Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Systematic reviews							
Shakespeare 2001	Assess the absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis (MS) patients	Through February 2001 (for MEDLINE) MEDLINE, EMBASE, reference lists, personal communications, drug manufacturers, manual searches of journals, collaborative MS trial registry, Cochrane database, National Health Service National Research Register	Double-blind, RCTs (either placebo-controlled or comparative studies)	<7 days duration	None	Independently abstracted by two reviewers and findings summarized	36/157 157 identified studies met inclusion criteria 23 placebo-controlled trials (5 oral baclofen, 4 dantrolene, 3 tizanidine, 3 botulinum toxin, 2 vigabitrin, 1 prazepam, 3 progabide, 1 brolitene, 1 L-threonine) 13 head-to-head trials met selection criteria (7 tizanidine vs. baclofen; 1 baclofen vs. diazepam, 1 diazepam vs. dantrolene, 2 ketazolam vs. diazepam, 2 tizanidine vs. diazepam) 1359 patients overall
Taricco 2000	Assess the effectiveness and safety of drugs for the treatment of long term spasticity in spinal cord injury patients	Through 1998 CCTR, MEDLINE, EMBASE, CINAHL	All parallel and crossover RCTs including SCI patients with "severe spasticity"	RCTs with <50% of patients with SCI	None	Data independently abstracted by two reviewers using data extraction form	9 of 53 studies met inclusion criteria (1 oral baclofen, 4 intrathecal baclofen, 1 amytal and valium, 1 gabapentin, 1 clonidine, 1 tizanidine) 8 crossover studies, 1 parallel group trial 218 patients overall

RCT = Randomized Controlled Trial; CCTR = Cochrane Controlled Trials Registry; CINAHL = Cumulative Index to Nursing and Allied Health; SCI = Spinal Cord Injury

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Systematic reviews					
Shakespeare 2001	Multiple sclerosis patients, age and severity varied between studies	Absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. Included studies characterized by poor quality (though more recent studies are higher quality), heterogeneous study designs, interventions, outcomes, and methods of assessment. Unable to do quantitative meta-analysis.	Not systematically reviewed.	GOOD.	
Taricco 2000	Crossover studies: 20/100 female, age range 16-62; 86/100 spinal cord injury, 14/100 multiple sclerosis Parallel study: 14/118 female, age range 15-69; mean duration of spinal cord injury 95 months	Tizanidine vs. placebo: Significant improvement of tizanidine for improving Ashworth score but now ADL performances Gabapentin, clonidine, diazepam, amytal, oral baclofen: No evidence for clinically significant effectiveness Unable to combine results because of poor quality, heterogeneous study designs, outcomes assessment, and method of reporting	Tizanidine vs. placebo: Increased drowsiness and xerostomia compared to placebo	FAIR. 14 retrieved studies had not yet been assessed.	

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Lataste 1994	Assess the comparative therapeutic profile of tizanidine and other antispastic medications using data from 20 double-blind studies conducted during the development program of tizanidine between 1977 and 1987	1977-1987 Not clear what methods used to identify relevant studies through database search; also used Sandoz database	Double-blind controlled studies comparing tizanidine with another muscle relaxant.	Not specified.	Authors employed by Sandoz and Athena. Not reported if funder held data.	Not reported	Number of excluded studies not reported 20 trials of tizanidine vs. active control, ranging from 4-8 weeks (385 patients on tizanidine, 392 on active control) 10 studies vs. baclofen in multiple sclerosis 2 studies vs. diazepam in multiple sclerosis 3 studies vs. baclofen in cerebrovascular disease 4 studies vs. diazepam in cerebrovascular disease 1 study vs. baclofen in amyotrophic lateral sclerosis

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Lataste 1994	43-48% multiple sclerosis, 45-57% cerebrovascular disease, 0-7% amyotrophic lateral sclerosis Gender, age, race not reported	Tizanidine vs. active control (all studies included in analysis) Muscle tone (improved): 64% vs. 66% Muscle spasms (improved): 50% vs. 58% Clonus (improved): 46% vs. 56% Muscle strength (improved): 34% vs. 36% Neurologic function (Kurtzke scale) and functional disability (Pedersen's scale): No differences (data not reported) Overall assessment of antispastic effect (moderate, good, or excellent): 67.5% vs. 64.6% Overall assessment of antispastic effect (good or excellent): 37.5% vs. 33.0% Total Ashworth score: -0.39 (NS) Global tolerability: Favors tizanidine vs. baclofen or diazepam	Tizanidine vs. active controls Withdrawal (overall): 14% vs. 19% Withdrawal (adverse events): 4% vs. 9%	POOR. Methods of database search not reported. No quality assessment of included studies. No assessmentn of heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined individual patient data for comparisons between interventions using 11/20 studies.	

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Meta-analyses (not systematic review)							
Groves 1998	Assess the efficacy and tolerability of tizanidine using studies recorded by Sandoz (Novartis), the European sponsor of tizanidine trials	Time period covered not clear Records of Sandoz searched	Controlled, doubled-blind, randomized studies in which tizanidine was compared to a positive control. Studies had individual patient data, three key outcome measures (Ashworth Rating Scale, measure of muscle strength, and Global Tolerability to Treatment Rating), and patients had multiple sclerosis or other cerebrovascular lesions	Studies without measurement of muscle tone or individual data for muscle strength or tone, use of a nonstandard or incomplete scale for muscle strength or tone, no exam at six weeks, and one study in patients with amyotrophic lateral sclerosis.	Authors employed by Athena, which licenses tizanidine in North America, Ireland, and U.K. Not reported if funder held data.	Not reported	10 studies excluded. 11 included studies involving 270 patients 8 studies used baclofen as control, 3 used diazepam

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Meta-analyses (not systematic review)					
Groves 1998	147 patients with multiple sclerosis 123 patients with other cerbrovascular lesions Mean age 38-48 years, 47-52% female, race not reported	Tizanidine vs. baclofen Mean change in total Ashworth score (scale 0 to 32): -3.2 vs. -3.0 (NS) Mean change in muscle strength (lower body Ashworth score, 0-160): -2.7 vs. -0.9 (p=0.07) Global Tolerability to Treatment (investigator rating, 1 (excellent) to 4 (poor): 2.0 vs. 2.3 (p=0.008) Tizanidine vs. diazepam Mean change in total Ashworth score: -5.6 vs. 4.0 (NS) Mean change in muscle strength: -4.4 vs. -2.7 (NS) Global Tolerability to Treatment: 1.8 vs. 2.6 (p=0.001)	Not reported	FAIR. No evaluation for heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined all individual patient data for comparisons between interventions.	Included studies previously evaluated in meta-analysis by Wallace.

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Wallace 1994	Combine data from three placebo-controlled and 11 active-controlled studies to evaluate efficacy of tizanidine	Time period covered not clear Sources used not clear, but appear to be unpublished data from studies sponsored by Sandoz	Not clear. Appear to be placebo controlled or active-controlled trials conducted by Sandoz.	Not reported	Authors employed by Athena, which licenses tizanidine in North America, Ireland, and U.K. Not reported if funder held data.	Not reported	3 placebo controlled studies (2 studies multiple sclerosis, 1 study spinal cord injury) with 525 evaluable patients 11 active-controlled studies (8 baclofen, 3 diazepam) with 5 studies on multiple sclerosis, 5 on patients with cerebral lesions, and 1 on amyotrophic lateral sclerosis with 288 patients

Evidence Table 1. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Population characteristics	Main results	Adverse events	Internal validity	Comments
Wallace 1994	Tizanidine vs. placebo: Mean age: 43.3 vs. 43.8 Gender: 53% female vs. 50% male Race (non-white): 11% vs. 11% Baseline demographics not reported for active-controlled studies	Tizanidine vs. placebo: Mean change in total Ashworth score for three lower-body muscle groups: -1.92 vs. -1.00 (p=0.01) Spasms and clonus: No statistically significant differences Global assessments: Placebo tolerated better than tizanidine, tizanidine more effective (NS) Muscle strength: No statistically significant differences Tizanidine vs. baclofen or valium (at end of week 6) Muscle strength: No difference at week 6 when all studies combined Global tolerance/patient assessment: No difference	Tizanidine vs. placebo Withdrawal (overall): 83/284 vs. 75/277 Withdrawal (adverse events): 44/284 vs. 15/277 Dry mouth: 49% vs. 27% Somnolence: 48% vs. 10% Asthenia: 41% vs. 16% Dizziness: 16% vs. 4% Headache: 12% vs. 13% UTI: 10% vs. 7% Insomnia: 8% vs. 8% Nausea: 7% vs. 7% Myasthenia: 6% vs. 6% Infection: 6% vs. 5% Adverse events for active-controlled trials not reported	FAIR. No evaluation for heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined all individual patient data for comparisons between interventions.	Active-controlled trials later analyzed in meta-analysis by Groves.

Evidence Table 2. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with musculoskeletal conditions

Author Year	Aims	Time period covered and sources used in literature search	Eligibility criteria	Exclusion criteria	Funding source and role	Method of appraisal	Characteristics of identified articles
Systematic reviews							
Browning 2001	Systematic review of cyclobenzaprine's effectiveness in the treatment of back pain	1966-1999 MEDLINE, PsycLit, CINAHL, EMBASE, AIDSLINE, HEALTHSTAR, CANCERLIT, Micromedix, Cochrane Library and Cochrane Database of Systematic Reviewers, Federal Research in Progress, reference lists, pharmaceutical companies contacted	Randomized, placebo-controlled, at least one group receiving cyclobenzaprine, and measurable outcomes reported	Not reported	None	Independently assessed by two reviewers using 6-item instrument	7 trials excluded 14 randomized placebo-controlled trials of 3315 patients on cyclobenzaprine; 6 studies also had diazepam as a control, 1 diflunisal, and 1 methocarbamol
Meta-analysis							
Nibbelink 1978	Assess the therapeutic response of cyclobenzaprine compared to diazepam and placebo	Time period covered not clear Not clear what methods used to identify relevant studies, but appears to include unpublished studies performed at Merck	Controlled clinical studies of patients with skeletal muscle spasm treated with cyclobenzaprine, diazepam, or placebo.	Studies outside the United States (3 studies) because of differences in protocol and data collection.	Authors employed by Merck. Not reported if funder held data.	Not reported	20 double-blind randomized trials of 1153 patients (434 cyclobenzaprine, 280 diazepam, 439 placebo) 46% posttraumatic, 14% musculoskeletal strain, 10% idiopathic, 8% postoperative, 6% osteoarthritis, 3% cervical root syndrome, 1% miscellaneous.

Evidence Table 2. Included systematic reviews and meta-analyses of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population characteristics	Main Results	Adverse events	Internal validity
Systematic reviews				
Browning 2001	Acute back pain and muscle spasm of varying degrees; age, race, and gender not reported	All studies had at least one problem with rated quality. Mean quality score 4.3 (scale 1-8) Cyclobenzaprine vs. placebo: Global improvement (10 studies, pooled risk difference): 0.37 (95% CI, 0.24-0.50) No statistically different results (though trends favored cyclobenzaprine) for local pain, muscle spasm, tenderness to palpation, range of motion, and ADL at 3 days, 1 or 2 weeks.	Cyclobenzaprine vs. placebo (percentages) Drowsiness: 20% vs. 2%, p<0.001 Dry mouth: 8% vs. 2%, p=0.02 Dizziness: 7% vs. 4%, p=0.04 Nausea: 2% vs. 2%, p=0.70 Any: 53% vs. 28%, p=0.002	GOOD.
Meta-analysis				
Nibbelink 1978	46% posttraumatic, 14% musculoskeletal strain, 10% idiopathic, 8% postoperative, 6% osteoarthritis, 3% cervical root syndrome, 1% miscellaneous. Gender 535/1065 female, 186/1153 >50 years, race not reported	Cyclobenzaprine vs. diazepam vs. placebo Global response: Cyclobenzaprine and diazepam significantly better than placebo, no significant differences between cyclobenzaprine and diazepam. Cyclobenzaprine vs. diazepam (symptoms absent or mild at week 2) Muscle spasms: 42% vs. 29% (p=0.035) Local pain: 24% vs. 33% (NS) Tenderness on palpation: 26% vs. 39% (p=0.044) Limitation of motion: 30% vs. 50% (p=0.006) Limitation of daily living: 31% vs. 48% (p=0.030)	Cyclobenzaprine vs. diazepam vs. placebo Drowsiness: 39% vs. 33% vs. 12% Dry mouth: 24% vs. 8% vs. 4% Ataxia/dizziness: 10% vs. 17% vs. 6% Bad taste: 3% vs. 1% vs. 0.4% Nausea: 2% vs. 1% vs. 3% Withdrawals not reported for different interventions	FAIR. No evaluation for heterogeneity. Insufficient detail of included studies. Not clear if studies summarised appropriately: combined all individual patient data for comparisons between interventions.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Bass 1988	Randomized crossover trial Canada Single center	A: Tizanidine titrated to mean of 17.4 mg/day B: Baclofen titrated to mean of 35 mg/day 2 weeks washout, 3 weeks titration, 5 weeks maintenance, 1 week withdrawal, 3 weeks crossover titration, 5 weeks maintenance (8 weeks per intervention)	Patients with clinically definite multiple sclerosis interfering with activities of daily living, spasticity stable for >2 months	Not reported	Not reported Not reported 66	18 withdrew or excluded after randomization 48	Initial intervention: Tizanidine vs. baclofen Mean age (years): 50 vs. 52 Female gender: 15/32 vs. 16/30 Race: Not reported Paraperesis: 90% vs. 80% Status at entry progressive: 25% vs. 37% Duration of spasticity (years): 8.7 vs. 7.5 Severity severe: 22% vs. 30% Prior muscle relaxant use/baclofen: 14/32 vs. 14/30 Prior muscle relaxant use/diazapam: 6/32 vs. 4/30 Prior muscle relaxant use/any: 22/32 vs. 20/30
Bes 1988	Randomized trial France Multicenter	A: Tizanidine mean 17 mg/day B: Diazepam mean 20 mg/day 2 weeks titration, 6 weeks maintenance	Spasticity interfering with daily activities following stroke or head trauma, stable for at least 2 months	Not reported	Not reported Not reported 105	23 91	Tizanidine vs. diazepam Mean age (years): 51 vs. 52 Female gender: 12/51 vs. 16/54 Race: Not reported Underlying condition/stroke: 46/51 vs. 43/54 Duration of symptoms (months): 20 vs. 23 Prior muscle relaxant use: 27% vs. 22%, specific medication not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Bass 1988	Spasms: 6 point ordinal scale Strength: 0 (normal) to 6 (no movement) Functional status: Kurtzke functional scale Disability: Pedersen functional disability scale Not clear when assessed	FAIR. Randomization, allocation concealment, blinding techniques not described, high loss to follow-up.	Tizanidine vs. baclofen Kurtzke functional scale (FS)/pyramidal (improvement >1): 2/48 vs. 2/48 (NS) Kurtzke FS/pyramidal (deterioration >1): 0/48 vs. 2/48 (NS) Kurtzke FS/cerebellar (improvement >1): 7/48 vs. 4/48 (NS) Kurtzke FS/cerebellar (deterioration >1): 3/48 vs. 7/48 (NS) Pedersen functional disability scale: No significant differences, raw data not reported Strength: No significant differences, raw data not reported Spasms: No significant differences (trend favored baclofen), raw data not reported Overall evaluation/patient (good or excellent): 13/53 (24%) vs. 20/51 (39%) (NS)
Bes 1988	Spasticity: 1 (absent) to 5 (severe) Functional status: walking Severity of contraction: 1-5 scale Muscle strength: Not clear how rated Clonus: Not clear how rated Assessed at 2 and 8 weeks	FAIR. Randomization, allocation concealment, and blinding techniques not reported, high overall loss to follow-up.	Tizanidine vs. diazepam Walking distance on flat ground (improvement, in meters): 224 ($p<0.05$ vs. baseline) vs. 406 Duration of contractures: No significant differences between treatments Resolution of clonus: 14/29 (48%) vs. 8/20 (40%) Muscle strength/improvement in quadriceps: 36% vs. 27% (NS) Overall assessment/investigators (great or slight improvement): 37/45 (82%) vs. 30/36 (83%) (NS) Overall assessment/patients (great or slight improvement): 73% vs. 70% (NS)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Bass 1988	Tizanidine vs. baclofen Muscle weakness: 11/46 (21%) vs. 17/46 (35%) (p<0.01) Somnolence: 15/46 (29%) vs. 9/46 (19%) (p<0.01) Dry mouth: 12/46 (23%) vs. 7/46 (14%) (p<0.05) Spasms: 8/46 (15%) vs. 2/46 (4%) (p<0.05) Headaches: 1/46 vs. 5/46 (NS) Dizziness: 2/46 vs. 7/46 (NS) Light-headedness: 3/46 vs. 2/46 (NS) Irritability: 3/46 vs. 5/46 (NS) Insomnia: 8/46 vs. 3/46 (NS) Nausea: 2/46 vs. 6/46 (NS) Vomiting: 0/46 vs. 4/46 (NS) Constipation: 3/46 vs. 0/46 (NS) Bladder urgency: 3/46 vs. 7/46 (NS) Leg dysesthesia: 3/46 vs. 1/46 (NS) Adverse event requiring dose reduction: 46% vs. 63% Withdrawals (overall): 5/46 vs. 13/46 Withdrawals (due to adverse events): 4/46 (weakness) vs. 12/46 (7 weakness, 5 nausea)	Not reported	High loss to follow-up; not clear how patients lost to follow-up accounted for in statistical analysis. Results of first intervention period not reported separately. Raw data for results not reported.
Bes 1988	Tizanidine vs. diazepam Drowsiness: 20/45 vs. 17/39 Fatigue: 9/45 vs. 10/39 Muscular weakness: 1/45 vs. 7/39 Orthostatic hypotension: 3/45 vs. 0/39 Vomiting: 2/45 vs. 2/39 Dry mouth: 5/45 vs. 1/39 Constipation: 2/45 vs. 2/39 Anxiety: 4/45 vs. 1/39 Sleep disturbance: 6/45 vs. 1/39 Disturbance of affect: 4/45 vs. 1/39 Overall tolerability: 61% vs. 54% Withdrawals (overall): 6/51 vs. 17/54 Withdrawals (due to adverse events): 6/51 vs. 15/54	Not reported	Specific prior muscle relaxants not reported. In patients on prior muscle relaxants, no difference between interventions for relief of spasticity. Not clear how withdrawn patients handled in data analysis.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Cartlidge 1974	Randomized crossover trial U.K. Single center	A: Baclofen 30 mg/day for 2 weeks and 60 mg/day for 2 weeks B: Diazepam 15 mg/day for 2 weeks and 30 mg/day for 2 weeks 4 weeks intervention, 4 weeks crossover	Spasticity, other eligibility criteria unclear	Not reported	Not reported Not reported 40	3 37	Age range (years): 22-61 Female gender: 19/40 Race: Not reported Underlying condition multiple sclerosis: 34/40 Baseline Ashworth score 3 or 4 in at least 1 lower limb Prior muscle relaxant use: Not reported
Eysette 1988	Randomized trial France Multicenter	A: Tizanidine titrated to 24 mg/day B: Baclofen titrated to 60 mg/day 2 weeks titration, 6 weeks maintenace	Patients age 18-70 with spasticity from multiple sclerosis	Not reported	Not reported Not reported 100	14/100 (14%) 86	Tizanidine vs. baclofen Mean age (years): 50 vs. 50 Female gender: 22/50 vs. 21/50 Race: Not reported Mean duration of gait disturbance (years): 11 vs. 13 Prior baclofen use: 73% overall, proportion for each group not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Cartlidge 1974	Spasticity: Ashworth scale	FAIR. Randomization, allocation concealment, blinding techniquest not described	Baclofen vs. diazepam Mean improvement in Ashworth score (low-dose vs. low-dose): 0.163 vs. 0.159 (NS) Mean improvement in Ashworth score (high-dose vs. high dose): 0.227 vs. 0.202 (NS) Patient's impressions (preferred): 19/37 vs. 15/37
Eysette 1988	Spasticity: 1 (absent) to 5 (spontaneous) Stretch reflex: 1-5 scale Locomotor function, patient's state in bed and in a chair, muscular strength, and difficulties with bladder control: unspecified methods General clinical status Overall efficacy and tolerability: unspecified methods Measured at 2 and 8 weeks	FAIR. Randomization, allocation concealment, blinding techniques not described.	Tizanidine vs. baclofen, results at 8 weeks Walking distance: No difference in ambulatory patients from baseline for either treatment (raw data not reported) Difficulty in transferring (improvement): 48% vs. 39% (NS) Difficulty in wheelchair use (improvement): 48% vs. 39% (NS) Difficulty in lying (improvement): 58% vs. 52% (NS) Flexor spasms (improvement): 55% vs. 48% (NS) Duration or angle of stretch reflex (improvement): No significant differences for any muscle group tested Clonus (no longer present): 8/28 vs. 6/28 Muscle strength at quadriceps (improvement): 34% vs. 29% (NS) Bladder function: No significant differences Overall status (improvement): 56% vs. 34% (significance not reported) Overall efficacy (very or moderately effective): 80% vs. 76% (NS) Overall efficacy (very effective): 42% vs. 24% (NS)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Cartlidge 1974	Baclofen vs. diazepam Sedation: 5/37 vs. 4/37 Weakness: 4/37 vs. 6/37 Lightheadedness: 1/37 vs. 0/37 Dry mouth: 1/37 vs. 0/37 Confusion: 2/37 vs. 1/37 Increasing stiffness: 2/37 vs. 3/37 Withdrawals (overall): Not clear Withdrawals (due to adverse events): 11/37 vs. 14/37	Not reported	
Eysette 1988	Frequent side effects: Tizanidine (n=50): 15 drowsiness, 14 dry mouth, 8 fatigue, 6 orthostatic hypotension, 7 insomnia Baclofen (n=50): 10 drowsiness, 12 fatigue, 10 muscular weakness, 9 disturbance of affect, 8 vomiting Tizanidine vs. baclofen Overall tolerability (well tolerated): 62% vs. 66% (NS) Withdrawals (overall): 8/50 vs. 6/50 Withdrawals (due to adverse events): 3/49 vs. 3/49	Not reported	73% of patients on baclofen prior to study entry, proportion in each intervention group not reported.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
From 1975	Randomized crossover trial Denmark Single center	A: Baclofen titrated to mean dose 61 mg/day B: Diazepam titrated to mean dose 27 mg/day 4 weeks initial intervention, 4 weeks crossover	Not reported	Not reported	Not reported Not reported 17	1 withdrew 16	Baseline characteristics not reported for each intervention group Mean age (years): 51 Female gender: 10/16 Race: Not reported Multiple sclerosis inpatients Mean duration of illness (years): 18 Unable to walk more than short distances: 14/16 Prior muscle relaxant use: Not reported
Glass 1974	Randomized crossover trial U.S. Single center	A: Dantrolene 100 mg qid B: Diazepam 5 mg qid C: Dantrolene 100 mg qid + diazepam 5 mg qid D: Placebo 4 2-week intervention periods	Not reported	Not reported	Not reported 62 16	5 withdrew 11	Demographics not reported Clinical conditions of patients enrolled not reported. In patients eligible, 39% CVA, 18% spinal cord injury, 12% MS, 4% CP, 4% miscellaneous (proportions not reported for each intervention group)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
From 1975	Spasticity: Ashworth scale, clinical exam Clinical exam: Global assessment, physical exam Preferences: Patient preferences Assessed at start of trial, and at 3 and 4 weeks of each intervention period	FAIR. Randomization, allocation concealment, blinding techniques not described, unable to compare baseline characteristics between intervention groups	Baclofen vs. diazepam Ashworth score for lower limbs added for all patients receiving intervention (improvement): 21 vs. 23 Clinical assessment of flexor spasms, clonus, bladder function, walking: No significant differences Patient preference: 12/16 vs. 0/16 (4/16 had no preference)
Glass 1974	Resistance to passive stretch: 1-6 scale (flaccid to marked resistance) Tendon jerk: 1-6 scale (absent to markedly hyperactive) Ankle clonus: 1-6 scale (absent to marked/sustained) General muscle strength: 1-6 scale (normal to paralyzed) Assessed weekly	FAIR. Randomization, allocation concealment, blinding techniques not described, high loss to follow-up, unable to compare baseline characteristics between intervention groups	Dantrolene vs. diazepam vs. dantrolene + diazepam vs. placebo Mean scores at end of treatment (no differences statistically significant between active treatments): Resistance to active stretch: 4.36 vs. 4.14 vs. 3.44 vs. 4.91 Tendon jerk: 3.70 vs. 3.00 vs. 2.70 vs. 5.45 Ankle clonus: 2.91 vs. 3.64 vs. 1.95 vs. 3.64 General muscle strength: 3.73 vs. 3.68 vs. 3.77 vs. 3.59

