The prime goal of health professionals treating pain is to alleviate the pain and suffering of their patients. The members of PAINSA by the very nature of their membership have an interest in the study of pain and its treatment. They will make use of all the diagnostic tools and treatment modalities to try and relieve pain.

Historically patients put their confidence in the practitioner and their professional ability and knowledge to do their best in order to manage and treat a problem. The very fundamental nature of this relationship is now being eroded on several fronts. The first problem encountered is the medical funder or medical aid that decides what a practitioner may or may not do depending on the health policy held by a patient. The funder may even decide which practitioner must be consulted. It would appear that these restrictions are made by financial considerations and are not based on “best practice” principles.

New technology may be effective though costly. This may sometimes be too costly for the funder who does not always understand the treatment principle. In many cases treatment authorization is refused by a clerk who has no comprehension of the pathology or its treatment and who simply refers to a handbook of treatment codes supplied by his employer. Years of clinical experience are simply dismissed. This leads to dissatisfaction between the health professional and the funder. This situation cannot be allowed to endure and solutions must be found so that patients will not be denied effective treatment because of financial principles.

The development of pharmaco-economic and cost-efficiency studies have partially resolved the problem but the matter does not simply end at this point. Funders are now looking for guidance for treatment of all medical conditions in the form of practice guidelines.

Pain management is not simply the property of a single medical discipline. Pain is a multidisciplinary multi-factorial problem. It would be extremely presumptuous of a single medical discipline to take ownership of pain because the effective treatment of pain or a pain syndrome may require the input of many medial and paramedical groups.

A case in point is that of lower back pain. No single medical discipline can claim to “own” this condition as there are multi-factorial causes of pain and as many methods for treatment of that pain. This problem makes it impossible for one group of practitioners to propose a dogmatic set of guidelines for the treatment of lower back pain. Such a comprehensive guideline will need input from all of the groups involved in the treatment of the condition. I would propose that all early endeavours for guidelines should be proposals rather than emphatic documents. These proposals can serve as templates until a final consensus document is achieved.

To this end I have included in this edition of the Journal a “Suggested guidelines for the non-surgical treatment of lower back pain”. The document will change with time and further input. It is well researched and referenced and should serve as the building block around which further recommendations can be added.

Dr. Milton Raff
BSc (WITS), MBChB (Pret), FFA (SA)

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4
Science Direct:

PAIN TOP 25 articles within the journal pain

9
Suggested guidelines: The non-surgical management of chronic low back pain

Corrie Avenant

29
Persistent pain and uncomfortable sensations in persons with multiple sclerosis

Olympia Hadjimichael, Robert D. Kerns, Marco A. Rizzo, Gary Cutter, Timothy Vollmer

37
Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia

Alex J. Zautra, Robert Fasman, Brendt P. Parish, Mary C. Davis

47
Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: A double blind sham controlled randomized clinical trial

Jan Van Zundert, Jacob Patijn, Alfons Kessels, Inge Lamé, Hans van Suijlekom, Maarten van Kleef

60
Opioid side effects

Ewan McNicol
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   *Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 5-9*
   Cao, Y.Q.

2 Algorithm for neuropathic pain treatment: An evidence based proposal
   *Pain, Volume 118, Issue 3, 1 December 2005, Pages 289-305*
   Finnerup, N.B.; Otto, M.; McQuay, H.J.; Jensen, T.S.; Sindrup, S.H.

3 To what extent do we share the pain of others? Insight from the neural bases of pain empathy • Review article
   *Pain, Volume 125, Issue 1-2, 1 November 2006, Pages 5-9*
   Jackson, P.L.; Rainville, P.; Decety, J

4 Gabapentin and postoperative pain - a systematic review of randomized controlled trials
   *Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 91-101*
   Ho, K.Y.; Gan, T.J.; Habib, A.S.

5 Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia) • Review article
   *Pain, Volume 124, Issue 3, 1 October 2006, Pages 242-263*
   Vierck, C.J.

6 Critical issues on opioids in chronic non-cancer pain:
   *Pain, Volume 125, Issue 1-2, 1 November 2006, Pages 172-179*
   Eriksen, J.; Sjogren, P.; Bruera, E.; Ekholm, O.; Rasmussen, N.K.

7 Acupuncture for patients with chronic neck pain
   *Pain, Volume 125, Issue 1-2, 1 November 2006, Pages 98-106*

8 Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations • Review article
   *Pain, Volume 125, Issue 3, 1 December 2006, Pages 208-215*

9 Emotional modulation of pain: A clinical perspective • Review article
   *Pain, Volume 124, Issue 3, 1 October 2006, Pages 264-268*
   Klossika, I.; Flor, H.; Kamping, S.; Bleichhardt, G.; Trautmann, N.; Treede, R.D.; Bohus, M.; Schmahl, C.

10 Site-specific increases in peripheral cannabinoid receptors and their endogenous ligands in a model of neuropathic pain
    *Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 102-114*

11 Calcium channel @a"2@d"1 subunit mediates spinal hyperexcitability in pain modulation
    *Pain, Volume 125, Issue 1-2, 1 November 2006, Pages 20-34*

12 Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens
    *Pain*
    Freynhagen, R.; Strojek, K.; Griesing, T.; Whalen, E.; Balkenohl, M.
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Treats pain and fever in children
13 Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values
*Pain, Volume 123, Issue 3, 1 August 2006, Pages 231-243*

14 Brain responses to dynamic facial expressions of pain
*Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 309-318*
Simon, D.; Craig, K.D.; Miltner, W.H.R.; Rainville, P.

15 Efficacy and safety of acupuncture for chronic uncomplicated neck pain: A randomised controlled study
*Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 245-255*

16 Physical therapy and active exercises - An adequate treatment for prevention of late whiplash syndrome?
*Pain, Volume 124, Issue 1-2, 1 September 2006, Pages 69-76*
Vassiliou, T.; Kaluza, G.; Putzke, C.; Wulf, H.; Schnabel, M.

17 Differential contribution of TRPV1 to thermal responses and tissue injury-induced sensitization of dorsal horn neurons in laminae I and V in the mouse
*Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 184-197*
Eckert, W.A.; Julius, D.; Basbaum, A.I.

18 Pain intensity and pain affect in relation to white matter changes
*Pain, Volume 125, Issue 1-2, 1 November 2006, Pages 74-81*
Oosterman, J.M.; van Harten, B.; Weinstein, H.C.; Scheltens, P.; Scherder, E.J.A.

19 Cost-effectiveness of acupuncture treatment in patients with chronic neck pain
*Pain, Volume 125, Issue 1-2, 1 November 2006, Pages 107-113*
Willich, S.N.; Reinhold, T.; Selim, D.; Jena, S.; Brinkhaus, B.; Witt, C.M.

20 Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years
*Pain, Volume 127, Issue 1-2, 1 January 2007, Pages 140-150*
von Baeyer, C.L.; Spagrud, L.J.

21 Spared nerve injury: an animal model of persistent peripheral neuropathic pain
*Pain, Volume 87, Issue 2, 1 August 2000, Pages 149-158*
Decosterd, I.; Woolf, C.J.

22 Duloxetine vs. placebo in patients with painful diabetic neuropathy
*Pain, Volume 116, Issue 1-2, 1 July 2005, Pages 109-118*
Goldstein, D.J.; Lu, Y.; Detke, M.J.; Lee, T.C.; Iyengar, S.

23 Screening for pain phenotypes: Analysis of three congenic mouse strains on a battery of nine nociceptive assays
*Pain, Volume 126, Issue 1-3, 1 December 2006, Pages 24-34*
Mogil, J.S.; Ritchie, J.; Sotocinal, S.G.; Smith, S.B.; Croteau, S.; Levitin, D.J.; Naumova, A.K.

24 Osteoarthritis and joint pain • Review article
*Pain, Volume 123, Issue 1-2, 1 July 2006, Pages 6-9*
Kidd, B.L.

25 The influence of prognostic factors on neck pain intensity, disability, anxiety and depression over a 2-year period in subjects with acute whiplash injury
*Pain, Volume 125, Issue 3, 1 December 2006, Pages 244-256*
Berglund, A.; Bodin, L.; Jensen, I.; Wiklund, A.; Alfredsson, L.
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Suggested Guidelines:
The non-surgical management of chronic low back pain

Dr Corrie Avenant M.B.Ch.B(Stell) DA(SA) FCA/GKN(SA)

Summary
These guidelines for the management of low back pain give a comprehensive picture. They begin with an analysis of the structural basis and etiology of low back pain. Information is then given on diagnostic techniques and treatment approaches for different types of low back pain. Detailed evidence of the effectiveness of a variety of treatments is provided, taken from a wide variety of studies. The information is summarised in two useful algorithms and a diagram illustrating the multidisciplinary approach to the management of low back pain.

1. Structural Basis:
For a structure to cause pain, it must fit the following description1:
• It should have a nerve supply;
• It should be susceptible to disease or injuries that are known to be painful;
• It should have been shown to be a source of pain in patients, using diagnostic techniques of known reliability and validity.

By using controlled, comparative, and double diagnostic blocks, it has been established that lower back pain is of the following types2:
• 40% is facet joint pain;
• 26% is discogenic pain;
• 2% is sacro-iliac joint pain;
• 13% is segmental dural/nerve root pain;
• 13% is unknown.

The causes of these types of low back pain are as follows:

1. Facet Joint Pain:
• Studies involving controlled diagnostic blocks of facet joints have demonstrated that facet joints are implicated in spinal pain for 45% of patients with low back pain.3,4

2. Intervertebral Discs:
• In 1934, Mixter and Barr described the disc as a source of pain.5
• In a controlled study, Schwarzer found that the low back pain of 39% of chronic sufferers was due to internal disc disruption.6

3. Dorsal Root Ganglion:
• The Dorsal Root Ganglion plays an important role in the mechanism of spinal pain.
• Experiments suggest that when the DRG is injured, oedema in the dorsal root ganglion underlies the production of nerve root pain in patients with disc herniation.7,8

4. Sacro-Iliac Joint:
• The Sacro-Iliac Joint is well innervated, fed by myelinated and unmyelinated axons capable of nociception.9,10
• In studies utilising controlled, comparative local anaesthetic blocks in patients with low back pain in whom there was a high index of suspicion for pathology, the prevalence of sacro-iliac joint dysfunction was established as 18.5%.11
• A high prevalence of pain caused in this way may be seen in patients with lumbar fusion.12

5. Post-Laminectomy Syndrome (FBSS):
• The term ‘Failed Back Surgery Syndrome’ is used to describe a cluster of syndromes resulting from surgery where the expectations of the patients and spine surgeon have not been met.
**Etiologies:**

The etiologies of low back pain are summarised as follows:

1. **Surgical:**
   - Stenosis

2. **Disc Disruption:**
   - Recurrent disc herniation
   - Retained disc fragment
   - Spondylolisthesis

3. **Non-Surgical:**
   - Epidural or intraneural fibrosis
   - Degenerative disc disease
   - Radicular pain
   - Facet joint pain
   - Sacro-iliac joint pain
   - Discitis
   - Arachnoiditis

Note: Epidural fibrosis is caused by FBSS in up to 36% of all cases.15,16

4. **Other:**
   - Facet joint arthritis
   - Incomplete (or inaccurate) surgical intervention
   - Fibromyalgia
   - Myofascial syndrome

Certain of these etiologies can be treated by interventional pain methods, e.g. epidural fibrosis, facet joint dysfunction, internal disc dysfunction, recurrent disc herniation, spinal stenosis.13,14

**Spinal Stenosis:**

Narrowing of the spinal canal resulting in:

- Symptoms and signs caused by entrapment and compression of intra-spinal vascular and nervous structures.17

The causes of narrowing of the spinal canal are:

- Disc bulging, protrusion and herniation
- Osteophytes and arthritic changes of facet joints18

Treatment options for Spinal Stenosis are as follows:

- Surgery
- Non-Operative:
  - Conservative Rx
  - Interventional Techniques

2. **Diagnosis**

2.1. **Clinical Examination:**

**Purposes**

The purposes of exploring the history of the condition, and of physical examination and special investigations are to9:

a) Determine “red flag” conditions, e.g.
   - Tumours;
   - Fractures;
   - Progressive Neurological outfall;
b) Determine if lower back pain is of mechanical (nociceptive) or neurogenic (neuropathic) origin. 

The following table outlines the differences between Radicular Pain and Somatic Referred Pain.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Radicular Pain:</th>
<th>Somatic Referred Pain:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Entire length of lower limb <strong>BUT</strong> Below knee &gt; above knee Narrow band Traveling</td>
<td>Traveling proximal &gt; distal Wide Area Relatively fixed in location</td>
</tr>
<tr>
<td>Quality</td>
<td>Shooting, lancinating, Like electric shock</td>
<td>Dull, aching, like an expanding pressure</td>
</tr>
<tr>
<td>Depth</td>
<td>Deep as well as superficial Radiofrequency</td>
<td>Deep only, lacks any cutaneous quality</td>
</tr>
</tbody>
</table>

MRI is the primary diagnostic imaging of choice. The indications for further diagnostic testing are:

- Foot drop
- Progressive weakness
- Fever
- Unexplained weight loss
- Change in bladder or bowel function
- Persistence or worsening of symptoms beyond 6 weeks

From this information a decision is made on the proper treatment.

2.2. Diagnostic Blocks:

Diagnostic blocks are used to diagnose in cases of low back pain. This is because most of the maneuvers in physical examination place stress on several structures simultaneously, making it difficult for a conclusive diagnosis to be reached. It must be acknowledged, however, that the accuracy of diagnoses based on these blocks cannot always be relied upon, as they vary in sensitivity, specificity, accuracy and quality. False positives, negatives and the placebo effect can exacerbate the difficulties of diagnosis.

**Types of Diagnostic Block**

Evidence-based diagnostic blocks for lower back pain include:

1. Facet (Zygapophysial) Blocks
2. Provocative Discography
3. Transforaminal Epidurals
4. SI Joint Infiltrations

**Mechanisms of Neural Blockades**

The postulate mechanism of a neural blockade is that it alters or interrupts nociceptive pain. It does so by:

a) Local Anaesthetic which interrupts the pain spasm cycle, dampening the C-fibre activity.

b) Corticosteroids which reduce the inflammation by inhibiting synthesis or release of pro-inflammatory substances. The methods of Corticosteroid action are:

- Membrane stabilisation
- Inhibition of neural peptide synthesis
- Blockade of Phospholipase A2
- Suppression of sensitisation of dorsal horn neurons

Detail with regard to each type of diagnostic block follows below:

1. **Facet (Zygapophysial) Blocks**

For facet (Zygapophysial) joint pain, controlled diagnostic blocks with two different Local Anaesthetics are the only means to confirm the diagnosis.
2. Provocative Discography

Provocative discography is a procedure that characterises the patho-anatomy of the intervertebral disc and thereby enables the physician to determine whether the disc is the source of the pain. The discography of normal discs is never painful.28,29 Discography has high accuracy rates,30 and is important in ensuring that informed decisions are made.30

3. Transforaminal Epidurals

The diagnostic selective nerve root block (Transforaminal Epidural) is indicated:

- Where a patient has persistent pain;
- When neither history, examination, imaging and other precision diagnostic injections, nor electrophysiological testing identify the pain generator;34
- Where the patient presents with radicular pain.

Sensitivity to this diagnostic block can be as much as 100%.

4. SI Joint Infiltrations

No history, examination, manpower or radiological feature can enable a definite diagnosis of SI Joint Pain.32,33

3. Levels of Evidence:

A wide range of evidence is presented in the following section, indicating the effectiveness of a variety of treatment systems. Criteria of the studies included in these guidelines were gathered from the Agency for Healthcare Research & Quality (AHRQ) and the Cochrane Review.

Different types of evidence have been included:

- Systematic Reviews;
- Randomised Clinical Trials;
- Observational Studies;
- Diagnostic Studies.

If randomised trials were not available for a particular procedure/technique, non-randomised trails or observational studies have been used.

The different levels of evidence are:

Level I:

- Conclusive: Research-based evidence from multiple relevant and high quality scientific studies;

Level II:

- Strong: Research-based evidence from at least one properly designated randomised, controlled trial of appropriate size (with at least 60 patients in the smallest group);

Level III:

- Moderate: Evidence from a well-designed small-randomised trial or evidence from well-designated trials without randomisation;

Level IV:

- Limited: Evidence from well-designed non-experimental studies from more than one centre or research group;

Level V:

- Intermediate: Opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees.

4. Treatment Options:

Treatment needs to be provided in a compassionate, co-ordinated fashion that addresses the multidimensional needs of the individual.35 For patients with extensive pain or disability, multidisciplinary care is essential, to optimise a positive and functional outcome.36

The team approach should focus on all of the following therapies:37

- Counselling
- Social work
- Physical therapy
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4.1 Non-Pharmacologic Management:

This includes:

• Exercise (strengthening exercises, walking, bicycling and swimming). Ideally exercises should be incorporated into a home program that becomes part of an on-going lifestyle.38
• Education of the sufferer towards protection of the spine during the normal activities of daily living.39

Treatment goals include:

• Preventing symptoms, if possible;
• Reducing pain severity or frequency;
• Improving physical functioning;
• Reducing psychological distress;
• Improving overall quality of life;
• Minimising possible adverse effects of treatment.

4.2 Pharmacological Management:

Nociceptive Pain

For Nociceptive pain, anti-inflammatory agents are the basis of treatment.40,41,42

Neuropathic Pain: 43,44

Most evidence for neuropathic pain treatment is derived from diabetic neuropathy and postherpetic neuralgia.45

First line drugs include:46,47
• Gabapentin;
• Tricyclic antidepressants;
• Opioids.

This will be discussed under the subject “Protocols for neuropathic pain”.

4.3 Therapeutic Blocks:

The time period for the therapeutic cortisone block is seen as:

• Short Term: Less than 6 weeks
• Long Term: Longer than 6 weeks

For the ablation techniques, short term and long term may be defined as:48
• Short Term: Less than 3 months
• Long Term: Longer than 3 months

4.3.1: Intra-Articular: Zygapophysial Blocks:

The evidence for intra-articular injections is indicated on the table below:

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodological Quality Score(s):</th>
<th>Initial Relief:</th>
<th>Long-term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHRQ Score(s)</td>
<td>Cochrane Score(s)</td>
<td>No. Patients</td>
<td>6 Weeks</td>
</tr>
<tr>
<td>Manchik anti et al (483)49</td>
<td>RA 8/10</td>
<td>6/10</td>
<td>73</td>
<td>100%</td>
</tr>
</tbody>
</table>

RA=randomized; P=positive; N=negative
Summary:
Moderate evidence for relief in the short term has been proven.
Limited evidence for relief in the long term has been proven.

