  

**Risk of bias**
Gascon 1989

<table>
<thead>
<tr>
<th>Methods</th>
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<tbody>
<tr>
<td>Randomised, double-blind crossover study.</td>
</tr>
<tr>
<td>Method of randomisation not stated.</td>
</tr>
<tr>
<td>Single centre North Dakota, USA.</td>
</tr>
<tr>
<td>Treatment periods of 6 weeks. Total duration of 12 weeks.</td>
</tr>
<tr>
<td>Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arm not stated</td>
</tr>
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</table>

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<tr>
<th>Participants</th>
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<tbody>
<tr>
<td>12 patients out of a group of 23 patients with myotonic dystrophy (confirmed by well-established criteria).</td>
</tr>
<tr>
<td>1 drop-out because of normal relaxation time.</td>
</tr>
<tr>
<td>6 patients were male, 6 female.</td>
</tr>
<tr>
<td>Mean age not stated. Range from 18-55 years.</td>
</tr>
<tr>
<td>Inclusion criteria: None stated.</td>
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<tr>
<td>Exclusion criteria: None stated.</td>
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<tr>
<th>Interventions</th>
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<tr>
<td>Imipramine from 50-375 mg/day on the basis of plasma concentrations.</td>
</tr>
<tr>
<td>Comparison treatment placebo.</td>
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</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Grip myotonia by measuring relaxation time after squeezing the examiner’s two fingers for 2-3 seconds.</td>
</tr>
<tr>
<td>Percussion myotonia thenar eminence after struck with reflex hammer by measuring time in seconds.</td>
</tr>
<tr>
<td>Three successive timings of grip and percussion myotonia were taken, and the mean of these three was used as the patient’s “score”</td>
</tr>
</tbody>
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| Notes |

**Risk of bias**

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</table>
**Grant 1987**

| Methods | Randomised, single-blind crossover study.  
|         | Method of randomisation not stated.  
|         | Single centre Glasgow, Scotland.  
|         | Treatment periods of 2 weeks. Total duration unclear.  
|         | Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arms not stated  

| Participants | 10 patients without withdrawals.  
|             | 10 patients with myotonic dystrophy.  
|             | 6 patients were male; 4 female.  
|             | Mean age 40.4 (SD not stated).  
|             | Inclusion criteria: Accepted clinical criteria and electromyographic characteristics.  
|             | Exclusion criteria: None stated.  

| Interventions | Nifedipine 10 mg 3x/day and nifedipine 20 mg 3x/day. Comparison treatment placebo.  

| Outcomes | Finger extension time of both hands measured as relaxation time after maximal voluntary contraction.  
|          | The mean value of the first five extension times was measured.  

| Notes |  

**Risk of bias**

| Bias | Authors' judgement | Support for judgement  
|------|--------------------|-----------------------  
| Allocation concealment (selection bias) | Unclear risk | B - Unclear |

**Kratz 1986**

| Methods | Randomised, double-blind crossover study.  
|         | Method of randomisation not stated.  
|         | Single centre, Washington, D.C., USA.  
|         | Treatment period not stated.  
|         | Total duration not clear.  
|         | Results presented as number of patients that improved. No insights in data. No washout period.  

| Participants | 6 patients without withdrawals.  
|             | 4 patients with myotonic dystrophy and 2 with myotonia congenita.  
|             | Number of males, females, mean age and inclusion/exclusion criteria not stated  

| Interventions | Mexiletine in doses up to 600 mg/day.  

| Outcomes | Grip strength. Relaxation time after making a fist, at room temperature and after the hand in ice water for 1 minute.  
|          | Length of myotonic discharges.  

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**Kratz 1986** *(Continued)*

### Notes

#### Risk of bias

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**Kwiecinski 1992**

#### Methods

Randomised, single-blind study. At beginning a crossover trial of phenytoin and placebo. Afterwards randomisation for disopyramide, tocainide or mexiletine.

Methods of randomisation not stated.

Single centre Poland.

Treatment periods of 4 weeks. Total duration unclear.

Results for the cross-over part of the study presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arms not stated.

Overall results presented as outcome measures after 4 weeks of treatment

#### Participants

30 patients with 2 withdrawals.

9 patients with myotonic dystrophy, 9 with dominant myotonia congenita and 12 with recessive myotonia congenita.

22 patients were male, 8 female.

Mean age 31.8 years old (SD not stated).

Inclusion criteria: Accepted clinical criteria and electromyographic characteristics for different diseases.

Exclusion criteria: None stated.

#### Interventions

Fenytoin 400 mg/day for two weeks and 600 mg/day for the last two weeks.

Disopyramide 300 mg/day for two weeks and 600 mg/day for the last two weeks.

Mexiletine 400 mg/day for two weeks and 600 mg/day for the last two weeks.

Tocainide 800 mg/day for two weeks and 1200 mg/day for the last two weeks.

Comparison treatment placebo.

#### Outcomes

Time needed to open eyes maximally after closure (Lid myotonia).