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
From 1975	Baclofen vs. diazepam Overall: 8/16 vs. 12/16 Sedation: 5/16 vs. 11/16 Depression: 2/16 vs. 0/16 Confusion: 0/16 vs. 1/16 Vertigo: 1/16 vs. 1/16 Nausea: 2/16 vs. 0/16 Weakness: 3/16 vs. 2/16 Withdrawal (overall): 1/16 vs. 0/16 Withdrawal (adverse event): 1/16 vs. 0/16	Not reported	Results of initial intervention period not reported.
Glass 1974	Withdrawal (adverse event): 3/16 vs. 1/16 vs. 1/16 vs. 0/16	Not reported	Results of initial intervention not reported. Adverse events not assessed. Not clear why 46/62 eligible patients were not entered into study. Not clear if patients who withdrew from one intervention received other interventions.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Hoogstraten 1988	Randomized trial Crossover Netherlands Single center	A: Tizanidine titrated, range 12-24 mg/day B: Baclofen titrated, range 15-60 mg/day 2-3 weeks titration period, 4 weeks on titrated dose, washout period, then crossover (6-7 weeks each intervention)	Multiple sclerosis patients with stable spasticity for >2 months, Kurtzke expanded disability status score 4-7	Severe cardiac insufficiency, diastolic blood pressure >110, severe hypotension, chronic alcoholism, history of mental illness or pretreatment with diazepam or dantrolene	Not reported Not reported 16	5 14	Baseline characteristics not reported for each intervention group Mean age (years): 55 Female gender: 6/16 Race: Not reported Average Kurtzke EDSS score: 6.1 Mean duration of illness: Not reported Prior muscle relaxant use: Not reported
Medici 1989	Randomized trial Uruguay Single center	A: Tizanidine titrated, mean dose 20 mg/day B: Baclofen titrated, mean dose 50 mg/day 2 weeks titration, 50 weeks maintenance	Outpatients with spasticity due to cerebrovascular disease	Heart disease, severe hypertension, orthostatic hypotension, alcoholism, insulin-dependent diabetes mellitus, impaired liver or renal function, abnormal blood chemistries, overt psychopathology	Not reported Not reported 30	2 deaths and 3 withdrawals 30	Tizanidine vs. baclofen Mean age (years): 50 vs. 49 Female gender: 4/15 vs. 2/15 Race: Not reported Duration of disability (years): 2.5 vs. 4.5 Type of disability: hemiparesis or hemiplegia): 14/15 vs. 15/15 Severity of spasticity (moderate or severe): 15/15 vs. 14/15 Severity of spasticity (severe): 7/15 vs. 4/15 Prior muscle relaxant use: Not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Hoogstraten 1988	Disability: Kurtzke Expanded Disability Status Scale Neurologic assessment of functional systems: Kurtzke Functional Systems Incapacitiy status: Minimal Record of Disability for Multiple Sclerosis Ambulation: Ambulation Index Spasticity/tone: Ashworth scale, patient self-report (0-5 scale) Reflexes/clonus Muscle strength Efficacy: -3 to +3 scale Tolerance: -3 to +3 scale	FAIR. Randomization technique not described, allocation concealment technique not described, inadequate blinding, unable to compare baseline characteristics between intervention groups	Tizanidine vs. baclofen No significant differences between interventions for overall efficacy, spasticity, spasms, mobility, or muscle strength (baseline scores not reported) Results for Ashworth score, Kurtzke scales not reported.
Medici 1989	Neurologic exam: Kurtzke method Overall disability status: Kurtzke scale Tone: Ashworth scale, score 0 (normal)-4 Muscle spasms: 0 (normal) to 4 (severe) Clonus: 0 (normal) to 2 Decreased muscle strength: 0 (normal) to 5 Functional assessment of disability: Pedersen scale Patient self-assessment of disability: Mild, moderate, severe, very severe Physician global assessment of clinical changes: Worse, no change, improvement, marked improvement Global assessment of antispastic efficacy by physicians and patients Assessed at 3, 6, and 12 months	FAIR. Randomization, allocation concealment, blinding techniques not described.	Tizanidine vs. baclofen Neurological exam, overall disability status: No significant differences Muscle tone (improvement): 87% vs. 79% Muscle spasm (improvement): 62% vs. 83% Clonus (improvement): 71% vs. 80% Muscle strength (improvement): 53% vs. 21% Functional assessment (Pedersen scale) (improvement): 40% vs. 43% Patient global assessment of clinical changes: No significant differences between interventions (raw data not reported) Physician global assessment of clinical changes: No significant differences between interventions (raw data not reported) Global assessment/physician (good to excellent): 60% vs. 40% (NS) Global assessment/patient (good to excellent): 66% vs. 47% (p=0.057) Functional assessment and activities of daily living: No differences between interventions

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Hoogstraten 1988	Tizanidine vs. baclofen Muscle weakness (first intervention period): 3/9 vs. 4/7 Somnolence (overall): 8/14 vs. 4/14 Dry mouth (overall): 5/14 vs. 2/14 Flushes (overall): 3/14 vs. 1/14 Nausea (overall): 2/14 vs. 3/14 Urine incontinence: 1/14 vs. 3/14 Dizziness (overall): 2/14 vs. 2/14 Sleep disturbance (overall): 2/14 vs. 0/14 Withdrawals (adverse events) during first intervention: 1/9 (depression) vs. 1/7 (weakness) Withdrawals (adverse events) during either intervention period: 1/16 vs. 4/16 (weakness)	Not reported	Data for Kurtzke scales and Ashworth scales not reported.
Medici 1989	Tizanidine vs. baclofen Somnolence: 5/15 vs. 4/15 Drowsiness: 0/15 vs. 1/15 Dizziness: 0/15 vs. 1/15 Diarrhea: 1/15 vs. 0/15 Muscular instability: 1/15 vs. 3/15 Weakness: 0/15 vs. 1/15 Dry mouth: 1/15 vs. 0/15 Withdrawals (overall): 1/15 vs. 4/15 Withdrawals (adverse events, not including deaths): 0/15 vs. 3/15 (weakness and muscular instability) Deaths (not thought related to drugs): 1/15 vs. 1/15	Not reported	Long duration of intervention (50 weeks).

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Nance 1994	Controlled clinical trial Canada Single center	A: Baclofen 20 mg qid B: Clonidine 0.05 mg bid C: Cyproheptadine 4 mg qid (results abstracted only for A and B)	Spinal cord injured patients with troublesome spasticity and original injury >1 year	Not reported	140 128 25	None reported 25	Age, gender, race not reported Severity: Frankel Grade A 11/25 Cervical injury: 16/25 Thoracic injury: 9/25 Prior muscle relaxant use: not reported
Newman 1982	Randomized crossover trial U.K. Single center	A: Tizanidine titrated to 16 mg/day B: Baclofen titrated to 40 mg/day 2 week titration, 4 weeks maintenance, 2 weeks crossover titration, 4 weeks crossover maintenance (6 weeks per intervention)	Patients with spasticity, neurologically stable	Not reported	Not reported Not reported 36	10 26	Age, gender, race not reported Multiple sclerosis: 32/36 Syringomyelia: 4/36 Severity 'severe': 17/36 Prior muscle relaxant use: not reported
Nogen 1976	Randomized crossover trial U.S. Single center	A: Dantrolene titrated to maximum 75 mg qid B: Diazepam titrated to maximum of 12 mg/day 3 weeks intervention, 3 weeks crossover	Children with cerebral palsy aged 2-8 years old, stable neurologically and physiologically	Children with contractures	Not reported Not reported 22	None reported 22	Age, gender, race not reported Severity and duration of illness not reported Prior muscle relaxant use: not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Nance 1994	Spasticity: Modified Ashworth scale using 1-5 scale and 0.5 gradations (raw data not reported) Spasticity: Video motion analysis of pendulum test Not clear when assessed	POOR. Does not appear randomized, allocation concealment technique not described, blinding not performed, unable to compare baseline characteristics between intervention groups	Baclofen vs. clonidine Spasticity (mean improvement): 0.8 vs. 0.8 Video motion analysis of pendulum test: No differences between treatments
Newman 1982	Spasticity: Ashworth scale Functional status: Kurtzke and Pedersen scales Assessed at baseline and on days 7, 14, and 42 of each intervention	FAIR. Randomization, allocation concealment, blinding techniques not described, unable to compare baseline characteristics between intervention groups	Tizanidine vs. baclofen Lower limb knee spasticity/tone (better): 8/26 vs. 4/26 (NS) Lower limb knee spasticity/tone (better): 7/26 vs. 6/26 (NS) Lower limb ankle spasticity/tone (better): 8/26 vs. 4/26 (NS) Lower limb ankle spasticity/tone (better): 8/26 vs. 4/26 (NS) Functional status: Results not reported
Nogen 1976	Tone: Unspecified method Tendon jerk: Unspecified method Clonus: Unspecified method Strength: Unspecified method Overall evaluation: Unspecified method Assessed twice weekly	FAIR. Randomizaton, allocation concealment, blinding techniques not described, unable to compare baseline characteristics between intervention groups	Dantrolene vs. diazepam Spasticity (best improvement on this medication): 9/22 vs. 7/22

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Nance 1994	None reported	Not reported	Non-randomized clinical trial. Similar improvement noted on cyproheptadine.
Newman 1982	Tizanidine vs. baclofen Drowsiness: 4/26 vs. 5/26 Dizziness: 2/26 vs. 4/26 Fatigue/lassitude: 1/26 vs. 1/26 Weakness: 2/26 vs. 4/26 Dry mouth: 0/26 vs. 1/26 Muscle pains: 4/26 vs. 5/26 Any adverse events: 17/26 vs. 17/26 Withdrawals (overall): 4/36 vs. 6/36 Withdrawals (adverse events): 2/36 vs. 6/36	Not reported	
Nogen 1976	Not clear. 'Only side effects were lethargy and drowsiness which usually disappeared'	Not reported	

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Rinne (1) 1980	Randomized trial Finland Single center	A: Tizanidine titrated, mean dose 14.3 mg/day B: Diazepam titrated, mean dose 15.0 mg/day 6 weeks	Not clear	Not reported	Not reported Not reported 30	4 withdrew 30	Tizanidine vs. diazepam Mean age (years): 42 vs. 40 Female gender: 9/15 vs. 10/15 Race: Not reported All patients had multiple sclerosis Disease severity "severe": 8/15 vs. 7/15 Duration of disease (years): 7 vs. 12 Prior muscle relaxant use: Not reported
Rinne (2) 1980	Randomized trial Finland Single center	A: Tizanidine titrated, mean dose 11.2 mg/day B: Baclofen titrated, mean dose 51.3 mg/day 4 weeks	Not clear	Not reported	Not reported Not reported 32	2 withdrew 31	Tizanidine vs. baclofen Mean age (years): 47 vs. 46 Female gender: 10/16 vs. 8/16 Race: Not reported Multiple sclerosis (24) or cervical myelopathy (8) Disease severity "severe": 9/16 (A) vs. 9/16 (B) Duration of disease (years): 14 vs. 12 Prior muscle relaxant use: Not reported
Roussan 1985	Randomized crossover trial U.S. Single center	A: Baclofen titrated, mean dose 47.3 mg/day B: Diazepam titrated, mean dose 28 mg/day 3 week washout, 5 week initial intervention, 3 week washout, 5 week crossover	Spasticity >3 months	Not reported	Not reported Not reported 13	None reported 13	Baseline characteristics not reported for each intervention group Mean age (years): 39 Female gender: 5/13 Race: Not reported 5 traumatic paraplegia, 7 multiple sclerosis, 1 transverse myelopathy Duration (years): 2-27 years Prior muscle relaxant use: Not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Rinne (1) 1980	Spasticity: Ashworth scale (numbers not reported) Assessed every 2 weeks	FAIR. Randomization technique not described, allocation concealment technique not described.	Tizanidine vs. diazepam Spasticity (marked improvement): 0/15 vs. 2/15 Spasticity (moderate or marked improvement): 5/15 vs. 5/15
Rinne (2) 1980	Spasticity: Ashworth scale (numbers not reported) Assessed at 2 week intervals	FAIR. Randomization technique not described, allocation concealment technique not described.	Tizanidine vs. baclofen: Muscle tone (marked improvement): 1/16 vs. 2/15 Muscle tone (marked or moderate improvement): 4/16 vs. 3/15
Roussan 1985	Global response to treatment: 0 (no improvement or worse) to 3+ (marked improvement) Assesssed weekly	FAIR. Randomization, treatment allocation, blinding techniques not described, unable to compare baseline characteristics between intervention groups.	Baclofen vs. diazepam Patient and physician preferences: No significant differences noted (trend favored diazepam)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Rinne (1) 1980	Tizanidine vs. diazepam, side effects at 2 weeks Drowsiness (severe): 0/15 vs. 7/15 Drowsiness (any): 8/15 vs. 13/15 Dry mouth: 5/15 vs. 0/15 Muscular weakness (severe): 1/15 vs. 4/15 Muscular weakness (any): 2/15 vs. 8/15 Dizziness: 1/15 vs. 2/15 Depression: 2/15 vs. 4/15 Constipation: 2/15 vs. 3/15 Overall tolerance (good or very good): 10/15 vs. 3/15 Withdrawal due to adverse event: 0/15 vs. 4/15 (weakness and drowsiness)	Not reported	May evaluate some of the same patients enrolled in Rinne (2). Outcome severity categories not defined.
Rinne (2) 1980	Tizanidine vs. baclofen (side effects at two weeks) Drowsiness (severe): 1/16 vs. 3/15 Drowsiness (any): 10/16 vs. 12/15 Dry mouth: 8/16 vs. 4/15 Muscular weakness (severe): 0/16 vs. 5/15 Muscular weakness (any): 3/16 vs. 6/15 Dizziness (severe): 0/16 vs. 2/15 Dizziness (any): 4/16 vs. 9/15 Nausea: 3/16 vs. 5/15 Overall tolerance (good or very good): 7/16 vs. 6/16 Withdrawal due to adverse event: 1/16 (urticaria) vs. 1/16 (weakness)	Not reported	May evaluate some of the same patients enrolled in Rinne (1). Outcome severity categories not defined.
Roussan 1985	Baclofen vs. diazepam Sedation: 1/13 vs. 5/13 Rebound spasticity: 7/13 vs. 3/13 Withdrawal: None reported	Not reported	

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Schmidt	Randomized trial	A: Dantrolene titrated to 75 mg qid	Multiple sclerosis patients with moderate or severe spasticity but relatively less ataxia or weakness	Severe dementia, ataxia, or tremor	250	4 withdrew	Demographics not reported
1976	Crossover	B: Diazepam titrated to 5 mg qid			Not reported	42	Multiple sclerosis, moderate to severe spasticity
	U.S.				46		Prior muscle relaxant use: No muscle relaxants or sedatives for 2 weeks before the study
	Single center	2 weeks low dose initial intervention, 2 weeks higher dose initial intervention, 2 weeks low dose crossover, 2 weeks higher dose crossover (4 weeks per intervention)					

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Schmidt 1976	Physical functions: Spasticity, clonus, and reflexes measured on 0 (absent) to 5 (marked) scale; deltoid strength, hip flexor strength, station stability, hand coordination, hand speed, foot speed, walking speed measured using techniques from ACTH Cooperative study Patient self-report: Subjective reports of symptom improvement or deterioriation by patients Assessed at 2 week intervals	FAIR: Randomization and allocation concealment techniques not reported, unable to compare baseline characteristics between intervention groups.	Dantrolene vs. diazepam, results on higher doses Spasticity: 9.54 vs. 9.40 (NS) Reflexes: 19 vs. 22 (p=0.001, favors dantrolene) Clonus: 3.2 vs. 3.4 (NS) Deltoid strength: 47 vs. 50 (p=0.10, favors dantrolene) Hip flexor strength: 122 vs. 127 (NS) Hand coordination: 147 vs. 134 (p=0.01, favors diazepam) Station stability: 46 vs. 34 (p=0.01, favors dantrolene) Hand speed: 250 vs. 227 (NS) Foot speed: 240 vs. 226 (NS) Walking speed: 11 vs. 17 (NS) Muscle cramps or spasms by patient report (improved): 60% vs. 76% (NS) Stiffness by patient report (improved): 38% vs. 48% (NS) Patient preference: 22/42 vs. 13/42 (7 chose neither drug) Long-term (6 month) use: 11/35 vs. 12/35 (9 on no study drug)

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Schmidt 1976	Dantrolene vs. diazepam Impaired gait: 52% vs. 75% Drowsiness: 31% vs. 67% Imbalance: 17% vs. 36% Incoordination: 10% vs. 29% Weakness: Not reported Withdrawals: 4 due to adverse events, intervention group not reported	Not reported	Results of initial intervention not reported separately. This appears to be the same study as Schmidt 1975, but some of the results and methodology are slightly different.

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Smolenski 1981	Randomized trial Switzerland Single center	A: Tizanidine titrated to 8 mg tid B: Baclofen titrated to 20 mg tid Average doses not reported 6 weeks intervention	Multiple sclerosis with spasticity and stable for 2 months	Cardiac, renal, hepatic disease, hypertension, epilepsy, chronic alcoholism, diabetes mellitus, or overt psychiatric illness	Not reported Not reported 21	None reported 21	Tizanidine vs. baclofen Mean age (years): 53 vs. 55 Female gender: 6/11 vs. 5/10 Race: Not reported Mean duration of symptoms (years): 17 vs. 27 Spasticity severe: 6/11 vs. 6/10 Prior muscle relaxant use: Not reported

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Smolenski 1981	Muscle strength: 0 (normal) to 5 (absence of voluntary movement) Muscle tone: Ashworth scale (0-4) Muscle spasms: 0 (normal) to 4 (all the time) Global assessment of change in condition Tolerance to medication Assessed weekly	FAIR: Randomization technique not described, treatment allocation technique not described, duration of illness appeared longer and more severe in baclofen group.	Tizanidine vs. baclofen Muscle tone and spasms (scores not reported): No significant differences Muscle strength (scores not reported): No significant differences Mean changes for functional abilities: No significant differences Physicians' assessments (improved) Overall spastic state: 10/11 vs. 9/10 Clonus: 5/11 vs. 5/10 Pain/stiffness: 9/11 vs. 7/10 Muscle strength: 5/11 vs. 5/10 Walking: 3/11 vs. 3/10 Bladder function: 3/11 vs. 0/10 Efficacy (good or excellent): 7/11 vs. 8/10 Tolerance (good or excellent): 10/11 vs. 9/10 Response compared to previous treatment (better): 7/11 vs. 5/10 Patients' global assessment of efficacy (good or excellent): 6/11 vs. 7/10 Patients' assessment of response compared to previous treatment (better): 6/11 vs. 4/10

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Smolenski	Tizanidine vs. baclofen	Not reported	Most patients previously on baclofen.
1981	Tiredness: 5/11 vs. 0/10 Weakness: 2/11 vs. 3/10 Dry mouth: 1/11 vs. 1/10 Ataxia: 1/11 vs. 0/10 Nausea: 0/11 vs. 1/10 Pyrosis: 0/11 vs. 1/10 Withdrawal: None reported		

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed	Population Characteristics
Stien 1987	Randomized trial Norway Single center	A: Tizanidine titrated, mean dose 23 mg/day B: Baclofen titrated, mean dose 59 mg/day 2 weeks titration, 4 weeks maintenance	Multiple sclerosis patients with stable disease for 3 months	Not reported	Not reported Not reported 40	2 withdrew 38	Tizanidine vs. baclofen Mean age (years): 50 vs. 45 Female gender: 9/18 vs. 12/20 Race: Not reported Multiple sclerosis patients in nursing home Duration of disease (years): 14 vs. 13 Severe spasticity: 5/18 vs. 10/20 Quadriparesis or quadriplegia: 8/18 vs. 12/20 Prior muscle relaxant use (baclofen): 10/18 vs. 16/20

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating	Outcomes
Stien 1987	Neurologic disability: Kurtzke scale Functional assessment: Pederson scale Muscle tone: Ashworth scale Clonus: Unspecified method Strength: Unspecified method Overall response: Unspecified method Assessed weekly	FAIR: Randomization technique not described, allocation concealment technique not described, eligibility criteria not specified, tizanidine group appears to have had less severe baseline disease	Tizanidine vs. baclofen Neurologic disability (Kurtzke scale): No significant differences between interventions (raw data not reported) Functional disability (Pedersen's method): No significant differences between interventions (raw data not reported) Statistical significance between interventions not reported: Clonus (improvement): 7/18 vs. 9/20 Clonus (worse): 1/18 vs. 8/20 Muscular resistance (improvement): 13/18 vs. 13/20 Provoked or spontaneous spasms (improvement): 12/18 vs. 13/20 Muscle strength (improvement): 2/18 vs. 2/20 Overall response (good)/physician assessment: 2/18 vs. 4/20 Overall response (good)/patient assessment: 1/18 vs. 6/20

Evidence Table 3. Head-to-head trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Adverse events	Funding Source and Role	Other comments
Stien 1987	Tizanidine vs. baclofen Tiredness, weakness, sleepiness, or dry mouth: 6/18 vs. 5/20 Withdrawals (adverse events): 1/18 (stiffness) vs. 1/20 (gastroenteritis) Rebound spasticity requiring re-initiation of medication: 1/18 vs. 5/20	Not reported	26/38 previously on baclofen. Abrupt discontinuation caused rebound spasticity in some patients requiring re-initiation of medication.