4.3.2: Median Branch:
The following table shows evidence for the effectiveness of Cortisone Median Nerve Blocks:

<table>
<thead>
<tr>
<th>Study:</th>
<th>Study Characteristics</th>
<th>Methodological Quality Score(s):</th>
<th>Initial Relief:</th>
<th>Long Term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AHRQ Score(s): Cochrane Score(s)</td>
<td>No. Pts.</td>
<td>&lt;6 Weeks</td>
<td>3 Mths: 6 Mths: Short-Term Relief &gt; 6 Weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Kleef et al50</td>
<td>PC, RA, DB</td>
<td>9/10</td>
<td>7/10</td>
<td>C=16 T=15</td>
<td>38% vs 67% 19% vs 47% 13% vs 47%</td>
</tr>
<tr>
<td>Dreyfuss et al51</td>
<td>P</td>
<td>8/8</td>
<td>15</td>
<td>93%</td>
<td>87% 87% 87%</td>
</tr>
<tr>
<td>Schofferman and Kine52</td>
<td>R</td>
<td>8/8</td>
<td>12</td>
<td>83%</td>
<td>83% 83% 83%</td>
</tr>
<tr>
<td>Schaefer53</td>
<td>R</td>
<td>7/8</td>
<td>117</td>
<td>NA</td>
<td>NA 68% N</td>
</tr>
<tr>
<td>Tzan and Tasker54</td>
<td>R</td>
<td>6/8</td>
<td>90</td>
<td>NA</td>
<td>NA 41% NA</td>
</tr>
<tr>
<td>North et al55</td>
<td>R</td>
<td>7/8</td>
<td>42</td>
<td>45%</td>
<td>45% 45% 45%</td>
</tr>
<tr>
<td>Vad et al56</td>
<td>P</td>
<td>8/8</td>
<td>12</td>
<td>83%</td>
<td>83% 83% 83%</td>
</tr>
</tbody>
</table>

R=Retrospective; P=Prospective; RA=Randomized; PC=Placebo Controlled; DB=Double Blind; C=Control; T=Treatment; N/A=Not available; P=Positive; N=Negative; LA=Local Anesthetic; RADIOFREQUENCY_TN=Radiofrequency Neurotomy

Summary:
Evidence of relief is moderate.

4.3.3 Median Branch Neurotomy:

Two types of Radiofrequency
There are two types of Radiofrequency which can be used:

1. Conventional or Continuous:
   - The temperature of the procedure is 45°C and more. At these temperatures nerve damage takes place.

2. Pulsed Radiofrequency:
   - As the temperature is less than 45°C, tissue does not coagulate further. The heat which is generated is dissipated between pulses. Only transient inhibition of evolved synaptic activity takes place.

The mechanism of action:

1. With pulsed Radiofrequency, the mechanism is definitely not heat. It is suggested that the electrical field rather than the temperature induces change in the nerve cells and has a Neuromodulatory effect on the pain procession mechanism.

2. Recently, a new theory of mechanism was published by van Zandert. He compared C-fos in pulsed Conventional Pulsed Radiofrequency and Sham groups. Under normal circumstances, the exposure of culture cells to an electric field leads to the up-regulation of C-fos. He found that Pulsed Radiofrequency and conventional Radiofrequency lead to similar increases in C-fos.

3. The persistence of expression of C-fos for 7 days and longer after Radiofrequency (exceeding the length of time of C-fos expression caused by effects of surgery) seems to be evidence of sustained activation of the pain-inhibitory mechanism.

Evidence:
The evidence of trials of Medial Branch Neurotomy (Percutaneous Radiofrequency) is as follows:
Evidence for short and long term is strong.

### 4.3.4. SI Joint:

Therapeutic injections which can be used for Sacro-Iliac Joint pain are:

- **a) Intra-articular injection**
- **b) Percutaneous Radiofrequency**

#### Evidence:

**a) The evidence of trials of the intra-articular injection is as follows:**

<table>
<thead>
<tr>
<th>Study:</th>
<th>Study Characteristics:</th>
<th>Methodological Quality Score(s):</th>
<th>No. Pts:</th>
<th>Initial Relief:</th>
<th>Long Term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breivik et al(^5)</td>
<td>RA, DB</td>
<td>AHRQ Score(s): 8/10 Cochrane Score(s): 7/10</td>
<td>C=19 T=16</td>
<td>&lt;6 Weeks: 25% vs 67%</td>
<td>3 Mths: 19% vs 63% 6 Mths: 20% vs 50%</td>
<td>P P</td>
</tr>
<tr>
<td>Bush and Hillier(^6)</td>
<td>RA, DB</td>
<td>AHRQ Score(s): 8/10 Cochrane Score(s): 8/10</td>
<td>C=11 T=12</td>
<td>&lt;6 Weeks: 100%</td>
<td>NA</td>
<td>NA 64% vs 83%</td>
</tr>
<tr>
<td>Matthews et al(^7)</td>
<td>RA/DB</td>
<td>AHRQ Score(s): 8/10 Cochrane Score(s): 7/10</td>
<td>C=34 T=23</td>
<td>&lt;6 Weeks: 56% vs 67%</td>
<td>NA</td>
<td>SMPR NA</td>
</tr>
<tr>
<td>Helsa and Breivik(^8)</td>
<td>RA/DB</td>
<td>AHRQ Score(s): 7/10 Cochrane Score(s): 7/10</td>
<td>69 crossover</td>
<td>NA</td>
<td>NA</td>
<td>NA 59% vs 25%</td>
</tr>
<tr>
<td>Revel et al(^9)</td>
<td>RA</td>
<td>AHRQ Score(s): 7/10 Cochrane Score(s): 6/10</td>
<td>Forceful Inj=29 Regular=31</td>
<td>NA</td>
<td>NA</td>
<td>NA 49% vs 19%</td>
</tr>
<tr>
<td>Meadeb et al(^10)</td>
<td>RA</td>
<td>AHRQ Score(s): 6/10 Cochrane Score(s): 6/10</td>
<td>D=16 D+G=15 G=16</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>McGregor(^11)</td>
<td>RA</td>
<td>AHRQ Score(s): 6/10 Cochrane Score(s): 5/10</td>
<td>Caudal=14 Interlaminar=16</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study:</th>
<th>Study Characteristics:</th>
<th>Methodological Quality Score(s):</th>
<th>No. Pts:</th>
<th>Initial Relief:</th>
<th>Long Term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maugars et al(^12)</td>
<td>RA</td>
<td>AHRQ Score(s): 6/10 Cochrane Score(s): 6/10</td>
<td>10 pts/ 13 w/ articulations</td>
<td>62%</td>
<td>62%</td>
<td>58%</td>
</tr>
<tr>
<td>Hanly et al(^13)</td>
<td>P</td>
<td>AHRQ Score(s): 5/8 Cochrane Score(s): -</td>
<td>19</td>
<td>SI</td>
<td>SI</td>
<td>NI</td>
</tr>
<tr>
<td>Slipman et al(^14)</td>
<td>R</td>
<td>AHRQ Score(s): 6/8 Cochrane Score(s): -</td>
<td>31</td>
<td>P</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^a=\)prospective; \(R=\)retrospective; \(RA=\)randomized; \(PC=\)placebo controlled; \(DB=\)double blind; \(C=\)control; \(T=\)treatment; \(N/A=\)not available; \(P=\)positive; \(N=\)negative; \(ND=\)Negative Discography; \(PD=\)Positive Discography; \(D=\)Disruption; \(G=\)Glucocorticoid

#### Summary:

Evidence for short and long term is strong.

**4.3.4. SI Joint:**

Therapeutic injections which can be used for Sacro-Iliac Joint pain are:

- **a) Intra-articular injection**
- **b) Percutaneous Radiofrequency**

#### Evidence:

**a) The evidence of trials of the intra-articular injection is as follows:**

<table>
<thead>
<tr>
<th>Study:</th>
<th>Study Characteristics:</th>
<th>Methodological Quality Score(s):</th>
<th>No. Pts:</th>
<th>Initial Relief:</th>
<th>Long Term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maugars et al(^12)</td>
<td>RA</td>
<td>AHRQ Score(s): 6/10 Cochrane Score(s): 6/10</td>
<td>10 pts/ 13 w/ articulations</td>
<td>62%</td>
<td>62%</td>
<td>58%</td>
</tr>
<tr>
<td>Hanly et al(^13)</td>
<td>P</td>
<td>AHRQ Score(s): 5/8 Cochrane Score(s): -</td>
<td>19</td>
<td>SI</td>
<td>SI</td>
<td>NI</td>
</tr>
<tr>
<td>Slipman et al(^14)</td>
<td>R</td>
<td>AHRQ Score(s): 6/8 Cochrane Score(s): -</td>
<td>31</td>
<td>P</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Summary:**

Evidence is moderate for short term\(^6\) and limited for long term.\(^5\)

#### Evidence:

**b) The evidence of trials of the Percutaneous Radiofrequency is as follows:**
### Intradiscal Electrothermal Therapy (IDET):

IDET is a minimally invasive interventional technique to achieve disc decompression. It is performed by introducing a flexible catheter (containing a resistive coil) into the disc.

### Evidence:

The evidence from trials of the Intradiscal Electrothermal Therapy (IDET) is as follows:

<table>
<thead>
<tr>
<th>Study: Study Characteristics:</th>
<th>Methodological Quality Score(s):</th>
<th>Initial Relief:</th>
<th>Long-Term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHRQ Score(s):</td>
<td>Cochrane Score(s):</td>
<td>No. Pts:</td>
<td>&lt;3 Mths:</td>
</tr>
<tr>
<td>Pauza et al 71</td>
<td>RA, DB, PC</td>
<td>10/10</td>
<td>10/10</td>
<td>C=27 T=37</td>
</tr>
<tr>
<td>Karasek &amp; Bogduk et al 72</td>
<td>P</td>
<td>9/10</td>
<td>-</td>
<td>C=17 T=35</td>
</tr>
<tr>
<td>Saal and Saal 73</td>
<td>P</td>
<td>6/10</td>
<td>-</td>
<td>58</td>
</tr>
<tr>
<td>Gerszten et al 74</td>
<td>P</td>
<td>6/10</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Mekhail and Kapural 75</td>
<td>P</td>
<td>5/10</td>
<td>-</td>
<td>32</td>
</tr>
<tr>
<td>Lee et al 76</td>
<td>P</td>
<td>5/10</td>
<td>-</td>
<td>62</td>
</tr>
<tr>
<td>Lutz et al 77</td>
<td>P</td>
<td>5/10</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Freedman et al 78</td>
<td>P</td>
<td>6/10</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>Spruit 79</td>
<td>P</td>
<td>5/10</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Derby et al 80</td>
<td>R</td>
<td>5/10</td>
<td>-</td>
<td>99</td>
</tr>
</tbody>
</table>

P = prospective; PC = placebo control; RA = randomized; R = retrospective; C = control; T = treatment; SI = significant improvement; NA = not available; NSI = no significant improvement; P = positive; N = negative

### Summary:

The evidence is undetermined.
Summary:
Evidence is strong for the short term and moderate for the long term.

4.3.6. Transforaminal Injections:
Transforaminal injections with cortisone can be used as a therapeutic technique.

Evidence:
The evidence from trials of the Transforaminal injections is as follows:

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodological Quality Score(s):</th>
<th>No. Pts:</th>
<th>Initial Relief:</th>
<th>Long Term Relief:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHRQ Score(s): Cochrane Score(s):</td>
<td>&lt;6 Weeks:</td>
<td>3 Mths:</td>
<td>6 Mths:</td>
<td>Short-Term &lt;6 Weeks:</td>
</tr>
<tr>
<td>Riew et al</td>
<td>RA, DB 8/10 7/10 IA=27 Los=28 33% vs 77% 33% vs 77% 33% vs 77%</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karppinen et al</td>
<td>RA, DB, PC 9/10 8/10 Ca=80 Ta=80 NA NA NA</td>
<td>N N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devulder et al</td>
<td>RA 6/10 5/10 60 NS NS NS</td>
<td>N N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vad et al</td>
<td>RA 7/10 7/10 48 48% vs 84% 8% vs 84% 8% vs 84%</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas et al</td>
<td>RA 6/10 5/10 Ca=15 Ta=16 SI SI SI</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutz et al</td>
<td>P 4/8 - 69 75% 75% 75%</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butterman #7</td>
<td>P 4/8 - 232 SI SI SI</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butterman #8</td>
<td>P 4/8 - 169 NA NA</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botwin #9</td>
<td>P 4/8 - 34 75% 75% 75%</td>
<td>P P</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=prospective; PC=placebo controlled; RA=randomized; DB=double blind; LA=Local Anesthetic; S=Steroids SI=significant improvement; C=control; T=treatment; NA=not available; P=positive; N=negative; vs=versus

Summary:
The evidence for:

a) Lumbar nerve root pair is:
   • Strong for short term
   • Moderate for long term
b) FBSS and spinal stenosis is limited
c) Disc extrusion is undetermined

4.3.7. Adhesiolysis:
The purpose of Adhesiolysis treatment is to eliminate the effects of scar formation, which can physically prevent the direct application of drugs to nerves or other tissue.

4.3.7.1. Epidural Adhesiolysis:
The evidence from trials of Epidural Adhesiolysis is as follows:
4.3.7.2. Endoscopy Adhesiolysis:
The evidence from trials of Endoscopy Adhesiolysis is as follows:

**Summary:**

a) The evidence for the effectiveness of an Epidural is strong for chronic low back pain and lower extremity pain.

b) The evidence for success of an endoscopy is:
   - Strong for short term relief;
   - Moderate for long term relief in chronic refractory low back pain and lower extremity pain.

5. Spinal Cord Stimulator (SCS):
The mechanism of the SCS is based on the Gate Control Theory. Stimulation of large, low threshold fibres would close the gate to reception of small fibre information (C & A delta fibres).

**Evidence: “Failed Back Surgery Syndrome” (FBSS):**

i) In a systemic review of FBSS patients, the aim was to determine whether SCS or Re-Operation was more effective for the relief of pain.

ii) A second aim was to investigate SCS as a “Late” or “Last Treatment” Strategy.
Managing the depths of severe pain.

MST Continus - oral controlled-release morphine sulphate tablets in terminally ill patients:

Safe and effective 12-hr dosing schedule (1)
Enhances patient comfort by improving medication compliance and allowing for a full night's sleep (1)

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- Melts in the mouth - does not need to be taken with water
- With a pleasant mint flavour

......with the established benefits of Tramadol

Effective for the treatment of moderate to moderately severe......

....ACUTE pain.
- Postoperative pain

....CHRONIC pain.
- Cancer pain - as step 2 analgesia
- Osteoarthritis
- Low back pain
- Neuropathic pain

References:
1. Registered

www.adcock.co.za

Addison Ingram Limited. Reg. No. 1948/03/385/06. Private BAG X98, Bryanston, 2011. Tel: (011) 846-3000
Study 1
In a review of 50 patients with “Failed Back Surgery Syndrome” who presented with Radicular Neuropathic Pain, patients were randomised to SCS or re-operation. The following outcomes were measured:

- 50% Pain relief;
- Patient preference for treatment;
- Opioids and analgesic use at follow-up.

Patients were followed up for 3 years.

Conclusions
The conclusion was that SCS is significantly more successful than re-operation.

- 47% of those treated with SCS had pain relief versus 12% of re-operated patients;
- 13% of those treated with SCS needed Opioids versus 42% of re-operated patients;
- 87% of those treated with SCS reported stable or decreased need for Opioids
- 21% of those treated with SCS crossed over, compared to 54% of re-operated patients.

Study 2
A meta-analysis was conducted of 65 case studies of FBSS-related Refractive Neuropathic Back/Leg Pain, treated with SCS. They were followed up for 10 years. Findings were as follows:

- 62% (> 50%) had pain relief;
- 53% no longer needed an Analgesic;
- 70% expressed satisfaction with the treatment;
- 40% were able to return to work.

6. Drug Delivery:
Oral / Systemic Administration
The following are problems experienced with oral/systemic administration of drugs:

- Therapeutic effects are limited or reduced because of partial degradation;
- Higher dosage leads to intolerable side effects;
- It is only an option when pain control with conventional medication leads to inadequate side effects.

Intra-spinal Drug Delivery
It is appropriate to use intra-spinal drug delivery when:

- The oral route and other less invasive methods are inadequate;
- The effectiveness of the analgesia has been tested;
- There is good communication among the staff, the patient and the patient's supporters;
- The general and psychological status of the patient is stable.

To optimise the chances of a successful treatment outcome, patients should be selected carefully and undergo a trial period.

Note: Bolus Intrathecal Injection of Morphine was equally as effective as Epidural Infusion and was less costly.

Side effects & prevention of side effects:
Side effects of long term spinal opioids e.g. hypogonadotropic hypocorticism:

- 15% developed central hypocorticism
- 15% developed growth hormone deficiency

Endocrinological side effects can be minimised by using hormonal supplementation.

Opioid inflammatory mass formulation can be minimised by ensuring high flow rates with low drug concentration.

6. Algorithm 1:
Interventional Techniques for Lower Back Pain
6. Algorithm 1: 
Interventional Techniques for Lower Back Pain

Algorithm 2: 
Radicular Back Pain:

Chronic Low Back Pain
Based on Clinical Evaluation

Facet Joint Blocks
Positive
Negative

Provocative Discography
Positive
Negative

SI Joint Injection
Positive
Negative

Discography
Positive
Negative

SI Joint Block
Negative
Positive

Radio Frequency (5)
Negative
Positive

IDET (3)
Positive
Negative

Facet Joint Blocks
Positive
Negative

Transformaminal Epidural Injection

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7. Figure 1: Multi Disciplinary Approach to Lower Back Pain

**Evidence:**

- **Morphine Implant**
  - 3
- **Neuro Stimulation**
  - 2
- **Strong Opioids + Antidepressants + Anticonvulsants**
  - 1
- **Adhesiolysis**
  - Epidural + Endoscopic
  - 2
- **Moderate Opioids + Antidepressants + Anticonvulsants**
  - 1
- **Infiltration - Radiofrequency**
  - 3
- **Mild Opioids + Antidepressants or Anticonvulsants**
- **Infiltrations - Local Anaesthetic + Cortisone**
  - 3
- **Paracetamol NSAIDs / COX II**
  - 1
- **Physiotherapy / Occupational Therapy / Psychology / Dietician**
  - ?