Time needed to open hand after firm closure (Hand opening).

Time needed to climb ten stairs (Stairtest).

EMG relaxation time (Afterdischarge).

Subjective responses.

Each test was repeated three times at intervals of at least ten minutes. The mean value from three such measurements was taken as the time value for each test

#### Notes

It is conspicuous that the sum of the number of patients in the different treatment groups of the randomisation part of the study exceeds the total number of included patients. Outcome measures were not measured in all patients (No reasons given)

### Risk of bias

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Continued

### Lewis 1966

#### Methods

Randomised, double-blind crossover study.  
Randomisation arbitrarily by secretary.  
Single centre United Kingdom.  
Treatment periods of 3 weeks. Total duration of 6 weeks.  
Results presented as combined data from both active treatment arms and both placebo arms. No washout period. Results first arm stated

#### Participants

20 patients and 13 controls.  
19 patients with myotonic dystrophy and 1 with myotonia congenita.  
Number of males and females not stated.  
Mean age not stated.  
Inclusion criteria: None stated.  
Exclusion criteria; None stated.

#### Interventions

Diazepam 5 mg 2x/day - 4x/day.  
Comparison treatment placebo.

#### Outcomes

Relaxation time with EEG surface electrodes on right forearm after 5 seconds of maximum voluntary contraction. Value was the mean of three measurements.  
Accurate progress notes with specific on grasp myotonia, percussion myotonia and toxic effects medication.

#### Notes

Great placebo effect; research into placebo tablets pointed out that they contain 0.5 mg quinine sulfate per tablet.

### Risk of bias

#### Bias

<table>
<thead>
<tr>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>
### Leyburn 1960

| Methods                        | Randomised, double-blind crossover study.  
|                               | Randomisation by statistician. 
|                               | Single centre United Kingdom. 
|                               | Treatment periods of three weeks. Total duration twelve weeks. 
|                               | Results presented as individual data for different interventions and as combined data for treatment arms and placebo arms. No washout period. Results first arm not stated |

| Participants                    | 20 patients with 4 withdrawals.  
|                                | 16 patients with myotonic dystrophy and 4 with myotonia congenita. 
|                                | 9 patients were male, 11 female. 
|                                | Mean age not stated. 
|                                | Inclusion criteria: None stated. 
|                                | Exclusion criteria: None stated. |

| Interventions                   | Quinine (5 grain sugar coated tablets): 5 grains 2x/day first week and 5 grains 3x/day second and third week. 
|                                | Procainamide (0.25 g tablets): 0.5 g q.i.d first week, 0.75 g q.i.d second week and 1.0 g q.i.d third week. 
|                                | Prednisone (5 mg tablets): 10 mg b.i.d first throughout the three week period. 
|                                | Comparison treatment placebo. |

| Outcomes                        | Objective myotonia by measuring 3 times the after discharge with EMG and by measuring 3 times clinical relaxation time. The result is the average of all six measurements. 
|                                | Subjective opinion. |

### Munsat 1967

| Methods                        | Randomised, double-blind crossover study. 
|                               | Method of randomisation not stated. 
|                               | Single centre Los Angeles, USA. 
|                               | Treatment periods of three weeks. Total duration 9 weeks. 
|                               | Results presented as combined data from four active treatment arms and both placebo arms. No washout period. Results first arm not stated |

| Participants                    | 9 patients without withdrawals. 
|                                | 7 patients with myotonic dystrophy and 2 with myotonia congenita. 
|                                | Number of males and females not stated. 
|                                | Mean age not stated. 
|                                | Inclusion criteria: Accepted clinical criteria, electromyography and muscle biopsy. Selected on the basis of intelligence and capability of being examined weekly and presented a spec- |
Munsat 1967  (Continued)