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Ashby 1972	Randomized crossover trial Australia Single center Inpatient	A: Cyclobenzaprine 60 mg/day B: Placebo Two weeks	Patients with cerebral or spinal spasticity.	15 14	Spinal patients (5) age range 16-38 (mean not reported) Cerebral patients (10) age range 8-69 Gender not reported Race not reported 5 patients with stablecervical/thoracic spinal cord damage of at least nine months' duration 10 patients with brain damage of 2-18 months' duration Mean spasticity severity not reported Previous muscle relaxant use not reported
Basmajian 1974	Randomized crossover trial United States Single center	A: Baclofen 5mg TID B: Placebo 5 weeks intervention, 1 week washout, 5 weeks crossover	Adult Outpatient Age 21-55 Spasticity for at least three months	15 11	Mean age not reported Gender ratio not reported Race not reported 8 Multiple Sclerosis 2 Traumatic paraplegia 1 Demyelinating spinal cord disease 1 Congenital quadriplegia Mean spasticity severity not reported Almost all patients had been on diazepam

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Ashby 1972	Muscle Tone (0=no resistance; 1=slight; 2=moderate; 3=marked; 4=complete) Muscle Power (Medical Research Council Scale) Tendon Hyperreflexia (0=absent; +=reduced; ++ = normal; +++ = increased; ++++ = markedly increased) Clonus (recorded in seconds) Functional Changes (unspecified) *All above clinical assessments performed daily. EMG and other objective assessments performed on last day of each treatment period.	FAIR. Method of random assignment unspecified. Allocation concealment adequate (pharmacy-controlled). Baseline similarity not reported. Blinding technique not reported.	Cyclobenzaprine vs. placebo: "Improvement": 3/14 vs. 3/14 Tone (upper or lower limbs): No significant between group differences Clonus, strength, deep tendon reflexes: No significant between group differences	Cyclobenzaprine (A) vs. placebo (B) Withdrawals (due to adverse events): 1/14 (rash) vs. 0/14 Other adverse events reported Patient 1: truncal rash(B) Patient 2: dry mouth(A) Patient 3: dizziness while on A; nausea & vomiting while on B Patient 4: nausea & vomiting while on both A and B
Basmajian 1974	Overall assessment of pain, motor status, and presence of spasms: methods not described Assessed weekly	FAIR. Randomization, allocation concealment techniques not reported. Unable to assess if intervention groups similar at baseline.	Baclofen vs. placebo Spasticity reduction "much superior or superior" (based on EMG and force recordings): 6/12 vs. 2/12 (4 inconclusive)	Withdrawals (overall): 4/12 (before intervention or early in treatment, group not specified) Withdrawal (adverse events): None No adverse events reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Basmajian 1975	Randomized crossover trial United States Single center	A: Baclofen; dose not reported B: Placebo 4 weeks on treatment; 1 week washout or duration required to return to pretreatment spasticity level, 4 weeks crossover	Patients with spasticity from multiple sclerosis	14 11	Age range 21-55 Gender not reported Race not reported Spinal cord injuries Demyelinating spinal cord disease Multiple sclerosis Previous muscle relaxant use not reported
Basmajian 1973	Crossover trial (not clear if randomized) United States Single center	A: Dantrolene 4 capsules/day, dose unclear B: Placebo 21 days treatment, then 21 days crossover	Motor spasticity caused by upper motor neuron disease	25 19	Age range 17-70 (mean age not provided) 70% female Race not provided 14 multiple sclerosis 5 spinal cord injury (4 of which were secondary to gunshot wounds) 4 other (stroke, dermoid cyst, meningioma) Severity not reported Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Basmajian 1975	Overall assessment of antispastic activity: methods not described Weekly assessment	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo (includes results of Basmajian 1974 MS patients, n=8) Spasticity Reduction (at least slightly superior): 9/19 vs. 4/19 (5 no difference) Spastiticy Reduction (superior or much superior): 5/19 vs. 3/19	Not reported
Basmajian 1973	Overall assessment of response to treatment by investigator: methods not described Assessments completed at end of each intervention and 7-10 days after study	POOR. Not clear if randomized, allocation concealment technique not described, unclear outcomes assessment, could not assess baseline differences between intervention groups.	Subjective overall clnical response: dantrolene preferred over placebo ($p<0.05$, raw data not reported)	Dantrolene vs. placebo Withdrawals (adverse events): 3/25 (weakness) vs. 1/25 (nausea and diarrhea) Frequent adverse events Weakness: "almost all patients" Dizziness: "several patients" Nausea: 2 patients Nausea and diarrhea: 3 patients

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Brar 1991	Randomized crossover trial United States Single center	A: Baclofen titrated from 5 mg/day up to 20 mg/day B: Placebo C: Stretching* D: Baclofen + stretching* 10 weeks Outcomes for these interventions not abstracted	Patients age 24-54 with clinically definite, mild-moderate MS 5.5 or less on Kurtzke Expanded Disability Status Scale (EDSS) Clinically stable for three months or more	38 30	Mean age not reported 70% female Race not reported Multiple Sclerosis 43% minimal spasticity in both legs 57% minimal in one leg and moderate in the other Prior muscle relaxant use not reported
Chyatte 1973	Randomized crossover trial United States Single center	A: Dantrolene sodium: initial dose of 5-25 mg QID; maximum dose of 100 mg QID B: Placebo 4 weeks intervention, 4 weeks washout, 4 weeks crossover	Patients with athetoid cerebal palsy	18 17	53% female Age range of 7-38 years Race not reported 15 birth-related brain damage (hypoxia) 1 brain injury (2 years post-injury) 1 encephalitis (4 years post-illness) Quadriplegia in five patients Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Brar 1991	Muscle tone (Ashworth Scale) Functional Ability (adapted from standard Minimal Record of Disability) Timing of assessment not reported	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Baclofen vs. placebo Ashworth score (improved): 30% vs. 20% (p not reported) Ambulating (improved): 10% vs. 17% (NS) Climbing (improved): 20% vs. 13% (NS) Household activities (improved): 17% vs. 20% (NS)	Withdrawals (overall): 8 overall, intervention group not reported Withdrawals (adverse events): 1, intervention group not reported No other adverse event information provided
Chyatte 1973	Overall clinical response: Includes spasticity (using unspecified 4-point scale) and motor function (unspecified scale) Activities of daily living: Included functional performance grading using 4-point scale (1=much easier; 2=easier; 3=no change; 4=more difficult) Timing of assessments not reported	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Overall clinical response: no results reported; numerical data from objective testing reported to be too "diffuse and variable" to analyze Improved motor control: 17/17 vs. 3/17 Better relaxation: 15/17 vs. 4/17 Less involuntary motion: 4/17 vs. 2/17 Improved excretory functions: 4/17 vs. 0/17 General improvement: 2/17 vs. 017	Dantrolene vs. placebo Withdrawals (overall): 0/17 vs. 1/18 Withdrawals (due to adverse events): 0 Numbers of adverse events not recorded for each intervention group

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Denhoff 1975	Randomized crossover trial United States Single Center	A: Dantrolene 1 mg/kg qid titrated to max of 3 mg/kg qid B: Placebo 6 week intervention, 2 weeks washout, 6 weeks crossover	Not reported	18 18	Age range 18 months to 12 years Female gender 43% Diagnoses Spastic quadriplegia: 15/28(54%) Spastic hemiplegia: 7/28(25%) Spastic diplegia: 4/28(14%) Mixed spasticity/athetosis: 1/28(4%) Mixed spasticity/rigidity: 1/28(4%) Degrees of severity Mild: 14/28(50%) Moderate: 5/28(18%) Severe: 9/28(32%)
Duncan 1976	Randomized crossover trial U.S. Single center	A: Baclofen 5 mg/TID titrated to max 100 mg/day B: Placebo 4 weeks intervention, 1 week washout, 4 weeks crossover	Duration of spasticity stability of 3 months or more	25 22	Average age: Multiple sclerosis group=36.4, non-multiple sclerosis group=38.8 Gender: 50% female Race: 100% White Diagnoses Multiple sclerosis: 11/22(50%) Other spinal cord lesions (including accidental and intraoperative trauma, compressive lesions and degenerative spinal cord disease): 11/22(50%) Extent of disability Ambulatory: 8/22 (36%) Paraplegia: 11/22(50%) Quadraplegia: 3/22(14%) Illness duration: MS patients=36.4, non-MS patients=5.1

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Denhoff 1975	*Measurement scales not specified Neurological measurements: strength, spasticity, tendon jerk reflexes and clonus Orthopedic measurements: active/passive range of motion (degrees) Motor performance: observational Activities of daily living: scales unspecified; observational ratings made by both program staff and parents Behavioral functioning: scales unspecified; observational ratings made by both program staff and parents Cognitive measurements: obtained by subtests from McCarthy Scales of Children's Abilities and Peabody Picture Vocabulary Test	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Neurological measurements (moderate or marked change): 6/28 vs. 2/28; p<0.04 Motor performance (moderate or marked change): 5/28 vs. 6/28; p=NS Staff evaluations (moderate or marked change): 8/28 vs. 0/28; p<0.02 Parent evaluations (moderate or marked change): 9/28 vs. 3/28; p<0.03 Cognitive measurements: no statistically significant group differences found	Dantrolene vs. placebo Any adverse event: 16/28 vs. 7/28; p<0.03 Frequent adverse events: irritability, lethargy, drowsiness, general malaise, exacerbation of seizures (4)
Duncan 1976	Resistance to passive movement: 5-point scale at the pretreatment visit (A=normal; E=immobile to passive movement) and change at each subsequent week rated using 5-point scale (1=worse; 5=marked improvement) Clonus: graded as none, minimal, moderate or severe at each visit Subjective impressions: included ratings of pain, use of spastic limbs, transfer activity, and general well-being Impression of current treatment: rated by patient in unspecified manner at end of each intervention phase Investigator therapy preference: rated before code broken	POOR. Randomization, allocation concealment, eligibility criteria, intention-to-treat analysis not performed. Blinding method described as providing baclofen and placebo tablets that were identical in size, shape, color and container.	Resistance to passive movement: A=11/20(55%) vs. B=1/20(5%), p<0.01 in increased resistance to passive movement Clonus: no consistent change seen in any patient; no significant between-group differences reported Subjective impressions: A=13(72%) vs. B=2(11%), p<0.01 in reduction of spasm frequency; A=9(75%) vs. B=0(0%), p<0.01 in reduction of nocturnal awakenings due to spasms; transfer activities reported as "generally improved", but no significant group differences were reported Impression of current treatment: Improvement reported as A=14/22(64%) vs. B=2/22(9%), p-value not reported but described as "significant" Investigator therapy preference: Improvement reported as A=14/22(64%) vs. B=0/22(0%), p-value not reported but described as "significant"	Withdrawals (due to adverse events): 2/25 patients on placebo Overall incidence: A=15, B=4 Frequent adverse events Lightheadedness: A=5, B=1 Nausea: A=5, B=1 Drowsiness: A=3, B=1 Dry Mouth: A=3, B=0 Weakness: A=2, B=0 Vomiting: A=1, B=0 Dizziness: A=1, B=1 Leg edema: A=1, B=0 Postural hypotension: A=1, B=0

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Feldman 1978	Randomized crossover trial United States Single center	A: Baclofen 15-80 mg/day B: Placebo 1 week washout, 4 weeks intervention, 1 week washout, 4 weeks crossover	Adult Established diagnosis of MS Spontaneous flexor contractions/spasticity for at least 3 months	33 23	Mean age 43 Gender not reported Race not reported Established diagnosis of Multiple Sclerosis Mean spasticity severity not reported. Previous muscle relaxant use not reported.
Gambi 1983	Randomized crossover trial Italy Single center	A: Dantrolene 25 mg BID titrated to maximum of 350 mg/day B: Placebo 2 weeks washout, 5 weeks interention, 1 week washout, 5 weeks crossover	Not reported	24 24	Mean age 41.3 Female gender: 50% Race not reported Multiple sclerosis: 12 patients with a mean spasticity period of 7.2 years Degenerative myelopathies: 12 patients with a mean spasticity period of 5.7 years Previous muscle relaxant use not specified

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Feldman 1978	Daily spasm frequency: method unspecified Knee clonus: method unspecified Resistence to passive movement: a (normal resistance) to f (immobile) Ambulation/transfer activity: Method unspecified Spastic limb pain/use of spastic limb: Subjective method unspecified Functional assessment: Barthel Index	FAIR. Randomization and allocation concealment techniques not reported.	Baclofen vs. placebo Daytime spasms (improved): 13/18 (72%) vs. 2/18 (11%) Nocturnal awakenings (improved): 9/12 (75%) vs. 0/12 (0%) Resistance to passive movement (improved): 11/20 (55%) vs. 1/20 (5%) Patient assesment (overall improvement): 14/22 (64%) vs. 2/22 (9%)	Baclofen vs. placebo Withdrawals: None reported on treatment Frequent adverse events (n=23) Drowsiness: 4 vs. 4 Paresthesia: 5 vs. 2 Blurred vision: 2 vs. 2 Dry mouth: 5 vs. 1 3-year long-term study Drowsiness: 2 Dizziness: 2 Anorexia: 1 Nocturia: 1 Constipation: 3
Gambi 1983	Degree of spasticity: 6-point scale (1=marked hypotonicity; 6=marked hypertonicity) Muscular strength: 6-point scale (1=normal; 6-absent) Clonus: 6-point scale (1=absent; 6=markedly steady) Knee and ankle tendon reflexes: 6-point scale (1=absent; 6=marked hyperactive) Articular flexor movement: evaluated using a degree scale Physician final assessment: 4-point scale (1=none; 4=marked) Patient acceptibility: 3-point scale (1=poor; 3=excellent) Assessments completed at the beginning and end of each treatment cycle	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene (A) vs. placebo (B) *Multiple sclerosis group* Degree of spasticity (reduction): A>B ($p<0.05$), data not reported Muscular strength: no significant differences Clonus: no significant differences Knee and ankle tendon reflexes: no significant differences Articular flexor movement: no significant differences Physician final assessment (of benefit): A>B ($p<0.05$) Patient acceptibility: no significant differences *Degenerative myelopathies group* Degree of spasticity (reduction): A>B ($p<0.005$), data not reported Muscular strength: no significant differences Clonus: no significant differences Knee and ankle tendon reflexes: no significant differences Physician final assessment (of benefit): A>B ($p<0.005$) Patient acceptibility: no significant group differences	Withdrawals (due to adverse events): A=2(9%) vs. B=3(13.6%) Any adverse event: 13/24 vs. 3/24 Headache: 2/24 vs. 1/24 Drowsiness: 7/24 vs. 2/24 Nausea: 4/24 vs. 0/24 Vomiting: 1/24 vs. 0/24 Gastric pain : 4/24 vs. 1/24 Malaise: 1/24 vs. 024 Muscular weakness: 3/24 vs. 1/24

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Gelenberg 1973	Crossover (not clear if randomized) U.S. Single center	A: Dantrolene 50-800 mg (mean dose not reported) B: Placebo 5 weeks intervention, 1 to 3 weeks washout, 5 weeks crossover	Patients with moderate-severe spasticity secondary to multiple sclerosis.	20 20	Mean age=49 55% Male Race unreported Multiple Sclerosis Moderate-Severe Spasticity (Mean unreported) Previous muscle relaxant use not reported
Haslam 1974	Randomized crossover trial United States Single center	A: Dantrolene 4mg/kg/day titrated to a maximum of 12mg/kg/day B: Placebo 2 weeks intervention, 10 days washoutk, 2 weeks crossover	Children with spasticity secondary to brain damage incurred at birth	26 23	Mean age (years): 6.5 65% female Race not reported Brain damage (e.g., prematurity, perinatal anoxia, kernicterus and neonatal meningitis) Mean IQ=45 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Gelenberg 1973	Spasticity, strength, clonus and tendon reflexes assessed weekly. Methods of assessment not specified.	POOR. Not clear if randomized. Allocation concealment technique not reported. Blinding technique may not have been adequate.	Dantrolene vs. placebo Patient preferred: 7/20 vs. 4/20 No other data provided	Dantrolene vs. placebo; n=20 Weakness: 15 vs. 0 Lightheadedness/drunkenness: 11 vs. 1 Nausea: 7 vs. 0 Dizziness: 6 vs. 0 Diarrhea: 6 vs. 0 Speech difficulty: 4 vs. 0 Drowsiness/lethargy: 3 vs. 0 Headache: 2 vs. 1 Short temper/irritable: 2 vs. 0 Photophobia: 1 vs. 0 Depression: 1 vs. 0 Cramps: 0 vs. 1
Haslam 1974	Spasticity: 5-point scale for clonus (0=absent-4=sustained) Passive Movement: 0=full range to 4=severely restricted Spontaneous Movement: 0=normal to 4=none Tone: 0=normal to 4=marked increase Reflexes: 0=normal to 4=very brisk Scissoring: 0=absent to 4=paraplegia-in-flexion Motor functions: step climbing, sitting position time, hand-knee position, roll-over time as measured by physical therapists; methods unspecified Self-help skills: reach for/transfer objects, pegboard test, wheelchair operation as measured by physical therapists; methods unspecified Daily activities: bathing, bracing, dressing, wheelchair transfer as measured by nursing staff; methods unspecified Assessed on days 4, 8, 11 and 15 of each treatment period	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene sodium vs. placebo Scissoring and reflexes: Improved in dantrolene vs. placebo, $p<0.05$, data not provided Passive range of motion, spontaneous range of motion, muscle spasticity: No differences between treatments	Withdrawals (overall): 3 (group not reported) Withdrawals (adverse events): 0 Frequent adverse events: minimal lethargy that resolved with first two days

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Hinderer 1990	Randomized United States Single Center	A: Baclofen, 40-80 mg/day B: Placebo 2.5-4.5 weeks washout, 2 weeks titration, 2.5-4.5 weeks at target dose (80 mg) (multiple baseline single-subject research design)	Patients with spasticity	5 5	Age range of 20-42 100% male Race not reported Spinal cord lesions of unspecified traumatic etiologies Previous muscle relaxant use not specified
Hulme 1985	Randomized crossover trial United Kingdom Single center Geriatric ward	A: Baclofen 10 mg TID B: Placebo 3-day titration, 18-day intervention, 7-day washout; 18 days crossover	Men and women over the age of 65 years in a geriatric ward who had muscle spasticity following a stroke	12 10	Gender: 7/12(58%) female Age range: 69-81 Race: not reported Baseline duration and severity of symptoms not reported
Jones 1970	Randomized crossover trial Australia Single center	A: Baclofen 15 mg/day titrated to 60 mg/day B: Placebo 14 days intervention followed by 14 days crossover	Hospitalized patients with quadriparetic or quadriplegic spinal cord injury	6 6	Age range (years): 17-41 Female gender: 2/6 Race: not reported Duration of illness: 5/6 less than 12 months Prior muscle relaxant use: All previously on diazepam 15-30 mg/day

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Hinderer 1990	Spasticity: unspecified method Anxiety: Beck Inventory Scale Assessed twice per week	POOR. Randomization, blinding techniques not described, intention-to-treat analysis not performed. Very small sample size. "Multiple baseline single-subjet research design" may be invalid.	Spasticity: 0 subjects demonstrated therapeutic reduction of spasticity measurements while taking baclofen Anxiety: 1/5 had significantly reduced Beck Inventory Score on baclofen	Not reported
Hulme 1985	*Methods not specfied: Spasticity Psychomotor functioning Mobility Self-care capacity Assessments completed initially and at weekly intervals thereafter	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Study stopped due to excess withdrawals, no data to assess efficacy.	Withdrawals (adverse events): 5/9 (drowsiness) vs. 1/6 (stroke) Drowsiness: 7/9 vs. 0/6
Jones 1970	Spasticity: 0 (normal) to 4 (rigid) Strength: British Medical Research Council Scale Ankle clonus: Duration Reflexes: 1 (normal) to 4 (markedly increased) Number of spasms Assessed daily	FAIR. Randomization, allocation concealment, blinding techniques not described.	Baclofen vs. placebo Muscle tone (improved): 5/6 vs. 0/6 Number of spasms: (fewer): 3/6 vs. 0/6 Reflexes: No differences	Baclofen vs. placebo Nausea: 5/6 vs. 2/6 Diarrhea: 2/6 vs. 2/6 Fatigue: Not clear Dizziness: None reported Dry mouth: None reported Weakness: None reported Any adverse event: Not clear Withdrawals: None reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Joynt 1980	Randomized United States Single center	A: Dantrolene 4 mg/kg/day titrated to maximum of 12 mg/kg/day B: Placebo 6 weeks	Children with cerebal palsy and spasticity interfering with function	21 20	Children, mean ages not reported Gender: not reported Race: not reported Diagnostic etiologies Diplegia: 7/20(35%) Quadriplegia: 7/20(35%) Hemiplegia: 5/20(25%) Paraplegia: 1/20(5%) Previous muscle relaxant use: not reported
Katrak 1992	Randomized crossover trial Australia Single center	A: Dantrolene 25 mg bid titrated to maximum 50 mg qid B: Placebo 2 weeks titration; 4 weeks maintenance; 1 week washout; 2 weeks crossover titration; 4 weeks crossover maintenance	Age 35-85; significant motor impairment; ability to comply with Cybex assessment	38 31	Average age 60.5 years 10% female Race not reported Within eight weeks post-CVA 14 left hemiparesis 17 right hemiparesis Previous muscle relaxant use not allowed