---

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IASP / Neuropathic Manuel


IASP / Neuropathic Manuel


Hoda PE, Brović H. Epidural anesthesia and epidual steroid injection for treatment of chronic low back pain and sciatica. Tidsskr Nor Laegeforen 1979; 99:936-939


Bogduk N, Karasek M. Two year follow-up of a controlled trial of intradiscal electrothermal ablation for chronic low back pain resulting from internal disc disruption. Spine J 2002; 2:343-350


Gerezen PC, Welch WC, McGraith PM, Willis SL. A prospective outcome study of patients undergoing intradiscal electrothermy (IDET) for chronic low back pain. Pain Physician 2002; 1:360-1364


We have always played open cards with you...

Composition: Ketorolac tromethamine 10 mg/mL, 20 mg/mL. Contains ethyl alcohol 10% v/v.

Indications: Short-term management of moderate post-operative pain.

Contra-indications: Active peptic ulcer, gastro-intestinal bleeding • Anticoagulant therapy • Haemorrhagic diathesis • Hypersensitivity to ketorolac or other NSAIDs, allergies to aspirin or other non-steroidal anti-inflammatory drugs • Ophthalmic cirrhosis, diabetes or asthma • Pregnancy or lactation • Children under 15 years of age or patients over 70 years of age.
Persistent pain and uncomfortable sensations in persons with multiple sclerosis

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Received 21 February 2006; received in revised form 24 June 2006; accepted 24 July 2006

Abstract

The experience of pain has been documented in small studies of individuals with multiple sclerosis (MS). The present study examines the prevalence of persistent pain and uncomfortable sensations among participants in the large North American Research Committee on MS (NARCOMS) Patient Registry. Registrants (10,176) responded to a questionnaire on pain and 7579 reported experiencing some level of pain during the month prior to the survey. Among the respondents 49% reported mild to severe pain and 49% of those indicated severe pain. Increased pain intensity was positively associated with gender (more women), multiple pain sites (51% of the severe pain group reported four or more pain sites), and constancy of pain (44% among the group with severe pain). There was also a positive association with increased MS-related disability, relapsing-worsening type of MS, and depression. Respondents with severe pain made greater use of the healthcare system and of prescribed analgesics, but were less likely to be satisfied with their doctors’ efforts to manage their pain. About one-third of the patients with moderate pain and 18% of those with severe pain reported no consultations for their pain. The effects of pain severity were fully evident in the respondents’ daily life, their work, mood, recreational activities and enjoyment of life. Our results indicate that the high prevalence of MS-related severe pain, low satisfaction with management of intense pain, and the perceived interference with quality of life indicators necessitate greater attention by healthcare providers to the management of pain and uncomfortable sensations in the MS population.

Keywords: Multiple sclerosis; MS-related pain; Painful sensations; Pain intensity; Pain sites; Quality of life

1. Introduction

Estimates of pain range from 13% to 86% (Goodin, 1999; Benrud-Larson and Wegener, 2000; Svendsen et al., 2003) among MS patients. Variations in methodology contribute to this wide range of estimates. Three studies were based on population samples, but were

small in size (Goodin, 1999; Ehde et al., 2003; Svendsen et al., 2003). Several studies placed prevalence estimates at about 50% of MS patients and provided some information about the specific pain conditions (Archibald et al., 1994; Indaco et al., 1994; Goodin, 1999; Rae-Grant et al., 1999; Ehde et al., 2003; Solaro et al., 2004). In only two studies reviewed was pain intensity quantified using a standardized measure (Archibald et al., 1994; Ehde et al., 2003). Dysesthetic leg pain was the most commonly reported problem, followed by chronic back pain and recurrent painful spasms of the legs (Rizzo, 2003; Solaro et al., 2004). The most
common acute pain conditions were neuralgias, Lhermitte’s sign, pain associated with optic neuritis, and brief painful tonic spasms (Indaco et al., 1994). Pain in MS patients was reported to be intermittent and to occur in more than one site (Archibald et al., 1994). Furthermore, a few of these investigators who report on pharmacologic management of MS-related pain show mostly use of non-opioid analgesics, and lesser use of adjuvant medications commonly used to treat neuropathic pain (Goodin, 1999; Brichetto et al., 2003; Ehde et al., 2003; Rizzo, 2003; Svendsen et al., 2003).

The aims of the current study are: (1) to provide data on the prevalence, sites, and types of persistent pain in a large, well-characterized sample of community dwelling persons with MS; (2) to examine the relationship between severity and number of pain sites, duration and constancy of pain; (3) to examine the relationship between severity of pain and MS subtype, disability, and perceived interference with activities; and (4) to describe healthcare utilization, medication use, and satisfaction with management of MS-related pain.

2. Methods

2.1. Patients

The NARCOMS (North American Research Committee on MS) Patient Registry, a project of the Consortium of MS Centers (CMSC), is a longitudinal database initiated in 1996 to provide a resource for clinical trials and long-term prospective studies (Vollmer et al., 1999). Patients are recruited through the National MS Society, pertinent publications, support groups, the internet, and neurologists’ offices. At the time of this special study (2002), the registry had 18,725 active participants and it has increased to over 24,000 (2005) since then.

IRB approval is received for each questionnaire that is mailed to the registrants, and it was received for this study as well.

Disability and handicap data are collected using validat-ed patient-driven instruments. Time sensitive data (e.g. current treatments, clinical status) are updated semiannually and new questions targeting specific hypotheses are investigated.

Data collected in 2002 focused on registrants’ experience of pain and uncomfortable sensations. There was a 54% (10,176) response to the update questionnaire and of these participants, 74.5% (7579) reported the presence of at least some pain. These respondents were asked to choose symptom descriptors, severity of pain, and whether the pain was constant or intermittent. The questionnaire instructed respondents to select all sites of pain experienced over the previous one month. For each site, respondents were asked to rate their overall satisfaction with their providers’ efforts to manage their pain on a 0 (none) to 10 (worst imaginable) rating scale. Respondents who reported “no pain” were used as a comparison group for some of the analyses.

2.2. Measures

2.2.1. MS-subtype

Participants in the registry are assigned a disease subtype based on the presence of relapses in the course of their disease and their disability progression. The subgroups are: (1) participants with ‘relapsing-stable’ MS who report a relapse at some time during the course of their disease but with improvement or no change in their disability level during the year prior to the time of completing the questionnaire; (2) participants with ‘relapsing-worsening’ MS who also report a relapse but indicate that their symptoms have worsened within the last year; and (3) participants with ‘primary progressive’ MS who have never experienced a relapse at any time in their disease course.

2.2.2. MS-related disability

Disability and handicap data are collected using two validated patient-driven instruments: (1) the PDSS (Patient-Determined Disease Steps) (Hohol et al., 1999) is an eight level ordinal scale (0 = normal to 8 = bedridden) that measures disability and correlates highly with EDSS (Kurtzke, 1983) (Spearman correlation = 0.93), and (2) the Performance Scales (Schwartz et al., 1999; Marrie et al., 2004) that measure handicap in nine domains of function, including pain. Participants who reported “no pain” were used as a comparison group for some of the analyses.

2.2.3. Pain experience

In the section of the questionnaire on pain and uncomfortable sensations, information was collected with a multi-level nested questionnaire developed specifically for this study. The questionnaire instructed respondents to select all sites of pain experienced over the previous one month. For each site, respondents were asked to choose symptom descriptors, severity of pain, and whether the pain was constant or intermittent. The list of symptom descriptors from which respondents could choose was determined empirically, largely from our collective clinical experiences, and then reviewed by patients within our clinic. Severity of pain/uncomfortable sensation was rated on a 0 (none) to 10 (worst imaginable) rating scale. Respondents were classified as having mild pain (scores 1–4), moderate pain (5–6), or severe pain (7–10), based on the highest rating in at least one site and type of pain. This classification was based on research that identified points on the ordinal scale that show distinct differences in pain-related interference (Serlin et al., 1995). Patients with pain were compared to those without pain.

Respondents were provided with a list of medications and healthcare providers for pain management, and were asked to identify healthcare providers they had seen and medications they had used. They were also asked to rate their overall satisfaction with their providers’ efforts to manage their pain on a 0 to 10 rating scale. Finally, the Medical Outcomes Study Pain Effects Scale (PES) (MSQLI, 1994) was employed as a measure of interference of pain with six quality of life factors. Each factor is rated on a scale of 1–5, and the total score can range from 6 (not at all) to 30 (interferes to an extreme degree).
3. Statistical analyses

Descriptive statistics were used to characterize the prevalence and characteristics of the pain experience. SAS (SAS, 1999) was used for all analyses. For comparisons among the pain intensity groups we used ANOVA (with Tukey's post hoc t-tests to control for multiple comparisons) and GLM for unbalanced classification. Multiple regression analyses were done to identify predictors of pain intensity (the dependent variable); MS-related disability, subtype of MS, length of disease, age, gender, duration and number of pain sites, and depression. All variables that met the 0.05 significance level were entered using stepwise selection. For the PES we used Bonferroni adjusted t-test pairwise comparisons to evaluate the difference between means among the groups.

4. Results

Demographic characteristics of the respondents to this survey were compared to those of the non-respondents in the Registry. The two groups were similar in gender distribution, years since diagnosis, and PDDS score, but the respondents were slightly older, and included fewer patients with primary progressive and worsening subtypes of MS, and less severe pain (Table 1). The higher prevalence of severe pain among non-responders, taken from previous NARCOMS questionnaires, may partly explain the non-response.

Table 1 shows the distribution of pain as it affects daily life activities of MS patients. Among participants, 35% were affected by mild to moderate pain, while 13% reported severe or totally disabling pain (10.6% plus 2.6%).

Respondents reported the frequency of different pain sites and associated symptoms (Table 2). Leg pain was the most commonly reported pain site (30%); less frequently reported sites were neck, face, eye, skin, bladder, abdomen, chest, rectum, and mouth.

Description of uncomfortable sensations varied by pain site. For example, the most frequent sensations in legs are spasms, aching, and tingling or crawling; in the back, aching, spasms, and sharp/stabbing pains; in feet and arms, aching, tingling/crawling, burning, and velvety numbness.

4.1. Pain severity comparisons

Among those who completed the pain/sensations intensity scale, 2071 (27%) were classified having mild symptoms, 1801 (24%) moderate symptoms, and 3707 (49%) severe symptoms (Table 3). Compared to respondents free of pain, all pain groups were slightly older \( (p < .0001) \), had shorter disease duration by one year \( (p = .015) \), but differed between the relapsing-stable and the other subtypes. Women were more likely to report severe pain \( (p < .0001) \), as were individuals without education after high school \( (p < .0001) \).

There was a strong association between pain intensity and MS-related disability reflected by the PDDS scores \( (p < .0001) \). Each pain group differed statistically from each other. Patients with relapsing-worsening MS were more likely to report increasing levels of pain than patients with stable disease, and this association was maintained after controlling for PDDS \( (p < .0001) \) (Table 3).

4.2. Pain characteristics

Table 4 shows increasing severity of pain was positively associated with a greater number of body sites,
long duration, and constant rather than intermittent pain ($p < .0001$).

### 4.3. Predictors of pain

Stepwise regression analysis of possible predictors of higher levels of pain showed the strongest predictor to be pain in multiple sites, but it accounted for only 17% of the pain ($p < .0001$). PDDS, gender, age, depression, MS-subtype, education, duration and constancy of pain were weak predictors, explaining an additional 6.6% of the pain. Reports of pain intensity may be influenced by the experience of pain in multiple sites; however, controlling for number of pain sites resulted in the same covariates as predictors, and no interactions were found significant. Race, duration of MS, and being treated with Disease Modifying Therapies had no predictive power.

### 4.4. Pain interference

Pain-related interference in daily life was significantly associated with increasing severity of symptoms as reflected in the PES scores (Table 5). This association remained strong after controlling for PDDS ($p < .0001$). Examination of individual scale items showed that respondents in the severe group had values indicating serious effects (i.e., ratings of 3 [quite a bit] to 5 [extreme degree]) in virtually all measured domains. The three highest rated areas where pain was perceived as having an effect were recreational activities, work, and ability to walk or move around.

#### Table 2

<table>
<thead>
<tr>
<th>Frequency of sites and their associated types of pain/sensations (includes all responses for each site)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leg(s)</strong></td>
</tr>
<tr>
<td>Frequency of pain sites</td>
</tr>
</tbody>
</table>

#### Table 3

Demographic and MS-related characteristics, by symptom severity group

<table>
<thead>
<tr>
<th>Pain/sensation symptom severity scale groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No pain</strong></td>
</tr>
<tr>
<td>Current age: mean (sd)</td>
</tr>
<tr>
<td>Years since diagnosis: mean (sd)**</td>
</tr>
<tr>
<td>Gender (%)</td>
</tr>
<tr>
<td>Female*</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Ethnicity/race (%)</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Education (%)</td>
</tr>
<tr>
<td>High School</td>
</tr>
<tr>
<td>Associate</td>
</tr>
<tr>
<td>Bachelor</td>
</tr>
<tr>
<td>Post college</td>
</tr>
<tr>
<td>Disability: PDDS mean (sd)***</td>
</tr>
<tr>
<td>MS subtype (%)</td>
</tr>
<tr>
<td>Relapsing stable</td>
</tr>
<tr>
<td>Relapsing worse</td>
</tr>
<tr>
<td>Primary progressive</td>
</tr>
</tbody>
</table>

* $p < .0001$ no pain vs. each pain group.

** $p < .01$ no pain vs. mild and severe groups.

*** $p < .0001$ each pain group different from no pain group and from each other.
4.5. Healthcare utilization

Frequency of healthcare visits was associated with heightened severity of pain (60% among the mild pain group, 72% among the moderate group, and 82% among the severe pain group). Most frequently, patients sought relief by visiting neurologists (mild group 39%, moderate 43%, severe 47%) and primary care physicians (14%, 21%, and 25%, respectively). The frequency of visits to other specialists was much lower (psychologists 6%, physical therapists 8%, and pain specialists 10%). Interestingly, only 3.6% of those with moderate to severe pain reported consulting a pain specialist, and 18% of those with severe pain reported that they had not sought any care.

Among all respondents, 66.7% reported using medications to manage their pain: 47% used one drug, 33% used two drugs, and 20% used three or more drugs. Aspirin or ibuprofen and acetaminophen were the most commonly used drugs (for 50% of the reported pains), but the severe pain group was more likely to use additional medications such as gabapentin (19%), amitriptyline (8%), oxycodone (6%), oxycodone CR (4%), clonazepam (7%), and carbamazepine (5%). Overall, the use of prescribed analgesics, including opioids, increased with pain severity (32% among those with mild pain, 39% among those with moderate, and 50% among those with severe pain).

Satisfaction with physicians’ efforts to manage symptoms was inversely associated with pain severity \((p < .0001)\). On a scale of 0–10, the mild pain group gave a mean satisfaction rating of 6.02 ± 3.56 with 29% reporting dissatisfaction (0–4 on the scale); the moderate pain group gave a rating of 5.59 ± 3.09 with 31% reporting dissatisfaction; and the severe pain group gave a rating of 5.47 ± 3.19 with 35% reporting dissatisfaction. Respondents reporting constant pain were significantly less satisfied with their pain management compared to those with intermittent pain (mean satisfaction rating 5.39 ± 3.2 vs. 5.94 ± 3.3).

5. Discussion

This study addressed concerns raised about prior studies by employing a large sample of individuals with MS who were assessed outside of a clinical setting, within a community environment, and already participating in routine surveys about the symptoms and experiences associated with MS. We collected data using standardized measures of key constructs (e.g., pain severity, disability, perceived interference with functioning). This enabled us to study not only the characteristics of those with pain versus those free of pain, but also, interrelationships between levels of increasing pain and several key variables.

Our findings extend prior research that documented a high prevalence of pain among persons with MS (Archibald et al., 1994; Goodin, 1999; Ehde et al., 2003; Solaro et al., 2004). Our results showed that pain intensity was significantly associated with reports of pain in multiple sites (extremities and back being the most common), longer duration, and presence of constant pain. Respondents used a wide array of adjectives to describe their condition, and there is evidence that the quality of the pain experience may vary with each site.

| Table 4 | Number of pain/sensations, their duration, and constancy, by symptom severity group |
|---|---|---|---|
| Number of pain sites (%) | Mild | Moderate | Severe |
| 1 | 42.2 | 23.5 | 11.8 |
| 2 | 29.3 | 24.4 | 16.4 |
| 3 | 14.9 | 20.3 | 20.2 |
| 4 or more | 13.6 | 31.8 | 51.5 |
| Duration of pain (%) | | | |
| 1-6 months | 21.4 | 16.8 | 15.8 |
| 7-12 months | 12.1 | 12.0 | 11.5 |
| 1-5 years | 35.5 | 36.5 | 33.8 |
| >5 years | 31.0 | 34.7 | 38.9 |
| Constancy of pain (%) | | | |
| Constant | 24.0 | 30.0 | 43.6 |
| On and off | 76.0 | 70.0 | 56.4 |

\(^* p < .0001.\)

| Table 5 | Pain effects scale (PES) |
|---|---|---|---|
| PES scores: (scales 1–5) mean (sd), \(^a\) | No pain | Mild | Moderate | Severe |
| Mood | 1.45 ± .77 | 1.82 ± .84 | 2.26 ± .96 | 2.77 ± 1.1 |
| Ability to walk or move around | 1.77 ± 1.2 | 2.14 ± 1.2 | 2.68 ± 1.2 | 3.19 ± 1.2 |
| Sleep | 1.45 ± .84 | 1.92 ± .92 | 2.43 ± 1.1 | 3.02 ± 1.2 |
| Normal work (both outside and at home) | 1.69 ± 1.2 | 2.06 ± 1.1 | 2.67 ± 1.2 | 3.26 ± 1.2 |
| Recreational activities | 1.80 ± 1.2 | 2.22 ± 1.2 | 2.86 ± 1.3 | 3.44 ± 1.2 |
| Enjoyment of life | 1.61 ± 1.0 | 1.99 ± 1.0 | 2.53 ± 1.1 | 3.13 ± 1.2 |
| Total PES score | 9.77 | 12.15 | 15.43 | 18.92 |

\(^p < .0001\) when adjusted for PDDS.

