Symptomatic Treatment of MS

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Symptomatic treatment of spinal cord and optic nerve damage

Symptomatic treatment

- Spasticity
- Gait function
- Bladder dysfunction
- Sexual dysfunction
- Pain
- Fatigue
- Cognitive rehabilitation
General guidelines for symptomatic therapy

- Before start of therapy make an agreement with the patient about what should be achieved
- Use only one medication at a time
- Increase the dose slowly
- Dose individually guided by efficacy and side-effects
- Adjust the dose frequently
- The patient has the final decision of the benefit of the therapy
Treatment of Spasticity
Spasticity - phenomenology

Spinal segmental type

Clonus, spasms (flexor), hyperactive tendon- and exteroceptive reflexes

Rostral type

Chronic, slowly developing, extensor, dystonia-like, involving the trunk
Spasticity in corticospinal tract injury

A

Supraspinal

- Reduced facilitatory input on ventromedial reticular formation
- Light spasticity

B

Spinal cord incomplete

- Interruption of inhibitory input on spinal interneuronal pool (dorsal reticulospinal tract)
- Severe spasticity

C

Spinal cord complete

- Interruption of facilitatory and inhibitory input on spinal interneuronal pool
- Moderate spasticity

Treatment of spasticity

Therapeutic considerations

- Antispasticity drugs are most helpful for treatment of painful spasms and for reduction of tonic co-contractions.
- Antispasticity drugs do seldom improve gait function.
- Antispasticity drugs can increase weakness and are most helpful in patients with near-normal strength.
## Antispasticity drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>GABA agonist, reduces pre-synaptic inhibition on interneurons</td>
<td>Weakness, fatigue, encephalopathy, GI</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Inhibits polysynaptic motor unit activity</td>
<td>Weakness, dry mouth, somnolence</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Enhances pre-synaptic inhibition by increasing affinity of GABA-receptors</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Direct action on muscles, decreases Ca-ion effect on contractability</td>
<td>Weakness, hepatic failure (0.3%)</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Neuromuscular presynaptic blockade</td>
<td>None</td>
</tr>
<tr>
<td>Nabiximols</td>
<td>Opioid receptor agonist. Delta-9-tetrahydrocannabinol (THC) and cannabidiol</td>
<td>Somnolence, dizziness</td>
</tr>
</tbody>
</table>
Case 1

- 49 years old woman with RRMS diagnosis at age 25 years and SPMS since age 41 years; EDSS 6.5, able to walk 50 meters with a walking stick
- Spastic paraparesis with clonus interfering with walking and painful flexor spasms in the morning
- ??
- Treatment with baclofen 25 mg three times daily partially effective, but sedation prohibit further increase of dose; EDSS and walking distance unchanged
- ??
- Add-on treatment with tizanidine not tolerated
- ??
- Nabiximols could be tried up to a maximum of 12 sprays in 24 hours or maximum tolerated dose
Treatment of spasticity

Practical approach

Spinal segmental spasticity
- Initially baclofen 10 mg at bedtime
- Increase dose with 5 mg every other day until optimal effect is achieved
- Maximum dose 100-150 mg

Rostral spasticity
- Initially tizanidline 6 mg at bedtime
- Increase dose with 6 mg every 3rd day
- Maximum dose 6-12 mg b.i.d.
Practical approach II

• Baclofen and tizanidine can be combined

• If the therapeutic response is insufficient, add
  Diazepam 5 - 10 mg at bedtime
  (Dantrolene 25 mg b.i.d. to 25-50 mg t.i.d)

• If the therapeutic response is insufficient, consider
  Nabiximols

• Severe spasticity not treatable with systemic drugs
  Intrathecal baclofen pump

• Focal severe spasticity
  Botox®
Nabiximols

- Nabiximols: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)(1:1)
- Oromucosal spray
- Each 100-µl actuation of active medication delivered 2.7 mg THC and 2.5 mg CBD to the oral mucosa
- Subjects were restricted to a maximum of 12 sprays in any 24-h period
Nabiximols

