

Appendix S2

Overview of included studies

Clinical studies

Study	Risk of bias	Reported outcomes						
		Muscle tone	Spasm	Disability	Gait	Overall efficacy	Subjective impression	Safety
<b>Oral baclofen vs. placebo</b>								
<b>Multiple sclerosis</b>								
Hudgson, 1971 <sup>1</sup>	Low	✓					✓	✓
Duncan, 1976 <sup>2</sup>	Low	✓	✓				✓	✓
Sachais, 1977 <sup>3</sup>	Low	✓		✓		✓		✓
Feldman, 1978 <sup>4</sup>	Low	✓	✓		✓			✓
Sawa, 1979 <sup>5</sup>	Unclear	✓						✓
Brar, 1991 <sup>6</sup>	Unclear	✓		✓		✓		✓
Ørsnes, 2000 <sup>7</sup>	Low	✓				✓		✓
<b>Cerebral palsy</b>								
Milla, 1977 <sup>8</sup>	Low	✓			✓		✓	✓
McKinley, 1980 <sup>9</sup>	Low	✓			✓			✓
<b>Stroke</b>								
Medaer, 1991 <sup>10</sup>	Low	✓		✓		✓		✓
<b>Oral baclofen vs. active comparators or open-label</b>								
<b>Multiple sclerosis</b>								
<b>Baclofen vs. tizanidine</b>								
Smolenski, 1981 <sup>11</sup>	Unclear	✓	✓	✓		✓	✓	✓
Newman, 1982 <sup>12</sup>	Low	✓	✓			✓		✓
Stien, 1987 <sup>13</sup>	Unclear	✓	✓	✓		✓		✓
Bass, 1988 <sup>14</sup>	Unclear	✓	✓	✓		✓		✓
Eyssette, 1988 <sup>15</sup>	Low	✓	✓		✓	✓		✓
Hooqstraten, 1988 <sup>16</sup>	Unclear	✓	✓	✓		✓	✓	✓
<b>Baclofen vs. diazepam</b>								
Cartledge, 1974 <sup>17</sup>	Low	✓					✓	✓
From, 1975 <sup>18</sup>	Low		✓				✓	✓
<b>Spinal cord injury</b>								
Jones, 1976 <sup>19</sup>	High	✓	✓					✓
Nance, 1994 <sup>20</sup>	Low	✓						✓
Aydin, 2005 <sup>21</sup>	Low	✓	✓	✓				✓
<b>Cerebral palsy</b>								
Bresolin, 2009 <sup>22</sup>	Low	✓			✓		✓	✓
<b>Brain injury</b>								
Medici, 1989 <sup>23</sup>	Low	✓	✓	✓		✓		✓
Meythaler, 2004 <sup>24</sup>	Unclear	✓	✓					✓

Summary of clinical studies by origin of spasticity, comparator and study design

Origin of spasticity	Comparator	Total no. studies	RCTs	Comparative studies	Open-label studies
<b>Spinal origin</b>					
Multiple sclerosis (MS)	Tizanidine (TIZ)	6	6	--	--
	Diazepam (DIA)	2	2	--	--
	Placebo (PLA)	7	7	--	--
	TOTAL	15	15	--	--
Spinal cord injury (SCI)	Transcutaneous electrical nerve stimulation (TENS)	1	--	1	--
	Clonidine (CLO) & Cyproheptadine (CYP)	1	--	1	--
	None	1	--	--	1
	TOTAL	3	--	2	1
<b>Cerebral origin</b>					
Cerebral palsy (CP)	Placebo (PLA)	2	2	--	--
	Eperisone (EPE)	1	1	--	--
	TOTAL	3	3	--	--
Brain injury (BI)	Tizanidine(TIZ)	1	1	--	--
	None	1	--	--	1
	TOTAL	2	1	--	1
Post-stroke	Placebo (PLA)	1	1	--	--
<b>Total</b>		<b>24</b>	<b>20</b>	<b>2</b>	<b>2</b>