\(^a\) Bonferroni adjusted \(t\)-test comparisons significant at .05.
Time since MS diagnosis and racial/ethnic differences were not found to be associated with pain, in agreement with previous studies (Archibald et al., 1994; Rae-Grant et al., 1999; Svendsen et al., 2003). However, women reported increased intensity and those reporting pain were found to be slightly older than those reporting its absence. The reporting of pain severity was significantly and inversely associated with education. These findings stand in contrast to much of the literature on MS that has not documented significant associations between pain and gender, age or other demographic variables (Archibald et al., 1994; Indaco et al., 1994; Ehde et al., 2003; Solaro et al., 2004). These relationships are commonly found among other groups with chronic non-cancer pain (Unruh, 1996; Edwards et al., 2001; Reid et al., 2002).

Prior research has been inconsistent in documenting a significant relationship between the presence or severity of pain and MS disability (Archibald et al., 1994; Indaco et al., 1994; Ehde et al., 2003; Solaro et al., 2004). In our sample, pain severity was found significantly associated with increasing levels of MS disability and relapsing-worsening MS subtype. Adjusted regression analysis showed pain in multiple sites to be the strongest predictor of severity, followed by depression, and increasing MS-related disability (PDDS). Even though depression does not cause pain, it can accentuate the experience of pain severity.

Pain-related interference in daily life, participants' mood, reduced recreational activities and enjoyment of life were also significantly associated with higher levels of severity, as seen in the PES. Such relationships have been reported in other groups with painful conditions (Kerns, 1996). There is evidence that patients with chronic pain consider improved functioning to be an important treatment objective (Casarett et al., 2001).

In our sample, greater use of the health care system was significantly associated with pain severity, but only two-thirds of respondents with pain reported the use of analgesics. Under-treatment of pain is consistent with other reports which show that current use of pain medication varies from 22% to 54%, and over the counter medications are the most commonly used (Ehde et al., 2004) representing individuals who have severe pain and are not inclined to participate, as our comparison with non-respondents showed. The data are cross-sectional in nature, not allowing us to determine causal relationships amongst the variables, i.e. whether there is a causal relationship between pain severity and disability/handicap.

Despite these limitations, the current study adds to the growing literature designed to better characterize the experience of pain among persons with MS. The final recommendation from this work is for further empirical investigations and greater attention to the problem of pain and uncomfortable sensations in the MS population.

Acknowledgements
We gratefully acknowledge the programming efforts of Rajani Yadaval and Ju Li, PhD.

References


SOUTH AFRICAN PERSPECTIVE

The disability caused by MS can be devastating and often the importance of pain in a patient with multiple problems can be overlooked. The value of a national registry for the disease is demonstrated by this study and support towards the South African registry is of great importance. It is also noticeable from this study that a large percentage of patients with MS suffering from pain do not consult their health care providers regarding pain management. In the local context it is likely that this figure might be even higher due to scarcities of specialist services. It is therefore important that in patients with a known diagnosis of MS particular attention should be given to questioning regarding the existence of pain. This would be of particular importance in patients with higher disability levels and also patients presenting with elements of depression since according to this study they are more likely to present with related problems. Of particular concern in this study is that patients presenting with pain related complaints had a very low level of satisfaction with treatment. Our experience is that pain treatment in more complicated patients is often sub optimal. A need for specific diagnostic and therapeutic approaches in patients with MS is needed and specific attention to the problem of pain related to the disease should be given in training programs for health care workers dealing with patients suffering from MS.

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Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia

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Abstract

We examined between and within-person variability, affective correlates, and diagnostic differences in daily fatigue in women with rheumatoid arthritis (RA), osteoarthritis (OA), and fibromyalgia syndrome (FMS). Two hundred and fifty-five female patients recruited from the community served as participants for this project. The patients had a physician-confirmed diagnosis of RA (n = 89), OA (n = 76), or FMS (n = 90). Individuals completed an initial questionnaire and up to 32 daily diaries assessing illness symptoms and psychosocial variables (i.e., fatigue, pain, sleep problems, depression, and affect). The primary outcome for the current project was variability in fatigue. We examined affective, pain, and sleep correlates of fatigue, and tested whether these relations varied by diagnosis. Results indicated that FMS patients had higher overall levels of and greater daily variability in fatigue compared with the other pain groups. For all patients, fatigue correlated highly with lower positive affect (PA). Moreover, day-to-day increases in fatigue were associated with decreases in PA, particularly among FMS patients, and with increases in negative affect (NA). Daily pain was associated with increased fatigue in all groups, although OA patients showed less pain reactivity than either FMS or RA patients. These findings indicate that fatigue is a common feature of rheumatologic conditions. Nonetheless, there are important differences between RA, OA, and FM patients in both the everyday manifestations and the biopsychosocial correlates of fatigue.

1. Introduction

Fatigue is a subjective feeling of low vitality that disrupts daily functioning, with a lifetime prevalence in the community of roughly 20% (Addington et al., 2001). Complaints of fatigue are common to nearly every major chronic illness (Evans, 1999) and are especially prevalent in pain disorders such as fibromyalgia syndrome (FMS: Wolfe, 1999), rheumatoid arthritis (RA: Belza, 1995; Singh et al., 2003; Jump et al., 2004), and osteoarthritis (OA: Wolfe, 1999; Fishbain et al., 2003). Clinically significant fatigue has been reported by over 40% of patients with OA or RA, and by 76% of patients with FMS (Wolfe et al., 1996). In fact, pain patients rate fatigue as a key factor leading to decreased quality of life (Swain, 2000).

Although fatigue is common in all three of these pain conditions, these disorders are marked by different etiological mechanisms, possibly resulting in distinct patterns of fatigue from one illness to another. Fibromyalgia is a disorder of unknown etiology, characterized by widespread pain in soft tissue areas that is often accompanied by symptoms of fatigue, insomnia, and affective disturbance (Roth, 2001; Staud and Domingo, 2001; Thieme et al., 2004). Fatigue in FMS has been associated with pain (Nicassio et al., 2002;
Bellamy et al., 2004), stiffness (Bellamy et al., 2004), depression (Kurtz and Svebak, 2001; Nicassio et al., 2002), and disordered sleep (Nicassio et al., 2002; Landis et al., 2003). Rheumatoid arthritis is an autoimmune disease with symptoms that include pain, swelling, and tenderness in multiple joints, and elevations in pro-inflammatory cytokines, chemotactic agents capable of promoting fatigue (Kelley et al., 2003). As in FMS, fatigue in RA has been associated with poor sleep, functional disability, greater pain, and depression (Belza, 1995; Wolfe et al., 1996; Stone et al., 1997). In OA, pain arises from inflammation in single joints, and often is also accompanied by symptoms of fatigue (Wolfe et al., 1996), particularly among patients with significant joint pain. Fatigue is one of the strongest predictors of functional impairment in OA (Wolfe, 1999).

Fatigue has been linked with pain, poor sleep, and depression in FMS, RA, and OA, but differences in the etiologies of these pain conditions suggest that underlying causes of fatigue may also be distinct across disorders. Moreover, focus on negative states, while illuminating, has left unexplored the contribution of positive affective resources to our understanding of fatigue. Positive affect is a dimension of health separate from depression and other types of negative affect (Zautra, 2003; Davis et al., 2004; Zautra et al., 2005), and may be an even stronger predictor of health and functional ability than negative affect (Benyamini et al., 2000). This study aims to examine similarities and differences in the experience of fatigue in FMS, RA, and OA. Based on prior studies, we suggest that fatigue varies between people as a function of the type of illness and also varies within people along with states of pain, poor sleep, depressive symptoms, and elevated negative affect. We also suggest that fatigue varies inversely with states of positive affect, independent from negative affect.

2. Methods

2.1. Participants

Participants in this research were drawn from two ongoing studies that recruited patients with chronic pain conditions from the greater Phoenix area. Both studies were reviewed by the Institutional Review Board of Arizona State University, and all participants provided written informed consent. The first study (Study 1) examined participants with RA. The second study (Study 2) examined participants with OA and FMS.

For Study 1, 89 participants between the ages of 21 and 79 (mean = 52.3 years) were recruited from physician’s offices, advertisements, senior citizen groups, mailings to members of the Arthritis Foundation as well as referrals from VA hospital rheumatologists. For inclusion in Study 1, participants were required to be female, between 21 and 80 years of age, have a physician-confirmed diagnosis of RA, report the absence of Lupus, and not be currently taking any cyclical estrogen replacement therapies. For the current analyses, RA patients were excluded if they did not evidence bilateral tenderness or swelling during a joint exam given by a rheumatologist for a separate laboratory study conducted on the same sample. Further, to aid comparison to the FMS and OA samples, only RA patients who reported pain greater than or equal to 20 on a 0–100 numerical rating scale 2 or more days of their 30 daily diaries were included. RA patients were allowed to have OA (5 received physician confirmation of OA and RA), but those RA patients who reported also having FMS were excluded from the analyses reported here.

Similar recruitment strategies for Study 2 yielded 166 participants between the ages 38 and 72 (mean = 57.2, OA = 59.1, FMS = 55.6). Study 2 required a physician-confirmed diagnosis of OA or FMS, no diagnosed autoimmune disorders, a pain rating above 20 on a 0 to 100 scale, and no involvement in litigation regarding their condition. Those with OA only were included in the OA group; participants were included in the FMS group if they had FMS only or if they had FMS and OA. Because there is some controversy regarding objective diagnosis of FMS and physicians may have differing diagnostic criteria, we supplemented the physician confirmations of diagnoses. To further assure differences between FMS and OA-only samples with soft tissue pain, we added inclusionary and exclusionary criteria based on participant reports during the diary phase. Only FMS patients who reported soft-tissue pain in all four quadrants using a body diagram on at least one day within the month of daily diaries were included in the current analyses. OA participants were excluded if they reported soft-tissue pain in all four quadrants on at least one day during their diary phase. These new requirements led to dropping 44 participants: 27 FMS patients and 17 OA patients.

2.2. Procedure

2.2.1. Study 1

After being screened into the study, participants were sent and returned by mail an informed consent form, documents authorizing the researchers to contact their doctor to confirm their RA diagnosis, and an initial packet of questionnaires containing demographic variables. After completing the initial assessment, participants were sent a packet of 30 paper diary questionnaires and 30 postage paid envelopes. Before beginning the diaries, they were phoned by a research assistant and given instructions to fill out the diaries one half hour before bedtime each day. To insure compliance in completing the diaries on a daily basis, participants were instructed to place the previous night’s completed diary in the prepaid envelope in the mail each morning. Postmark verification was monitored to substantiate compliance with instructions. After satisfactory completion of the diary portion of the study, participants were compensated up to $90 for their time: two dollars for each diary completed, with a bonus of one dollar per diary if completing over 25 diaries. The overall rate of completion was 94%. Among other questions, the daily diary contained measures of fatigue, positive and negative affect, and daily pain. Following completion of the diaries, participants were mailed another packet of questionnaires containing measures of sleep quality and depression.
2.2.2. Study 2

After being screened into the study, participants in Study 2 completed measures similar to those in Study 1 with the following differences. Daily diaries were administered via laptop computers, which were provided to participants along with training in their use at the research lab. Built-in date checking within the software prevented data entry on days other than the correct day. At a subsequent home visit the participants were administered the sleep quality measure and the depression measure, received payment for their efforts as in Study 1, and returned the laptop. The overall rate of completion was 92%.

2.3. Measures

2.3.1. Fatigue

Daily fatigue was assessed by asking the participant: "What number between 0 and 100 best describes your average level of fatigue today? A zero (0) would mean 'no fatigue' and a one hundred (100) would mean 'fatigue as bad as it can be'". (Jensen et al., 1986). Day to day test-retest reliabilities were computed, yielding a correlation of .64 for both studies combined (RA = .67, OA = .60, FMS = .45). In addition, the validity of this single item fatigue scale was probed by examining its correlates with other similar measures on both a daily basis and over time. Changes in daily level of fatigue varied with daily fatigue measured with the PANAS-X (Watson and Clark, 2003; all participants (r = .61, p < .01; RA = .57, OA = .57, FMS = .61). Further, participants who reported greater fatigue on average across the 30 days also reported higher scores on fatigue (all participants r = .63, p < .01; RA = .59, OA = .58, FM = .63). Average between-person fatigue also strongly negatively correlated with the SF-36 Vitality subscale (Ware and Sherbourne, 1992); all participants (r = -.60, p < .01; RA = -59, OA = -46, FMS = -.48).

2.3.2. Positive affect (PA) and negative affect (NA)

PA and NA were measured in the daily diary using the Positive and Negative Affect Schedule (Watson and Clark, 2003). Participants rated 10 standard mood adjectives each for PA and NA using a 5-point scale from 1 (very slightly or not at all) to 5 (extremely). Scores for the 2 scales were computed by aggregating each participant’s items across all days. Cronbach’s z was .97 for PA (RA = .95, OA = .98, FMS .95), and .92 for NA (RA = .92, OA = .92, FMS = .90). Within-person estimates of reliability were computed by transforming item scores into z-scores within each participant. Within-person Cronbach’s z for PA was .87 (RA = .87, OA = .87, FMS = .88) and for NA was .77 (RA = .77, OA = .76, FMS = .79).

2.3.3. Sleep

The Pittsburgh Sleep Inventory (PSI: Buysse et al., 1998) was administered in both studies after the diary phase. Cronbach’s z overall was .77 (RA = .76, OA = .78, FMS = .67).

2.3.4. Depression

Pro-rated raw scores from the Hamilton Depression Inventory-Short Form (Reynolds and Kobak, 1995) were used to assess levels of depression. Cronbach’s α on the 9-item scale yielded .84 for both studies combined (RA = .72, OA = .89, FMS = .87).

2.3.5. Pain

Daily pain was measured in each diary with the standard instruction for a numerical rating scale (Jensen et al., 1986; Zautra et al., 2001). “Please choose a number between 0 and 100 that best describes the average level of pain you have experienced today due to your ‘Rheumatoid arthritis’ in Study 1 and ‘Fibromyalgia or Osteoarthritis’ in Study 2’. A zero (0) would mean ‘no pain’ and a one hundred (100) would mean ‘pain as bad as it can be’”. Test-retest reliabilities were computed across days to yield a day-to-day correlation of .73 for both studies combined (RA = .75, OA = .65, FMS = .53).

2.4. Data analysis methods

Daily diary observations from the three diagnostic groups were combined to create a dataset with a hierarchical nested structure (up to 30 observations nested within each of the 255 participants). Multilevel analyses were conducted using the SAS PROC MIXED software (Littell et al., 1996) to differentiate between and within-person sources of variance in daily fatigue. Specifications for the multilevel models were selected following Singer (1998) to identify the best fitting model of the variances and covariances of the variables under study.

The first set of multilevel analyses estimated the extent to which daily fatigue varied between and within individuals in each diagnostic group. These analyses were conducted by estimating the proportion of variance accounted for by the intercept (between-person) and residual (within-person) for a null model (i.e., no independent variables entered) predicting fatigue. Because these two estimates added together represented the total variance in daily fatigue, a ratio of the estimates for each person (i.e., ID) or Residual variance over their sum represented the partitioning of between and within-person sources of variance in fatigue, respectively. These “null model” analyses were followed by those that added positive and negative affect measures as predictors, recording changes in proportion of variance accounted for in fatigue with the introduction of these predictors. To differentiate between and within-person effects for predictor variables, certain data computations were necessary to create average and deviation (person-centered) scores. Between-person variables were created by computing average score on predictor variables across the 30 days for each participant. Within-person variables were created by subtracting each participant’s mean score from their daily scores on the predictor variables.
The second set of analyses examined the fixed effects of within- and between-person variables on daily fatigue. Procedures for constructing multi-level models and equations predicting effects of Level 1 (between-person), Level 2 (within-person), and cross-level interaction (Level 1 × Level 2) variables have been detailed in other papers by our research team (Zautra et al., 2001, 2005; Davis et al., 2004), and will not be explained in detail in this paper. The dependent variable (fatigue) was modeled as a random variable, and goodness of fit tests were employed to examine whether the daily deviations in within-person variables varied randomly across participants.

3. Results

3.1. Sample characteristics

We began our analyses with a comparison of the study variables between the three diagnostic groups. Descriptive statistics as well as post hoc comparisons between groups are provided in Table 1. The OA group was significantly older than the RA group, but there were no significant differences in average income or education level. The FMS patients reported significantly greater levels of fatigue compared to the OA and RA groups. The three groups differed significantly in pain reports, with FMS patients reporting the highest levels, OA patients more moderate levels, and RA patients the lowest levels of pain. It is also important to note that the FMS group evidenced higher disturbance on several key psychological and physical health measures. The FMS participants reported significantly more sleep problems, depressive symptomology, pain, and negative affect, as well as lower levels of positive affect, compared to the other two groups.

3.2. Examination of variance components of fatigue

We next explored the nature of fatigue by estimating between and within-person sources of variance in daily fatigue in a null multi-level model. As shown in Table 2, FMS patients were subject to more day-to-day variation in fatigue than were patients with RA and OA. The proportion of variance in OA fatigue was similar for between (52.6%) and within (47.4%) person sources. The between-person variance was slightly greater than the within-person variance in RA (56% vs. 44% within). In contrast, for FMS patients, within-person variance accounted for 69.6% of fatigue variance compared to only 30.4% for between-person variance. In Fig. 1 we display the day-to-day reports of fatigue using one illustrative case for each diagnostic group.

An examination of PA and NA as predictors of the between and within-person sources of variance in daily fatigue was conducted next. As shown in Table 3, approximately 19% of the between-person variance in fatigue was accounted for by differences between subjects in their reports of PA, averaged across the 30 daily diary accounts. Individual differences in average NA accounted for 17% of the between-subject variance in fatigue. Taken together, between-subject differences in both PA and NA accounted for 28% of the between-subject variance in fatigue. (The total amounts of variance accounted are not simply the sum of the two effects due to collinear relations between positive and negative affects.) Holding these influences constant, the analyses proceeded with comparisons of residual (within-person) variance before and after entry of daily change scores in daily PA and/or NA. Approximately 13% of the within-person variance in fatigue was accounted for by daily fluctuations in PA.