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Joynt 1980	Family observations: muscle spasm, range of motion, activities of daily living, child's daily performance and drug's helpfulness; all rated using 9-point scale, with 5 being the pre-treatment baseline score (higher numbers indicated improvement) Tone: rated 0-6; 3=normal Clonus: rated 0-6; 0=normal Strength: rated 0-5; 5=normal Reflexes: rated 0-6; 3=normal Spasms: rated 0-3; 0=normal General activities of daily living: measured by various functional tests Mobility: measured by various functional tests Evaluated at weeks 3 and 6	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Spasm (improvement): 3/11 (27%) vs. 0/9, p=0.089 Range of motion (improvement): 7/11 (64%) vs. 2/9 (22%), p=0.064 Other family observations: No significant differences Physical examinations: no significant differences for Tone, Clonus, Strength, Reflexes, or Spasms General activities of daily living (improvement): 8/11 (72%) vs. 2/9 (22%) Mobility: no significant differences	Dantrolene vs. placebo Withdrawal (adverse events): 1/11 vs. 0/9 Any adverse events: 10/11 (91%) vs. 3/9 (33%), p<0.008 Frequent adverse events (intervention not specified): fatigue (n=5), drowsiness (n=3), anorexia (n=2), diarrhea (n=1) and vomiting (n=1)
Katrak 1992	Tone: 0-5 scale (1=flaccid; 5=severe) Motor function: Motor Assessment Scale (eight areas of motor function on 0-6 scale) Activities of daily living: Barthel ADL scale Assessed at 1) Baseline; 2) completion of titration; 3) end of maintenance phase 1; 4) completion of washout; 5) completion of crossover titration; 6) completion of crossover maintenance phase; 7) completion of final washout	FAIR. Allocation concealment, blinding techniques not described.	Dantrolene vs. placebo Tone: No between-group differences Motor function: No between-group differences Activities of daily living: No between-group differences	Dantrolene vs. placebo Withdrawals (overall): 7 (group not specified) Lethargy/drowsiness: 14/20 vs. 6/20 (p=0.03) Slurred speach: 6/31 vs. 0/31 (p=0.01)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Ketel 1984	Randomized United States Single center	A: Dantrolene 25 mg BID or TIID titrated to average dose165.4mg B: Placebo Phase I: 6-week open-label dantrolene Phase II: randomized to 6 weeks of A or B	Patients with a history of cerebrovascular accident and limited return of function	18 14	Mean age of 61 Gender: Female=10/18(56%) Race: 100% White Cerebrovascular thrombosis: 17/18(94%) Cerebrovascular hemorrhage: 1/18 (6%) Left hemiparesis: 12/18 (67%) Right hemiparesis: 6/18(33%)
Knutsson 1982	Randomized crossover trial Sweden Single center	A: Tizanidine, maximum 10 mg/day B: Placebo 3-4 weeks intervention, 3-4 weeks crossover	Not reported	13 12	Gender: 4/17 (24%) female Age range: 23-80 Race: not reported Illness duration: 2 months to 42 years Wheelchair-bound: 3/17 (18%) Walking-aid dependent: 8/17 (47%) Prior antispastic medication use Baclofen: 4/14 (29%) Dantrolene sodium: 1/4 (25%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Ketel 1984	Neurological examination Spasticity: method not reported Strength: method not reported Clonus: method not reported Reflexes: method not reported Activities of daily living: method not reported Therapeutic goal Spasticity: method not reported Motor ability: method not reported Assessments completed at 3-week intervals	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed. 7/9 patients randomized to placebo switched to dantrolene.	Dantrolene vs. placebo Neurological examination Spasticity improvement: 5/5 (100%) vs. 0/8 (0%) Strength improvement: 4/5 (80%) vs. 0/8 Clonus improvement: 5/5 (100%) vs. 0/9 Reflexes improvement: 5/5 (100%) vs. 0/8 Improvement in activities of daily living: 5/5 (100%) vs. 0/8 Therapeutic goal Spasticity improvement: 5/5(100%) vs. 0/9 Motor ability improvement: 5/5(100%) vs. 0/9	Dantrolene vs. placebo Withdrawals (due to adverse events): 3 Rebound spasticity: 0/5 vs. 7/9 (78%) Any adverse events:: 9/12(75%) vs. 1/9(11%) Frequent adverse events: lethargy, weakness, fatigue, drowsiness, depression, dizziness, diarrhea, periorbital rash
Knutsson 1982	Resistance to passive movement: 5-point Ashworth scale Clonus: unspecified 3-point scale Functional disability: unspecified subjective assessment	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Tizanidine vs placebo Passive resistance/Ashworth scale (improvement): 5/12 (42%) vs. 3/12 (25%), NS Clonus (improvement): 3/12 (25%) vs. 3/12 (25%), NS Functional disability (improvement): 1/12 (8%) vs. 2/12 (17%), NS	Withdrawals (due to adverse events): 1 (patient on placebo) Tizanidine vs. placebo Drowsiness: 4/12 (33%) vs. 3/13 (23%) Dry mouth: 2/12 (17%) vs. 1/13 (8%) Muscle weakness: 1/12 (8%) vs. 0 Sleep disturbance: 1/12 (8%) vs. 0 Increased dysphasia: 1/12 (8%) vs. 0 Nausea: 0 vs. 1/13 (8%) Nycturia: 0 vs. 1/13 (8%) Dyspnea: 1 vs. 1/13 (8%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Lapierre 1987	Randomized Canada Single center	A: Tizanidine 2 mg/day titrated to maximum 32 mg/day B: Placebo 3-weeks titration, 5-weeks maintenance	Age between 18 and 60 years; definite diagnosis of multiple sclerosis; at least moderate degree of spasticity, severe enough to interfere with functional performance in daily life; stability of spasticity for two months or more	66 66	Tizanidine vs. placebo Mean age: 47.6 vs. 43.8 Gender: Female = 17 (52%) vs. 16 (48%) Race not reported Mean disease duration: 15.2 vs. 11.6 Severity "severe": 8 (25%) vs. 11 (33%) Monoparesis=7(22%) vs. 1(3%) Hemiparesis=0(0%) vs. 0(0%) Paraparesis=29(91%) vs. 32(97%) Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Lapierre 1987	Neurological evaluation: included scoring of limb power, tone, deep tendon reflexes, clonus, cerebellar function, sensory function, mental status and cranial nerves (unspecified methods) Functional evaluation: included scoring of neurological status (Kurtzke), functional disability assessment (Kurtzke), ambulation index and upper extremities index Assessments at weeks 0, 2, 3 and 8	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Neurological evaluation: no significant between-group differences for any outcomes measures Neurological status scale/Kurtzke (improved): 3/33 vs. 3/33 Kurtzke EDSS: No between-group differences Cumulative limb tone score (change from baseline): 3.86 vs. 1.49, p<0.05 (favors tizanidine) Cumulative deep tendon reflex score (change from baseline): 1.14 vs. -0.20, p<0.01 (favors tizanidine) Investigator overall judgement of effectiveness (good to excellent): 27% vs. 10%	Tizanidine vs. placebo Withdrawals (overall): 5/33 (15%) vs. 2/33 (6%) Withdrawals (due to adverse events): clear data not provided Tolerability: 53% vs. 85% Frequent adverse events Drowsiness: 48% vs. 27% Dry mouth: 48% vs. 27% Abdominal pain: 2(6%) vs. 0(0%) Sleep disturbances: 2(6%) vs. 2(6%) Tremor: 2(6%) vs. 0(0%) Rash: 2(6%) vs. 2(6%) Bladder disturbances: 1(3%) vs. 1(3%) Dizziness: 1(3%) vs. 2(6%) Gait disturbances: 1(3%) vs. 1(3%) Hallucination: 1(3%) vs. 0(0%) Muscle weakness: 1(3%) vs. 2(6%) Constipation: 0(0%) vs. 2(6%)

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Losin 1966	Randomized United States Single center Inpatient clinic	A: Chlorzoxazone, average dose of 20 mg/lb. body weight B: Placebo 9-10 weeks	Children with severe spasticity, mental retardation, and bedridden Concomitant use of anticonvulsants, antibiotics or vitamins allowed	30 27	Mean age (years): 10 Female gender: 37% Race not reported Diffuse encephalopathy: unknown cause (15), birth trauma (5), prematurity (3), postnatal meningoencephalitie (2), other (5) Previous muscle relaxant use not reported
Luisto 1982	Randomized crossover trial Finland 2 centers	A: Dantrolene sodium 75mg TID titrated to 400 mg QID over 21 days B: Placebo 25 days intervention, 1 week washout, 25 days crossover	Patients with moderate-severe spasticity	17 14	Mean age (years): 38 Female gender: 24% Race not reported Spinal cord injuries: 9/17 Multiple sclerosis: 3/17 Other: 5/17 Spasticity duration (range): >1-15 years Moderate to severe spasticity Confined to bed or wheelchair: 15/17

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Losin 1966	Limb posture, passive stretch resistance, pain: 4 point scale (0=normal, 1+=mildly abnormal, after which there were increasing degrees of severity up to 4+) General nursing care, feeding: 3 point scale ("+"=improvement, "0"=no change, "-"=worse) Timing of assessment not reported	POOR. Inadequate randomization (arbitrary assignment by investigator), one investigator not blinded, allocation concealment technique not described.	Chlorzoxazone vs. placebo Limb posture, passive stretch resistance, pain: "Improvement" in 3/5 on chlorzoxazone; no other data provided General nursing care, feeding: Spasticity severity increase for 2/3 on chlorzoxazone; no placebo data provided; no Feeding data provided	Withdrawals (overall): not reported Withdrawals (due to adverse events): not reported Frequent adverse events: sonorous respiration (1/6); light brown urine (5/0) Serious adverse events (resulting in death): aspiration pneumonia (1/2)
Luisto 1982	Spasticity: 1 (flaccid) to 6 (marked) Muscle strength: 1 (normal) to 6 (paralyzed) Clonus: 1 (absent) to 6 (sustained, marked) Reflexes: 1 (absent) to 6 (hyperactive, marked) Functional evaluation (methods not specified)	FAIR. Randomization, allocation concealment techniques not reported.	Dantrolene sodium vs. placebo Spasticity (sum of scores): 33.5 vs. 71.5 (p=0.05) Strength (sum of scores): 57 vs. 48 (p=0.05) Clonus (sum of scores): 40.5 vs. 64.5 (p=0.05) Reflexes: 36 vs. 69 (p=0.05) Activities of daily living: No improvement on either treatment	Withdrawals (overall): 3 (intervention group not specified) Withdrawals (adverse events): 3 (at least 2 from dantrolene group) Dantrolene vs. placebo Any adverse events: 100% vs. 35% Drowsiness: 15/17 vs. 6/17 Dizziness/vertigo: 4/17 vs. 1/17/1 Headache: 3/17 vs. 0/17 Nausea: 3/17 vs. 1/17 Numbness in hands/feet: 3/17 vs. 0/17 Others adverse events occurred in 1 or 2 patients

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
McKinlay 1980	Randomized crossover trial U.K. Single center School for physically handicapped children	A: Bacofen 0.5 mg/kg/day titrated to maximum dose 60 mg/day over 2 weeks B: Placebo 4 weeks titration/intervention, 2 weeks washout, 4 weeks crossover	Children with spasticity, no other criteria reported	20 18	Gender: "even sex distribution" (data not reported) Age range: 7-16 (mean not reported) Race: not reported Etiology Prenatal: 5 (25%) Perinatal: 10 (50%) Postnatal: 2 (10%) Unknown: 3 (15%)
Medaer 1991	Randomized crossover trial Belgium Single center Multiple sclerosis and rehabilitation center	A: Baclofen titrated to mean 30 mg/day B: Placebo 6 week washout, 2 weeks titration, 4 weeks intervention, 1 week washout, 2 weeks crossover titration, 4 weeks crossover intervention	Post-stroke spasticity	20 20	Female gender: 13/20 Mean age: 65 Race not reported Hemiplegia: 18/20 Monoparesis: 2/20 Mean duration: 4 years Patients on prior antispasticity agents excluded

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
McKinlay 1980	Muscle tone: Ashworth scale Tendon reflexes, extrapyramidal symptoms, cerebellar sympotms: graded clinically, methods not specified Manual dexterity: assessed using materials from standard tests (not specified) Speed of tongue movements: movement of tongue side-to-side 10 times Articulatory speed: time to say "buttercup" 10 times Assessments completed at initial visit and at weekly intervals Gait: Physiotherapist evaluation (method not specified) Muscle tone or better movement: Physiotherapist evaluation (method not specified)	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo Muscle tone: no significant differences Tendon reflexes: no significant differences Extrapyramidal symptoms: no significant differences Cerebellar symptoms: no significant differences Manual dexterity: no significant differences Speed of tongue movements: no significant differences Articulatory speed: no significant differences Muscle tone by physical therapy evaluation (improved): 14/20 vs. 5/20 (p=0.064) Gait (improved): 8/20 vs. 4/20	Baclofen vs. placebo Withdrawals (overall): 0 Any adverse event: 8/20 vs. 1/20 Drowsiness: 12/20 vs. 0/20 (p<0.001) "Sickness": overall 2 Dizziness: overall 2 Nocturnal enuresis: overall 2 Absence states: overall 2 Slurred speech: overall 2 Weakness: overall 1
Medaer 1991	Muscle Tone: Ashworth Scale Functional Status: Oswestry Rating Scale, Incapacity Status Scale Clinical Global Impression Scale: 4 point scale Extrapyramidal symptoms, cerebellar symptoms, clonus, reflexes, walking ability, range of abduction, impariment of self-help, and impairment of dexterity: Unspecified scales Improvement in spasticity: Unvalidated 4 point scale Assessed before treatment and after each intervention period	FAIR. Randomization and allocation concealment techniques not described. Unable to determine baseline differences between intervention group.	Baclofen vs. placebo Mean scores after treatment Ashworth: 2.95 vs. 3.75 (p<0.001) Oswestry: 3.8 vs. 3.2 (p<0.014) Incapacity status scale: 12.4 vs. 12.8 (NS) Clinical global impression scale (moderate of excellent improvement): 65% vs. 40% (p=0.009) Preferred treatment: 6/20 vs. 1/20 (13 undecided or wanted neither treatment)	Withdrawals: None reported Baclofen vs. placebo Any adverse event: 10/20 vs. 3/20 Somnolence: 1/20 vs. 0/20 Weakness: 4/20 vs. 0/20 Dizziness: 6/20 vs. 0/20 Difficulty walking: 2/20 vs. 0/20 Confusion: 0/20 vs. 1/20

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Meythaler 2001	Randomized crossover trial United States Single center Outpatient and inpatient rehabilitation center	A: Tizanidine 12-36 mg/day B: Placebo 6-weeks titration/treatment phase; 1-week taper; 1-week washout; 6-week crossover; 1-week taper; 1-week washout	Severe, chronic spastic hypertonia in at least 1 lower extremity (LE); spasticity of > 6 months' duration; Tone of >3 on Ashworth Scale Spasm of >2 on Penn Spasm Frequency Scale (PSFS); failure to respond satisfactorily to modalities and therapy for spasticity	17 17	Female gender: 3/17 (18%) Average age: 44 years Non-white race: 1/17 (6%) Black 7/17 (41%) hemiplegia 9/17 (53%) stroke 8/17 (47%) traumatic brain injury Tone >3 on Ashworth Scale Spasm >2 on Penn Spasm Frequency Scale (PSFS) 100% of patients had undergone a previous trial of oral baclofen and not responded adequately or could not tolerate the side effects
Milla 1977	Randomized crossover trial U.K. Multicenter	A: Baclofen 10 mg/day titrated to maximum 30-40 mg/day in children aged 2-7 and 60 mg/day in children aged 8 and above B: Placebo 4-weeks intervention, 4-weeks crossover	Children with spasticity; aged 2-16	20 20	Female gender: 11/20 (55%) Mean age: not reported Race: not reported Functional disability Diplegia: 5/20(25%) Hemiplegia: 7/20(35%) Quadriplegia: 8/20(40%) Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Meythaler 2001	Muscle Tone: Ashworth scale Spasticity: Penn Spasm Frequency Scale (PSFS) Deep tendon reflex: Using unspecified deep tendon reflex scale Range of Motion (ROM): Measured using goniometer Motor strength: Measured using International 6-point motor scale (0=absent; 5=normal) Mobility: Measured using FIM instrument and Craig Handicap Assessment and Reporting Technique (CHART) Assessments completed at start of arms 1 and 2 and at weeks 2, 4, 6, and 8 of treatment	FAIR. Randomization, allocation concealment, intention-to-treat analysis not described.	Tizanidine vs. placebo Muscle tone: A>B in reduction of lower extremity motor tone after 4 weeks of treatment (p=0.0006); A>B in reduction of upper extremity motor tone after 4 weeks of treatment (p=0.0007) (differences between interventions not reported) Spasticity: no significant differences Deep tendon reflex: no significant differences Range of Motion (ROM): no significant differences Motor strength: no significant differences Mobility: no significant differences Assessments completed at start of arms 1 and 2 and at weeks 2, 4, 6, and 8 of treatment	Withdrawals (adverse events): None Common adverse events on tizanidine Somnolence: 7/17 (41%) Increased LFT's: 3/17 (18%) Dry mouth: 2/17 (12%) Hypertonia: 2/17 (12%) Myasthenia 2/17 (12%) Pain 2/17 (12%) Other adverse events occurred in 1 patient
Milla 1977	Records were kept of: 1) spasticity, 2) extra-pyramidal signs, 3)cerebellar signs, 4) clonus, 5) tendon reflexes, 6) walking ability, 7) passive limb movements, 8) degree of self-help and 9) manual dexterity *All assessment methods unspecified except spasticity (rated using Ashworth scale) Assessments completed at 7-day intervals	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Baclofen vs. placebo Spasticity (improved): 14/20 (70%) vs. 2/20 (10%), p<0.001 Placebo group results not reported for other outcome measures	Baclofen vs. placebo Withdrawals (adverse events): 0 Any adverse event: 5/20 vs. 0/20 Sedation: 4/20 vs. 0/20 Hypotonia: 3/20 vs. 0/20

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Monster 1974	Randomized crossover trial U.S. and Canada Multicenters	A: Dantrolene 50 mg QID titrated to 100 mg QID B: Placebo 5 weeks intervention, 5 weeks crossover	Patients with spasticity of various causes	200 147	Age: Range from 35 to 50 years depending on underlying diagnosis Female gender: About 50% Race not reported Spasticity secondary to spinal cord, stroke, "unclassified" and multiple sclerosis etiologies (proportion of each not reported) Previous muscle relaxant use not reported
Nance 1994	Randomized U.S. and Canada Multicenter	A: Tizanidine 4 mg/day titrated to maximum 36 mg/day B: Placebo 3 weeks titration, 4 weeks maintenance, 1 week tapering (8 weeks intervention)	Patients 18 years or older with spinal cord injury, Frankel grade of A, B, or C and Ashworth scale score of 2 or greater in one or more muscle groups	124 118	Tizanidine vs. placebo Age range (years): 15-69 Female gender: 9/59 vs. 5/59 Non-white race: 31% vs. 36% Mean duration of spinal cord injury (months): 101 vs. 89 Frankel grade A: 32/59 vs. 34/59 Previous muscle relaxant use: not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Monster 1974	Overall clinical response (OCR): measured by 3-point scale (0=no/mild change; +1=moderate improvement; +2=marked improvement) Disability: methods not reported; included Activities of Daily Living (ADL) assessment Spasticity: various EMG measurements, including Clonus	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Overall clinical response (OCR): substantial improvement in 83% of patients on Dantrolene sodium (data/p-value not reported) Disability: substantial improvement in 43% of patients on Dantrolene sodium (data/p-value not reported) Spasticity: reduction in clonus in 90% of patients on Dantrolene sodium (data/p-value not reported)	Dantrolene sodium vs. placebo Withdrawals (overall): 53 (intervention not clear) Withdrawals (due to adverse events): less than 10% (exact number and intervention unclear) Frequent side effects: general malaise, fatigue, weakness, drowsiness, nausea, anorexia and dizziness (numbers not reported)
Nance 1994	Spasticity: Ashworth scale and video motion analysis of the pendulum test Frequency of spasms Muscle strength: Unspecified method Functional status: modified Klein-Bell scale Global evaluation: Unspecified method Assessed at each visit	FAIR. Randomization, allocation concealment, blinding techniques not described. High dropout rate (78/118 completed trial)	Tizanidine vs. placebo Ashworth score (mean improvement): 4.41 vs. -0.44 ($p<0.0001$) Pendulum test (mean improvement) 13.32 vs. 1.50 ($p=0.004$) Daily spasm frequency: No difference at end of treatment Muscle strength: No differences Global evaluation: No significant differences Functional status (Klein-Bell): No differences	Tizanidine vs. placebo Withdrawals (overall): 21/59 (36%) vs. 19/59 (32%) Withdrawals (adverse events): 15/59 (25%) vs. 5/59 (8%) Any adverse event: 81% vs. 53% ($p=0.002$) Somnolence: 24/59 vs. 4/59 Dizziness: 10/59 vs. 2/59 Weakness: Not reported Dry mouth: 23/59 vs. 4/59 Asthenia: 18/59 vs. 9/59 Headache: 12/59 vs. 9/59 Diarrhea: 2/59 vs. 5/59