**Adverse events with oral baclofen vs. placebo or active comparator, as reported in the clinical studies**

Study	Adverse event	Number of patients, n (%)		
		Oral baclofen	Comparator	
<b>Oral baclofen vs. placebo</b>				
<b>Multiple sclerosis</b>				
Hudgson, 1971 <sup>1</sup>	Nausea	3 (13)	1 (4)	
	Transient vertigo	1 (4)	—	
	Supraorbital pain	1 (4)	—	
	Sleepiness	1 (4)	—	
	Blurring of vision	—	1 (4)	
	Upper respiratory tract infection	—	1 (4)	
Duncan, 1976 <sup>2</sup>	Lightheadedness	5 (23)	1 (5)	
	Nausea	5 (23)	1 (5)	
	Drowsiness	3 (14)	1 (5)	
	Dry mouth	3 (14)	—	
	Weakness	2 (9)	—	
	Vomiting	1 (5)	—	
	Dizziness	1 (5)	1 (5)	
	Leg edema	1 (5)	—	
	Postural hypotension	1 (5)	—	
	Severe spasm during washout period	1 (5) (withdrawn)	—	
	Profuse diarrhea	—	1 (5) (withdrawn)	
		Skin rash	—	1 (5)
Sachais, 1977 <sup>3</sup>	Somnolence	60 (71)	29 (36)	
	Vertigo	19 (22)	6 (7)	
	Excessive weakness	17 (20)	9 (11)	
	Nausea	14 (16)	5 (6)	
	Headache	10 (12)	7 (9)	
	Frequency of urination	10 (12)	1 (1)	
	Constipation	9 (11)	2 (2)	
	Insomnia	9 (11)	7 (9)	
	Depression	4 (5)	5 (6)	
	Excessive weakness, lower extremity	4 (5)	2 (2)	
		Vomiting	4 (5)	—
	Feldman, 1978 <sup>4</sup>	Paresthesia	5 (21.7)	2 (8.7)
Dry mouth		5 (21.7)	1 (4.3)	
Drowsiness		4 (17.4)	4 (17.4)	
Blurred vision		2 (8.7)	2 (8.7)	
Sawa, 1979 <sup>5</sup>	Sedation	6 (29)	—	
	Nausea	5 (24)	—	
	Headache	3 (14)	—	
	Increased weakness	3 (14)	—	
	Euphoria	2 (10)	—	
	Depression	2 (10)	—	
	Dizziness (non-specific)	2 (10)	—	
	Balance disturbance	2 (10)	—	
	Vomiting	2 (10)	—	
	Abdominal pain	2 (10)	—	
	General malaise	2 (10)	—	
	Diarrhea	1 (5)	—	
	Dry mouth	1 (5)	—	
	Weight gain	1 (5)	—	
Ørsnes, 2000 <sup>7</sup>	Fatigue	5 (38)	1 (8)	
	Dizziness	3 (23)	1 (8)	
	Better sleep	2 (15)	—	
	Nausea	1 (8)	—	
	Decreased diplopia	1 (8)	—	
	Bad temper	1 (8)	—	
	Obstipation	1 (8)	—	
	Diarrhea	1 (8)	1 (8)	
	Worsened incontinence	1 (8)	—	
		More frequent urination	1 (8)	—
<b>Cerebral palsy</b>				
Milla, 1977 <sup>8</sup>	Sedation	4 (20)	—	
	Hypotonia	3 (15)	—	
McKinley, 1980 <sup>9</sup>	Drowsiness	5 (25)	—	
	Sickness	2 (10)	—	
	Dizziness	2 (10)	—	
	Nocturnal enuresis	2 (10)	—	
	Epileptiform	2 (10)	—	
	Slurred speech	2 (10)	—	
	Weakness	1 (5)	—	
<b>Stroke</b>				
Medaer, 1991 <sup>10</sup>	Dizziness	6 (30)	—	
	Weakness	4 (20)	—	
	Difficulties walking	2 (10)	—	
	Incontinence	1 (5)	—	
	Tiredness	1 (5)	—	
	Diplopia	1 (5)	—	
	Loss of appetite	1 (5)	—	
	Stomach upset	—	1	
	Confusion	—	1	
		Agitation	—	1
			—	1
<b>Oral baclofen vs. active comparators or open-label</b>				
<b>Multiple sclerosis</b>				
<b>Baclofen vs. tizanidine</b>				
Smolenski, 1981 <sup>11</sup>	Tiredness	—	5 (45)	
	Weakness	3 (30)	—	
	Dry mouth	1 (10)	1 (9)	
	Ataxia	—	1 (9)	