Table 1
Descriptive statistics for demographic and study variables

<table>
<thead>
<tr>
<th></th>
<th>OA (n = 76)</th>
<th>RA (n = 89)</th>
<th>FMS (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>59.1 (8.1)</td>
<td>52.3 (12.7)</td>
<td>55.2 (8.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Income</strong></td>
<td>17.6% &lt; $25k mean $30k–$40k</td>
<td>28.6% &lt; $25k mean $30k–$40k</td>
<td>37.2% &lt; $25k mean $25k–$30k</td>
</tr>
<tr>
<td><strong>Education:</strong></td>
<td>11.9% H.S. 85.1% college</td>
<td>13.3% H.S. 84.0% college</td>
<td>14.9% H.S. 83.8% college</td>
</tr>
<tr>
<td>Pittsburgh sleep inventory</td>
<td>8.2 (4.0)</td>
<td>8.4 (4.1)</td>
<td>12.3 (3.5)</td>
</tr>
<tr>
<td>Hamilton depression</td>
<td>5.9 (4.4)</td>
<td>6.1 (4.1)</td>
<td>10.3 (5.6)</td>
</tr>
<tr>
<td>Pain (0–100)</td>
<td>43.6 (15.6)</td>
<td>35.5 (17.3)</td>
<td>62.7 (12.0)</td>
</tr>
<tr>
<td>Fatigue (0–100)</td>
<td>37.4 (19.4)</td>
<td>33.5 (17.3)</td>
<td>55.8 (12.9)</td>
</tr>
<tr>
<td>Negative affect</td>
<td>1.3 (0.3)</td>
<td>1.3 (0.3)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>Positive affect</td>
<td>2.8 (0.9)</td>
<td>2.8 (0.7)</td>
<td>2.2 (0.6)</td>
</tr>
</tbody>
</table>

*Note.* Different superscripts within a row represent significantly different groups in Tukey HSD Post Hoc comparisons at p < .05.

Table 2
Estimates of within and between-person variance in fatigue for each diagnostic group

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>OA</th>
<th>FMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between-person</strong></td>
<td>291.89</td>
<td>365.65</td>
<td>154.98</td>
</tr>
<tr>
<td><strong>Within-person</strong></td>
<td>232.98</td>
<td>329.5</td>
<td>355.81</td>
</tr>
<tr>
<td><strong>Percent between</strong></td>
<td>56%</td>
<td>52.6%</td>
<td>30.4%</td>
</tr>
<tr>
<td><strong>Percent within</strong></td>
<td>44%</td>
<td>47.4%</td>
<td>69.6%</td>
</tr>
</tbody>
</table>

*Note.* Variance estimates obtained from SAS proc mixed variance components analyses.
A decade of DUROGESIC® now with advanced DTrans® matrix technology offers:

- Comparable efficacy and safety to the reservoir patch ¹
- Reliable and consistent delivery of fentanyl ²
- Thinner, translucent and more flexible ²
- Easier to apply and more comfortable to wear ²
- Outpatients can be switched directly from reservoir patch to any dosage titration ¹

---

INDICATIONS: DUROGESIC® is indicated for the management of moderate to severe pain in adults who have failed or are intolerant to other analgesics, concomitant use with another opioid or in non-cancer cases. CONTRAINDICATIONS: DUROGESIC® is contraindicated in: pregnant and breastfeeding women, patients with a known hypersensitivity to the transdermal fentanyl system. WARNINGS: DUROGESIC® should not be used in the treatment of acute or breakthrough pain. The administration of fentanyl in the presence of an opioid receptor antagonist could result in hyperalgesia. In an acute pain setting, patients who have experienced opioid toxicity should be monitored for at least 72 hours after the DUROGESIC® patch is removed. The administration of opioid antagonists is contraindicated in patients who are receiving DUROGESIC®. Dr. Michael Yaffe, Clinician, San Diego, CA, comments: "There is no place for DUROGESIC® except in patients with a significant morphine equivalent." The management of patients receiving opioid agonist therapy during treatment of pain is the selection and management of response to treatment with DUROGESIC®. The management of patients receiving opioid antagonists for the treatment of pain is the selection and management of response to treatment with DUROGESIC®. DOSAGE AND DURATION: DUROGESIC® patches should be prescribed based on a number of factors, including the patient's current and past medical status, the patient's current and past medical history, and the patient's current and past medical status. The duration of DUROGESIC® treatment should be determined based on the patient's current and past medical status. The duration of DUROGESIC® treatment should be determined based on the patient's current and past medical status.

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Dosage:

- DUROGESIC 100 mcg/24 hours
- DUROGESIC 250 mcg/24 hours
- DUROGESIC 500 mcg/24 hours
- DUROGESIC 1000 mcg/24 hours

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In contrast, only 5% of within-person variability in fatigue was accounted for by daily NA fluctuations. Combined, daily PA and NA accounted for a total of 14% of within-person variance in fatigue.

We then followed up suspected differences in fatigue variability between diagnostic groups revealed in the initial analyses with multi-level tests of interactions between contrast-coded diagnosis factors and within-person deviations in daily PA. Within-person increases in PA were associated with less fatigue across all conditions, but, mirroring diagnostic differences in the day-to-day variability in fatigue, PA had the strongest influence for FMS patients ($\beta = -1.64$, $SE = 0.74$, $t(7187) = -2.23$, $p < .05$). In this analysis, the interaction term (daily PA by FMS diagnosis) displayed significant random effects and improved the fit statistics, and was therefore modeled as a random variable. In subsequent analyses, the addition of control and affect variables (depression, sleep quality, average, and daily pain, average and daily PA/NA) did not affect the significance of this interaction effect.

3.3. Affective and behavioral predictors of fatigue

To further examine the relations between fatigue and affective states, preliminary analyses were conducted to develop a model that would control for other correlates of fatigue that were likely to play an influential role. As expected, average pain and daily pain were significant predictors of daily fatigue. As shown in Table 4, fatigue scores varied directly with average and daily pain. Fatigue was also inversely related to day in the study. Although sleep quality and depression scores significantly affected fatigue when entered in the preliminary model, these variables were not significant once pain and affect were entered. However, sleep quality and depression were left in further models because of their influence on fatigue in prior research (e.g., Nicassio et al., 2002; Schanberg et al., 2005).

Next, PA and NA, at both the between and within-person levels, were added to the model along with the control variables. Daily pain and daily PA were modeled as random variables because they displayed significant random effects and improved the fit statistics. Interestingly, at the between-person level positive affect was predictive of lower fatigue, whereas the effects of negative affect were only marginal. At the within-person level, both positive and negative affect were significant predictors of daily fatigue above and beyond depression and pain. Days with higher levels of negative affect were associated with greater fatigue. Controlling for the effects of pain and negative affect, days with higher levels of positive affect were associated with lower levels of fatigue. As revealed in Table 4, the strength of the association between PA and fatigue was more than twice that of the relationship between NA and fatigue.

Because pain was a strong correlate of fatigue but may stem from distinct sources across the three illnesses, we conducted further analyses on whether the pain-fatigue relationship varied by diagnosis. Multi-level interaction effects were tested comparing each diagnostic group with the other two on the effects of daily changes in pain on fatigue. These analyses (see Table 4) showed that the OA patients’ fatigue was not associated with daily fluctuations in their arthritis pain to the same extent that it was for the other two diagnostic groups.

Finally, we explored whether daily affective changes preceded or followed changes in daily fatigue. We

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Variance</th>
<th>Change</th>
<th>% Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null model</td>
<td>355.80</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Positive affect only</td>
<td>287.96</td>
<td>67.84</td>
<td>19</td>
</tr>
<tr>
<td>Negative affect only</td>
<td>296.30</td>
<td>59.50</td>
<td>17</td>
</tr>
<tr>
<td>Positive and negative affect</td>
<td>254.88</td>
<td>100.92</td>
<td>28</td>
</tr>
<tr>
<td><strong>Within</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null model</td>
<td>311.93</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Positive affect only</td>
<td>272.85</td>
<td>39.08</td>
<td>13</td>
</tr>
<tr>
<td>Negative affect only</td>
<td>297.36</td>
<td>14.57</td>
<td>5</td>
</tr>
<tr>
<td>Positive and negative affect</td>
<td>267.84</td>
<td>44.09</td>
<td>14</td>
</tr>
</tbody>
</table>

Note: Changes in variance derived by subtractions from null model variance when fixed affects were added for positive affect, negative affect, or positive and negative affect together.
constructed lagged and lead indicators on the key study variables and analyzed the data probing whether fatigue predicted next day’s positive and negative affect, and whether changes in affect had effects on fatigue that extended to the next day. We found that neither daily fatigue nor affect ratings showed effects that extended into the subsequent day, when controlling for prior day elevations in the criterion variable. However, there was evidence that when daily pain was higher than average, fatigue was elevated the following day ($b = .08, SE = .02, t(6753) = 4.59, p < .01$).

4. Discussion

In this paper, we examined reports of fatigue among patients with chronic pain finding considerable variance in levels of fatigue both between patients and over time. We compared three chronic pain conditions and found group differences in both average level of fatigue and also extent of day-to-day variability. Pain, the cardinal symptom of chronic musculoskeletal conditions, was among the strongest predictors of fatigue. Individuals with higher average levels of pain reported greater fatigue, and daily increases in pain were related to daily increases in fatigue, including elevations in fatigue the next day.

When we examined affective correlates of fatigue, we found strong evidence for the association between positive affect and fatigue. These findings held even after controlling for better known correlates of clinical fatigue: depression, pain, sleep quality, and negative affect. The absence of PA played a significant role in predicting fatigue for all groups. The strong links between FM and low PA found in prior research (Zautra et al., 2005) are found here as well, with low PA more strongly associated with increases in daily fatigue for FMS than for RA and OA. We are led by these findings to surmise that FMS may be characterized best by attending both to what is missing in their emotional lives as well as what is present. FMS patients show a shortage of restorative affective responses, a likely source of the elevations in symptomatic fatigue on days of lower PA.

The findings on sleep quality, depression, and negative affect are only partially consistent with past research on individual differences in fatigue (Nicassio et al., 2002; Schanberg et al., 2005). Patients who reported greater fatigue on average also reported more depression, more sleep problems, and higher levels of negative affect than patients with less fatigue. However, when controlling for pain and the influence of positive affective states, individual differences in depression, sleep quality, and average negative affect were no longer consistent predictors of fatigue. Daily variations in NA were associated with fatigue, but those relationships were less substantial than those found for levels of pain and positive affect.

The differences found in the patterns of self-report of fatigue among OA, RA, and FMS groups reveal distinctive patterns of variability in this symptom for participants with different diagnoses. RA and OA patients

| Table 4 |
|-----------------|------------|----------------|-----------------|----------------|
| Fatigue with affect and diagnostic interactions in model |
| Covariance parameter estimates | Subject | $\beta$ | Std. error | $Z$ | $p$ |
| **Random effects: prediction of daily fatigue** | | | | | |
| Intercept | ID | 123.43 | 12.05 | 10.24 | <.01 |
| Positive affect | ID | 28.72 | 5.71 | 5.02 | <.01 |
| Pain | ID | 0.05 | 0.008 | 6.47 | <.01 |
| AR(1) | ID | 18 | 0.01 | 13.55 | <.01 |
| Residual | ID | 213.66 | 3.90 | 54.76 | <.01 |
| **Predictor variables control variables** | | $\beta$ | Std. error | DF | $t$ | $p$ |
| **Fixed effects** | | | | | | |
| Day | –0.12 | 0.02 | 7187 | –5.01 | <.01 |
| Hamilton depression | 0.29 | 0.21 | 247 | 1.39 | 0.16 |
| Pittsburgh sleep inventory* | 0.16 | 0.21 | 247 | 0.77 | 0.44 |
| Average pain (0–100) | 0.62 | 0.04 | 247 | 14.39 | <.01 |
| Pain | 0.39 | 0.02 | 7187 | 16.79 | <.01 |
| OA | –1.16 | 1.64 | 247 | ~0.71 | 0.48 |
| **Level 2 affect** | | | | | | |
| Average negative affect | 5.06 | 2.65 | 247 | 1.91 | 0.057 |
| Average positive affect | –3.40 | 1.06 | 247 | –3.21 | <.01 |
| **Level 1 affect** | | | | | | |
| Negative affect | 3.54 | 0.51 | 7187 | 6.92 | <.01 |
| Positive affect | –8.05 | 0.0 | 7187 | –16.05 | <.01 |
| **Level 1 x Level 2** | | | | | | |
| Pain x OA | –0.10 | 0.04 | 7187 | –2.66 | <.01 |

*Daily sleep disturbance was also assessed, but because it was measured differently in the two studies and did not affect the results, it was not included in these analyses.
displayed the most stable patterns of fatigue. FMS patients, on the other hand, show a pattern of high levels of day-to-day variability in fatigue and covariation between fatigue and PA that may be characteristic of the illness’s unpredictable course and of central disturbances in affective regulation (Wolfe et al., 1995, 1996; Zautra et al., 2005). Fatigue in OA participants, on the other hand, may be less influenced by daily pain fluctuations because of the relatively simple and localized “wear and tear” nature of this condition compared to the other two groups.

Observations closer in time to the occurrence of painful episodes and those that probe neuroendocrine changes may reveal further similarities and differences in physiological processes between diagnostic groups responsible for the differences we have found here in self-reported fatigue. Without a healthy control group for comparison, we cannot tell whether the diminished reactivity to pain among the OA group compared to other pain groups is similar to that found among people without chronic pain. There may also be significant gender differences in pain-contingent and affect-contingent fatigue that could not be examined in our data, which were drawn entirely from women. In any case, the relatively low pain-contingent fatigue recorded for this group invites additional study. More generally, the findings encourage further examination of patterns of fatigue between groups and over time that would yield disease-specific profiles valuable in diagnostic work.

Our FMS sample included some OA patients, potentially blurring differences between these two groups. These participants with both FMS and OA reported that they could distinguish between pain resulting from the two conditions, and they all reported that pain from FMS was more severe. Although differences in the experience of fatigue may differ between FMS patients with OA and FMS patients without OA, because OA is common in FMS, the inclusion of FMS patients with OA here provides us with a more conservative test of differences between groups and likely a more representative sample of the FMS population.

The associations found between fatigue and everyday affect point to the relevance of a biopsychosocial approach to this phenomenon. Fatigue and its counterpart, “energy”, represent global indicators of health or its absence (Ryan and Frederick, 1997). There are likely illness-related and psychosocial influences on fatigue, and thoughtful studies are likely to reveal key causes and consequences of this state. The relatively small contribution of negative affect and depression to fatigue compared with positive affect in the current study encourages a broad conceptual framework for understanding fatigue: one that acknowledges it is not simply a derivative of psychological and physiological distress (Hickie et al., 2003). Discrimination of these features of fatigue can also guide us to develop more sophisticated interventions that take into account distinct disease-related and psychosocial influences on energy gains and losses.

Although causal relationships among the variables were not a focus of this study, the absence of next-day associations for affect predicting fatigue, and fatigue predicting affective states deserves comment. We suspect that there are bi-directional relationships between affect and fatigue, but those effects do not extend into the next day. It is likely that any influence of affective state on fatigue and vice versa would give rise to compensatory mechanisms that would reestablish homeostasis, but this study did not probe for those mechanisms. Indeed, within-day repeated measures as well as laboratory studies are needed to clarify the causal relationships among variables found to be associated with daily fluctuations in fatigue. Longitudinal research is needed to identify the role of individual differences in shaping the fatigue responses. The use of multifactorial measures of fatigue (Rupp et al., 2004) as well as behavioral manifestations of exhaustion (Kop et al., 2005) should also advance our understanding of the underlying components of the fatigue response.

In sum, this research alerts researchers and clinicians alike to the varying manifestations of fatigue in rheumatic conditions. This symptom is central to all three conditions studied: RA, OA, and FMS, but the type of chronic pain condition played a role in defining the fatigue response observed in the diary studies. Affective correlates were strong both between and within subjects, revealing a particularly central role for positive affect in restoration of energy, alongside pain and other negative affective states that are fatiguing. Behavioral and pharmacological interventions that aim to restore health and well being among those with chronic pain would profit from greater attention to the affective dimensions of fatigue uncovered here. Moreover, the dynamics of fatigue, and its counterpart, vitality, warrant consideration by physicians in the examination room and those engaged in research on musculoskeletal illnesses. Such work may advance our ability to identify signs of a patient’s capacity to sustain good health and show resilience in the face of physical challenge as well as further our understanding of pathological signs of ill health in specific rheumatic conditions.

Acknowledgements

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References


LOCAL PERSPECTIVE: Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia (FMS).

This article highlights the relevance of fatigue as a prominent symptom in 3 common pain disorders. As expected, higher levels of pain in patients predicted greater fatigue, with also a correlation with depression scores and sleep problems.

FMS patients reported the highest pain levels and significantly greater levels of fatigue, which may possibly be a reflection of the central serotonergic mechanisms involved in pain perception in FMS patients. Sleep disturbances are a prominent feature in FMS patients, most of the body’s growth hormone is produced – low growth hormone levels may contribute to poor healing of muscle microtrauma and increased pain in FMS patients. Poor sleep has now been shown in various studies to contribute to fatigue and lowering pain threshold in various pain disorders – this sleep-pain relation is bidirectional. Pain clinicians should therefore assess sleep and review sleep-hygiene in all chronic pain patients. Analgesics (in particular caffeine-containing analgesics) and even certain hypnotics may disturb the sleep architecture and contribute to the pain experience of the patient. Tricyclic antidepressants and antiepileptic agents have been shown to reduce sleep interference and to improve pain levels in subsets of chronic pain patients.