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Nogen 1979	Randomized trial U.S. Single center	A: Dantrolene titrated to 5.6-7.9 mg/kg/day B: Placebo All patients titrated on dantrolene, 1 week washout, then unclear duration of intervention	Pediatric patients with spasticity and epilepsy	21 21	Age range: 7 months to 19 years Female gender: 11/22 Race: not reported Mental retardation: 19/22 Hypoxia at birth or in utero: 6/22 Hemiparesis: 8/22 Other diagnoses: Tumor, encephalitis, vascular malformation, hydrocephalus Anticonvulsant use: 9 phenobarbitol, 7 clonazepam, 13 phenytoin (7 patients more than one) Prior muscle relaxant use: not reported
Orsnes 2000	Randomized crossover trial Denmark Multicenter	A: Baclofen 5 mg TID titrated to maximum 15 mg TID B: Placebo Titration to maximum tolerated dose (duration variable); 11 days maintenance; 1-week taper; 2-week washout; crossover titration; 11 days crossover maintenance; 1-week crossover taper	Patients with clinically definite MS	14 14	Median age=42 Clinically-definite MS; stable for at least one month Kurtzke's Expanded Disability Status Scale (EDSS) median score of 5 Neurologic Rating Scale (NRS) median score of 67 MS-impairment scale (MSIS) median score of 3 Ambulation index (AMB) median score of 3 Ashworth index of spasticity median score of 0.8 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Nogen 1979	Spasticity: Unspecified method Strength: Unspecified method Reflexes: Unspecified method Clonus: Unspecified method Functional status: Unspecified method Seizures: EEG and frequency	FAIR. Randomization, allocation concealment, blinding techniques not described	Dantrolene vs. placebo Seizure frequency (increased): 1/11 vs. 2/10 Spasticity and other outcomes not reported	Dantrolene vs. placebo Drowsiness: 9/11 vs. 0/10 Increased drooling: 3/11 vs. 0/10 Headaches: 2/11 vs. 0/10 Leg cramps: 1/11 vs. 0/10 Dizziness: Not reported Dry mouth: Not reported Weakness: Not reported Withdrawals (overall): 1, group not reported Withdrawals (adverse events): None reported
Orsnes 2000	Postural stability: measured by force-plate Strength: Medical Research Council scale (0-5) Passive movement resistance: Ashworth scale (5-point scale) Tendon reflexes: 6-point scale (0=hyporeflexic; 5=severe clonus) Assessments before each of 2 treatment periods and after 11 days of treatment at the maximum dose	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo Postural stability: insignificant trends Strength: insignificant trends Passive movement resistance: insignificant trends Tendon reflexes: insignificant trends	Baclofen vs. placebo Withdrawals: not reported Any adverse event: 9/14 vs. 1/14 Fatigue: 5/14 vs. 1/14 Dizziness: 3/14 vs. 1/14 Better sleep: 2/14 vs. 0/14 Nausea: 1/14 vs. 0/14 Diarrhea :1/14 vs. 1/14 Other adverse events occurred in 1 patient

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Sachais 1977	Randomized trial United States Multicenter Combined inpatient and outpatient setting	A: Baclofen, 5 mg tid (outpatients) or 10 mg tid (inpatients) titrated to 70-80mg/day B: Placebo 2-week titration, 5-week intervention	Inpatient or outpatient adults (18 years or older) Spasticity secondary to MS (duration not specified)	166 106	Mean age=43 59% Female 92% White 87% Outpatient Multiple Sclerosis Mean Disease Duration - 11 years One-Month Spasticity Stabilization - 70% Quadraplegia - 10/5 Paraplegia - 30/33 Hemiplegia - 6/3 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Sachais 1977	Mental State (Depression, Euphoria, Irritability); Flexor Spasms (Pain, Frequency); Resistance to Passive Joint Movement (Ankle Flexion, Ankle Extension, Knee Flexion, Knee Extension, Hip Abduction, Hip Extension); Tendon Stretch Reflexes (Left Knee Jerk, Right Knee Jerk); and Global Disease Severity - all assessed through unspecified methods at baseline and at weeks three and five Physician Global Impressions (5=marked; 4=moderate; 3=slight; 2=no change; 1=worse) - assessed at end of study Patient Self-Evaluation of Condition (0=little of the time to 3=all the time) and Disability (1=minimal to 6=very severe) - rated at baseline and final visit	FAIR. Randomization, allocation concealment, blinding techniques not described.	Baclofen (A) vs. placebo (B) Mental State: No significant differences for depression, euphoria, and irritability Flexor Spasms: Pain: -1.10 vs. -0.08 (p<0.001) Frequency: -0.63 vs. -0.14 (p<0.005) Resistance to Passive Joint Movements: Baclofen significantly better for ankle flexion, knee flexion, knee extension Global Disease Severity: -0.26 vs. -0.19 (NS) Physician's Assessment of Neurological Findings: No significant differences for ankle clonus or knee clonus Flexor spasms (improvement): 17/37 vs. 6/37 (p=<0.02) Patient Self-Evaluation ratings (improvement from baseline): Baclofen significantly better for muscle spasms, clonus, and stiffness	Baclofen vs. placebo Withdrawals (overall): 31/85 vs. 29/81 Withdrawals (adverse events): not reported Somnolence=71% vs. 36% Vertigo=22% vs. 7% Excessive Weakness=20% vs. 11% Headache=12% vs. 9% Frequenct Urination=12% vs. 1% Insomnia=11% vs. 9% Depression= 5% vs. 6% Lower Extremity Weakness=5% vs. 2% Nausea=16% vs. 6% Constipation=11% vs. 2% Vomiting=5% vs. 0%

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Sawa 1979	Randomized crossover trial Canada Single center	A: Baclofen 5mg TID titrated to a maximum of 60mg B: Placebo 21-days intervention, 7-days washout, 21-days crossover	Patients with clinically definite MS of chronic myelopathy (presumed MS)	21 18	Mean age of 49 for males and 36 for females 29% male Race not reported Clinically definite MS of chronic myelopathy (presumed MS) Mean duration of illness of 14 years for males and 9 years for females Previous muscle relaxant use not reported
Sheplan 1975	Randomized trial United States Single Center	A: Dantrolene titrated to maximum of 200mg QID 5-week intervention, 2-week washout, 5-week crossover	Males with spasticity of a neurological etiology	Not reported Not reported 18 enrolled	Mean age=47.8 100% male Race not reported Multiple sclerosis - 8 Stroke - 4 Cervical spondylosis - 3 Other - 3 Wheelchair-confined - 6 Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Sawa 1979	Spasticity: 0 (normal) to 5 (in the absence of voluntary contraction, the leg will stay extended and require a significant degree of force to overcome the extensor spasticity)	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Baclofen vs. placebo Spasticity mean grade change (improvement in score): 1 vs. 0 (p not reported) Spasticity (improved): 13/18 vs. 0/18 (p<0.001) No other data reported	Baclofen vs. placebo Withdrawals (overall): 3/21 Withdrawals (adverse events): 1/21 (intervention not reported) Any adverse event: 71% vs. 19% Frequent Adverse Events in Baclofen Patients (n=21): Sedation(6), Headache(3), Mood Changes(4), Dizziness(2), Balance Disturbance(2), Weakness(3), Nausea(5), Vomiting(2), Diarrhea(1), Abdominal Pain(2), General Malaise(2), Dry Mouth(1), Weight Gain(1) Placebo patient adverse event data not reported
Sheplan 1975	Spasticity: rigidity and clonus measured by unspecified methods carried out weekly Hyperreflexia: measured by tendo-achilles myotatic reflex Patient acceptance (improvement in activities of daily living): measured by unspecified methods	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Spasticity Clonus (complete remission): 78% vs. not reported Rigidity (complete remission): 50% vs. not reported Hyperreflexia (complete remission): 83% vs. not reported Patient acceptance: no data provided	No withdrawal data provided. Frequent adverse events: weakness, incoordination, "rubber legs", headache, dizziness, GI disturbance, somnolence, fatigue; no data provided

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
Smith 1994	Randomized trial United States Multicenter (14)	A: Tizanidine titrated to maximum 36 mg/day B: Placebo 2 weeks titration, 9 weeks maintenance, 1 week withdrawal	Patients with multiple sclerosis	256 220	Mean age (years): 45.3 62% female Race reported as being mostly White, but percentage unspecified. Muscle spasticity secondary to MS Average baseline spasticity severity values Tizanidine - 12.99 Placebo - 14.95 Previous muscle relaxant use not reported.
Tolosa 1975	Randomized trial United States Single center	A: Dantrolene 25mg QID titrated to maximum 800 mg/day B: Placebo 8 weeks intervention	Patients with multiple sclerosis	23 23	Age, gender and race not reported Multiple sclerosis 48% severely disabled/confined to wheelchair Previous muscle relaxant use not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
Smith 1994	Primary Efficacy: Mean muscle tone (Ashworth Scale) and type/frequency of muscle spasms/clonus (patient diaries) (0-3 scale) Secondary Efficacy Assessment: Deep tendon reflexes/clonus (unspecified scale), pain/disability secondary to muscle spasm/clonus (0-2 scale), muscle strength (British Medical Research Council scale), functional capacity (e.g. walking time, activities of daily living) (unspecified scale) and global evaluation of antispastic efficacy (11.5 cm visual analog scale) Assessed weekly titratio, every 3 weeks during maintenance, and 1 week after intervention	FAIR. Method of randomization not reported. Method of treatment allocation concealment not reported. Unspecified suspected treatment crossover deviations reported, high withdrawal/loss to follow-up.	Tizanidine vs. placebo Muscle tone/spasticity (change in Ashworth score, improvement): 2.03 vs. 2.73 (NS) Muscle tone/spasticity (improved): 60% vs. 58% (NS) Spasms/clonus daily count (percent improvement): -61 vs. -41 Patient global assessment (mean score): 5.91 vs. 4.33 (p=0.01) No other significant differences in secondary outcomes (improvements generally small)	Tizanidine vs. placebo Withdrawals (overall): 28/111 (25%) vs. 33/109 (30%) Withdrawals (adverse events): 14/111(13%) vs. 6/109 (6%) Any adverse event: 101/111(91%) vs. 66/109(61%) Dry mouth: 57% vs. 15% (p<0.001) Asthenia: 48% vs. 18% (p<0.001) Somnolence: 48% vs. 3% (p<0.001) Nervous system: 84% vs. 38% (p<0.001) Dizziness: 19% vs. 5% (p=0.001) Drug-induced hepatitis: 1/111 vs. 0/111 (resolved after drug discontinued) Severe hallucinations: 1/111 vs. 0/109 (resolved after drug discontinued) SGOT increase: 6(5%) vs. 0 (p=0.029)
Tolosa 1975	Spasticity: (0=flaccid to 6=extreme resistance)	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene vs. placebo Muscle Spasticity Reduction: 42% vs. 27% (signifiance not reported)	Dantrolene vs. placebo Withdrawals (overall): 2/12 vs. 0/11 Withdrawals (adverse events): 2/12 (weakness, diarrhea) vs. 0/11 Weakness: 50% vs. 9% Dizziness, vertigo and GI effects were noted as being "common," but no data reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics
United Kingdom Tizanidine Trial Group 1994	Randomized trial United Kingdom Multicenter (16)	A: Tizanidine mean dose 25 mg/day B: Placebo 3-week titration, 9-week intervention	Spasticity due to clinically-definite, lab-supported or probable MS. Stable MS during previous month.	187 187	Mean age (years): 47 vs. 47 Female gender: 63% vs. 67% Race not reported Multiple sclerosis patients: Mean baseline muscle tone score 18.5 vs. 16.8 1 patient (placebo) with previous Tizanidine treatment. All other patients, except 1 (placebo), had previously taken other unspecified medication(s) for spasticity.
Weiser 1978	Randomized crossover trial United Kingdom Single center	A: Dantrolene 25 mg qid titrated to 100 mg qid B: Placebo 4 weeks intervention, 1 week washout, 4 weeks crossover	Symptomatic lower limb spasticity from spinal cord injury	35 27	Age range: 28 to 76 Female gender: 21/35 Race not reported Multiple sclerosis: 9/35 Myelopathy: 11/35 Hereditary spastic paraplegia: 8/35 Syringomyelia: 4/35 Other: 3/35 Severity and duration not reported

Evidence Table 4. Placebo-controlled trials of skeletal muscle relaxants in patients with spasticity (continued)

Author Year	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments	Outcomes	Adverse Events
United Kingdom Tizanidine Trial Group 1994	Primary Efficacy Assessment: Ashworth Scale administered weekly during 3-week titration phase; every three weeks during maintenance therapy; and at end of trial Secondary Efficacy Assessment: Muscle Strength: British Medical Research Council Scale Functional status/disability: Kurtzke Functional System Scale (FSS)/Kurtzke Expanded Disability Status Scale (EDSS) Reflexes: unspecified 8-point tendon reflex scale Spasms: unspecified 4-point spasm/spontaneous movement scale Timed 8 meter walking test	FAIR. Randomization method not reported. Allocation concealment technique not reported.	Tizanidine vs. Placebo Muscle Tone (sum Ashworth score) Change (%): 21 vs. 9 (p=0.004) Secondary Muscle Strength Change (%): +4 vs. +3 (NS) Muscle Spasm Frequency Change (%): -13 vs. -15 (NS) Muscle Spasm Pain Change (%): -10 vs. -4 (NS) Deep Tendon Reflexes Change (%): -9 vs. -4 (NS) Timed Walking Change (%): +4 vs. -10 (NS) No. of Steps Change (%): -3 vs. -3 (NS) Intermediate functions (improved): 20% vs. 10% Upper limb functions (improved): 6% vs. 5% Patient comfort (improved): 39% vs. 15% Sleep quality (improved): 43% vs. 33% Overall assessment by patient (very good or good): 28% vs. 14% (p=0.012)	Withdrawals (overall): 29/94 vs. 22/93 Withdrawals (due to adverse events): 12/94(13%) vs. 5/93(5%) Any adverse event: 87% vs. 61% Overall tolerability (very good or good): 40% vs. 85% Frequent adverse events Dry mouth: 45% vs. 0% Drowsiness: 54% of all patients in study
Weiser 1978	Tone: 0 (normal) to 3 (pronounced hypertonia) Clonus: 0 (absent) to 2 (sustained) Number and severity (scale not specified) of spasms Walking performance: Time to walk 40 minutes and time to climb up and down 21 step staircase Gait: Not specified Weekly intervals	FAIR. Randomization, allocation concealment, blinding techniques not specified. Results reported for more patients than enrolled in trial for some outcomes.	Dantrolene vs. placebo Tone (treatment preferred): 14/24 vs. 3/24 (p=0.012) Knee clonus (treatment preferred): 17/40 vs. 5/40 (p=0.016) Ankle clonus (treatment preferred): 24/52 vs. 6/52 (p=0.002) Walking time: NS Staircase time: NS Gait (improved): 15/20 vs. 1/20 (p<0.004) Spasms (improved): 14/20 vs. 0/20 (p<0.002)	Dantrolene vs. placebo Withdrawals (any): 4/35 (11%) vs. 2/35 (6%) (2 not clear which intervention) Withdrawals (adverse events): 4/35 (11%) vs. 2/35 (6%) Drowsiness or 'lightheadedness': 8/35 vs. 0/35 Weakness: 8/35 vs. 2/35 Depression: 3/35 vs. not reported

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Aiken 1978a	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg tid titrated up to 20 mg tid B: Diazepam 5 mg tid titrated up to 10 mg tid C: Placebo 14 days intervention	Outpatients with moderate to severe acute (<30 days) muscle spasm associated with traumatic strains of the neck or low back	Central nervous system etiology, comorbid secondary conditions, pregnant women, receiving analgesics, steroids, or tranquilizers, conditions for which study drugs were contraindicated	Not reported Not reported 117	17 114
Basmajian 1978	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg tid titrated up to 20 mg tid (mean dose not reported) B: Diazepam 5 mg tid C: Placebo 18 days	Patients with clinically palpable muscle spasm, limitation of motion, limitation of activities of daily living, local pain, and tenderness on palpation	Other neurologic or general medical conditions	Not reported Not reported 120	15 105 completed study, but results only reported for 52
Boyles 1983	Randomized trial U.S. Multicenter	A: Carisoprodol 350 mg qid B: Diazepam 5 mg qid 7 days	Outpatients between 19 and 65 years with acute (<7 days) sprain or strain of the lower back (no cervical involvement) with moderate pain and local spasm	Cervical strain, litigation, pregnant, nursing, allergy to interventions, patients requiring analgesics (except acetaminophen or aspirin), anti-inflammatories, or sedatives, history of drug abuse, chronic medical problems	Not reported Not reported 80	9 not analyzable 71

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Aiken 1978a	Cyclobenzaprine vs. diazepam vs. placebo Age (>50 years): 4/37 vs. 3/38 vs. 7/39 Female gender: 18/37 vs. 13/38 vs. 22/39 Race: Not reported Posttraumatic: 35/37 vs. 35/38 vs. 34/39 Neck pain: 24/37 vs. 25/38 vs. 26/39 Back pain: 13/37 vs. 13/38 vs. 13/39 Severity (moderate/severe or severe): 27/37 vs. 25/38 vs. 20/39 Prior muscle relaxant use: Not reported	Muscle spasm on palpation: 1 (absent) to 5 (severe) scale Limitation of motion: 1 to 5 scale Limitation of activities of daily living: 1 to 5 scale Pain: 1 to 5 scale Tenderness on palpation: 1 to 5 scale Global response: 5 point scale (worse to marked improvement) Assessed at baseline, day 3, day 7, day 14	FAIR. Randomization, blinding, and allocation concealment techniques not described.
Basmajian 1978	Age, gender, race: Not reported Cyclobenzaprine vs. diazepam vs. placebo Neck spasms: 10/34 vs. 10/36 vs. not described Lumbar spasms: 24/34 vs. 26/36 vs. not described Severity or duration: Not reported Prior muscle relaxant: Not reported	Muscle spasm: 1 (absent) to 5 (severe) scale Weighted mean of EMG index (these results not abstracted) Timing of evaluation not reported but appears to be at baseline and at end of intervention	POOR. Randomization and allocation concealment techniques not described; very high loss to follow-up and not clear how patients lost to follow-up analyzed; unable to compare baseline characteristics between intervention groups.
Boyles 1983	Carisoprodol vs. diazepam Mean age (years): 39 vs. 39 Female gender: 53% vs. 51% Race (non-white): 8% vs. 14% Baseline severity (5 point verbal rating scale) Pain severity: 4.28 vs. 4.31 Impairment of activity: 4.14 vs. 4.29 Prior muscle relaxant use: Not reported	Muscle spasm: 1 (none) to 5 (severe) Tenderness: 1 (none) to 5 (severe) Mobility restriction: 1 (none) to 5 (severe) Pain, stiffness, activity, sleep impairment, tension: 5 point verbal rating scale (VRS) and 100 mm visual analogue scale Assessed at baseline and days 3 and 7 of treatment	FAIR. Allocation concealment technique not described.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Aiken 1978a	Cyclobenzaprine vs. diazepam vs. placebo Improvement in mean scores at weeks 1 and 2 Muscle spasm: 1.5** vs. 0.7 vs. 0.8; 1.9 vs. 1.4 vs. 1.3 Local pain: 1.0 vs. 0.6 vs. 0.7 and 1.5* vs. 1.2 vs. 1.1 Tenderness on palpation: 1.1* vs. 0.6 vs. 0.7; 1.5* vs. 1.2 vs. 1.1 Limitation of motion: 1.1* vs. 0.6 vs. 0.6; 1.6** vs. 1.3 vs. 1.1 Limitation of activities of daily living: 0.9** vs. 0.4 vs. 0.5; 1.4 # vs. 1.2 vs. 0.9 Total spasm score: 5.4** vs. 3.2 vs. 3.3 and 8.2** vs. 6.4 vs. 5.4 *p<0.05 for difference between cyclobenzaprine and diazepam **p<0.01 for difference between cyclobenzaprine and diazepam #p<0.05 for difference between cyclobenzaprine and placebo Global response (marked or moderate improvement): 28/37 vs. 15/38 vs. 16/39 Global response (marked improvement): 22/37 vs. 11/38 vs. 6/39 (p<0.01 for cyclobenzaprine vs. diazepam and placebo)	Cyclobenzaprine vs. diazepam vs. placebo Withdrawals (overall): 5/38 (13%) vs. 6/40 (15%) vs. 6/39 (15%) Withdrawals (adverse events): 1/38 (3%) vs. 0/40 vs. 0/39 Any adverse event: 29/38 (76%) vs. 28/38 (72%) vs. 25/39 (64%) Drowsiness: 25/38 vs. 26/38 vs. 18/39 Dizziness: 7/38 vs. 8/38 vs. 9/39 Nausea: 1/38 vs. 0/38 vs. 4/39 Dry mouth: 2/38 vs. 1/38 vs. 1/38 Lightheadedness: None reported	Editorial assistance provided by Merck, funding source otherwise not clear	
Basmajian 1978	Cyclobenzaprine vs. diazepam vs. placebo Task performance time (% change from pretreatment): -12.5 vs -9.1 vs -6.5 (NS) Muscle spasm/back (change from pretreatment score): -1.0 vs. -1.0 vs -1.0 (NS) Muscle spasm/neck (change from pretreatment score): -0.9 vs. -0.7 vs. -0.7	Not reported	Not reported	
Boyles 1983	Carisoprodol vs. diazepam (estimated from graphs) Mean improvement in VRS scores: Pain: 1.9 vs. 1.7 Muscle stiffness: 2.0 vs. 1.3 (p<0.05 at day 6) Activity impairment: 2.0 vs. 1.8 Sleep impairment: 2.0 vs. 1.8 Tension: 1.9 vs. 1.3 (p<0.05 at day 7) Relief: 4 vs. 3.2 (p<0.05 at day 6) (Similar results for visual analogue scales) Overall relief (very good to excellent): 68% vs. 45% (NS)	Carisoprodol vs. diazepam Drowsiness/tired: 5/40 vs. 12/40 Dizzy/blackout: 5/40 vs. 3/40 Headache: 2/40 vs. 1/40 Dry mouth: Not reported Any adverse event: 9/40 (22%) vs. 14/40 (35%) Withdrawals (overall): 4/40 vs. 5/40 Withdrawals (adverse event): 1/40 vs. 2/40	Not reported	

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Bragstad 1979	Randomized trial Norway Single center	A: Tizanidine 2 mg po tid B: Chlorzoxazone 500 mg po tid 7 days	Spasms of the back muscles from degenerative lumbar disk disease	Impaired liver or renal function, severe hypertension, heart disease, epilepsy, cerebral insufficiency, or pregnant	Not reported Not reported 27	1 26
Brown 1978	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg po tid B: Diazepam 5 mg po tid C: Placebo 14 days	Moderate to severe pain in the lumbar or posterior cervical regions for more than 12 months	Not reported	Not reported Not reported 49	None reported 49
Fryda-Kaurimsky 1981	Randomized trial Germany Single center	A: Tizanidine 4-8 mg po tid B: Diazepam 5-10 mg po tid 10 days	Inpatients with acute muscle spasm due to degenerative spinal disease	Not reported	Not reported Not reported 20	None reported 20