Study	Adverse event	Number of patients, n (%)	
		Oral baclofen	Comparator
	Nausea	1 (10)	—
	Pyrosis	1 (10)	—
Newman, 1982 <sup>12 a</sup>	Muscle pains	9 (35)	4 (15)
	Drowsiness	4 (15)	4 (15)
	Weakness	4 (15)	4 (15)
	Dizziness	3 (12)	2 (8)
	Bladder or bowel disturbance	3 (12)	3 (12)
	Depression	2 (8)	—
	Fluid retention	2 (8)	—
	Lassitude	1 (4)	1 (4)
	Headache	1 (4)	—
	Sleeplessness	1 (4)	2 (8)
	Visual disturbance	1 (4)	—
	Speech disturbance	1 (4)	1 (4)
	Abdominal pain and upset	1 (4)	1 (4)
	Weight gain	1 (4)	—
	Tremor	1 (4)	2 (8)
Clumsiness	1 (4)	—	
Stien, 1987 <sup>13</sup>		Weakness Tiredness	Tiredness Muscular weakness Sleepiness
Bass, 1988 <sup>14</sup>	Muscle weakness <sup>b</sup>	17 (35)	11 (21)
	Somnolence <sup>b</sup>	9 (19)	15 (29)
	Dry mouth <sup>b</sup>	7 (14)	12 (23)
	Dizziness	7 (14)	2 (4)
	Bladder urgency	7 (14)	3 (6)
	Nausea	6 (13)	2 (4)
	Headaches	5 (10)	1 (2)
	Irritability	4 (8)	3 (6)
	Vomiting	4 (8)	—
	Insomnia	3 (6)	8 (15)
	Light-headedness	2 (4)	3 (6)
	Spasms <sup>b</sup>	2 (4)	8 (15)
	Leg dysesthesia	1 (2)	3 (6)
	Constipation	—	3 (6)
Eyssette, 1988 <sup>15</sup>	Fatigue	12 (27)	8 (19)
	Daytime drowsiness	10 (23)	15 (36)
	Muscular weakness	10 (23)	—
	Disturbances of affect	9 (20)	—
	Vomiting	8 (18)	—
	Dry mouth	—	14 (33)
	Insomnia	—	7 (17)
	Orthostatic hypotension	—	6 (14)
Hoogstraten, 1988 <sup>16</sup>	Subjective muscle weakness	11 (79)	4 (29)
	Somnolence	4 (29)	8 (57)
	Nausea	3 (21)	2 (14)
	Urinary incontinence	3 (21)	1 (7)
	Dry mouth	2 (14)	5 (36)
	Dizziness	2 (14)	2 (14)
	Flushes	1 (7)	3 (31)
	Depression	1 (7)	2 (14)
	Blurred vision	1 (7)	—
	Headache	1 (7)	—
	Dysarthria	1 (7)	1 (7)
	Burning hands or feet	1 (7)	—
	Sleep disturbance	—	2 (14)
Bladder retention	—	1 (7)	
<b>Baclofen vs. diazepam</b>			
Cartledge, 1974 <sup>17 c</sup>	Sedation alone	6 (16)/5 (14)	5 (14)/4 (11)
	Sedation associated with other effects	3 (8)/1 (3)	5 (14)/6 (16)
	Weakness	2 (5)/4 (11)	6 (16)/6 (16)
	Insomnia	1 (3)/1 (3)	—
	Light-headedness	—/1 (3)	—
	Confusion	1 (3)/2 (5)	—/1 (3)
	Diarrhea and frequency of micturition	1 (3)/—	—
	Urgency of micturition	—/1 (3)	—
	Incontinence of urine	1 (3)/1 (3)	1 (3)/1 (3)
	Dry mouth	1 (3)/1 (3)	—
	Sore mouth	2 (5)/1 (3)	—
	Loss of taste and smell plus vertigo	1 (3)/1 (3)	—
	Depression	—/1 (3)	—/1 (3)
	Weakness and confusion	—	1 (3)/1 (3)
	Diarrhea and confusion	—	1 (3)/1 (3)
Diarrhea	—	1 (3)/1 (3)	
Nausea and vertigo	—	1 (3)/1 (3)	
From, 1975 <sup>18</sup>	Sedation	5 (31)	11 (69)
	Weakness	3 (19)	2 (13)
	Depression	2 (13)	—
	Nausea	2 (13)	—
	Euphoria	1 (6)	1 (6)
	Vertigo	1 (6)	1 (6)
	Headache	1 (6)	—
	Diarrhea	1 (6)	—
	Confusion	—	1 (6)
<b>Spinal cord injury</b>			
Jones, 1976 <sup>19</sup>	Drowsiness	8 (7)	—
	Dreams	4 (4)	—
	Hallucinations	3 (3)	—
	Paranoia	2 (2)	—
	Euphoria (temporary)	2 (2)	—
	Depression	2 (2)	—
	Headache	2 (2)	—