Mean & 95% C.I. by week  

P=0.048

N=65  

N=124

NRS spasticity score: changes from baseline

GW-1000-02  
Placebo

Week 6/End of treatment

Nabiximols

≥ 20% reduction in NRS spasticity score

Novotna et al. Eur J Neurol 2011
**Nabiximols**

### Adverse effects

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>CBM ($n = 124$)</th>
<th>Placebo ($n = 65$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>40 (32.3)</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (10.5)</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13 (10.5)</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11 (8.9)</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Balance impaired</td>
<td>9 (7.3)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (7.3)</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (6.5)</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7 (5.6)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>6 (4.8)</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (4.8)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>
Intrathecal baclofen with implantable reservoir pump

Indications:
• Insufficient effect of oral administration
• Unacceptable side-effects of oral administration
• Spasticity primarily affecting the lower extremities

Type of delivery pumps:
A) Volume-guided (computer controlled, battery-powered)
   - fixed drug concentration, variable infusion speed
B) Concentration-guided (gas-driven)
   - constant flow, variable drug concentration

Adverse effects and complications
• Treatment failure
  • dislocation, bending, disconnection of catheter
  • mechanical pump defect, exhausted battery
• Infections – pump pouch or catheter
• Overdose
Improvement of Gait Function
Patients with MS rate difficulty walking as the impairment that concerns them most.

MS Patient Rating of What Functional Impairments Concern Them Most

- Walking
- Power Coordination of Hands
- Normal Skin Sensations
- Lack of Pain
- Bladder Control
- Bowel Control
- Visual Function
- Wakefulness and Alertness
- Thinking and Memory
- Speech
- Swallowing
- Mood
- Sexuality

Fampridine enhances neurological function by improving impulse conduction across demyelinated axons

- 4-aminopyridine (4-AP)
- Prolonged-Release Fampridine Tablets (prolonged-release)
  - Long duration of effect
  - Avoids high plasma peaks
  - Overcomes significant food effects

Without Fampridine
- Action potentials propagate more slowly along demyelinated axons compared with myelinated axons

With Fampridine
- Fampridine is a potassium channel blocker which reduces the leakage of ionic current through these channels.
- This improves action potential propagation in demyelinated axons.

Clinical Relevance in Fampridine Pivotal Trials

Percent of Patients with ≥20% Increase in Walking Speed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage of Patients</th>
<th>Change in MSWS-12</th>
<th>Clinically Meaningful Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=190)</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR-Fampridine (n=343)</td>
<td>32.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean Change in 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

- Placebo: <20% Increase in Walking Speed (n=231)
- PR-Fampridine Treated: ≥20% Increase in Walking Speed (n=112)

PR=prolonged release.*Changes of -4 to -6 points have been shown to be clinically meaningful.

Patient EDSS 5.5: On and Off Treatment

Off Treatment

On Treatment
**ENABLE Study Design**

### PR-Fampridine Clinical Responders (n=708)
Faster walking speed on Timed 25-Foot Walk (T25FW) at Weeks 2 and 4 AND improvement on the 12-item Multiple Sclerosis Walking Scale (MSWS-12) at Week 4.

### Nonresponders (n=139)
Not faster on T25FW at Weeks 2 and 4 OR no improvement on MSWS-12 at Week 4. Optional allocation to control group.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timed 25-Foot Walk</td>
<td>X X X X</td>
</tr>
<tr>
<td>12-item Multiple Sclerosis Walking Scale</td>
<td>X X</td>
</tr>
<tr>
<td>Short-Form-36 Question Health Survey</td>
<td>X X X X</td>
</tr>
<tr>
<td>Multiple Sclerosis Impact Scale</td>
<td>X X X X</td>
</tr>
<tr>
<td>Work Productivity and Impairment-Specific Health Problems Questionnaire</td>
<td>X X X X</td>
</tr>
<tr>
<td>Patient-Reported Indices For Multiple Sclerosis*</td>
<td>X X X X</td>
</tr>
<tr>
<td>EuroQol 5-Dimensions</td>
<td>X X X X</td>
</tr>
</tbody>
</table>