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Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: A double blind sham controlled randomized clinical trial

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Abstract

Cervical radicular pain affects approximately 1 on 1000 adults per year. Although many treatment modalities are described in the literature, the available evidence for efficacy is not sufficient to allow definitive conclusions on the optimal therapy to be made. The effect of pulsed radiofrequency treatment for this type of patients was evaluated in a prospective audit that showed satisfactory pain relief for a mean period of 9.2 months, justifying a randomized sham controlled trial. Twenty-three patients, out of 256 screened, met the inclusion criteria and were randomly assigned in a double blind fashion to receive either pulsed radiofrequency or sham intervention. The evaluation was done by an independent observer. At 3 months the pulsed radiofrequency group showed a significantly better outcome with regard to the global perceived effect (>50% improvement) and visual analogue scale (20 point pain reduction). The quality of life scales also showed a positive trend in favor of the pulsed radiofrequency group, but significance was only reached in the SF-36 domain vitality at 3 months. The need for pain medication was significantly reduced in the pulsed radiofrequency group after six months. No complications were observed during the study period. These study results are in agreement with the findings of our previous clinical audit that pulsed radiofrequency treatment of the cervical dorsal root ganglion may provide pain relief for a limited number of carefully selected patients with chronic cervical radicular pain as assessed by clinical and neurological examination.

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Keywords: Pulsed radiofrequency; Cervical radicular pain; Global perceived effect; Visual analogue scale; Spurling test; Dorsal root ganglion; Randomized clinical trial

1. Introduction

Cervical radicular pain affects approximately 1 on 1000 adults per year (Radhakrishnan et al., 1994), and has a high impact on the patient’s quality of life (Daffner et al., 2003). It is most commonly caused by an irritation or injury of the cervical spinal roots due to herniated intervertebral disc or narrowing of the intervertebral foramen (Merskey and Bogduk, 1994). Although many treatment modalities are described in the literature, the available evidence for efficacy is not sufficient to allow definitive conclusions on the optimal therapy to be made (Bogduk, 1999; Rathmell and Benzon, 2004). According to two randomized controlled trials (RCT’s) (van Kleef et al., 1996; Slappendel et al., 1997) and two systematic
reviews, there is limited evidence that RF of the cervical DRG is more effective than placebo in chronic cervical radicular pain (Geurts et al., 2001; Niemisto et al., 2003). In both RCT’s, diagnosis was made based on clinical and neurological screening methods. However, this was not always described in detail, which probably resulted in heterogeneous study populations.

Radiofrequency lesioning adjacent to the DRG remains controversial due to the potential risk of deafferentation syndrome (Sluijter, 2001). For this reason a modification of the technique, resulting in less neural damage, would be more attractive for chronic pain management. In 1998, Sluijter et al. introduced the isothermal RF treatment known as pulsed radiofrequency (PRF) for the relief of chronic pain (Sluijter et al., 1998).

The precise mode of action of PRF is not yet clear. Sluijter et al. suggested that the electric field rather than temperature may induce changes in the nerve cells, which may contribute in the observed clinical effect (Sluijter et al., 1998). It has recently been reported that the electric fields generated by PRF may be capable of modifying neuronal membranes (Cosman and Cosman, 2005). In neurobiology studies, an early (Higuchi et al., 2002) and late (Van Zundert et al., 2005) temperature-independent cellular activity was demonstrated in the rat dorsal horn after exposure of the cervical DRG to PRF. Furthermore, the biological effect of PRF appeared to be selective to small diameter C- and A-δ-fibers, and unlikely to be related to thermal damage (Hamann et al., 2006). The concept that PRF may produce inhibition of excitatory C-fiber responses using a phenomenon such as long-term depression was proposed in an accompanying editorial to be an attractive hypothesis. The author stressed the need for confirmation of the clinical value of PRF in RCT’s (Richebe et al., 2005), which up to now have been lacking.

In a previous clinical audit, we reported long lasting pain relief after PRF adjacent to the cervical DRG for the management of chronic cervical radicular pain (Van Zundert et al., 2003). The positive therapeutic results of this audit was the reason to perform a sham controlled RCT with follow-up of 6 months in chronic cervical radicular pain to evaluate the efficacy and side effects of PRF treatment. The results of the first RCT on PRF are presented.

2. Methods

2.1. Participants

Two hundred fifty-six patients with cervicobrachialgia, referred to the multidisciplinary pain centers of the University Hospital Maastricht, Maastricht, The Netherlands; Ziekenhuis Oost-Limburg, Genk, Belgium and Catharina Hospital, Eindhoven, The Netherlands, were screened for inclusion in the study by a pain physician with at least 5 years experience (JVS and JVZ) under the supervision of a staff neurologist (JP). Because the participating institutions have a function as “third line referral center” for chronic pain patients, most of the patients were referred by medical specialists (neurologists, neurosurgeons, orthopedic surgeons, rheumatologists and rehabilitation physicians).

The institutional Ethics Review Board of each of the participating centers approved the trial and all patients signed an informed consent form.

Patients were eligible for the study if they reported of neck pain radiating over the posterior shoulder area to the arm that has been present for more than 6 months and conventional therapy, which included medication, physical therapy and transcutaneous electrical nerve stimulation, was not effective. Their signs and symptoms should suggest involvement of the cervical spinal nerve and be perceived along the affected nerve root. Pain from C5 extends into the upper arm, while that from C6 and C7 extends from the neck and shoulder into the forearm and hand. In both instances, the pain occurs in the lateral border of the upper limb, but that of C7 extends more onto the dorsal aspect (Slipman et al., 1998; Bogduk, 1999). In order to select a homogeneous patient population, the routine neurological examination was extended with a protocol of physical examination to exclude shoulder motion restriction as the cause of brachialgia. Only patients with a positive Spurling test as sign of root involvement were included in the study (Spurling and Scoville, 1944). The average pain intensity measured on a visual analogue scale (VAS) (0 = no pain, 100 = “the worst pain imaginable”) should be higher than 35.

Medical imaging techniques and electrophysiological studies were performed according to clinical indications, but the results were not used as inclusion criteria, because of lack of data on their specificity and sensitivity in the diagnosis of cervical radicular pain. Moreover, prospective studies in asymptomatic subjects have shown abnormal magnetic resonance imaging (MRI) of the cervical spine in 19–28% of the patients depending on their age (Teresi et al., 1987; Boden et al., 1990).

Exclusion criteria were as follows: younger then 20 years or older than 75 years, a history of cancer, fractures of the cervical vertebral, myelopathy, previous cervical fusion or laminectomy, systemic diseases or connective tissue diseases, diabetes mellitus, coagulation disorders and use of anticoagulants, multiple sclerosis, pregnancy, shoulder pathology, the presence of a cardiac pacemaker or spinal cord stimulator and previous RF or PRF treatment of the cervical DRG. Patients with a score of 45 or higher on the Pain Catastrophizing Scale were first referred to the psychologist for further investigation (Van Damme et al., 2000).

After the clinical diagnosis of cervical radicular pain was made, the segmental level that appeared to be involved was confirmed in all patients by three separate diagnostic blocks at the cervical DRG of C5, C6 or C7, respectively. The technique used was previously described by van Kleef et al. (1993, 1996). Overflow into the epidural space and intravascular injection was avoided by careful observation of the spread of contrast medium by fluoroscopic real time imaging. After the location of the cervical DRG was confirmed by injecting a small volume (approximately 0.5–1 ml) of iohexol contrast medium (Amersham health, Cork, Ireland), an equal volume of 2% lidocaine (AstraZeneca, Karlskoga, Sweden) was slowly injected.
Pain relief was assessed 10, 20 and 30 min after the procedure. A diagnostic block was considered positive if it resulted in a minimum of 50% pain reduction, measured on the VAS within 30 min. The level that responded with the largest pain reduction was selected for intervention (sham or PRF). After having given written informed consent, the patients were randomly allocated to one of the two study groups according to a computer-generated randomization list, stratified for the centre and in variable block size (2 or 4 patients).

An independent observer provided the treating physician with a sealed envelope numbered in advance according to the computer-generated randomization list. The envelope was opened in the operating room as soon as the intervention cannula was positioned in the patient’s cervical area. Immediately after the procedure the randomization form, together with the patient’s identity and the technical details of the performed intervention, was placed in an envelope, which was sealed and returned to the randomization centre. The independent observer, the data manager and the neurologist were never in the operation facility during the treatment and were thus unaware of the nature of the performed intervention. The sealed envelopes with the codes were opened after the last evaluation of the last included patient.

### 2.2. Intervention technique

A technique similar to the one for performing diagnostic nerve blocks was used for the interventions (van Kleef et al., 1993, 1996). The C-arm of the fluoroscopy unit (Philips BV 25, Eindhoven, The Netherlands) was positioned with the beam parallel to the axis of the intervertebral foramen (25–35° anteriorly and 10° caudally). The entry point was located by projecting a metal ruler over the caudal and posterior part of the foramen. The 22 G cannula (SMK Pole needle 54 mm with 4 mm active tip, Cotop International BV, Amsterdam, The Netherlands) was positioned with the stylet of the cannula was then replaced by the RF probe (SMK-TC 5, Radionics, Burlington, MA). After checking the impedance, indicating a normal, closed electrical circuit, stimulation was started at a frequency of 50 Hz to obtain a sensory stimulation threshold in all patients. A paresis was elicited along the tested cervical nerve root at less than 0.5 V in all patients, and was considered to indicate adequate proximity of the DRG (Ford et al., 1984).

The PRF current was applied during 120 s from the lesion generator (Radionics RFG 3 C Plus, Burlington, MA) as described by Sluijter et al., 1998. During the procedure, the display of the generator was kept out of sight of the patient and auditory signals were turned off.

For the sham intervention the identification of the target point, electrode placement, and the sensory stimulation was performed in the same way as for the patients undergoing active treatment. Instead of passing current through the electrode, however, the treating physician merely manipulated the generator without starting the procedure. During the intervention, the same information regarding start, progress and end of the procedure was provided to both groups of patients. Two experienced pain specialists performed all procedures (21 patients JVZ, 2 patients JVS). The patients had no previous experience of PRF adjacent to the cervical DRG, and the applied current had a frequency outside the sensory range. During and after the treatment, however, none of the patients were asked about the sensations they experienced during the procedure. All precautions were taken to maintain blinding of patients and evaluators. None of the patients had asked to which group they were allocated.

Based on the experience with previous sham controlled RCTs in our center, and the problems we had observed with patients’ long-term adherence to the study protocol, we did not ask the subjects to guess, at the different evaluation points, which treatment they received (Turner et al., 2002). Patients experiencing too much pain were offered oral (co)analgesics in an ascending step-wise protocol as rescue treatment.

### 2.3. Outcome measurements

Evaluations were performed by an independent observer, blinded to the subjects’ condition and the treatment given, at four time points: immediately prior to the intervention (T0), at 4 weeks (T1), and at 3 months (T2). Thereafter, patients with a favorable outcome at T2 were also evaluated 6 months (T3) after the intervention. Pain intensity was assessed by averaging three daily VAS measurements, ranging from 0 to 100 according to Jensen and McFarland (1993), for four consecutive days during the week prior to the evaluation visits. The data manager phoned the patient to remind him/her to fill in the pain score diary. Global perceived effect (GPE) was scored by the patient on a 7-point Likert scale (from \(75\%\) worse = very bad to \(75\%\) improvement = very good) as illustrated in Table 1 (Likert, 1932; Farrar et al., 2001). The use of pain medication was scored as follows: WHO step I, peripheral analgesics = 1; co-analgesics = 1; WHO step II, weak opioids = 2; WHO step III, strong opioids = 3. The minimal score for pain medication was 0, and the maximal score 4 (Steedman et al., 1992).

Two validated instruments were used to assess the quality of life; SF-36 (Ware and Sherbourne, 1992) (Dutch version) (Aaronson et al., 1998) and Euroqol (1990; Brooks, 1996). Side

<table>
<thead>
<tr>
<th>Score</th>
<th>% Change</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>(75%) improvement</td>
<td>Very good</td>
</tr>
<tr>
<td>6</td>
<td>50–74% improvement</td>
<td>Good</td>
</tr>
<tr>
<td>5</td>
<td>25–49% improvement</td>
<td>Fairly good</td>
</tr>
<tr>
<td>4</td>
<td>0–24% improvement or worse</td>
<td>Same as before</td>
</tr>
<tr>
<td>3</td>
<td>25–49% worse</td>
<td>Fairly bad</td>
</tr>
<tr>
<td>2</td>
<td>50–74% worse</td>
<td>Bad</td>
</tr>
<tr>
<td>1</td>
<td>(75%) worse</td>
<td>Very bad</td>
</tr>
</tbody>
</table>

Table 1
Likert scale 7-point scoring system: global perceived effect

Based on the experience with previous sham controlled RCTs in our center, and the problems we had observed with patients’ long-term adherence to the study protocol, we did not ask the subjects to guess, at the different evaluation points, which treatment they received (Turner et al., 2002). Patients experiencing too much pain were offered oral (co)analgesics in an ascending step-wise protocol as rescue treatment.

Based on the experience with previous sham controlled RCTs in our center, and the problems we had observed with patients’ long-term adherence to the study protocol, we did not ask the subjects to guess, at the different evaluation points, which treatment they received (Turner et al., 2002). Patients experiencing too much pain were offered oral (co)analgesics in an ascending step-wise protocol as rescue treatment.
effects and complications were noted during the intervention, and a neurological examination was performed at each follow-up visit with special attention paid to changes in sensibility in the dermatomes C5, C6 and C7 measured by pinprick. Changes from the baseline values were considered anomalous and rated; 0 (normal) to 2 (strong anomaly).

The primary-outcome measurement of our trial was success or failure of the treatment 3 months (T2) after the intervention. Success was defined as at least 50% improvement of the GPE (6 or 7 on a 7-point Likert scale) and 20-points reduction in pain intensity on the VAS score. Improvement was also judged by a reduction in the need for pain medication.

Secondary outcome measurements included all the primary-outcome parameters but measured at 4 weeks (T1) and 6 months (T3). Patients with a lack of pain relief after 3 months were offered an alternative treatment and considered as a failure for further analysis. The influence of the treatment on the quality of life (QOL), was measured by the SF-36 questionnaire and Euroqol at 4 weeks (T1), 3 months (T2) and 6 months (T3).

Six months after termination of the study, the patients were contacted by phone to determine whether they had undergone cervical spine surgery since the end of the trial.

2.4. Statistical analysis

According to the experience in our centre with a previous sham controlled RCT on conventional RF in a similar patient population, a 20-point reduction on a 100-point VAS score, 3 months after the intervention can be considered clinically relevant (Farrar et al., 2001; Salaffi et al., 2004). This study indicated that a standard deviation in VAS score of 27 points could be expected. For a power of 80% and 5% significance to reject the nil hypothesis (one-sided), 21 patients per treatment group or a total of 42 patients were required.

Analysis of the primary-outcome measurement was by intention to treat. The differences in the baseline values and outcome measurement, GPE, VAS, SF-36 and Euroqol, between sham and PRF intervention were analyzed, dependent on the scale of variable, using the Student’s t-test or the Chi-square test and if appropriate with Fisher’s exact test. To adjust for differences in the baseline values, the analyses were also performed using a multivariate logistic regression model. Consumption of medication was compared using the Mann-Whitney U test. Significance was reached if P was less than 0.05.

3. Results

Between February 2002 and September 2004, 256 patients referred with cervicobrachialgia were included in the study. As the slow inclusion rate even slowed further down. After the decision to stop the study was taken, the last evaluation of the last included patient was done and encoded. A period of 9 months elapsed between the decision to stop the study and the last evaluation of the last included patient. Twenty-three patients were randomly allocated to PRF treatment (n = 11) or sham intervention (n = 12). The trial profile is illustrated in Fig. 1. One patient dropped out of the study after the first evaluation point (4 weeks). He was treated surgically and his data were considered a failure. The patient baseline characteristics are shown in Table 2. There were significant differences in age and VAS scores. In the sham group the patients were older (52.9 versus 42 years) and started with a higher VAS score (76.2 vs. 55.7).

3.1. Primary outcome

The primary outcome consisted of three measurements 3 months after the intervention. The first, success defined as at least 50% pain improvement of the GPE (6 or 7 on the Likert scale), was achieved in 9/11 (82%) patients in the PRF group and in 4/12 (33%) in the sham group. The differences between the two treatment groups are statistical by significant (P = 0.03).

The second primary-outcome measurement, a 20-points reduction in pain intensity measured by VAS...
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¹Reference: 1. Brufen® Tablets and Brufen® Pendible Suspenion Package Insert. Suggested indications, Schedule 2. B.P. Pharmacopoeia Classification: 3.2.1 – Antiinflammatory. Antiinflammatory activity: PROPRIETARY NAME (Code number): Brufen® 500 mg Tablets, Brufen® 150 mg Tablets, Brufen® 300 mg Tablets, Brufen® Ibuprofen Tablets. Brufen® Pendible Suspension. Brufen® pendible Suspension: COMPOSITION: Each tablet contains: 500 mg ibuprofen in a 158 mg starch, 438 mg lactose, 182 mg magnesium stearate, 102 mg magnesium stearate. NOVOCORT® 1% Amphilex and 0.5% Amphilex, and 0.1% Amphilex and 0.05% Amphilex. 2. Recommended dosage of Brufen® 7.75 mg/kg/day in three divided doses. The time to efficacy of Brufen® should not exceed 60 mg. Brufen® is not recommended for children under 12 years. Recommended daily dose: 7.75 mg/kg of body weight. Recommended dose: 150 mg twice a day, methoxsalen whole with grains of Bold. Brufen® PENDIBLE SUSPENSION should be given to children less than 12 years. Children with aspirin intolerance. Bronchial asthma and patients in whom aspirin intolerance may result in cardiovascular adverse reaction. Systolic, chronic, or recurrent oliguria, pregnancy, hypertension, renal disease, diabetes mellitus, infectious mononucleosis, and systemic lupus erythematosus. Patients with hepatic and kidney diseases. Patients with aspirin intolerance. Bronchial asthma and patients in whom aspirin intolerance may result in cardiovascular adverse reaction. Safety is not established in children and should not be less than 12 years. Transient side effects: hypotension, nausea, vomiting, headache, dizziness, rash, tinnitus, flushing, urticaria, angioedema, indigestion, flatulence, dryness/diaphoresis, anorexia, diarrhea, dyspepsia, dizziness, nervousness, pain, fever. Bronchial asthma and patients in whom aspirin intolerance may result in cardiovascular adverse reaction. Systolic, chronic, or recurrent oliguria, pregnancy, hypertension, renal disease, diabetes mellitus, infectious mononucleosis, and systemic lupus erythematosus. Patients with hepatic and kidney diseases. Patients with aspirin intolerance. Bronchial asthma and patients in whom aspirin intolerance may result in cardiovascular adverse reaction. Safety is not established in children and should not be less than 12 years. Transient side effects: hypotension, nausea, vomiting, headache, dizziness, rash, tinnitus, flushing, urticaria, angioedema, indigestion, flatulence, dryness/diaphoresis, anorexia, diarrhea, dyspepsia, dizziness, nervousness, pain, fever.
FREE

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• Duration of pain relief 4-6 hours

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• Additional pain relief in combination with dextropropoxyphene

Contains L-glutamine:
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• Important in the synthesis of collagen and connective tissue
• Improves immune cell function

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References:

Further information available on request.

