UPDATE IN NEUROLOGY

J. D. Bartleson, MD
Mayo Clinic
Rochester, MN

Update 1 – New Recommendations for Treating Acute and Chronic Low Back Pain

The emerging public health epidemic of prescription opioid-related morbidity and mortality in the United States has prompted guidelines from the Centers for Disease Control and Prevention (CDC),[1] a position paper from the American Academy of Neurology (AAN) by our colleague, Dr. Gary M. Franklin,[2] and "a call to action" by the U.S. Surgeon General.[3] The guidelines, recommendations, and "action" call for using opioid analgesics only when the benefits on reduced pain and improved function are expected to outweigh risks. Opioid analgesics include codeine, tramadol, oxycodone, hydrocodone, hydromorphone, morphine, and fentanyl. Non-opioid therapy is recommended for chronic pain and short-term use in acute low back pain.

What are the nonsurgical options for treating acute and chronic low back pain?

- Pharmacologic agents including:[4]
  - Muscle relaxants which are modestly helpful for acute back pain, and may be additive with analgesics.
  - COX-2 inhibitors and non-steroidal anti-inflammatory drugs which have modest benefit and can adversely affect the kidneys, gastrointestinal tract, and liver.[5] These drugs may be associated with cardiovascular risks.
  - Acetaminophen (known as paracetamol in Europe) has recently been shown to have no significant benefit for back pain.[6,7,8,9]
  - Tricyclic agents such as amitriptyline and nortriptyline which are thought to be helpful for radicular pain.
  - Neuro-modulating drugs such as gabapentin and pregabalin, which are also thought to be helpful for radicular pain.
  - Some herbal medications.[10]

- Non-pharmacologic therapies including cognitive-behavioral therapy, exercise, spinal manipulation, and interdisciplinary rehabilitation which are more helpful than acupuncture, massage, yoga, functional restoration, and heat for low back pain.[11,12,13]

- Non-surgical interventional therapies for low back pain such as:
  - Radiofrequency ablation of medial branch nerves supplying pain-generating facet joints.
  - Many non-surgical interventional therapies such as facet joint injection, intradiscal steroid injection, and intradiscal radiofrequency thermal coagulation have not been shown to be effective.[14]

- New, potentially helpful medications include:

  - Duloxetine monotherapy for chronic low back pain.[15]
  - Cannabis for chronic pain.[16,17,18,19]
    - The use of cannabis for pain is not legal in all states.
    - Its use is not approved by the U.S. Federal Government.
    - Where legal, its use is not always approved for back pain.
    - For these reasons, the use of cannabis for acute and chronic back pain is controversial.
- New American College of Physicians Clinical Practice Guidelines on the nonpharmacologic, systemic pharmacologic, and noninvasive therapies for low back pain were very recently published in the *Annals of Internal Medicine*.[20,21,22,23]

References

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016. JAMA 2016; 315(15):1624-1645.

2. Franklin GM. Opioids for Chronic Noncancer Pain. Neurology 2014; 83:1277-1284.

3. Murthy VH. Ending the Opioid Epidemic – A Call to Action. N Engl J Med 2016; 375(25): 2413-2415.

4. Chou R. Pharmacological Management of Low Back Pain. Drugs 2010; 70(4):387-402.

5. Enthoven WTM, Roelofs PDDM, Deyo RA, et al. Non-steroidal Anti-inflammatory Drugs for Chronic Low Back Pain. Cochrane Library DOI: 10.1002/14651858.CD012087, 2016.

6. Saragiotto BT, Machado GC, Ferreira ML, et al. Paracetamol for Low Back Pain. Cochrane Database of Systematic Reviews (6)CD012230, 2016.

7. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and Safety of Paracetamol for Spinal Pain and Osteoarthritis: Systematic Review and Meta-Analysis of Randomised Placebo Controlled Trials. BMJ 2015; 350:h1225.

8. Sands-Lincoln M, Goldmann DR. Acetaminophen in the Management of Acute and Subacute Low Back and Neck Pain. Am J Med 2016; 129(8):806-807.

9. Williams CM, Maher CG, Latimer J, et al. Efficacy of Paracetamol for Acute Low-Back Pain: A Double-Blind, Randomised Controlled Trial. Lancet 2014; 384:1586-1596.