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Bragstad 1979	Tizanidine vs. chlorzoxazone Mean age (years): 37 vs. 37 Female gender: 7/14 vs. 7/13 Race not reported Hospitalized: 2/14 vs. 5/13 Average muscle tension score: 2.57 vs. 2.69 Prior muscle relaxant use: Not reported	Muscle tension, pain intensity, tenderness, limitation of movement, protective posture, interference with normal activities: All rated on 0 (none) to 3 (severe) scale Baseline, 2, 3, 5, and 7 days of treatment	FAIR. Randomization and allocation concealment techniques not described.
Brown 1978	20-64 years old 27/49 female Race not reported Demographics not reported for each intervention group Cyclobenzaprine vs. diazepam Underlying conditions Musculoskeletal strain: 4/16 vs. 4/16 Posttraumatic: 5/16 vs. 6/16 Postoperative: 6/16 vs. 5/16 Other: 1/16 vs. 1/16 Severity or duration: Not reported Prior muscle relaxant use: Not reported	Global evaluation: Worse, no change, slight improvement, moderate improvement, marked improvement Evaluated at 1 and 2 weeks	FAIR. Randomization, treatment allocation, blinding techniques not described; unable to compare baseline characteristics between intervention groups.
Fryda-Kaurimsky 1981	Tizanidine vs. diazepam Mean age (years): 54 vs. 50 Female gender: 6/20 (30%) overall Race not reported Underlying condition Low back syndrome: 50% vs. 60% Low back and cervical syndrome: 30% vs. 20% Cervical syndrome: 20% vs. 20% Severity (severe): 50% vs. 50% Duration of degenerative spinal disease (days): 102 vs. 110 Prior muscle relaxant use: Not reported	Pain: 0 (none) to 3 (severe) Tenderness: 0 (none) to 3 (severe) Muscle spasm: 0 (normal) to 2 (markedly increased) Abnormal posture: 1 (slight, correction possible but slightly painful) to 3 (very marked, correction not possible) Day-to-day activities: 0 (normal) to 3 (immobile) Patient's self-evaluation: 0 (no incapacity) to 3 (severe incapacity) Restriction of movement (centimeters or degrees, measured in various joints) (not abstracted here) Assessed at baseline, 2, 3, 4, 5, and 7 days	FAIR. Randomization, treatment allocation, and blinding techniques not described.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Bragstad 1979	Tizanidine vs. chlorzoxazone Muscle pain (improvement): 1.43 vs. 1.58 (NS) Muscle tension (improvement): 1.86 vs. 2.25 (NS) Tenderness (improvement): 1.36 vs. 1.91 (NS) Limitation of movement (improvement): 1.00 vs. 1.25 (NS) Protective posture (improvement): 1.50 vs. 1.62 Prevention of normal activity (imprvoement): 1.43 vs. 1.64 (NS) Overall assessment/patient (good or excellent):11/14 (79%) vs. 9/13 (69%) Overall assessment/patient (excellent): 8/14 (57%) vs. 3/13 (23%)	Tizanidine vs. chlorzoxazone Any adverse events: 0/14 vs. 2/13 (diarrhea and fatigue) Withdrawal (overall): 0/14 vs. 1/13 Withdrawal (adverse events): None reported	Not reported	
Brown 1978	Cyclobenzaprine vs. diazepam vs. placebo Global evaluation (marked or moderate improvement): 11/16 (69%) vs. 8/16 (50%) vs. 5/17 (29%) (NS for difference between active treatments) Global evaluation (marked improvement): 8/16 (50%) vs. 6/16 (38%) vs. 2/17 (12%)	Cyclobenzaprine vs. diazepam vs. placebo Drowsiness: 7/16 (p<0.05 vs. placebo) vs. 2/16 vs. 0/17 Dry mouth: 8/16 (p<0.05 vs. placebo) vs. 2/16 vs. 0/17 Dizziness: 4/16 (p<0.05 vs placebo) vs. 2/16 vs. 0/17 Withdrawals: None reported	Not reported	
Fryda-Kaurimsky 1981	Tizanidine vs. diazepam Pain (improvement): 1.7 vs. 1.9 Tenderness (improvement): 1.8 vs. 1.8 Muscle spasm (improvement): 1.6 vs. 1.7 Day-to-day activities (improvement): 1.6 vs. 1.6 Patient's self-evaluation (improvement): 1.6 vs. 1.9 Combined scores for six variables pain, tenderness, spasm, abnormal posture, day-to-day activities, and self-evaluation (improvement): 8.5 vs. 9.1 (NS) Efficacy by physician evaluation (complete relief): 8/10 (80%) vs. 8/10 (80%)	Tizanidine vs. diazepam Any adverse effects: 2/10 vs. 5/10 Precordial discomfort: 1/10 vs. 0/10 Dry mouth: 1/10 vs. 1/10 Dizziness and fatigue: 1/10 vs. 5/10 Withdrawals: None	Not reported	

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Hennies 1981	Randomized trial Germany Single center	A: Tizanidine 4 mg tid B: Diazepam 5 mg tid 7 day	Acute painful cervical or lumbar spasm	Liver or renal disease, cardiovascular disease, active infection or malignancy in spine, rheumatic disease, psychologically unstable, or pregnant	Not reported Not reported 30	1 30
Preston 1984	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg po tid B: Methocarbamol 1500 mg po qid C: Placebo 7 days	Localized muscle spasm due to pain secondary to traumatic or inflammatory causes of less than 14 days	Spasm due to disease of the spinal cord, cerebral disease, psychological causes; no injectable analgesics, skeletal muscle relaxants, tranquilizers, sedatives, or anti-inflammatories within last 48 hours, pregnancy, <18 years except with parental consent, other significant co-morbid medical conditions, alcohol or drug abuse, glaucoma	Not reported 232 227	30 197
Rollings 1983	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg po qid B: Carisoprodol 350 mg po qid 8 days	Outpatients between 19 and 65 with acute back strain (no neck involvement), moderate pain and local muscle spasm, tenderness and limited mobility, and <7 days duration	Cervical strain, patients involved in litigation, pregnant women, nursing mothers, women of childbearing potential not using contraceptives, known allergy or intolerance, patients requiring therapy other than bed rest or moist heat, patients requiring other medications for symptoms, known drug abuse, and other serious medical medications	Not reported Not reported 78	20 58

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Hennies 1981	Tizanidine vs. diazepam Mean age (years): 46 vs. 49 Female gender: 11/15 vs. 9/15 Race: Not reported Score for pain (mean): 2.3 vs. 2.2 Score for spasm (mean): 2.3 vs. 2.1	Pain: 0 (absent) to 3 (severe) Tension: Unspecified method Protective posture: Unspecified method Daily living activity: Unspecified method Limitation of lumbar mobility: Centimeters Lasegue test: Degrees Patient self-assessment: Unspecified method Evaluated at baseline, day 3, and day 7	FAIR. Randomization and allocation concealment techniques not described.
Preston 1984	Cyclobenzaprine vs. methocarbamol vs. placebo Mean age (years): 42 vs. 40 vs. 41 Female gender: 59% vs. 63% vs. 52% Non-white: 13% vs. 8% vs. 10% Duration of spasm (days): 3.8 vs. 3.8 vs. 4.3 Severity of muscle spasm (moderate or severe): 100% vs. 100% vs. 100% Prior muscle relaxant use: Not reported	Nine-point ordinal scale 0 (absent) to 8 (very severe) for following: Muscle spasm Local pain and tenderness Limitation of normal motion Interference with normal activities Baseline, interim visit, and at final visit (day 7)	FAIR. Randomization, allocation concealment techniques not described, high loss to follow-up and no intention-to-treat analysis; results excludes patients with initially mild scores from analysis.
Rollings 1983	Cyclobenzaprine vs. carisoprodol Mean age (years): 43 vs. 41 Female gender: 10/28 (36%) vs. 17/30 (57%) Non-white: 13% vs. 11% Pain severity score: 4.07 vs. 3.89 Duration of symptoms: Not reported Prior muscle relaxant use: Not reported	Pain severity: Verbal rating scale (VRS) 1 (none) to 5 (severe) and visual analogue scale (VAS) 0 (none) to 100 (worse) Muscle stiffness: VRS and VAS Activity impairment: VRS and VAS Sleep impairment: VRS and VAS Tension: VRS and VAS Evaluated on days 4 and 8	FAIR: High loss to follow-up and no intention-to-treat analysis.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Hennies 1981	Tizanidine vs. diazepam Muscle tension (number improved): 9/11 vs. 12/15 (NS) Muscle tension (mean improvement in score): 1.5 vs. 1.2 Muscle pain (number improved): 13/14 vs. 11/15 (NS) Muscle pain (mean improvement in score): 1.7 vs. 1.1 Daily living activities (number improved): 13/14 vs. 14/15 (NS) Daily living activities (mean improvement in score): 1.7 vs. 1.4 Self-assessment (number improved): 13/14 vs. 12/15 (NS)	Tizanidine vs. diazepam Any adverse event: 1/15 vs. 0/15 Withdrawals (overall): 1/15 (7%) vs. 0% Withdrawals (adverse events): 1/15 (7%) vs. 0% Somnolence: None reported Dizziness: None reported Weakness: None reported Dry mouth: None reported	Not reported	Most patients on both treatments had improved by day 7.
Preston 1984	Cyclobenzaprine vs. methocarbamol vs. placebo (study only reported results from first interim analysis and excluded patients with initially mild scores) Muscle spasm (absent or mild): 33% vs. 40% vs. 35% (NS for A vs. B) Local pain (absent or mild): 40% vs. 48% vs. 32% (p=0.05 for A vs. B) Limitation of motion (absent or mild): 35% vs. 49% vs. 34% (NS for A vs. B) Interference with daily activities (absent or mild): 41% vs. 48% vs. 32% (NS for A vs. B)	Cyclobenzaprine vs. methocarbamol vs. placebo Any adverse event: 37/87 (42%) vs. 29/94 (31%) vs. 7/46 (15%) Severe adverse event: 14/47 (30%) vs. 7/34 (21%) vs. 0 CNS adverse event (including drowsiness, dizziness): 60/87 (58%) vs. 30/94 (31%) vs. 2/46 (4%) Dry mouth: 8/87 (9%) vs. 1/94 (1%) vs. 1/46 (2%) Withdrawal (overall): 12/87 (14%) vs. 12/94 (13%) vs. 6/46 (13%) Withdrawal (adverse events): 6/87 (7%) vs. 6/94 (6%) vs. 1/46 (2%)	Not reported	By end of trial, most patients (including placebo) had improved. Results only reported for interim (day 1-4) visit.
Rollings 1983	Cyclobenzaprine vs. carisoprodol (difference in scores from baseline) Pain (VRS): 1.6 vs. 1.9 (NS) Muscle stiffness (VRS): 1.5 vs. 1.6 (NS) Activity impairment (VRS): 1.6 vs. 1.7 (NS) Sleep impairment (VRS): 1.3 vs. 1.7 (NS) Tension (VRS): 1.1 vs. 1.0 (NS) Relief (VRS): 3.2 vs. 3.3 (NS) No significant differences in physician ratings for the above, or in assessment of overall improvement	Cyclobenzaprine vs. carisoprodol Any adverse event: 24/37 (65%) vs. 24/39 (62%) Drowsiness: 15/37 (40%) vs. 16/39 (41)% Dizzy: 3/37 (8%) vs. 10/39 (26%) Dry mouth: 14/37 (38%) vs. 4/39 (10%) (p<0.05) Headache: 1/37 (3%) vs. 3/39 (8%) Paresthesia: 0 vs. 3/39 (8%) Constipation: 3/37 (8%) vs. 1/39 (3%) Withdrawal (overall): 9/37 (24%) vs. 11/39 (28%) Withdrawal (due to adverse events): 3/37 (8%) vs 3/39 (8%)	Authors employed by A.H. Robins Company. Not clear if data held by funder.	

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Exclusion Criteria	Screened Eligible Enrolled	Withdrawals or lost to follow-up Analyzed
Scheiner 1978 (1)	Randomized trial U.S. Single center	A: Cyclobenzaprine 30-40 mg/day B: Diazepam 15-20 mg/day C: Placebo 14 days	Moderate to severe neck or low back muscle spasm of local origin and recent (<30 days) onset	Other serious medical or psychiatric conditions, spasticity of neurologic origin, pregnant patients, abnormal lab values, arthritic conditions	Not reported Not reported 96	18 96
Scheiner 1978 (2)	Randomized trial U.S. Single center	A: Cyclobenzaprine 30-40 mg/day B: Diazepam 15-20 mg/day C: Placebo 14 days	Moderate to severe neck or low back muscle spasm of local origin and recent (<30 days) onset	Other serious medical or psychiatric conditions, spasticity of neurologic origin, pregnant patients, abnormal lab values, arthritic conditions	Not reported Not reported 75	10 69

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Population Characteristics	Method of Outcome Assessment and Timing of Assessment	Overall Rating and comments
Scheiner 1978 (1)	Cyclobenzaprine vs. diazepam vs. placebo Mean age (years): 33 vs. 38 vs. 36 Female gender: 10/34 vs. 12/32 vs. 12/30 Non-white: Not reported Duration <7 days: 34/34 vs. 31/32 vs. 26/30 Severity (severe): 6/34 vs. 8/32 vs. 5/30 Location back: 16/34 vs. 15/32 vs. 14/30 Location neck: 18/34 vs. 17/32 vs. 16/30 Posttraumatic: 15/34 vs. 9/32 vs. 13/30 Strain: 13/34 vs. 11/32 vs. 8/30 Other: 6/34 vs. 12/32 vs. 9/30 Prior muscle relaxant use: Not reported	Muscle spasm (consistency), local pain, tenderness, limitation of motion, and limitation of activities of daily living: All assessed using 1 (absent) to 5 (severe) scale Global evaluation: 5 point scale (worse to marked improvement) Assessed at baseline, day 7, and day 14	FAIR: Randomization and allocation concealment techniques not reported; high loss to follow-up in cyclobenzaprine group (12/34).
Scheiner 1978 (2)	Cyclobenzaprine vs. diazepam vs. placebo Mean age (years): 35 vs. 32 vs. 34 Female gender: 6/24 vs. 6/21 vs. 15/24 Non-white: Not reported Duration <7 days: 17/24 vs. 17/21 vs. 13/24 Severity (severe): 1/24 vs. 1/21 vs. 1/24 Location back: 13/24 vs. 10/21 vs. 13/24 Location neck: 11/24 vs. 11/21 vs. 11/24 Posttraumatic: 18/24 vs. 13/21 vs. 14/24 Strain: 5/24 vs. 6/21 vs. 5/24 Other: 1/24 vs. 2/21 vs. 5/24 Prior muscle relaxant use: Not reported	Muscle spasm (consistency), local pain, tenderness, limitation of motion, and limitation of activities of daily living: All assessed using 1 (absent) to 5 (severe) scale Global evaluation: 5 point scale (worse to marked improvement) Range of motion: Goniometry (results not abstracted) Assessed at baseline, day 7, day 10, and day 14	FAIR: Randomization and allocation concealment techniques not reported.

Evidence Table 5. Head-to-head trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Outcomes	Adverse events	Funding Source and Role	Other comments
Scheiner 1978 (1)	Cyclobenzaprine vs. diazepam vs. placebo Mean improvement in score at weeks 1 and 2 Muscle spasm: 1.4 vs. 0.9 vs. 0.5 and 2.5 vs. 1.9 vs. 1.1 Local pain: 1.3 vs. 0.9 vs. 0.4 and 2.4 vs. 1.8 vs. 1.2 Tenderness: 1.4 vs. 1.1 vs. 0.5 and 2.6 vs. 1.8 vs. 1.1 Limitation of motion: 1.5 vs. 1.0 vs. 0.5 and 2.5 vs. 1.8 vs. 0.9 Limitation of activities of daily living: 1.4 vs. 1.0 vs. 0.4 and 2.5 vs. 1.9 vs. 1.0 Differences significant for cyclobenzaprine and diazepam vs. placebo, not significant for cyclobenzaprine vs. diazepam except for tenderness on palpation at week 2 ($p<0.05$), and limitation of motion at weeks 1 and 2 ($p<0.01$) Global evaluation (marked or moderate improvement): 29/34 vs. 28/32 vs. 17/30 Global evaluation (marked improvement): 25/34 vs. 17/32 vs. 4/30 ($p<0.01$ for cyclobenzaprine vs. diazepam or placebo)	Cyclobenzaprine vs. diazepam vs. placebo Withdrawals (overall): 12/34 (35%) vs. 3/32 (9%) vs. 3/30 (10%) Withdrawals (adverse events): None reported Drowsiness: 8/34 vs. 9/32 vs. 3/30 Dry mouth: 10/34 vs. 2/32 vs. 0/30 Dizziness: 3/34 vs. 9/32 vs. 0/30 Ataxia: 0/34 vs. 3/32 vs. 0/30 Nausea: 0/34 vs. 0/32 vs. 1/30 Any side effect: 11/34 (32%) vs. 9/32 (28%) vs. 3/30 (10%)	Editorial assistance provided by Merck, funding source otherwise not clear	
Scheiner 1978 (2)	Cyclobenzaprine vs. diazepam vs. placebo Mean improvement in score at weeks 1 and 2 Muscle spasm: 1.9 vs. 1.5 vs. 0.3 and 2.7 vs. 2.2 vs. 0.5 Local pain: 1.8 vs. 1.3 vs. 0.2 and 2.7 vs. 2.1 vs. 0.4 Tenderness: 2.0 vs. 1.4 vs. 0.2 and 2.7 vs. 2.1 vs. 0.4 Limitation of motion: 2.0 vs. 1.5 vs. 0.2 and 2.8 vs. 2.3 vs. 0.4 Limitation of activities of daily living: 2.0 vs. 1.5 vs. 0.2 and 2.8 vs. 2.2 vs. 0.4 Differences significant ($p<0.01$) for cyclobenzaprine and diazepam vs. placebo, and significant ($p<0.05$) for cyclobenzaprine vs. diazepam except NS for muscle spasm and limitation of motion at week 1 Global evaluation (marked or moderate improvement): 24/24 vs. 18/21 vs. 1/24 Global evaluation (marked improvement): 18/24 vs. 6/21 vs. 1/24 ($p<0.01$ for cyclobenzaprine vs. diazepam or placebo)	Cyclobenzaprine vs. diazepam vs. placebo Withdrawals (overall): 2/26 (8%) vs. 5/24 (21%) vs. 3/25 (12%) Withdrawals (adverse events): None reported Drowsiness: 20/24 vs. 14/21 vs. 1/24 Dry mouth: 11/24 vs. 3/21 vs. 1/24 Dizziness: 4/24 vs. 11/21 vs. 1/24 Ataxia: 0/24 vs. 2/21 vs. 0/24 Nausea: None reported Any side effect: 12/24 (50%) vs. 14/21 (67%) vs. 1/24 (4%)	Editorial assistance provided by Merck, funding source otherwise not clear	

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Aiken 1978b	Randomized trial United States Single center	A: Cyclobenzaprine 10 mg qD (range 20-60 mg qD) B: Placebo 2 weeks intervention	Outpatients with moderate to severe skeletal muscle spasm associated with traumatic strains of the neck and low back	50 44	Cyclobenzaprine vs. placebo Female gender: 12/25 vs. 10/25 Age (>45 years): 3/25 vs. 3/25 Race not reported Posttraumatic: 23/25 vs. 23/25 Neck: 14/25 vs. 15/25 Back: 11/25 vs. 10/25 Severity (severe): 13/25 vs. 6/25	Muscle spasm, limitation of activities of daily living, pain, tenderness: 1 (absent) to 4 (severe) Overall response: worse to excellent Assessed at day 3 or 4, 1 week, and 2 weeks
Baratta 1976	Randomized trial United States Single center	A: Carisoprodol 350 mg QID B: Propoxyphene 65 mg QID C: Placebo 14 days	Patients with low back syndrome	105 94	Average age: A=38, B=36, C=37 Female gender: 18% vs. 31% vs 21% Non-white:Race: 9% vs. 22% vs. 10% Underlying conditions: lumbosacral sprain, cervical sprain, sacroiliac sprain, thoraco-lumbar sprain, thoraco-spinalis sprain Baseline severity and duration not reported Previous muscle skeletal relaxant use not reported	Functional measurements: flexion, extension, rotation, etc. Pain symptoms: active and passive Other symptoms: discomfort, stiffnes and anxiety Sleep patterns: early and middle insomnia and total hours of sleep *All assessed on 4 point scale Global improvement: rated by investigator using 3-point scale ("satisfactory", "mild", or "no relief") Assessments completed at baseline and 2x/week

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Aiken 1978b	FAIR. Allocation concealment, blinding techniques not described.	Cyclobenzaprine vs. placebo Mean scores at 2 weeks Spasm: 1.6 vs. 2.2 (p<0.01) Limitation of motion: 1.4 vs. 2.0 (p<0.01) Limitation of activities of daily living: 1.7 vs. 2.5 (p<0.01) Pain and tenderness: 1.9 vs. 2.5 (p<0.05) Global evaluation (excellent or good): 19/22 vs. 3/22 Global evaluation (excellent): 9/22 vs. 1/22	Cyclobenzaprine vs. placebo Withdrawals (all): 3/25 vs. 3/25 Withdrawals (adverse events): 1/25 vs. 0/25 Any adverse event: 24/25 vs. 12/25 Drowsiness: 21/25 vs. 3/25 Dizziness: 9/25 vs. 6/25 Weakness: 4/25 vs. 3/25 GI upset: 3/25 vs. 1/25 Sweating: 3/25 vs. 0/25 Dry mouth: 1/25 vs. 0/25
Baratta 1976	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Results only for carisoprodol vs. placebo (p<0.01 unless noted) Flexion: 12.3 vs. 5.7 Back extension: 1.2 vs. -0.2 Passive sit-up: 44.4 vs. 13.9 Knee flex on abdomen: 39.3 vs. 6.6 Side bend to knee joint: 1.8 vs. 0.7 Squat off heels: 3.9 vs.1.4 Stiffness relief: 1.0 vs. 0.1 Discomfort relief: 0.8 vs. -0.1 Pain symptoms: no significant differences Sleep patterns: 1.0 vs. 0.2 (p=0.01) for falling asleep; 1.3 vs. 0.8 (p<0.02) in reducing number of awakenings Global improvement (satisfactory): 19/33(58%) vs. 4/29(14%) (p<0.01)	No adverse reactions were recorded for any of the patients in the study

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Baratta 1982	Randomized United States # of centers not reported	A: Cyclobenzaprine 10mg TID B: Placebo 10 days or until patient became asymptomatic	Moderate-severe degree of muscle spasm for not longer than 30 days.	120 117	Cyclobenzaprine vs. placebo Mean age (years): 35 vs. 38 Female gender: 24/58 vs. 24.59 Race not reported 118 acute musculoskeletal strain 2 post-traumatic origin Moderate-severe spasticity Previous muscle relaxant use not reported	Muscle spasm Local pain Tenderness on palpitation Limitation of motion Limitation of activities of daily living *All recorded using 5-point rating scale (1=absent to 5=severe) Assessment #1 completed 2-3 hours post-first dose of test drug; #2 within days 2-4; #3 within days 5-7; #4 within days 8-12
Basmajian 1988	Randomized Canada Multicenter (18)	A: Cyclobenzaprine 5mg bid + diflunisal 500mg bid B: Diflunisal 500mg bid C: Cyclobenzaprine 5mg bid D: Placebo 10 days	Patients with muscle spasm secondary to acute trauma or musculoskeletal strain of 7-10 days' duration.	175 175	Age not reported Gender not reported Race not reported Acute trauma or musculoskeletal strain of 7-10 days' duration Severity not reported Previous muscle relaxant use not reported	Presence of local pain; Presence of muscle spasm; Presence of muscle tenderness on palpation; Limitation of range of motion; Limitation of activities of daily living: Methods of assessments not reported Assessments completed at Baseline and at Days 2, 4 and 7-10