*Activity limitations scale only. Macdonell R et al. Presented at AAN; March 16–23, 2013; San Diego, CA. P03.218.
ENABLE Interim Analysis: SF-36 Physical Component Scale Changes from Baseline at Weeks 12 and 24

Graph represents mean change from baseline.
### Phase 3 studies: Most frequent AEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=191)</th>
<th>PR-fampridine (n=348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>10.5%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Falls</td>
<td>16.2%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.6%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.1%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.9%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>2.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.1%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

AE=adverse event.
Studies MS-F203 and MS-F204: all AEs seen in >5% of PR-fampridine-treated patients.
Case 2

- 54 year old man with PPMS since 15 years
- Progressive spastic paraparesis; EDSS 6.0
- Timed 25-foot walking: 10.4 sec.
- Multiple Sclerosis Walking Scale: 72 points (0-100 points)
- ?
- Fampridine 10 mg twice daily
- After 2 weeks: Timed 25-foot walking: 8.1 sec.
- Multiple Sclerosis Walking Scale: 66 points
- ?
- Improvement in Timed 25-foot walking: 22 % (>20% improvement is clinical significant)
- Improvement in Multiple Sclerosis Walking Scale: -6 points (-4 points response is clinically significant)
- Responder: continue fampridine
Treatment of Bladder Dysfunction
Bladder control and micturation

Control of Bladder Function

Micturation

Storage phase

Bladder hyperreflexia

Normal micturation
Detrusor-sphincter dyssynergia
Atonic bladder
Classification of bladder dysfunction in MS

Failure to store
Bladder hyperreflexia (spastic bladder):
detrusor-instability

Failure to empty
Bladder hyporeflexia (atonic bladder):
detrusor-hypocontractility
Failure to relax the urethral sphincter

Failure to store and empty
Detrusor-sphincter-dyssynergia

50-80 %
30-40 %
20-60 %
# Drugs with effect on bladder function

<table>
<thead>
<tr>
<th>Promote storage</th>
<th>Promote emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinergics</strong></td>
<td><strong>Muscle relaxants</strong></td>
</tr>
<tr>
<td>Inhibit detrusor contractions</td>
<td>Reduce detrusor muscle tone</td>
</tr>
<tr>
<td>Tolterodin*</td>
<td>Oxybutynin</td>
</tr>
<tr>
<td>Emepron*</td>
<td>Flavoxat*</td>
</tr>
<tr>
<td>Propatheline (Pro-Banthine®)</td>
<td>Imipramin</td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
</tr>
</tbody>
</table>

* Desmopressin

* Baclofen

* Not included in the category
Case 3

- 39 year old woman with RRMS since age 30
- Increasing problems with bladder control. Frequent micturition during day time with a few cases of incontinence
- ?
- Test for urinary tract infection (no signs of infection) and measurement of residual urine volume: 35 ml
- ?
- Anticholinergics (Tolterodin, Emepron)
- Treatment effective, but 3 years later increasing problems with incontinence
- ?
- Test for urinary tract infection (no signs of infection) and measurement of residual urine volume: 155 ml
- ?
- Triple voiding, alpha-blocker (doxazosin, prazocin, terazocin) – if unsuccessful: Clean intermittent self-catheterization (ISC)
Algorithm for management of bladder dysfunction

Test for urinary tract infection

- No
  - Measure residual urine volume
    - No
      - Anticholinergics
    - Yes
      - RUV < 80-100 ml
      - Desmopressin
      - Local anticholinergics
      - Catheter
  - Yes
    - RUV > 80-100 ml
    - Triple voiding
    - Alpha-blocker
    - Clean intermittent self-catheterization (ISC)
  - Treat infection

RUV > 80-100 ml

RUV < 80-100 ml

If insufficient
Thank you for your attention