10. Gagnier JJ, Oltean H, van Tulder MW, et al. Herbal Medicine for Low Back Pain: A Cochrane Review. Spine 2016; 41(2):116-133.

11. Chou R, Loeser JD, Owens DK, et al. Interventional Therapies, Surgery, and Interdisciplinary Rehabilitation for Low Back Pain. Spine 2009; 34(10):1066-1077.

12. Chou R, Huffman LH. Nonpharmacologic Therapies for Acute and Chronic Low Back pain: A Review of the Evidence for an American Pain Society/American College of Physicians Clinical Practice Guideline. Ann Intern Med 2007; 147:492-504.

13. Chou R, Deyo R, Friedly J, et al. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

14. Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical Interventional Therapies for Low Back Pain. Spine 2009; 34(10):1078-1093.

15. Konno S, Oda N, Ochiai T, Alev L. Randomized, Double-blind, Placebo-controlled Phase III Trial of Duloxetine Monotherapy in Japanese Patients with Chronic Low Back Pain. Spine 2016; 41(22):1709-1717.

16. Choo EK, Feldstein SW, Lovejoy TI. Opioids Out, Cannabis In – Negotiating the Unknowns in Patient Care for Chronic Pain. JAMA 2016; 316(17):1763-1764.

17. Azofeifa A, Mattson ME, Grant A. Monitoring Marijuana Use in the United States – Challenges in an Evolving Environment. JAMA 2016; 316(17):1765-1766.

18. Medical Letter on Drugs and Therapeutics. Cannabis and Cannabinoids. JAMA 2016; 316(22):2424-2425.

19. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-Analysis. JAMA 2015; 313(24):2456-2473.

20. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017; doi:10.7326/M16-2459.

21. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017; doi:10.7326/M16-2458.

22. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2017; doi:10.7326/M16-2459.

23. Atlas SJ. Management of Low Back Pain: Getting From Evidence-Based Recommendations to High-Value Care. Ann Intern Med 2017; DOI: 10.7326/M17-0293.

Update 2 – What's New in Spine Imaging?

My colleagues in Rochester in the last couple of years have reported on a specific pattern of gadolinium enhancement in spondylotic myelopathy and how to discriminate between long myelitis of neuromyelitis optica and neurosarcoidosis.

"Pancake-like" gadolinium enhancement suggests compressive myelopathy due to spondylosis.[1,2]

- Flanagan, et al, reported on 56 patients with spondylotic myelopathy and gadolinium enhancement of the cervical spinal cord who underwent spine surgery; 93 percent affected the cervical spinal cord, and 7% affected the thoracic spinal cord. All patients had longitudinal spindle-shaped T2-signal hyperintensity and spinal cord enlargement accompanied by a characteristic transverse, pancake-like band of gadolinium enhancement in three-fourths of the 56 patients.
- The gadolinium enhancement was typically immediately caudal to the site of maximal spinal stenosis. The majority of patients had been diagnosed as having a neoplastic or inflammatory myelopathy before decompressive surgery, which was often delayed (by a median of 11 months). The gadolinium enhancement persisted for months to years following decompressive surgery in many patients. Recognition of this imaging finding is needed to prevent inappropriate interventions (e.g., spinal cord biopsy) or delayed consideration of potentially beneficial decompressive surgery.

Flanagan, et al, also reported on "discriminating long myelitis of neuromyelitis optica from sarcoidosis."[3]

- They identified 71 patients who had an episode of myelitis accompanied by a spinal cord lesion spanning ≥ three vertebral segments between 1996 and 2015. All patients had either spinal cord sarcoidosis (SCS) or neuromyelitis optica spectrum disorder (NMOSD). There were 34 patients with SCS and 37 patients with NMOSD. About half of the SCS patients were initially diagnosed as NMOSD or idiopathic transverse myelitis. Median delay to diagnosis was longer for SCS than NMOSD (5 versus 1.5 months).
- NMOSD myelitis patients were more commonly women, had concurrent or prior optic neuritis or intractable vomiting episodes more often, had shorter time to maximum deficit, and had systemic autoimmunity more often than SCS patients. SCS patients had constitutional symptoms, cerebrospinal fluid (CSF) pleocytosis, and hilar adenopathy more frequently than NMOSD. Low CSF glucose and elevated angiotensin-converting enzyme levels were exclusively found in SCS patients. Dorsal spinal cord subpial gadolinium enhancement extending over ≥ two vertebral segments, and persistent enhancement for > two months favored SCS and ring-like enhancement favored NMOSD. Abnormalities suggestive of sarcoidosis on chest x-ray (7 of 18, 39%), chest CT (22 of 30, 73%), and FDG PET (7 of 8, 88%) were seen exclusively in SCS patients. In 3 of 7 patients with SCS, FDG PET showed hypermetabolism in the spinal cord. Maximum disability was similar in both disorders. The authors conclude that SCS is an under-recognized cause of longitudinally extensive myelitis and commonly mimics NMOSD.