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Baratta 1982	FAIR. Allocation concealment method not reported.	Flexeril vs. Placebo Muscle spasm mean decrease (mean score difference) Days 2-4: -0.7 vs. -0.2 (p<0.01) Days 5-7: -1.4 vs. -0.8 (p<0.01) Days 8-12: -1.9 vs. -1.2 (p<0.01) Local pain mean decrease (mean score difference) Days 2-4: -1.1 vs. -0.6 (p<0.01) Days 5-7: -1.6 vs. -1.0 (p<0.01) Days 8-12: -2.0 vs. -1.5 (p<0.01)	Withdrawal (due to adverse events): 0 Any adverse event: 25/58(43%) vs. 17/59(29%) <u>Frequent adverse events</u> A: n=58; B: n=59 Dizziness: 36% vs. 15% (p<0.01) Drowsiness: 31% vs. 10% (p<0.01) Nausea: 12% vs. 3% (NS) Dry mouth: 10% vs. 5% (NS) Sweating: 3% vs. 0 (NS) GI upset: 2% vs. 3% (NS) Fatigue: 2% vs. 0 (NS) Weakness: 2% vs. 2% (NS) Epigastric distress: 0 vs. 2% (NS)
Basmajian 1988	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Presence of local pain: No significant between groups differences Presence of muscle spasm: No significant between groups differences Presence of muscle tenderness on palpation: No significant between groups differences Limitation of range of motion: No significant between groups differences Limitation of activities of daily living: No significant between groups differences Global response: No significant between groups differences except at Day 3(improvement rates): A=32/46(70%), B=24/40(60%), C=26/44(59%); (p=0.006)	Withdrawals: not reported Overall incidence: "no significant adverse events attributable to therapy"

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Bennett 1988	Randomized United States Multi-center (2) Outpatient rheumatology clinics	A: Cyclobenzaprine: 10 mg qpm; titrated to a maximum dose of 40 mg/day B: Placebo 12 weeks	Musculoskeletal pain of at least three months' duration; presence of at least 7 tender points; increased shoulder/neck tension; morning fatigue secondary to sleep disturbance; am stiffness/aching accentuation	120 120	97% female Mean age of 49 Race not reported 44% primary fibrositis 56% fibrositis associated with trauma or arthritis Previous muscle relaxant use not reported	Patient symptoms: weekly assessment of local pain, sleep quality, am stiffness, and fatigue using a visual analog scale (1-10) Tender point analysis: rated using 5-point scale (1=absent; 5=severe) at weeks 1, 2, 4, 8 and 12 Muscle tightness/musculoskeletal pain: rated using 5-point scale (1=absent; 5=severe) at weeks 1, 2, 4, 8 and 12 Overall response to therapy: assessed by physician
Bercel 1977	Randomized United States Single Center	A: Cyclobenzaprine, 20-40 mg (mean dose not reported) B: Placebo 2 weeks	Cervical or lumbosacral osteoarthritis (confirmed by x-ray) Moderate-severe muscle spasm for 30 days or longer	54 54	Mean age=54.4 56% female Race not reported 31 posterior neck spasm 23 lower back spasm Moderate-severe muscle spasticity Previous muscle relaxant use not reported	Muscle spasm duration (absent, mild, moderate, moderately severe, or severe) Global evaluation of therapeutic response (markedly, moderately, slightly) Ratings completed before and after treatment

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Bennett 1988	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, not performed. Intention-to-treat analysis utilized.	Cyclobenzaprine (A) vs. placebo (B) Patient symptoms: significant improvements in pain severity (A>B; p<0.02) and sleep quality (A>B; p<0.02) at weeks 2-12; no between-groups differentiation for morning stiffness; improvement in fatigue at weeks 2 and 4 (A>B; p<0.02) Tender point analysis: significant reduction in number and severity of tender points at week 2 and 4 (A>B; p<0.03) Muscle tightness/musculoskeletal pain: significant global pain improvement at weeks 2 and 4 (A>B; p<0.05) Overall response to therapy (n=117): A>B; p<0.04	Cyclobenzaprine vs. placebo Withdrawals (overall): 35% vs. 60% Withdrawals (due to adverse events): 8% vs. 5% Any adverse event: 89% vs. 64% (p=0.002) Frequent adverse events (n=62 vs. 58): dry mouth (57 vs. 17); drowsiness (34 vs. 17); constipation (8 vs. 2); dizziness (7 vs. 5); palpitation (7 vs. 4); tachycardia (5 vs. 4); fatigue (5 vs. 2); depression (5 vs. 2); headache (3 vs. 9); nausea (2 vs. 7); generalized pain (2 vs. 4)
Bercel 1977	FAIR. Randomization technique not reported; treatment allocation concealment techniques not reported	Cyclobenzaprine vs. placebo Muscle spasm duration improvement Week 1: 81% vs. 41% (significance not reported) Week 2: 77% vs. 41% (significance not reported)	Withdrawals (due to adverse events): none <u>Frequent adverse events:</u> Cyclobenzaprine (n=27) vs. Placebo (n=27) Drowsiness: 9(33%) vs. 5(19%) Dry mouth: 1(4%) vs. 4(15%) Dizziness: 3(11%) vs. 0 Nausea: 1(4%) vs. 0 Ataxia/weakness: 1(4%) vs. 1(4%)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Berry 1988	Randomized United Kingdom Multicenter (7)	A: Tizanidine, 4 mg TID + ibuprofen, 400 mg TID B: Placebo + ibuprofen, 400 mg TID 7 days	Patients with low back pain of at least moderate severity, of recent onset, with painful limitation of movement of the lumbar spine; aged 18-65	105 94	Tizanidine vs. placebo Mean age (years): 43 vs. 42 Female gender: 47% vs. 43% Race: not reported Functional disability and underlying severity: not reported Diagnostic etiologies: not reported	Limitation of movement: 4-point scale (severely, moderately, mildly restricted, not restricted) Sciatica: 4-point scale (absent, mild, moderate, severe) Pain: 4-point scale (none, mild, moderate, severe) Subjective assessments: overall helpfulness and whether patient was better or worse were rated by unspecified methods Assessments completed at baseline and days 3 and 7
Berry 1988	Randomized United Kingdom Multicenter (20)	A: Tizanidine, 4 mg tid B: Placebo 7 days	Patients aged 18-70 years with acute low-back pain of at least moderate severity, of recent onset, with or without sciatica, together with painful limitation of movement of the lumbar spine	112 96	Tizanidine vs. placebo Mean age (years): 44 vs. 38 Female gender: 49% vs. 49% Race: not reported Functional disability and mean severity: not reported Prior muscle relaxant use: Not reported	Restriction of movement: 4-point scale (severely, moderately, mildly restricted, not restricted) Sciatica: 4-point scale (absent, mild, moderate, severe) Pain: 4-point scale (none, mild, moderate, severe) on movement, at rest and at night Subjective assessments: overall helpfulness (no help, some help or very helpful) and rating of patient's condition compared to baseline (much better, better, same, worse, much worse) Assessments completed at baseline and days 3 and 7

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Berry 1988	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, intention-to-treat analysis not performed.	Tizanidine + ibuprofen (A) vs. placebo + ibuprofen (B) Pain at night (percent with moderate-severe severity): 18% vs. 37% (p=0.025) Pain at rest: no treatment differences Pain on movement (mean changes in diary visual analogue score assessment): 23 vs. 19 (p=0.029) Restriction of movement: no significant differences between groups Sciatica (marked improvement): A>B (p=0.002) at Day 3 of patients with moderate to severe pain at baseline Helpfulness of tablets (helpful): 88% vs. 69% (p=0.05) at day 3; between group difference not significant at day 7 Overall improvement: No significant between group differences reported	Withdrawals (due to adverse events): 6 Frequent adverse events (n=51) Central nervous system: A=17(33%), B=5(9%); p=0.025 Gastro-intestinal: A=3(6%), B=11(20%); p=0.002 Types of CNS adverse events in Group A: Drowsiness(n=10), Dry mouth(n=3), Tiredness(n=2), Light-headedness(n=2), Sedation(n=1), Vertigo(n=1)
Berry 1988	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Tizanidine vs. placebo Pain at night: no significant between group differences on patients' daily visual analogue scale assessments or four-point scale assessments Pain at rest: no significant between group differences shown in patients' diary visual analogue scale assessments Restriction of movement: no significant between group differences patients' daily visual analogue scale assessments or four-point scale assessments Sciatica: no significant between group differences Helpfulness of tablets: no significant between group differences	Withdrawals (due to adverse events): A=5/59(8%), B=1/54(2%) Overall incidence: A=24(41%), B=11(21%) Frequent adverse events Drowsiness and other central nervous system side-effects 19/59 (32%) (22% drowsiness) vs. 5/53(9%); p=0.003 Gastro-intestinal side-effects: B>A (p=0.018)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Bianchi 1978	Randomized U.S. Single center	A: Cyclobenzaprine 10 mg tid B: Placebo 14 days	At least moderately severe acute muscle spasm of local origin	48 35	Cyclobenzaprine vs. placebo Female gender: 8/24 vs. 14/24 Mean age (years): 47 vs. 45 Race: not reported Mean duration (days): 4.1 vs. 3.5 Severity (moderate-severe): 19/24 vs. 21/24 Location back: 17/24 vs. 19/24	Muscle consistency, spontaneous local pain, tenderness, limitation of motion, limitation of activities of daily living, global evaluation: 1 (absent) to 5 (severe) Assessed during week 1 and at day 14
Borenstein 1990	Randomized Open-label # centers not reported	A=Naprosyn; 500 mg/day initially then 250 mg q 6 hrs B=Naprosyn + cyclobenzaprine 10 mg po q 8 hrs 14 days	Patients with mild-moderate acute low back pain (duration of 10 days or less), between the ages of 18 and 60.	40 40	Naprosyn vs. naprosyn + cyclobenzaprine Mean age (years): 32 vs. 37 Female gender: 35% vs. 25% Race not reported Acute mild-moderate low back pain Mean duration of pain before treatment (days): 2.5/3 Previous muscle relaxant use not reported	Functional Capacity: 0=usual activities performed without discomfort or difficulty to 3=usual activities could not be performed-scale completed daily by patient Muscle Spasm:: 0=none to 3=severe Tenderness to palpitation: 0=no pain to 3=withdraws Pain: Numerical scale: 0-20; also 0 (no pain) to 3 (severe pain) scale" - both scales completed daily Lumbosacral spine range of motion; straight-leg raising test; Schober's test; degree of difficulty in arising from a supine position Assessments completed at initial evaluation and at three follow-up visits (days 3, 7 and 14) Overall Efficacy: 0=poor to 4=excellent completed at final assessment by patient Overall remaining limitation of function: 0=none to 4=incapacitating

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Bianchi 1978	FAIR. Blinding, allocation concealment techniques not reported.	Cyclobenzaprine vs. placebo Mean scores at day 7 and day 14 Muscle consistency: 1.3 vs. 2.2 (p<0.01); 1.0 vs. 1.3 (NS) Pain: 1.3 vs. 1.9 (p<0.05;1.0 vs. 1.3 (NS) Tenderness: 1.5 vs. 2. 3 (p<0.01) and 1.0 vs. 1.3 (NS) Limitation of motion: 1.5 vs. 2.3 (p<0.01); 1.0 vs. 1.3 (NS) LImitation of activities daily limitation:1.4 vs. 2.0 (p<0.05); 1.0 vs. 1.2 (NS) Global evaluation (complete or satisfactory relief): 20/22 vs.14/20 (p<0.01); 20/20 vs. 15/15 (NS) Global evaluation (complete relief): 17/22 vs. 6/20; 19/20 vs. 11/15	Cyclobenzaprine vs. placebo Any: 10/24 vs. 5/24 Withdrawals (overall): 4/24 vs. 9/24 Withdrawals (adverse events): None Drowsiness: 7/24 vs. 2/24 Dizziness: 1/24 vs. 1/24 Dry mouth: 2/24 vs. 0/24 Gastric pain: 0/24 vs. 1/24
Borenstein 1990	POOR. Randomization, allocation concealment not described. Open-label study.	Naprosyn vs. naprosyn + cyclobenzaprine Functional Capacity (cumulative score for intervention): 15 vs. 9 (NS) Muscle Spasm: 3 vs. 2 (p=<0.05) Tenderness: 3 vs. 2.5 (p=<0.05) Days to resolution of pain: No significant difference between groups in Patient rating (12.5 vs. 8.5) or Physician Rating (14 vs. 7) No significant difference between groups in Days to maximum anterior flexion/extension (14 vs. 7) or Days to sit without pain (7 vs. 5) Schober's test range (cm): 2.0-7.0 vs. 4.5-6.0 (p<0.05) Other assessment results not reported	Naprosyn (n=20) vs. naprosyn + cyclobenzaprine (n=20) Withdrawals not reported Any adverse event: 4/20 vs. 12/20 (p<0.05) Drowsiness: 0 vs. 3/20 Dyspepsia: 1/20 vs. 2/20 Nervousness: 0/20 vs. 2/20 Others (reported by 1 patient each): abdominal pain, constipation, headaches, dizziness, diarrhea, dyspepsia/drowsiness, dyspepsia/diarrhea, dispepsia/dizziness

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Carette 1994	Randomized Canada Multicenter (11)	A: Amitriptyline 10mg/day week 1, 25 mg/day weeks 2-12, 50 mg/day for last 12 weeks B: Cyclobenzaprine 10 mg/day week 1, 20mg/day weeks 2-12, 10 mg qam and 20mg qpm for last 12 weeks C: Placebo 6 months	18 years of age or older; American College of Rheumatology (1990) criteria; Score equal to or greater than 4 on at least one of two visual anolog scales measuring pain and global assessment of symptoms; normal lab results	208 186	Amitriptypline vs. cyclobenzaprine vs. placebo Mean age (years): 44.1 vs. 43.4 vs 47.1 Female gender: 92.9 vs. 95.1 vs. 92.9 Race not reported Fibromyalgia Duration of fibromyalgia (months): 60 vs. 36 vs. 60 months Patient global evaluation: 70.0 vs. 69.6 vs. 72.6	Visual analog assessments: Pain(0=none; 10=severe); Fatigue(0=none; 10=severe fatigue); Sleep(0=no difficulty; 10=extreme difficulty); Feeling on awakening(0=feeling find and refreshed; 10=feeling exhausted); Morning stiffness(0=none; 10=very severe); Global assessment of fibromyalgia (0=not troublesome at all; 10=extremely troublesome) McGill Pain Questionnaire Functional disability: Sickness Impact Profile (SIP); Health Assessment Questionnaire (HAQ) Psychological status: Arthritis Impact Measurement Scales (AIMS); MMPI Fibromyalgia point tenderness: 9-kg dolorimeter; global assessment of fibromyalgia using 10-cm visual analog scale (0=doing extremely well; 10=doing extremely poorly)
Casale 1988	Randomized Italy Single center	A: Dantrolene sodium 25 mg/day B: Placebo 4 days	Patients suffering from chronic low back pain in the acute phase	20 20	Dantrolene (n=10) vs. placebo (n=10) Mean age (years): 47 vs. 47 Female gender: 30% vs. 20% Race not reported Illness duration (days): 12.4 vs. 14.7 Previous muscle relaxant use not reported	Muscle spasm: measured by means of manual semiotic maneuvers Pain behavior: measured by Scott and Huskinsson's visual analog scale (VAS) Muscle force: measured at knee and hip

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Carette 1994	FAIR. Adequate method of randomization (table of random numbers) in blocks of 5; allocation concealment not described.	Amitriptyline vs. placebo results only One-month improvement: 21% vs. 0% (p=0.002) Six-month improvement: 36% `vs. 19% (p=0.08) Visual analog scale scores: Significant improvement for each variable (no data provided) McGill Pain Questionnaire: No significant difference except pain rating index at month 1 (no data) for cyclobenzaprine Functional disability (SIP, HAQ): No significant differences except SIP physical dimension score at month 3 (no data) for cyclobenzaprine Psychological status (AIMS, MMPI): No significant AIMS scores differences	Amitriptyline vs. cyclobenzaprine vs. placebo Withdrawals (overall): 14/82 vs. 24/78 vs. 14/40 Withdrawals (due to adverse events): 5/82 vs. 11/78 vs. 2/40 Any adverse events: 95% vs. 98% vs. 62% Frequent adverse events: somnolence (4 vs. 3 vs. 1); dizziness (0 vs. 5 vs. 1); abdominal pain (1 vs. 3 vs. 0); rash (1 vs. 1 vs. 0); headache (0 vs. 1 vs. 0); weight gain (1 vs. 0 vs. 0)
Casale 1988	FAIR. Inadequate description of randomization, allocation concealment, and blinding techniques.	Dantrolene vs. placebo Muscle spasm (improvement): 85% vs. 10% by day 3 (p<0.001) Pain behavior (improvement): 90% at 3 days and 100% at 4 days vs. 40% (p<0.001; VAS pain measurement decrease in 50% vs. 8.6% (p<0.001) Muscle force: extension of the knee improvement in 77% vs. 8% (p<0.01)	Indication that patients did not report any weakness. No other information provided

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Cullen 1976	Randomized United States Single center	A: Carisoprodol 350 mg qid B: Placebo 10 days	Patients with acute, traumatic conditions affecting the cervical, thoracic and lumbar regions of the back	65 63	Carisoprodol vs. placebo Mean age (years): 41 vs. 37 Female gender: 12/32 vs. 11/33 Non-white: 0/32 vs. 1/33 Primary diagnoses: Lumbosacral, cervical, sacroiliac, or thoracic sprain	Muscle pain: method not reported Muscle spasm: method not reported Limitation of motion: method not reported Patient improvement: rated on 4-point scale (none to severe) Global improvement: rated on 6-point scale (complete relief to worsened considerably) Assessments completed pretrial and on days 5 and 10
Dapas 1985	Randomized United States Multicenter	A: Baclofen, 30-80 mg/day B: Placebo 14 days	Paravertebral muscle spasm and functional disability of less than 2 weeks' duration and at least moderate severity	200 178	Baclofen vs. placebo Mean age: 42 Female gender: 48% vs. 56% Race: Not reportedGender: Pain severity Moderate: 77/200(39%) Severe or extreme: 123/200(61%) Prior muscle relaxant use not reported	Efficacy variables included: 1) Lumbar pain; 2) Tenderness; 3) Paravertebral muscle spasm; 4) Interference with daily activity; 5) Global; 6) Physician's opinion; 7) Patient's opinion; 8) Active straight leg raising (degrees); 9) Forward flexion (inches) Assessment methods were not reported for any efficacy variables Assessments were completed at baseline and on two additional occasions during 14-day treatment period

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Cullen 1976	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described.	Carisoprodol (A) vs. placebo (B) Muscle pain (average) at Day 5: 2.1 vs. 2.7, p<0.01 At Day 10: 1.3 vs. 2.0, p<0.01 Muscle spasm (average) at Day 5: 1.5 vs. 2.2, p<0.01 At Day 10: 1.2 vs. 1.7, p<0.01 Limitation of motion (average) at Day 5: 1.6 vs. 2.4, p<0.01 At Day 10: 1.1 vs. 1.8, p<0.01 A=1.1, B=1.8 (p<0.01) Global improvemen (complete remission): 72% vs. 36% (p<0.01)	Carisoprodol (A, n=32) vs. placebo (B, n=33) Withdrawals (due to adverse events): A=1(dizziness), B=2(generalized giant hives, subarachnoid hemorrhage) Frequent adverse events Drowsiness: A=4, B=1 Dizziness: A=6, B=1
Dapas 1985	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	In patients with 'severe' initial pain: A>B, (p<0.05) for all efficacy variables at Visit 2, except paravertebral muscle spasm and forward flexion; and for all efficacy variables at Visit 3 In patients with 'moderate' initial pain: A>B, (p<0.05) for 'Interference with daily activities' and 'Global limitation of function' at visit 2; no other significant between group differences were observed at visit 2 or 3	Baclofen vs. placebo Withdrawals (due to adverse events): 17/98 vs. 0/97 Any adverse events: 68% vs. 30%, p not reported but described as "significant" Frequent adverse events Sleepiness/fatigue: 49% vs. 21% Dizziness/lightheadedness: 28% vs. 2% Vertigo: 10% vs. 0% Nausea: 38% vs. 13% Dry mout: 5% vs. 1% Other adverse events occurring in < 10% of patients not reported here shown in table 4 of study

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Diamond 1966	Randomized U.S. Single center	A: Metaxalone 800 mg qid B: Placebo (lactose) 10 days	Muscle spasm, pain, tenderness, and restriction of motion of acute onset, location not specified	100 100	Metaxalone vs. placebo Age range (years): 17-89 vs. 16-77 Female gender: 'Similar' Race: Not reported Baseline severity: Not reported Prior muscle relaxant use: Not reported	Muscle spasm: 5 point scale (worse to excellent) Pain: 4 point scale (not present prior to therapy, completely relieved by therapy, partially relieved by therapy, or unaffected by therapy) Assessed daily
Fogelholm 1992	Randomized crossover trial Finland Single center	A: Tizanidine, 6 mg/day to 18 mg/day B: Placebo 6 weeks intervention; 2 weeks washout; 6 weeks crossover	Women less than 60 years of age who had been treated in the past few years for chronic tension-type headache in the outpatient clinic of a neurology department	45 37	Gender: 100 percent female Median age: 47 years Race: not reported Baseline severity: not reported Prior muscle relaxant use not reported	Daily headache severity: documented in patient diary by marking a Visual Analogue Scale (VAS) of 100 mm (0 mm=no headache; 100 mm=the most severe headache) and also using a 5-point Verbal Rating Scale (VRS) (1=no headache; 5=most severe headache)
Gold 1978	Randomized United States Single center	A: orphenadrine 100 mg BID B: phenobarbital 32 mg BID C: placebo 7 days	Patients with moderate-severe low-back syndrome pain that had been precipitated within 48 hours of study entry and was causing some degree of disability regarding work or normal activities	60 60	Age not reported Gender not reported Race not reported Severity not reported Previous muscle relaxant use not reported	Symptomotology/pain intensity: method not specified Pain relief: method not specified Assessments completed at days 2, 4 and 7