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score, was also statistically significant with more improvement achieved in 9/11 (82%) patients in the PRF group compared with 3/12 (25%) in the sham group ($P = 0.02$). The individual VAS scores are shown in Fig. 2.

The third primary-outcome was the reduction in intake of pain medication. A reduction was noted in the PRF group but no significance was reached after 3 months. The evolution of the intake of pain medications is illustrated in Fig. 3.

### 3.2. Secondary outcome

The secondary outcome with regard to the evolution of GPE between T1 and T3 is shown in Fig. 4. The differences in success (GPE and VAS) between the PRF and sham groups, with the odds ratios and 95% confidence interval over the three observation points are presented as unadjusted values and as values adjusted for variations in baseline characteristics in Fig. 5. A value above 1 is a statistical significant improvement of PRF versus sham treated patients. At T1 the outcome of sham is better than PRF for the adjusted and for the unadjusted values; at T2 the outcome of PRF is better than sham for adjusted and unadjusted values and at T3 the unadjusted value for the outcome of PRF is better than for sham, while statistical significance is just not reached for the adjusted values. Although the statistical

### Table 2

Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>PRF treatment group $n = 11$</th>
<th>Sham treatment group $n = 12$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean [SD])</td>
<td>42 [12.2]</td>
<td>52.9 [11.9]</td>
</tr>
<tr>
<td>Total duration of pain (months [SD])</td>
<td>53.6 [40.0]</td>
<td>60.3 [65.0]</td>
</tr>
<tr>
<td>PCS (mean [SD])</td>
<td>16.6 [12.1]</td>
<td>26.2 [7.6]</td>
</tr>
<tr>
<td>VAS (mean [SD])</td>
<td>55.7 [17.3]</td>
<td>76.2 [14.2]</td>
</tr>
<tr>
<td>SF-36 (mean [SD])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>68.5 [15.3]</td>
<td>50.7 [24.6]</td>
</tr>
<tr>
<td>Social functioning</td>
<td>65.9 [25.1]</td>
<td>59.4 [28.3]</td>
</tr>
<tr>
<td>Physical role limitations</td>
<td>22.0 [31.3]</td>
<td>8.3 [28.9]</td>
</tr>
<tr>
<td>Emotional role limitations</td>
<td>71.7 [41.7]</td>
<td>51.5 [30.3]</td>
</tr>
<tr>
<td>Mental health</td>
<td>74.2 [18.3]</td>
<td>63.7 [24.7]</td>
</tr>
<tr>
<td>Vitality</td>
<td>52.7 [17.4]</td>
<td>49.2 [22.8]</td>
</tr>
<tr>
<td>Pain</td>
<td>47.1 [11.4]</td>
<td>29.1 [19.3]</td>
</tr>
<tr>
<td>General health</td>
<td>71.8 [15.2]</td>
<td>48.6 [23.1]</td>
</tr>
<tr>
<td>Euroqol (mean [SD])</td>
<td>62.6 [22.0]</td>
<td>50.3 [23.8]</td>
</tr>
<tr>
<td>Medication</td>
<td>1.6 [1.0]</td>
<td>1.3 [1.1]</td>
</tr>
</tbody>
</table>

Gender
- Male: 5 (46) vs 5 (42) (P = 0.67)
- Female: 6 (54) vs 7 (58) (P = 0.70)

Marital status
- Single: 4 (36) vs 1 (8) (P = 0.01)
- Married/living together: 7 (64) vs 11 (92) (P = 0.01)

Educational level
- Low: 8 (73) vs 7 (58) (P = 0.67)
- Middle/high: 3 (27) vs 4 (32) (P = 0.80)

Employment status
- Employed: 4 (36) vs 3 (25) (P = 0.67)
- Unemployed: 5 (46) vs 8 (67) (P = 0.04)

Medication
- No: 2 (18) vs 3 (25) (P = 0.40)
- WHO step I: 2 (18) vs 4 (33) (P = 0.40)
- WHO step II: 5 (46) vs 3 (25) (P = 0.25)
- WHO step III: 2 (18) vs 2 (17) (P = 0.89)

DRG level of treatment
- C5: 3 (28) vs 3 (25) (P = 0.80)
- C6: 4 (36) vs 4 (33) (P = 0.80)
- C7: 4 (36) vs 5 (42) (P = 0.25)

Treatment location
- Left: 7 (64) vs 8 (67) (P = 0.80)
- Right: 4 (36) vs 4 (33) (P = 0.80)

Fig. 2. Scatterplot of the visual analogue scale before treatment versus 3 months after the intervention.

Fig. 3. Evolution of intake of pain medication from baseline to T2 (3 months).
significance was lost at 6 months, there was still a large improvement. The use of pain medication was significantly decreased in the PRF group at T3 compared to baseline \((P = 0.02)\). The QOL as evaluated by the Euroqol scale and SF-36 indicated a trend towards a better result after 4 weeks in the sham group and after 3 months and 6 months in the PRF group, but no statistical significance was reached. The differences in scores of the SF-36 items between T0 and T2 and Euroqol for both groups are shown in Table 3, there was a statistically significant improvement of the domain vitality in the PRF group. No side effects or complications were noted in either group during the study period. The telephone inquiry revealed that 4 out of the 23 patients were referred for neck surgery: 3 patients from the sham group and 1 from the PRF group.

4. Discussion

Scoring treatment satisfaction is used as an outcome measure for pain management. It reflects quality of care and also predicts other significant patient behavior (McCracken et al., 2002). Therefore, we defined treatment success as minimum 50% improvement on the GPE and a 20-point reduction on VAS score. After 4 weeks there was a tendency for improvement in the sham group. This time frame was chosen to evaluate side effects and is too short to evaluate treatment efficacy in chronic pain patients. Our results indicated that PRF treatment of the cervical DRG for chronic cervical radicular pain provided better pain relief than sham intervention 3 and 6 months after the procedure, but significance was only reached after 3 months. Although the significance was lost at 6 months, there was still an improvement in outcome. The need for pain medication, which was defined as rescue treatment in the study protocol, was reduced in the PRF group and increased in the sham group. Statistical significance was reached after 6 months. There was a tendency towards better outcome in QOL for sham patients after 4 weeks, measured by SF-36 and Euroqol, but, after 3 and 6 months, there was a trend towards a better improvement of QOL in the PRF-group although statistical significance was only reached for the domain vitality. No side effects or neurological complications were noted in either group during the study period.

To our knowledge, this is the first RCT of PRF treatment in patients with chronic pain. Because of lack of a gold standard for the diagnosis of cervical radicular pain, special attention was paid to selection of patients to form a homogeneous study population. The
You call the shots!

Physician confidence
10.0 mg/ml: Surgical Anaesthesia

Patient benefit
7.5 mg/ml: Anaesthesia with Analgesia

Early mobilisation
2.0 mg/ml: Pain Management

5.0 mg/ml: Peace of mind

 ropivacaine HCL

AstraZeneca

Control through choice
examined could be included (Geurts et al., 2003). The brosacral radicular pain, where only 83 of the 1001 patients recent RCT on RF lesioning of the DRG for chronic lum-
das, 2003). This is in accordance with the experience in a patients (256 were screened), which makes it difficult to
not to participate in the study (Sackett, 2000).
may also have a strong influence causing the patient
consent when there is 50% chance of receiving a "place-
dness of our study, the low inclusion rate, which resulted
This was probably related to the most important weak-
on the adjusted analysis for GPE and VAS pain score.
and significance was no longer reached after 6 months
and variations in baseline characteristics were presented.
was shown that a positive Spurling test has a high predictive value for cervical disc prolapse detected on MRI. Moreover,
these authors reported a significant correlation between
for cervical disc prolapse detected on MRI. Moreover,
Spurling test. Despite high selectivity but low sensitivity,
this test is considered a valuable aid in the clinical diag-
nosis of patients with cervical radicular pain (Viikari-
Juntura et al., 1989). It has been validated in a con-
trolled trial using electromyography as reference, with
comparable results (sensitivity: 30%, specificity: 93%)
(Tong et al., 2002). In a recent publication, it was shown
that a positive Spurling test has a high predictive value
for cervical disc prolapse detected on MRI. Moreover,
these authors reported a significant correlation between
the results of the Spurling test and the root-canal diam-
eter (Shah and Rajshekhar, 2004).
mostly related to the most important weak-
ness of our study, the low inclusion rate, which resulted
in an underpowering for different parameters. It is often
difficult to convince the patient to sign the informed
consent when there is 50% chance of receiving a "place-
bo" intervention. Not only is the patient reluctant to
enter a sham-controlled trial, but referring specialists
may also have a strong influence causing the patient
not to participate in the study (Sackett, 2000).
We could only include 23 patients of the 42 needed
patients (256 were screened), which makes it difficult to
extrapolate our results into daily practice (Carr and Gou-
das, 2003). This is in accordance with the experience in a
recent RCT on RF lesioning of the DRG for chronic lum-
boSacral radicular pain, where only 83 of the 1001 patients
examined could be included (Geurts et al., 2003). The
problem of patient recruitment and low inclusion we
encountered in this sham-controlled interventional trial
has already been reported in other studies and systematic
reviews of interventional pain management techniques
(Koes et al., 1999; Geurts et al., 2001; Nelemans et al.,
2001; Niemisto et al., 2003). A double blind sham/placebo
controlled randomized clinical trial is considered to pro-
vide the highest level of evidence according to evidence-
based medicine guidelines (1992) and Guyatt et al.
(1995), but the true value of placebo/sham interventions
in pain management trials is under debate (Hrobjartsson
A RCT has the objective to compare the effects of a treat-
ment with the natural course of the disease. The question
of whether sham intervention really reflects the natural
course of the disease is becoming more controversial,
one reason being that PET studies have documented that
placebo and opioids activate the same brain regions
(Petrovic et al., 2002).
We performed this study in patients with chronic cer-
vical radicular pain because the available evidence in the
literature did not provide any indication for the best
treatment option. In case of intractable pain, cervical
spine-surgery is often performed (Rathmell et al.,
2004). However, there is a lack of evidence to support
this treatment, which is associated with a small but def-
inite risk of complication (Fouyas et al., 2002; Jacobs
et al., 2004). For this reason, during the last decade
interest has been directed to less invasive percutaneous
interventional pain management. Other less invasive
techniques, such as cervical interlaminar epidural ste-
roids (Stav et al., 1993), have limited evidence of efficacy
(Peloso et al., 2005). Recently, several case reports indi-
cate the possibility of serious complications such as
spinal-cord lesions after cervical transfomaminal epidural
steroids, which are hypothesized to be related to intra-
arterial injection of particulate steroid with occlusion
of critical vessels that supply the spinal cord (Brouwers
et al., 2001; Baker et al., 2003; Karasek and Bogduk,
2004; Rosenkranz et al., 2004). Hence, some colleagues
have questioned the suitability of this approach
(Rathmell and Benzon, 2004), and even suggest tempo-
urally abandoning the transfomaminal approach above
the L3 level until more scientific data are available
(Huntoon and Martin, 2005).
Two RCT’s concerning RF techniques adjacent to the
cervical DRG for chronic cervical radicular pain
have been published (van Kleeft et al., 1996; Slappendel
et al., 1997) with limited evidence according to two
systematic reviews (Geurts et al., 2001; Niemisto et al.,
2003). Our study included a comparable number of
patients compared with van Kleeft et al. (1996), whereas
Slappendel et al. (1997) included larger patient groups.
Our study had a longer follow-up period than the other
two, for up to 6 months. In both the other RCT’s, the
diagnosis was made based on clinical and neurological

| Table 3 | Results of the SF-36 and Euroqol outcome measurements at 3 months |
|---------|-----------------|-----------------|----------------|----------------|
| Item    | PRF mean difference (SD) | Sham mean difference (SD) | P value |
| Euroqol | 12.6 (19.7) | 4.7 (30.8) | 0.5   |
| Physical functioning | 9.0 (16.6) | 6.9 (15.0) | 0.8   |
| Social functioning | 12.5 (28.0) | 1.0 (28.4) | 0.3   |
| Physical role restriction | 23.5 (48.6) | 24.3 (26.9) | 0.9   |
| Emotional role restriction | 24.2 (36.8) | 0.0 (53.7) | 0.2   |
| Mental health | 6.9 (12.9) | 0.3 (22.2) | 0.4   |
| Vitality | 17.3 (17.1) | 2.1 (16.0) | 0.04   |
| Pain | 9.8 (20.5) | 9.3 (25.8) | 0.9   |
| General health | 4.1 (10.0) | 2.3 (19.0) | 0.7   |

* Statistical significance.
screening methods. However, they were not always described in detail, which may have resulted in some degree of heterogeneity in the intervention groups. By specific testing of shoulder motion range and including the Spurling test, we believed that a more homogeneous study population was achieved.

An important issue in clinical practice for choosing between conventional RF and PRF is the risk for neurological side effects and complications. Drawing conclusions on safety based on studies involving low numbers of patients is not justifiable, which is a weakness of most sham-controlled studies in interventional pain medicine. Therefore, data from large well-designed cohort studies may provide more valid information on safety. It has been demonstrated that these studies do not systematically overestimate the effect of the intervention in comparison with RCT’s (Concato et al., 2000).

Future research should concentrate on elucidating the mode of action of PRF. At present 5 neurobiology trials are published. They indicate that PRF and sham treatments have different biological effects (Higuchi et al., 2002; Cahana et al., 2003; Erdine et al., 2005; Van Zundert et al., 2005; Hamann et al., 2006), the mode of action is temperature-independent (Higuchi et al., 2002; Erdine et al., 2005; Van Zundert et al., 2005; Hamann et al., 2006), and that neural destruction with conventional RF and PRF is dependent on the distance between the electrode and the tissue, but is less pronounced and transient with PRF (Erdine et al., 2005; Van Zundert et al., 2005; Hamann et al., 2006), the mode of action is temperature-independent (Higuchi et al., 2002; Erdine et al., 2005; Van Zundert et al., 2005; Hamann et al., 2006), and that neural destruction with conventional RF and PRF is dependent on the distance between the electrode and the tissue, but is less pronounced and transient with PRF (Erdine et al., 2005; Van Zundert et al., 2005; Hamann et al., 2006). Furthermore, PRF appears to have selective effects on small-diameter C and A-δ-fibers according to one neurobiology trial (Hamann et al., 2006). The frequency at which PRF should be applied in order to optimize the therapeutic outcome in clinical practice needs to be investigated. The pathology causing cervical radicular pain may be present at more than one level and the question whether simultaneous PRF treatment at different levels yields a better outcome remains unanswered.

In conclusion, the results of our study are in accordance with the findings of the clinical audit (Van Zundert et al., 2003). PRF treatment of the cervical DRG may provide pain relief for a limited number of carefully selected patients with chronic cervical radicular pain caused by an irritation or injury of the cervical spinal roots due to herniated intervertebral disc or narrowing of the intervertebral foramen (Merskey and Bogduk, 1994). Considering the presumed less neurodestructive nature of PRF, this approach may have a better risk/benefit ratio than continuous RF lesioning, but this hypothesis needs to be confirmed in larger observational studies.

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Radiofrequency (RF) ablation is a common procedure for spinal and neck pain in South Africa. It is usually performed by medical practitioners who have been trained to do RF as it is not an innocuous procedure and does have well described complications. RF is usually done in a fluoroscopy suite or in an operating room using a C-arm. I must stress that it is not a procedure that should be undertaken without a prior positive test performed using a local anaesthetic block of the suspected trigger site.

Internationally there is much debate about whether the standard radio frequency ablation should be performed or whether pulsed radio frequency should be done. It has been suggested that the pulsed variety is less destructive and is thus safer for use in areas where motor nerves are in close proximity to the targeted sensory nerve. This still remains the choice of the individual practitioner. Most of the procedures done are for lower back pain and facets and dorsal root ganglia are the most frequently targeted areas. The more common procedure in the neck is for the facets. This article suggests another target for patients with neck pain. Judging by the conclusions it is certainly worth investigating and may prove to be a useful additional tool for the pain specialist. The authors of this article are internationally renowned for RF therapy and as such their conclusions can be taken at face value.

Dr. Milton Raff
Opioids are first-line analgesic therapy for moderate to severe acute pain and for life-threatening illnesses such as cancer. Evolving evidence suggests that opioids may also be useful in chronic noncancer pain, although controversy exists as to the long-term effectiveness and appropriate dosing regimens in this population. Research on opioid efficacy and safety, and on the treatment of opioid side effects, is more abundant in the acute than the chronic setting. Nonetheless, opioids are frequently used for long periods, sometimes for years.

Successful opioid therapy of any duration requires that the benefits of analgesia outweigh treatment-related adverse events. Opioid side effects in patients with chronic pain can impair quality of life, increase morbidity, and may cause a patient to discontinue therapy. Many side effects (with the exception of constipation) diminish or resolve with continued opioid use; conversely, some side effects such as immune and sexual dysfunction are more apparent after long-term therapy. Consequently, in anticipating or treating opioid side effects, consideration should be given to the expected duration of therapy, the likelihood of side effects, and their potential severity.

Many side effects diminish or resolve with continued opioid use; conversely, some side effects are more apparent after long-term therapy.

This issue of Pain: Clinical Updates surveys evidence and empiric practice for the treatment of opioid side effects, primarily in patients with cancer pain but also in those with chronic noncancer pain. The treatment of opioid side effects in the acute setting will not be addressed because the approach to doing so often involves opioid-sparing techniques such as regional anesthesia and multimodal analgesia that are not fully generalizable to the chronic setting. Because of space constraints, this discussion of long-term opioid effects will not encompass tolerance, physical dependence, and addiction.

What Are the Most Important Side Effects?