References

1. Flanagan EP, Marsh RW, Weinshenker BG. Teaching NeuroImages: "Pancake-like" Gadolinium Enhancement Suggests Compressive Myelopathy Due to Spondylosis. Neurology 2013; 80(21):e229.

2. Flanagan EP, Krecke KN, Marsh RW, et al. Specific Pattern of Gadolinium Enhancement in Spondylotic Myelopathy. Ann Neurol 2014; 76:54-65.

3. Flanagan EP, Kaufmann TJ, Krecke KN, et al. Discriminating Long Myelitis of Neuromyelitis Optica from Sarcoidosis. Ann Neurol 2016; 79:437-447.

Update 3 – Do Oral Corticosteroids Help an Acute Radiculopathy Due to a Herniated Lumbar Disk?

Have you ever given a patient with an acute lumbar (or cervical) disk a course of oral corticosteroids with that hope that they will get better faster? Goldberg, et al conducted a randomized, double-blind, placebo-controlled clinical trial of 269 adults with radicular lower limb pain for three months or less.[1] Patients were followed for one year. Patients received a 15-day course of oral prednisone (5 days of 60 mg per day, 5 days of 40 mg per day, and 5 days of 20 mg per day or matching placebo). All patients had an Oswestry Disability Index (ODI) of ≥ 30, indicating moderate dysfunction and a herniated lumbar disk confirmed by magnetic resonance imaging (MRI). Results were as follows:

- At 3 weeks and 52 weeks, there was no difference in pain reduction in the prednisone versus placebo groups. The prednisone-treated group showed a modest improvement in the ODI at 3 weeks and 52 weeks. There were no differences in surgery rates at 52 weeks of follow-up. About half of the patients who received prednisone had an adverse event. Adverse events were about twice as common in the prednisone group as compared to the placebo group.
- Compared to placebo, a 15-day course of a tapering dose of oral prednisone may provide some improvement in functional outcome but no change in pain. The benefits of a course of oral prednisone are probably roughly comparable to the benefits from an epidural injection of corticosteroid, and the risks may be similar as well. A course of oral steroids for acute radiculopathy does not require pretreatment advanced imaging of the spine which is required before an epidural steroid injection.
- One commentator stated that, "In individuals with acute symptoms at high risk for developing chronic pain (e.g., those with co-existing psychosocial issues) and at low risk for side effects, a course of oral steroids seems like a reasonable treatment option."[2]
- The results give very modest support to this form of treatment.

References

1. Goldberg H, Firtch W, Tyburski M, et al. Oral Steroids for Acute Radiculopathy Due to a Herniated Lumbar Disk – A Randomized Clinical Trial. JAMA 2015; 313(19):1915-1923.

2. Cohen SP. Oral Steroids for Improved Function but Not Pain in Acute Radiculopathy Due to Disc Herniation. Evid Based Med 2015; 20(4):138.

Update 4 – Do Epidural Steroid Injections Help Patients with Lumbar Spinal Stenosis?

Injections of all kinds are given to the spine, both for therapeutic and diagnostic purposes. One of the very common injections is a lumbar epidural steroid injection for symptomatic lumbar spinal stenosis. Friedly, et al reported on a randomized trial of epidural corticosteroid injections for spinal stenosis with surprising results.[1]

- Four hundred patients with lumbar central spinal stenosis and moderate to severe lower limb pain and disability were randomly assigned to receive epidural injections of corticosteroids plus lidocaine or lidocaine alone. Patients received one or two injections before the primary outcome evaluation which was performed after six weeks. Primary outcomes were the Roland-Morris Disability Questionnaire (RMDQ) and the rating of the intensity of leg pain.