Study	Adverse event	Number of patients, n (%)	
		Oral baclofen	Comparator
	Blurred vision	2 (2)	
	Nausea	2 (2)	
	Jerking, tremor	2 (2)	
	Visual illusions	1 (1)	
	Vagueness (temporary)	1 (1)	
	Aphrodisiac effect	1 (1)	
	Anxiety	1 (1)	
	Diplopia	1 (1)	
	Sweating	1 (1)	
	Weakness	1 (1)	
Aydin, 2005 <sup>21</sup>	Dryness of mouth	3 (30)	—
	Fatigue	2 (20)	
<b>Cerebral palsy</b>			
	Asthenia	9 (60)	3 (17)
	Hypoesthesia in lower limbs	4 (27)	—
	Sleepiness	4 (27)	—
	Amenorrhoea	1 (7)	—
	Anorexia	1 (7)	—
	Cramps	1 (7)	—
	Heat in lower limbs,	1 (7)	—
	Hypocondrial pain	1 (7)	—
	Nausea	1 (7)	—
	Paresthesia	1 (7)	—
	Sciatica	1 (7)	—
	Vertigo	1 (7)	—
Bresolin, 2009 <sup>22 d</sup>	Epigastric pain	—	2 (11)
	Insomnia	—	2 (11)
	Cramps	—	1 (6)
	Dyspepsia	—	1 (6)
	Eczema	—	1 (6)
	Headache	—	1 (6)
	Hypertension	—	1 (6)
	Hypotonia	—	1 (6)
	Itching	—	1 (6)
	Leukocytosis	—	1 (6)
	Shivering	—	1 (6)
	Sleepiness	—	1 (6)
	Sweating	—	1 (6)
<b>Brain injury</b>			
	Muscular instability	3 (27)	1 (7)
	Drowsiness	1 (9)	—
	Headache	1 (9)	1 (7)
	Dizziness	1 (9)	—
	Incoordination	1 (9)	—
	Gastric pain	1 (9)	—
	Hypertension	1 (9)	—
	Increased weakness	1 (9)	—
	Increased rigidity	1 (9)	—
Medici, 1989 <sup>23 e</sup>	Somnolence	—	5 (36)
	Nervousness	—	1 (7)
	Diarrhea	—	1 (7)
	Gastric intolerance	—	1 (7)
	Epigastric burning	—	1 (7)
	Dry mouth	—	1 (7)
	Hypotension	—	1 (7)
	Pain in lower limb	—	1 (7)
	Increased spasticity	—	1 (7)
Meythaler, 2004 <sup>24</sup>	Sleepiness	6 (17)	—
	Problems with urination	1 (3)	—
	Furuncles	1 (3)	—

<sup>a</sup>During the final 4 weeks of drug treatment; <sup>b</sup>observed during the maintenance period (rates were higher during the titration period, with muscle weakness in 57% of baclofen patients vs. 32% of tizanidine patients); <sup>c</sup>low dose/high dose; <sup>d</sup>versus eperisone; <sup>e</sup>versus tizanidine – all baclofen adverse events rated as severe, apart from increased rigidity, while all tizanidine adverse events were rated as mild