Limited evidence describes the most common opioid side effects in cancer and chronic noncancer pain. A recent systematic review of opioids for chronic noncancer pain found that six side effects occurred significantly more often in those taking opioids than in those given a placebo: constipation; nausea; dizziness or vertigo; somnolence or drowsiness; vomiting; and dry skin, itching, or
pruritus.\(^1\) Similar findings were reported in patients receiving opioids for neuropathic pain.\(^2\) Another systematic review found that 22\% of patients with chronic noncancer pain discontinue opioid therapy because of side effects.\(^3\) Evidence of prevalence of opioid side effects in cancer pain is restricted to reports of specific side effects, and numbers are often confounded by the contribution of comorbidities or concurrent medications. Many trials are of insufficient duration or simply do not assess side effects that occur after long-term opioid administration; therefore, these side effects may be underreported.

The most commonly prescribed opioids and treatments for their side effects have been off patent for decades

There is a scarcity of literature that addresses which opioid side effects are most important to patients; however, clinical experience suggests that they may differ for patients with noncancer pain versus those with cancer pain. For example, a patient with advanced cancer may be less bothered by opioid-induced somnolence than a patient with chronic pain who attaches more importance to functionality.\(^4\) Research in a small group of patients with chronic noncancer pain suggests that constipation is the most bothersome side effect, based on its impact on life and the frequency with which it occurs.\(^5\) By consensus, the Clinical Practice Guidelines Committee of the American Pain Society considered the following side effects to be the most relevant to patients with cancer pain: constipation, nausea and vomiting, urinary retention, pruritus, hallucinations/confusion, respiratory depression, sedation/somnolence, dizziness, myoclonus, and dysphoria.\(^6\)

Evidence-Based Treatment

A 2003 evidence-based report on the treatment of opioid side effects in cancer pain and chronic noncancer pain highlighted the lack of high-quality evidence for either population.\(^7\) These findings are not surprising given the difficulty in performing randomized, controlled trials in palliative care settings. Further, the most commonly prescribed opioids and treatments for their side effects have been off patent for decades, reducing regulatory and commercial motivation for carrying out large randomized controlled trials in this area. An updating of the 2003 review during the preparation of the present survey shows little interim progress in the quantity and quality of evidence, with the exception being new publications on peripherally acting opioid antagonists to treat constipation. In addition, the treatment of opioid-induced dizziness and urinary retention has still not been addressed outside of the acute pain population. The following recommendations, therefore, are based on a combination of limited evidence, consensus guidelines, and standard practice.

General Approaches

Comorbidities and concurrent medications that contribute to the incidence and severity of side effects should be assessed and treated or discontinued as feasible. Pharmacological ap-

proaches to preventing or treating opioid side effects include an opioid-sparing regimen (addition of a nonsteroidal anti-inflammatory or adjuvant analgesic), symptomatic treatment (e.g., the use of an anti-emetic), use of an opioid antagonist to directly reverse opioid effects (e.g., naltrexone, small doses of naloxone for respiratory depression), or changing to another opioid ("opioid rotation").

Constipation is the most commonly occurring adverse effect of chronic opioid therapy

Opioid rotation exploits differences in efficacy and side-effect profiles of specific opioid molecules. Different opioids have different intrinsic efficacies at opioid receptor types and subtypes. Preclinical and clinical evidence suggests that analgesic tolerance develops more rapidly with opioids that have high intrinsic efficacy, thus reducing the frequency of required dose increases and their associated side effects.\(^8\)\(^9\) For most side effects there are no long-term, head-to-head comparisons that demonstrate increased tolerability of one opioid over another.\(^10\) Transdermal fentanyl may produce less constipation and daytime drowsiness than oral morphine.\(^11\) Differences in side-effect profiles may in part be due to individual opioid metabolites. Certain metabolites may have antianalgesic effects, neuroexcitatory effects (e.g., normeperidine), or both (morphine-3-glucuronide). Despite the relatively common practice of opioid rotation, there are no randomized trials that validate its effectiveness.\(^12\)

Nausea and Vomiting

The incidence of opioid-induced nausea and vomiting is estimated to be 10–40% depending on the opioid administered and the disease state studied, although untreated pain itself can induce nausea.\(^13\) Nausea and vomiting are both rated as highly distressing by patients.\(^14\) Opioids exert their emetogenic effects through multiple mechanisms, such as by stimulating the medullary chemoreceptor trigger zone, by causing gastric stasis, or through enhancing vestibular sensitivity. Gradual dose titration may forestall the occurrence of nausea. Additionally, these symptoms often subside with chronic therapy. It has been suggested that high doses of opioids may, in fact, reduce nausea and vomiting by interaction with mu receptors in the anantiemetic center.\(^15\)

Untreated pain itself can induce nausea

Currently, no medications are specifically licensed for the treatment of opioid-induced nausea and vomiting.\(^16\) Antiemetic therapy should be directed at precipitating mechanisms, although drug combinations are often necessary. While the oral route is preferable, parenteral administration may be required for initial dosing until the oral route becomes reliable. Commonly, with initial opioid dosing, nausea is caused by stimulation of the chemoreceptor trigger zone, in which case the dopamine antagonists prochlorperazine or haloperidol can be used. Alternatively, serotonin antagonists may be administered; they generally have a superior safety profile and are now priced
Success is built on a solid clinical foundation.
comparably to dopamine antagonists since the advent of generic ondansetron.13 Studies assessing the effectiveness of ondansetron are contradictory depending on route of administration and the disease state studied.15,17 Nausea induced by gastric stasis may be relieved by the prokinetic metoclopramide.16 For nausea exacerbated by motion, diphenhydramine or transdermal scopolamine may be helpful.18 Evidence supporting the efficacy of opioid antagonists in reducing either the incidence or the severity of nausea and vomiting is equivocal.19 Antiemetics themselves are associated with a number of side effects including sedation, confusion, and extrapyramidal symptoms, and for this reason they are usually introduced only when symptoms appear.

Pruritus

Pruritus (itching) occurs in about 1% of patients after systemic administration of opioids, but its incidence rises to 8% and 46% when epidural or intrathecal routes are employed, respectively. The mechanisms underlying the pruritogenic effects of opioids are still not completely understood; however, the high incidence of pruritus seen with intraspinal opioid administration suggests the involvement of spinal opioid receptors.20 Opioids cause histamine release from mast cells to varying degrees, which may account for the sensation of itch; however, fentanyl and sufentanil have not been shown to cause histamine release, yet they still cause itching.21 Other proposed mechanisms include opioid-induced dishabituation of itch-specific neurons22 or activation of central 5-hydroxytryptamine subtype 3 (5-HT3) receptors.

Despite controversy about the role of histamine, opioid-induced pruritus is routinely treated with antihistamines.

Despite controversy about the role of histamine, opioid-induced pruritus is routinely treated with antihistamines. Diphenhydramine is employed with varying degrees of success. Its sedating effect may be as important in relieving symptoms as its antihistaminic properties, although increased sedation may be undesirable in patients who are already suffering from opioid-induced sedation. Under these circumstances a less sedating antihistamine, such as hydroxyzine, may be employed. Mixed agonist/antagonists (e.g., nalbuphine) or pure opioid antagonists, such as nalmefene, can reverse itching, but dosing must be carefully titrated to prevent reversal of analgesia and precipitation of acute opioid abstinence. Limited evidence supports the use of the 5-HT3 antagonist ondansetron and alosetron, which may relieve pruritus through an inhibitory effect on the dorsal horn of the spinal cord.23,24 Finally, nonpharmacological interventions such as cool compresses or moisturizers may offer relief.

Sedation

Sedation most frequently occurs at initiation of opioid therapy or when a significant dose increase occurs. Symptoms frequently resolve after a few days, in which case reassurance and education (such as warning the patient to avoid alcohol and driving) should prove sufficient. Sedation for extended periods may be caused by comorbidities (dementia, metabolic encephalopathy, or brain metastases) or concurrent medications.24 Antihistamines, antidepressants, and anxiolytics can cause sedation directly or can reduce metabolism and hence increase the effects of opioids.

If the above approaches fail, opioid rotation,25,26 addition of a psychostimulant,26,27 or in refractory cases neurosurgical procedures to permit lowering of opioid requirements may provide some benefit. Two small studies demonstrate the effectiveness of the Alzheimer’s medication donepezil.28,29

Myoclonus

The incidence of opioid-induced myoclonus is estimated at between 3–87% depending on the patient population and methods of assessment.30 Although the mechanisms by which opioids induce myoclonus are not well characterized, the effect is often a function of both dose and duration of therapy and may be precipitated by metabolites of the parent drug. Myoclonus tends to occur when patients are drowsy or entering light sleep.31 It is usually mild and self-limiting, though in rare circumstances it persists and can be distressing for both patients and family. Signs range from mild twitching of the extremities to generalized spasms that can exacerbate pain by causing involuntary movement of, for example, a painful limb.31

Myoclonus often resolves with rotation to a different opioid

Myoclonus often resolves with rotation to a different opioid. When symptoms persist, and when other causes have been eliminated (dehydration, hypoglycemia, concurrent medications), treatment with a benzodiazepine or skeletal muscle relaxant (such as dantrolene and baclofen) has been recommended.43,32 Naloxone appears to be mostly ineffective and may actually precipitate seizures in normeperidine-induced myoclonus.30 Case reports have demonstrated that the use of local anesthetics or antiseizure medications may control symptoms.34,35

Delirium

Delirium is an acute confusional state that commonly occurs in terminally ill patients, complicating the assessment of an opioid contribution; however, it is estimated that opioids are a contributing factor in two-thirds of cases.36 Patients are at increased risk of delirium if they have renal dysfunction, are receiving chronic high doses of opioids, already have a degree of cognitive impairment, are dehydrated, or are taking other psychoactive drugs.32 The degree to which different opioids precipitate delirium has not been well characterized, but it has been suggested that route of administration and lipophilicity of the opioid are factors—the more rapid the receptor occupancy, the greater the probability of cognitive changes.21

Opioid rotation is commonly used to alleviate opioid-induced delirium.28 When rotation fails or is impractical, and when other causes have been excluded, neuroleptics are often
administered to patients with agitated delirium. The addition of a benzodiazepine is another option, though in some patients, paradoxically, doing so may exacerbate delirium.\textsuperscript{31,32} Case reports describing successful treatment with acetylcholinesterase inhibitors, such as donepezil and physostigmine, suggest that delirium may be precipitated via an opioid-induced disorder of central cholinergic neurotransmission.\textsuperscript{49}

**Respiratory Depression**

Respiratory depression is a potentially fatal side effect, but tolerance to this opioid effect usually occurs rapidly. It is rare in patients receiving chronic opioid therapy for two reasons. First, patients with chronic pain generally take their medications orally, thereby averting very high peak plasma concentrations. Second, dose escalation usually occurs gradually. When respiratory compromise does occur in this population, an alternative explanation should be sought, such as pneumonia, pulmonary embolism, or cardiomyopathy;\textsuperscript{7} or the coadministration of another sedating medication such as a benzodiazepine. Opioids act on respiratory centers in the brainstem to produce dose-dependent reductions in both respiratory rate and tidal volume. However, in the majority of patients, mild hypoventilation causes CO\textsubscript{2} to accumulate, which in turn stimulates central chemoreceptors, leading to a compensatory partial normalization of respiratory rate.\textsuperscript{30} Individual opioids are thought to cause comparable degrees of respiratory depression at equianalgesic doses; however, the complex pharmacokinetics of methadone may place patients at higher risk of hypoventilation than other opioid agonists.\textsuperscript{41,42}

**Respiratory depression is a potentially fatal side effect, but tolerance usually occurs rapidly**

Due to the risk of precipitating an acute abstinence syndrome with elevations of heart rate and blood pressure and reversal of analgesia, the opioid antagonist naloxone should only be given for impending or symptomatic respiratory depression (fewer than eight breaths per minute), and in small, titrated doses. Naloxone’s short half-life may necessitate repeated dosing, particularly in patients receiving long-acting opioids such as methadone. Some studies suggest that hypoventilation due to the mixed agonist-antagonist buprenorphine may be relatively resistant to the effects of naloxone.\textsuperscript{41}

**Constipation**

Definitions of constipation vary. Quantitative criteria define constipation as being present if two or more of the following symptoms have existed for more than 3 months: (1) straining at least 25\% of the time, (2) hard stools at least 25\% of the time, (3) incomplete evacuation at least 25\% of the time, (4) three or fewer bowel movements per week.

These criteria, in particular the chronicity requirement, may be overly stringent in patients receiving opioids.\textsuperscript{44} Constipation may be related to the patient’s underlying disease or comorbidity, for example inactivity, dehydration, or spinal cord compression. It is also commonly induced by medications such as antidepressants, antacids, anticholinergics, and diuretics. Opioids can delay gastric emptying, decrease peristalsis, and slow bowel motility.\textsuperscript{44} These actions in turn produce not only constipation, but also a constellation of symptoms including incomplete evacuation, bloating, abdominal distension, and increased gastric reflux.\textsuperscript{44} Together these symptoms are termed “opioid bowel dysfunction.” Estimates of the incidence of this condition are lacking, but constipation is estimated to occur in 25–50\% of patients with cancer and is the most commonly occurring adverse effect of chronic opioid therapy in patients with advanced cancer.\textsuperscript{6} Estimates in patients with noncancer pain are slightly lower (15–40\%), perhaps due to the lower prevalence of comorbidities in this population.\textsuperscript{45}

Constipation is one of the side effects of opioids to which patients rarely develop tolerance; therefore, a bowel regimen should be initiated at commencement of opioid therapy. Regimens are generally anecdotally based, but it is commonly accepted that both a stool softener and a stimulant are required, usually docusate sodium and senna, respectively. The long-term effectiveness and safety of such a regimen is unclear. Bulk laxatives such as psyllium and osmotic laxatives such as lactulose are also commonly employed. A psyllium regimen requires that the patient maintain adequate fluid intake, lest fecal impaction occur, and for this reason it is rarely a good choice in patients with advanced cancer. Metoclopramide may improve symptoms for patients with depressed gastric motility. Four randomized controlled trials employing opioid antagonists have been performed in patients with chronic opioid-induced constipation.\textsuperscript{49} Two small trials involving the nonspecific opioid antagonist naloxone, and one each involving the peripherally acting antagonists alvimopan (n = 168) and methylnaltrexone (n = 22), have been performed in mixed populations. Meta-analysis of these trials has demonstrated that opioid antagonists improve time to, number of, and satisfaction with bowel movements compared to placebo. These drugs appear to be safe in the short term and impair analgesia no more than placebo. The peripherally acting antagonists alvimopan and methylnaltrexone have been developed specifically for the treatment of opioid bowel dysfunction, although studies in patients with chronic pain have focused on constipation per se. These two drugs may in theory have a potentially superior safety profile than traditional antagonists in that the latter may act centrally to reverse analgesia. Both are at the phase III stage of development. The U.S. FDA’s approval of alvimopan has been delayed pending further long-term safety data.

**Side Effects of Long-Term Opioid Use**

Potential adverse effects of prolonged opioid therapy include abnormal pain sensitivity, hormonal changes, and immune modulation.\textsuperscript{2} The prevalence of, risk factors for, and mechanisms that perpetuate these effects have not been fully established; consequently, prophylaxis or treatment is either unavailable or has not yet been validated.

Abnormal pain sensitivity due to opioid-induced pronociception may be difficult to differentiate from opioid tolerance (desensitization) in clinical practice. Possible opioid-induced mechanisms for abnormal pain sensitivity include the production of anti-analgesic opioid metabolites, enhancement of NMDA receptor function, and increased release of spinal...
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Table 1

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Antiemetics, metoclopramide, anticholinergics, opioid rotation</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Antihistamines, opioid antagonists, propofol or 5-HT3 antagonists, nonpharmacological treatments</td>
</tr>
<tr>
<td>Sedation</td>
<td>Discontinuation of other sedating medications; opioid rotation, psychostimulants, donepezil</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Opioid rotation, benzodiazepines, skeletal muscle relaxants</td>
</tr>
<tr>
<td>Delirium</td>
<td>Opioid rotation, haloperidol, benzodiazepines, anticholinesterase</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Naloxone (emergency situations only)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Prophylactic treatment with a stool softener and bowel stimulant, nonabsorbable laxative (lactulose, polyethylene glycol), metoclopramide, opioid antagonists</td>
</tr>
<tr>
<td>Long-term side effects</td>
<td>Abnormal pain sensitivity: reduce opioid dose? Hypogonadism: testosterone or estrogen replacement</td>
</tr>
</tbody>
</table>

Prolonged opioid therapy may lead to abnormal pain sensitivity, hormonal changes, and immune modulation

Hormonal changes were historically described in subjects receiving methadone maintenance but are now increasingly described in those prescribed opioids for chronic pain. The general health of patients receiving methadone maintenance may confound the true incidence of opioid-induced changes. However, testosterone depletion and other signs and symptoms of androgen deficiency such as osteoporosis have been described in men receiving intrathecal opioid therapy for chronic pain. Testosterone (or in women, estrogen) replacement is currently the clinical standard of treatment, but the long-term risks of hormone replacement therapy in increasing the occurrence of hormone-dependent tumors are now being debated.

Until alternative nonopioid regimens exist, the monitoring and treatment of opioid side effects will continue to be an essential element of a patient’s therapy

Opioids may have a direct effect on the immune system. Additionally, different opioids appear to cause varying degrees of immunosuppression. Current, other than reducing dose or discontinuing opioid therapy, no treatment for this side effect has been tested or suggested.

Conclusion

Opioids remain the analgesics of choice for moderate to severe acute and cancer pain and are increasingly employed in the treatment of chronic oncologic pain of the same severity. Until equally effective nonopioid regimens exist, the monitoring and treatment of opioid side effects will continue to be essential elements of each patient’s therapy (see Table 1). Although many opioid side effects are recognized or suggested (e.g., periodontal disease from chronic dry mouth), only nausea and vomiting, respiratory depression, pruritus, and constipation have been investigated in randomized controlled trials. The lack of controlled trials relating to other side effects and to the practice of opioid rotation may result from their unpredictability or from the difficulty in reproducing the adverse effects in a controlled investigation. Until the true incidence, underlying mechanisms, and clinical implications of long-term responses to opioid therapy are fully understood, the optimal treatments for such events will likely remain undetermined and underdeveloped.

References

7. Chris Evans, MAPI values. Boston MA. Personal communication.