- At six weeks, there were no significant between-group differences! A secondary subgroup analysis stratified the results according to type of injection (interlaminar versus transforaminal), which likewise showed no significant differences at six weeks.
- "You could have fooled me." Epidural steroid injections for temporary symptomatic relief of pseudoclaudication due to lumbar spinal stenosis are widely used in spine centers and pain clinics with presumed benefit. Of course, if lumbar spinal stenosis symptoms are provoked by neural compression rather than inflammation, perhaps the results of this study are understandable, if not predictable.
- Although I do not order as many epidural steroid injections for my lumbar spinal stenosis patients after reading this article, I have not completely abandoned the practice. The editorialist said the same thing.[2] Shame on us.

References

1. Friedly JL, Comstock BA, Turner JA. A Randomized Trial of Epidural Glucocorticoid Injections for Spinal Stenosis. N Engl J Med 2014; 371(1):11-21.

2. Andersson GBJ. Epidural Glucocorticoid Injections in Patients with Lumbar Spinal Stenosis. N Engl J Med 2014; 371(1):75-76.

Update 5 – Is Simultaneous Fusion Helpful for Patients Undergoing Laminectomy for Lumbar Spinal Stenosis?

Have you ever wondered why so many fusions are performed? Are they always necessary? Between 2002 and 2007, the use of surgical decompression alone to treat lumbar spinal stenosis declined slightly in the United States, whereas the use of a combined procedure of decompression and fusion increased by a factor of 15 during this period![1] Decompression with fusion is performed in about half of all patients with lumbar spinal stenosis who undergo spine surgery and 96% of the subgroup of patients who have concomitant spondylolisthesis.

Back-to-back articles in the *New England Journal of Medicine* one year ago reported on a randomized trial of laminectomy plus fusion versus laminectomy alone for patients with lumbar spinal stenosis with and without spondylolisthesis,[2] and a smaller study randomizing patients with symptomatic lumbar spinal stenosis and degenerative spondylolisthesis to undergo either decompressive laminectomy alone or laminectomy with posterolateral instrumented fusion.[3]

Försth, et al conducted a randomized, controlled trial of fusion surgery for lumbar spinal stenosis.[2] Two hundred forty-seven patients who had lumbar spinal stenosis at one or two adjacent vertebral levels were randomized to undergo either decompression surgery (laminectomy) plus fusion (fusion group) or decompression surgery alone (decompression-alone group). Patients with and without preoperative degenerative spondylolisthesis were included. Outcomes included patient-reported measures, a six-minute walk test, a health economic evaluation, and the Oswestry Disability Index (ODI) two years after surgery.

- There were no significant differences between the groups after two years. In addition, the results were similar between patients with and without spondylolisthesis.
- A subset of patients underwent follow-up evaluation five years after surgery, and again there were no significant differences between the groups in clinical outcomes at five years. The mean length of hospitalization was 7.4 days in the fusion group and 4.1 days in the decompression-alone group. Operating time was longer, the amount of bleeding was greater, and surgical costs were higher in the fusion group than in the decompression-alone group.
- During a mean follow-up of 6.5 years, additional lumbar spine surgery had been performed on 22% of patients in the fusion group and in 21% of those in the decompression-alone group.
- The authors conclude that in patients with symptomatic lumbar spinal stenosis with or without degenerative spondylolisthesis, decompression surgery plus fusion does not result in better clinical outcomes at two and five years than decompression-alone.

Ghogawala et al randomized 60 patients who had stable degenerative spondylolisthesis (ranging from 3-14 mm) and symptomatic lumbar spinal stenosis to undergo either decompressive laminectomy alone (decompression-alone group) or laminectomy with posterolateral instrumented fusion (fusion group).[3] The primary outcome

measure was change in the physical-component summary score of the Medical Outcomes Study 36Item Short-Form Health Survey (SF-36) two years after surgery (higher scores indicate better quality of life). A secondary outcome measure was the ODI (higher scores indicate worse disability). Patients were followed for four years.

- Follow-up was 89% at one year, 86% at two years, and 68% at four years.
- At two, three, and four years, SF-36 physical-component summary scores remained higher in the fusion group than in the decompression-alone group. With respect to reductions in disability related to back pain, changes in the ODI scores two years after surgery did not differ significantly between the two groups. The improvement on the SF-36 was just above the minimal clinically important difference. The ODI is thought to be a better, more disease-specific functional scale.[1]
- Understandably, more blood loss and longer hospital stays occurred on the fusion group.
- In this study, the cumulative re-operation rate was 14% in the fusion group and 34% in the decompression-alone group.