<table>
<thead>
<tr>
<th>Exclusion criteria: None stated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
</tr>
<tr>
<td>Diphenylhydantoin 100 mg 2x/day first week, 3x/day second week and q.i.d third week.</td>
</tr>
<tr>
<td>Procainamide 1 g 2x/day first week, 3x/day second week and 4x/day third week.</td>
</tr>
<tr>
<td>Comparison treatment placebo.</td>
</tr>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Ergographic evaluation of hand grasp after five seconds of maximum voluntary contraction.</td>
</tr>
<tr>
<td>Subjective report regarding efficacy or toxicity or both.</td>
</tr>
<tr>
<td>Repeated ECG utilizing standard leads.</td>
</tr>
<tr>
<td>Notes</td>
</tr>
<tr>
<td>Researcher could recognize medicine of patients by kind of adverse events</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfonsi 2007</td>
<td>Case study.</td>
</tr>
<tr>
<td>Backman 1990</td>
<td>Non-randomised uncontrolled study.</td>
</tr>
<tr>
<td>Benstead 1987</td>
<td>Case study.</td>
</tr>
<tr>
<td>Birnberger 1975</td>
<td>Non-randomised uncontrolled study.</td>
</tr>
<tr>
<td>Brumback 1983</td>
<td>Non-randomised open study.</td>
</tr>
<tr>
<td>Cook 1984</td>
<td>Case study.</td>
</tr>
<tr>
<td>Durelli 1982</td>
<td>Non-randomised study.</td>
</tr>
<tr>
<td>Garai 1954</td>
<td>Case study.</td>
</tr>
<tr>
<td>Geschwind 1955</td>
<td>Case study.</td>
</tr>
<tr>
<td>Griggs 1977</td>
<td>Non-randomised study.</td>
</tr>
<tr>
<td>Griggs 1978</td>
<td>Non-randomised open study.</td>
</tr>
<tr>
<td>Reference</td>
<td>Type of Study</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Griggs 1989</td>
<td>No myotonia as outcome measure.</td>
</tr>
<tr>
<td>Guilleminault 1984</td>
<td>Non-randomised study.</td>
</tr>
<tr>
<td>Hughes 1991</td>
<td>Case studies.</td>
</tr>
<tr>
<td>Jackson 1994</td>
<td>Case study.</td>
</tr>
<tr>
<td>Karli 1974</td>
<td>Case study.</td>
</tr>
<tr>
<td>Matsumura 2004</td>
<td>Non-randomised open study.</td>
</tr>
<tr>
<td>Mielke 1985</td>
<td>Non-randomised study.</td>
</tr>
<tr>
<td>Milner-Brown 1990</td>
<td>Non-randomised uncontrolled study.</td>
</tr>
<tr>
<td>Müller 1980</td>
<td>Non-randomised open study.</td>
</tr>
<tr>
<td>Orndahl 1986</td>
<td>Non-randomised study.</td>
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<tr>
<td>Orndahl 1994</td>
<td>No myotonia as outcome measure.</td>
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<tr>
<td>Penderenda 1974</td>
<td>Case study.</td>
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<tr>
<td>Péanisson-Besnier 2008</td>
<td>No myotonia as outcome measure.</td>
</tr>
<tr>
<td>Ricker 1980</td>
<td>Non-randomised open study.</td>
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<tr>
<td>Rüdel 1980</td>
<td>Non-randomised study.</td>
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<tr>
<td>Samaha 1964</td>
<td>Non-randomised study.</td>
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<tr>
<td>Schneider-Gold 2003</td>
<td>No myotonia as outcome measure.</td>
</tr>
<tr>
<td>Sechi 1983</td>
<td>Non-randomised study.</td>
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<tr>
<td>Streib 1987</td>
<td>Case study.</td>
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<tr>
<td>Sugino 1998</td>
<td>Non-randomised open study.</td>
</tr>
<tr>
<td>Tarnopolsky 2004</td>
<td>No myotonia as outcome measure; Only muscle forces, functional measures and activities of daily living scales</td>
</tr>
<tr>
<td>Vlachopapadopoulou 1995</td>
<td>No myotonia as outcome measure.</td>
</tr>
<tr>
<td>Walter 2002</td>
<td>No myotonia as outcome measure.</td>
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DATA AND ANALYSES
This review has no analyses.

ADDITIONAL TABLES
Table 1. Methodological Quality of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation concealment</th>
<th>Patient blinding</th>
<th>Observer blinding</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Outcome measures</th>
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<tr>
<td>Antonini 90</td>
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<td>Grant 87</td>
<td>B</td>
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<td>A</td>
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<td>A</td>
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<td>Kwiecinski 92</td>
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<td>A</td>
<td>D</td>
<td>A</td>
<td>B</td>
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<td>Lewis 66</td>
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<td>A</td>
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<td>Leyburn 60</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Munsat 67</td>
<td>B</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>A</td>
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<tr>
<td>Kratz 86</td>
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<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

Key: A: Adequate
     B: Unclear
     C: Inadequate
     D: Not done

WHAT'S NEW
Last assessed as up-to-date: 29 July 2009.
**History**

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2006

<table>
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<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 August 2009</td>
<td>New search has been performed</td>
<td>Searches updated to 30 July 2009 and minor edits undertaken. No new randomised controlled trials were identified.</td>
</tr>
<tr>
<td>29 April 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>25 February 2008</td>
<td>New search has been performed</td>
<td>Searches updated to 31 December 2007. One additional study, Alfonsi 2007 added to excluded studies.</td>
</tr>
<tr>
<td>5 October 2005</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
</tbody>
</table>

**Contributions of Authors**

Jeroen Trip wrote the first draft. Jeroen Trip and Karin Faber independently reviewed the titles and abstracts from the electronic search to identify trial reports. They graded the methodological quality and performed the data extraction. Karin Faber, Gea Drost and Baziel van Engelen commented on the first and subsequent drafts. All authors agreed the final text.

**Declarations of Interest**

Authors were supported by the Princess Beatrix Foundation (MAR04-0118).
SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• Princess Beatrix Foundation (MAR04-0118), Netherlands.

INDEX TERMS

Medical Subject Headings (MeSH)
Myotonia [*drug therapy]; Myotonic Dystrophy [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words
Humans