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Diamond 1966	FAIR. Allocation concealment technique not described.	Metaxalone vs. placebo Spasm (excellent response): 11/50 (22%) vs. 12/50 (24%) (NS) Spasm (good or excellent response): 26/50 (52%) vs. 23/50 (46%) (NS) Pain (completely relieved): 14/50 (28%) vs. 13/50 (26%) (NS) Pain (completely or partially relieved): 33/50 (66%) vs. 36/50 (72%) (NS)	Not clear ('minor and related to vomiting and nausea')
Fogelholm 1992	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Tizanidine vs. placebo Daily headache severity Visual Analogue Scale (VAS) median sum: 408 vs. 680, p=0.018 Verbal Rating Scale (VRS) six-week sum: 70 vs. 81, p=0.012 Global Rating (milder headache): 90 vs. 60, p=0.001 Analgesic use (median # tablets): 4 vs. 10, p=0.001	Tizanidine vs. placebo Withdrawals (overall): 4/37 vs. 3/37 (1 not specified) Withdrawals (adverse events): 2 vs. 0 Tolerability (ratings of 'good' or 'moderately good'): 90% vs. 100%, p=0.007
Gold 1978	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described, outcomes assessment and patient population not described.	Orphenadrine vs. phenobarbital vs. placebo Overall improvement symptomotology/pain intensity A=7/20(35%)* B=3/20(15%)* C=0/20(0%) *>Placebo(p<0.01) Pain relief (at 48 hours) A=9/20(45%)* B=3/20(15%) C=4/20(20%) *>Phenobarbital or placebo (p<0.01)	Withdrawals not reported Any adverse effects A: 5/20(25%) B: 2/20(10%) C: 1/20(5%) <u>Frequent adverse events</u> A: 5 patients complained of heartburn, dry mouth, slight drowsiness or "high" feelings with shakiness or insomnia B: 2 patients complained of drowsiness C: 1 patient complained of sleepiness

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Hindle 1972	Randomized United States Single center	A: carisoprodol 350 mg TID B: butabarbital 15 mg/day tid C: Placebo	Low back pain, not otherwise reported	48 43	Carisoprodol vs. batbarbital vs. placebo Gender (overall): 44% female Mean age (years): 37 vs. 35 vs. 44 Race: 100% hispanic Duration of symptoms 0-12 hours: 6% vs. 19% vs. 13% 12-24 hours: 88% vs. 69% vs. 75% 24-48 hours: 6% vs. 13% vs. 13%	Pain: 4-point scale (1=none; 4=severe) Spasm: 4-point scale (1=none; 4=severe) Interference with daily activities: 4-point scale (1=none; 4=severe) Limitation of motion: 4-point scale (1=none; 4=severe) Anxiety/tension: 4-point scale (1=none; 4=severe) Degree of limitation of motion: "finger to floor" test Pain intensity: 100 point VAS Global evaluation: assessment completed by investigator on 5-point scale (Excellent, Good, Fair, Poor, Worse) Assessments completed at baseline and at days 2 and 4
Lance 1972	Randomized crossover Australia Single center	A: Cyclobenzaprine, 30-60 mg/day B: Placebo One month	Chronic tension headache, not otherwise reported	20 20	Age range: 19-66 Female center: 60% Race: not reported Illness duration range: mean 8 years Headache characteristics: 19/20(95%) bilateral; 13/20(65%) bifrontal; 2/20(10%) bitemporal; 1/20(5%) occipital; 3/20(15%) "all over the head"	Headache severity: rated on 3-point scale ("virtually headache free", "condition more than 50% improved", "condition unchanged")

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Hindle 1972	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described. Randomization conducted using a table of random numbers	Carisoprodol vs. placebo (average improvement at day 4) Pain: 1.4 vs. 0.0 (p=0.01) Spasm: 1.3 vs. 0.1 (p=0.01) Interference with daily activities: 1.9 vs. -0.3(p<0.01) Limitation of motion: 1.7 vs. 0.0 (p<0.01) Anxiety/tension: 1.0 vs.- 0.2 (p<0.01) Degree of limitation of motion: 19.6 vs. -1.3 (p=0.01) Pain intensity: 70.5 vs. 1.5 (p<0.01) Global evaluation: 1.5 vs. 0.0 (p<0.01) *Group B (Butabarbital) outcomes were not abstracted	Carisoprodol vs. placebo Withdrawals (due to adverse events): None Adverse events: None reported
Lance 1972	POOR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described	<u>Cyclobenzaprine vs. placebo</u> <u>Headache severity</u> Virtually headache free: 25% vs. 0 More than 50% improved: 25% vs. 25% No change: 35% vs. 70% Withdrew: 15% vs. 5%	Withdrawals (due to adverse events): 0 vs. 1/20 Frequent adverse events (n=20) Drowsiness: A=4, B=5 Insomia: A=0, B=1 Heaviness in legs: A=1, B=0 Nausea: A=1, B=2 Epigastric discomfort: A=1, B=0 Dizziness: A=1, B=2 Dry mouth: A=4, B=0 Weight gain: A=1, B=1 Constipation: A=1, B=0 Frequency of micturition: A=1, B=0 Tremor: A=1, B=0 Blocked nose: A=2, B=1 Blurred vision: A=0, B=1

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Latta 1989	Randomized crossover trial U.K. Single center	A: Orphenadrine 100 mg qhs B: Placebo 1 month intervention, 1 month crossover	Elderly patients in care facilities with painful nocturnal leg cramps	59 59	Mean age (years): 64 Female gender: 35/59 Race: Not reported Baseline severity of nocturnal leg cramps: Not reported Previous muscle relaxant use: Not reported	Number of nocturnal leg cramps in a 1 month period
Lepisto 1979	Randomized Finland Single center Inpatient	A: Tizanidine 2 mg/day (n=15) B: Placebo (n=15) 7 days	Between age 18 and 62; suffering from moderate-severe muscle spasm of the lumbar (26 patients) or thoracic (4 patients) regions	30 28	Tizanidine vs. placebo Mean age (years): 42.5 vs. 40.8 Female gender: 47% vs. 53% Race not reported Lumbar muscle spasm: 87% vs. 87% Thoracic muscle spasm: 13% vs. 13% Previous muscle relaxant use not reported	The following were rated using a 4-point scale (absent, slight, moderate, severe): Pain in the back; Tenderness on palpation; Muscle tension; Limitation on movement; Protective posture Straight leg raising: measured in degrees Assessments performed before study entry and at days 2, 3, 5 and 7
McGuinness 1983	Randomized England # of centers not reported	A: Orphenadrine + paracetamol, doses not reported B: Paracetamol alone Duration appears to be 10 days	Male or female patients; aged 18-70; suffering from painful musculoskeletal disorders	32 28	Orphenadrine + paracetamol vs. paracetamol Female gender: 64% vs. 36% Mean age (years): 35.7 vs. 41.9 Race: not reported <u>Diagnostic etiologies</u> Back pain: 57% vs. 57% Other pain: 43% vs. 43%	Assessments were made using a 4-point scale of severity, ranging from normality to severe distress and included (1) Pain; (2) Stiffness; and (3) Functional impairment These evaluations were carried out on the first attendance and at days 5 and 10

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Latta 1989	FAIR. Randomizaton, allocation concealment, blinding techniques not described.	Orphenadrine vs. placebo (results of first intervention) Mean number of nocturnal leg cramps/1 month: 3.28 vs. 9.93 (p<0.0001)	No episodes of lightheadedness, dizziness, dry mouth, excess somnolence reported Any adverse event: 2/59 on orphenadrine Withdrawals (adverse events): None reported
Lepisto 1979	FAIR. Randomization, allocation concealment, blinding techniques not described.	Pain in the back: no significant group differences Muscle tension (mean score decrease): Day 3=1.60 vs. 0.93 (p-value significant, but not reported); Day7=2.27 vs. 1.58 (p-value significant, but NR) Tenderness on palpation (mean score decrease): Day 2=0.53 vs. 0.27(p-value significant, but NR); Day 3=1.00 vs. 0.73(p-value significant, but NR) Limitation on movement: no significant group differences Protective posture: no significant group differences Straight leg raising (mean score decrease): Day 2=13 vs. 1.7(p-value significant, but NR) Physician's ratings: A better than B(p<0.001)	Tizanidine vs. placebo Any adverse event: 33% vs. 40% <u>Frequent adverse events</u> Light somnolence: 5/15 vs. 1/15 Dizziness: 0/15 vs. 3/15 Nausea: 0/15 vs. 1/15 Sweating: 0/15 vs. 1/15 Dry mouth: None reported
McGuinness 1983	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	<u>Orphenadrine + paracetamol vs. paracetamol</u> <u>Pain (mean score improvement at day 10):</u> 1.2 vs. 0.8 <u>Stiffness (mean score improvement at day 10)</u>: 1.8 vs. 0.6 Function (mean score improvement at day 10): 2.0 vs. 1.0	Withdrawals (due to adverse events): 1(nausea) on combination No other adverse event information provided

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Murros 2000	Randomized Finland # of centers: not reported	A: Tizanidine modified release (MR), 6 mg/day B: Tizanidine MR, 12 mg/day C: Placebo 6 weeks	Men and women, aged 18 or older, who fulfilled the International Headache Society criteria for chronic tension type headache (CTTH)	201 160	Tizanidine 6 mg vs. tizanidine 12 mg vs. placebo Mean age (years): 41 vs. 46 vs. 45 Female gender: 77% vs. 73% vs. 74% Race: not reported Mean headache duration (months): 90 vs. 116 vs. 92	Headache severity: measured using visual analogue scale (VAS) Days free of headache: method of measurement unspecified Daily duration of headache: method of measurement unspecified Use of paracetamol: method of measurement unspecified Assessments completed at weeks 2, 4 and 6
Quimby 1989	Randomized trial U.S. Single center	A: Cyclobenzaprine 10 mg qhs titrated to 30 mg qhs + 10 mg qam B: Placebo 10-14 day washout, 6 weeks intervention	Fibromyalgia syndrome and no evidence of secondary causes of pain	45 40	Female gender: 40/40 Mean age (years): 45 Race: not reported Mean duration: 11 years Mean number of tender points: 7 No significant differences between groups for baseline severity, depression, sleep scales	Depression: Beck depression inventory Fatigue, stiffness, pain, sleep, overall rating: Minus 1 (got worse) to 3 (marked improvement) Assessed at baseline, 3 weeks, and 6 weeks

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Murros 2000	FAIR. Randomization, allocation concealment, blinding techniques not described.	VAS: no significant group differences Days free of headache: no significant group differences Daily duration of headache: no significant group differences Use of paracetamol: no significant group differences	Withdrawals (due to adverse events): 14, group not specified Withdrawals (overall): 25, group not specified Frequent adverse events Tiredness: *A+B=21(17%) vs. C=9(15%) Dry mouth: *A+B=27(22%) vs. C=0 Tolerability (poor): *A+B=12/105 vs. 2/55 *A+B=all patients on active drug
Quimby 1989	FAIR. Randomization and allocation concealment techniques not described	Fatigue: no significant group differences Pain: no significant group differences Patient rated stiffness and aching: favored cyclobenzaprine (p<0.05) Patient rated poor sleep: favored cyclobenzaprine (p<0.05) Patient overall rating: favored cyclobenzaprine (p<0.05)	Cyclobenzaprine vs. placebo Withdrawals (overall): 2/23 vs. 3/22 Withdrawals (adverse events): 1/23 vs. 1/22 Dry mouth: 13/19 vs. 6/18 Lightheadedness, weakness, fatigue: Not reported

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Reynolds 1991	Randomized crossover Canada Single center Inpatient/Outpatient sleep disorders clinic	A: Cyclobenzaprine 10 mg TID B: Placebo 2 week washout, 4 weeks treatment, 2 weeks washout, 4 weeks crossover	Fibromyalgia and no previous cyclobenzaprine	12 9	Female gender: 83% Mean age: 43 Race: not reported Fibromyalgia severity: not reported	Tender point severity count: 16 anatomatic regions rated using 5-point scale (1=absent; 5=severe) Pain: 7-point scale (0-no pain; 6=worse possible pain) Fatigue: unspecified questionnaire which consisted of 7 statements (1=full of energy; 7=totally physically exhausted) Sleepiness: Stanford Sleepiness Rating Scale Sleep measurements: included Total sleep time, Latency Stage 2, Latency REM, Sleep efficiency, Alpha-non-REM, Movements, Stage Changes
Salvini 1986	Randomized Italy Single center	A: Ibuprofen 200 mg TID + dantrolene 25 mg/day B: Ibuprofen 200 mg TID Eight days	Not reported	60 59	Low back pain (LBP) (n=30) Mean age (years): 47.1 Female gender: 53% Race not reported Cervicobrachialgia (CBA) (n=30) Mean age (years): 53.2 Female gender: 37% Race not reported Severity and duration of symptoms not reported.	Active and passive articular mobility: in angular degrees Muscle contracture: 4-point scale (0=absent; 3=severe) Muscle strength: 5-point scale (0=normal; 4=paralysis) Pain on movement: 4-point scale (0=absent; 3=severe without movement) Rest pain: 4-point scale (0=absent; 3=severe and constant) Physician judgment of effect: visual analog scale Patient judgment of effect: visual analog scale Assessments performed at days 0, 4 and 8

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Reynolds 1991	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Tender point severity count: no significant between group differences Pain: no significant between group differences Fatigue: no significant between group differences for am; A=4.4, B=5.1; p<0.05 Sleepiness: no significant between group differences Sleep measurements: no significant between group differences	Withdrawals (overall): 0 vs. 1 (1 withdrew during washout) Withdrawals (adverse events): 0 vs. 1 (excess sleepiness) Overall incidence: not reported Frequent adverse events: not reported
Salvini 1986	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Dantrolene (A) vs. placebo (B) Low back pain patients Muscle contracture (after 4 days): A>B(p=0.04) Muscle strength (after 4 days): A>B(P=0.05) Pain on movement: no significant difference Rest pain: no significant difference Physician judgment of effect: A>B (p<0.01) Patient judgment of effect: A>B (p=0.01) Cervicobrachialgia patients Muscle contracture (after 4 days): A>B(p=0.001) Muscle strength (after 4 days): A>B(P=0.0006) Pain on movement: no significant difference Rest pain: A>B (p=0.01) Physician judgment of effect: A>B (p<0.001) Patient judgment of effect: A>B (p=0.001)	Dantrolene vs. placeboWithdrawals (due to adverse events): 0/30 vs. 1/30 Any adverse event: 1/30 vs. 2/30 Frequent adverse events=epigastric pain, heartburn

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Sirdalud Ternelin Asia-Pacific Study Group 1998	Randomized Asia-Pacific region Multicenter (16) Type(s) of clinics: Not reported	A: tizanidine, 2 mg BID + diclofenac, 50 mg BID B: placebo + diclofenac, 50 mg BID 7-days	Men and women aged 18 to 70 years with acute pain in the back, neck or shoulder girdle, a clinical impression of m muscle spasms and onset of pain <7 days previously	405 361	Tizanidine + diclofenac vs. placebo + diclofenac Female gender: 49% vs. 54% Meean age (years): 40 vs. 40 Race: 100% asian-pacific Pain location Back: 53% vs. 50% Neck: 18% vs. 26% Shoulder: 29% vs. 24%	Pain: 4-point scale (0=absent; 3=severe) on palpitation, during movement, at night and at rest Severity of muscle spasm: 4-point scale (0=not present; 3=severe) Restriction of body movement: 4-point scale (0=no restriction; 3=marked restriction) Patients' self-assessment of disability due to pain: 5-point scale (0=no disability; 4=complete disability, need to stay in bed) Sleep quality: 4-point scale (0=no sleep disturbance; 3=>8 hours of daytime bed rest necessary) Overall efficacy: assessed by investigators using categorical scale Assessments completed at baseline, after 3 days and after 7 days
Soyka 1979	Randomized United States Multicenter	A: Soma compound (carisoprodol 200 mg + phenacetin 160 mg + caffeine 32 mg) 2 tabs qid B: Carisoprodol 400 mg qid C: Phenacetin/ Caffeine D: Placebo 6 days	Aged 18-65; suffering from acute, painful musculoskeletal condition of the lumbar and/or cervical region of not more than 7 days' duration; pain of moderate or greater severity	414 336	Soma compound vs. carisoprodol vs. phenacetin + caffeine vs. placebo Median age (years): 35 vs. 36 vs. 36 vs. 36 Female gender: 48% vs. 50% vs. 48% vs. 47% A=43(52%) male vs. 40(48%) Non-white: 13% vs. 9% vs. 6% vs. 8% Musculoskeletal etiology and severity not reported Previous muscle relaxant use not reported	Pain severity: 5-point scale (1=none; 5=very severe) Muscle spasm: 5-point scale (1=none; 5=very severe) Activity impairment: 5-point scale (1=none; 5=complete) Sleep impairment: 4-point scale (1=none; 4=severe) Global improvement: 8-point scale (1=complete improvement with no residual pain or impairment; 5=no change; 8=markedly worse or completely disabled) Assessments completed at days 3 and 6

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Sirdalud Ternelin Asia-Pacific Study Group 1998	FAIR. Allocation concealment, eligibility criteria, blinding techniques not described. Randomization conducted using a table of random numbers	Tizanidine + diclofenac (A) vs. placebo + diclofenac (B) Pain(decrease from baseline scores): A>B (p<0.05) for rest, during movement and at night; A>B (p<0.001) on palpitation Severity of muscle spasm(mean values): Day 4: 0.77 vs. 1.20 (p<0.001); Day 8: 0.29 vs. 0.77(p<0.001) Restriction of body movement(mean values): Day 4: 0.72 vs. 0.94 (p<0.001); Day 8: 0.48 vs. 0.93 (p<0.001) Patients' self-assessment of disability due to pain(mean values): Day 4: 0.98 vs. 1.27 (p<0.001); Day 8: 0.61 vs. 0.92 (p<0.001) Sleep quality(mean values): no significant group differences at either Days 4 or 8 Overall efficacy (% good to very good): 72% vs. 58%(p<0.05)	Withdrawals (due to adverse events): 0 Frequent adverse events: GI adverse events: 12% vs. 32% (p<0.001) Central nervous system adverse events: 18% vs. 10% (p<0.05)
Soyka 1979	FAIR. Randomization, allocation concealment, eligibility criteria, blinding techniques not described.	Carisoprodol vs. placebo results only Pain severity (mean improvement): 1.73 vs. 1.27 (p=0.08) Muscle spasm (day 6 mean improvement): 1.82 vs. 1.11 (p=0.015) Activity impairment (day 6 mean improvement): 1.75 vs. 1.18 (p=0.04) Sleep impairment: 1.45 vs. 0.75 (p=0.07) Global improvement (day 6 mean scores): 2.04 vs. 3.16 (0.02) Average symptomatic improvement(mean improvement): 1.69 vs. 1.08 (p=0.048)	Carisoprodol vs. placebo results only Withdrawals due to adverse events: 1/104 vs. 0/104 <u>Frequent adverse events</u> Dizziness: 18% vs. 3% Drowsiness: 8% vs. 1% Nausea: 2% vs. 1% Dry mouth: 0% vs. 0% Description of other adverse events which occurred in 1 % or less of the total patient population in Table XI

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Type of Study, Setting	Interventions Dose Duration	Eligibility Criteria	Enrolled Analyzed	Population Characteristics	Method of Outcome Assessment and Timing of Assessment
Steingard 1980	Randomized U.S. Multicenter	A: Cyclobenzaprine 30 mg/day B: Placebo 1-2 weeks	Acute muscle spasm of the neck or low back	121 106	Cyclobenzaprine vs. placebo Mean age (years): 38 vs. 37 Female gender: 26/59 vs. 25/52 Race: Not reported Musculoskeletal strain: 51/59 vs. 45/62 Others: Posttraumatic, idiopathic, cervical root syndrome Prior muscle relaxant use: Not reported	Global evaluation: Unspecified method Muscle spasm: Unspecified method Local pain: Unspecified method Tenderness on palpation: Unspecified method Limitation of motion: Unspecified method Functional status: Unspecified method Total symptom score: Unspecified method Assessed at baseline, and during weeks 1 and 2
Valtonen 1975	Randomized Finland Single center	A: Orphenadrine 100 mg bid B: Placebo C: Chlormezanone D: Orphenadrine + acetaminophen (only results of A vs. B abstracted) 7 days	Low back or neck pain with tense, contracted muscles	200 (interventions A or B only) 200	Age, gender, race: Not reported Neck or cervical syndrome: 69% vs. 66% Back syndromes: 26% vs. 28% Ischial syndrome: 5% vs. 6% Prior muscle relaxant use: Not reported	Overall effect: 3 point scale (no effect to good pain relief)

Evidence Table 6. Placebo-controlled trials of skeletal muscle relaxants in patients with musculoskeletal conditions (continued)

Author Year	Overall Rating and comments	Outcomes	Adverse Events
Steingard 1980	FAIR. Not clear if randomized. Allocation concealment and blinding techniques not reported.	Cyclobenzaprine vs. placebo Global evaluation (marked improvement): 34% vs. 27% (NS) Global evaluation (marked or moderate improvement): 55% vs. 46% (NS) Muscle spasm (marked or moderate improvement): 62% vs. 60% (NS) Local pain (marked or moderate improvement): 62% vs. 53% (NS) Tenderness on palpation (marked or moderate improvement): 66% vs. 47% (NS) Limitation of motion (marked or moderate improvement): 55% vs. 43% (NS) Limitation of daily activities (marked or moderate improvement): 52% vs. 47% (NS) Total symptom score (improvement): 8.8 vs. 7.2 (NS)	Cyclobenzaprine vs. placebo Drowsiness: 24% vs. 3% Fatigue: 17% vs. 2% Dry mouth: 12% vs. 3% Dizziness: 5% vs. 2% Any adverse event: 54% vs. 23% Withdrawal (adverse event): None reported
Valtonen 1975	FAIR. Blinding may not have been adequate (different frequency of dosing). Allocation concealment technique not described.	Orphenadrine vs. placebo Overall effect (moderate or good): 66% vs. 53% (NS) Overall effect (good): 26% vs. 25%	Orphenadrine vs. placebo Withdrawals: Not reported Any adverse event: Not reported Drowsiness: 5% vs. 4% Vertigo: 4% vs. 4% Dry mouth: 0% vs. 0% Weakness: Not reported Feeling unwell: 4% vs. 2% Rash: 0% vs. 3% Heart pains: 1% vs. 3% Diarrhea: 2% vs. 0%