Systematic reviews

Study details	Risk of bias (score out of 10)	Efficacy of oral baclofen in spasticity	Adverse events with oral baclofen
<b>Oral baclofen vs. intrathecal baclofen</b>			
<b>Spinal spasticity</b>			
Dario, 2004 <sup>25</sup> 17 trials, 1,501 patients with severe spasticity	Unclear (6.5)	Favorable risk-benefit assessment Effective in severe spasticity, comparable with tizanidine	Incidence 10–75% Reversible, not severe Mainly sedation or somnolence, excessive weakness, vertigo, psychological disturbances Usually appear at dosages >60 mg/day
<b>Oral baclofen vs. tizanidine</b>			
<b>Multiple sclerosis or brain injury</b>			
Lataste, 1994 <sup>26</sup> 14 trials, 632 MS or BI patients	Unclear (4.5)	Comparable with tizanidine and diazepam at improving muscle tone, spasms and clonus in MS or CVD patients	Greater muscle weakness than tizanidine (>10% patients) Tolerability rated worse than tizanidine by physicians in MS or CVD patients
Groves, 1998 <sup>27</sup> 7 trials, 196 MS or BI patients	Unclear (5.0)	Similar spasticity reducing effects to tizanidine and diazepam Improvement in muscle strength, but greatest with tizanidine	Greater muscle weakness than tizanidine Tizanidine better tolerated than baclofen and diazepam Mainly sedation, fatigue, muscle weakness, hypotension
<b>Oral baclofen vs. antispastic oral drugs</b>			
<b>Multiple sclerosis</b>			
Paisley, 2002 <sup>28</sup> 7 trials, 182 mainly MS patients	Unclear (6.5)	Significantly more effective than placebo at higher doses; no difference with lower doses Efficacy comparable with tizanidine and diazepam Greater preference for baclofen than diazepam	AEs common: drowsiness, weakness, paresthesia, dry mouth Fewer AEs than diazepam and dantrolene Side effects with baclofen did appear to limit the dose tolerated, but were fewer and more readily tolerated than those caused by diazepam
Beard, 2003 <sup>29</sup> 12 trials, 403 MS patients	Low (7.0)	Same results as Paisley 2002 <sup>28</sup> Limited evidence of the effectiveness of baclofen, tizanidine, diazepam, dantrolone in MS	Same results as Paisley 2002 <sup>28</sup> Little evidence that tizanidine caused less muscle weakness
Shakespeare, 2003 <sup>30</sup> 13 trials, MS patients	Unclear (5.0)	Inclusive results in placebo-controlled studies No significant differences between antispasticity drugs	Some reports of increased muscle weakness with baclofen vs. tizanidine
Nicholas, 2009 <sup>31</sup> 4 trials, 138 MS patients	High (2.5)	No conclusions could be made for efficacy of baclofen on spasticity compared with placebo or active comparators	Similar level of AEs compared with tizanidine (muscle weakness, sedation, dry mouth)
<b>Musculoskeletal conditions</b>			
Chou, 2004 <sup>32</sup> 30 trials	Low (7.0)	Dantrolene, baclofen, and tizanidine all appear effective in patients with spasticity The best available evidence suggests that tizanidine is roughly equivalent to baclofen for most clinical outcomes Insufficient evidence to determine the efficacy of dantrolene compared to baclofen	Overall rate of AEs between tizanidine and baclofen is similar, but tizanidine is associated with more dry mouth and baclofen with more weakness
<b>Cerebral palsy or brain injuries</b>			
Montané, 2004 <sup>33</sup> 3 trials, 55 CP or CVD/head trauma patients	Low (8.0)	Efficacy of all antispastic agents was marginal No significant difference between baclofen and tizanidine	High incidence of muscle weakness, sedation and drowsiness (25–27%) Neurologic events seemed to be dose-related, and tended to disappear when doses were reduced

AEs, adverse events; BI, brain injury; CP, cerebral palsy; CVD, cerebrovascular; MS, multiple sclerosis