Both trials show clearly that for most patients, lumbar stenosis surgery should be limited to decompression unless patients have:[1]

- Proven spinal instability as confirmed on flexion-extension radiographs.
- Vertebral destruction caused by trauma, tumor, or infection.
- Associated spine deformity such as congenital spondylolisthesis or scoliosis.
- Foraminal stenosis with compressed exiting spinal nerves caused by postsurgical disk collapse.

The addition of instrumented fusion to decompression for lumbar spinal stenosis appears to be inappropriate in most patients.

- Lumbar fusion for chronic low back pain without neural compression is no better than non-operative care.[4,5]

Please send your patients with symptomatic lumbar spinal stenosis with or without spondylolisthesis who are considering surgery to a spine surgeon who is likely to perform decompression without simultaneous fusion.

References

1. Peul WC, Moojen WA. Fusion for Lumbar Spinal Stenosis – Safeguard or Superfluous Surgical Implant? N Engl J Med 2016; 374(15):1478-1479.

2. Försth P, Ólafsson G, Carlsson T, et al. A Randomized, Controlled Trial of Fusion Surgery for Lumbar Spinal Stenosis. N Engl J Med 2016; 374(15):1413-1423.

3. Ghogawala Z, Dziura J, Butler WE, et al. Laminectomy Plus Fusion versus Laminectomy Alone for Lumbar Spondylolisthesis. N Engl J Med 2016; 374(15):1424-1434.

4. Hedlund R, Johansson C, Hägg O, et al. The Long-Term Outcome of Lumbar Fusion in the Swedish Lumbar Spine Study. Spine J 2016; 16(5):579-587.

5. Mannion AF, Brox J-I, Fairbank JC. Consensus at Last! Long-Term Results of All Randomized Controlled Trials Show that Fusion is No Better than Non-Operative Care in Improving Pain and Disability in Chronic Low Back Pain. Spine J 2016; 16(5):588-590.

Update 6 – Is Stem Cell Therapy the Next Big Thing in the Treatment of Discogenic Low Back Pain?

Intervertebral disk (IVD) degeneration is ubiquitous and increases with age. IVD degeneration affects more than 70% in the age group of 50 years or younger, and over 90% in those older than 50. As an imaging finding, IVD degeneration is age-related and frequently asymptomatic. However, there is a population in which the disk becomes painful, often termed discogenic pain. Discogenic pain is estimated to account for 25-80% of all low back and neck pain.

The IVD is largely avascular and hypoxic. Nutrients such as glucose and oxygen diffuse from the capillaries across the cartilaginous end plate and through dense disk material. IVD degeneration is characterized by cell death and degeneration of extracellular matrix. A decrease in extracellular matrix synthesis and an increase of extracellular matrix degeneration are associated with loss of cells and an inflammatory response. Dehydration of the nucleus pulposus, fissures in the annulus fibrosis, protrusion and extrusion of the nucleus pulposus, and a cascade of inflammatory reactions perpetuate loss of the normal matrix. Innervation of the normal IVD is confined to the outer third of the annulus and end plate, but there is evidence that so-called sinuvertebral nerves, situated posterolaterally, can grow into the superficial layers of the degenerating IVD and mediate pain.

Over the past decade, there has been increasing interest in treating IVD degeneration with stem cells.[1,2,3,4,5]

- A systematic review of IVD regeneration with stem cells in animal controlled trials found that despite statistical heterogeneity, stem cells transplanted to the IVD in quadruped animals slowed or arrested the IVD degenerative process.[1]
- Some early clinical human data support the safety and feasibility of bone marrow-derived mesenchymal stem cells for the treatment of low back pain due to uncontrolled degenerative disk disorders.
- A double-blind, controlled, randomized clinical study with an adequate number of patients and validated endpoint measures is under way.[5]

The potential of stem cell therapy is exciting, but most “newest greatest” therapies for chronic spine pain do not pan out.

References

1. Wang Z, Perez-Terzic CM, Smith J, et al. Efficacy of Intervertebral Disc Regeneration with Stem Cells – A Systematic Review and Meta-Analysis of Animal Controlled Trials. Gene 2015; 564:1-8.

2. Zeckser J, Wolff M, Tucker J, Goodwin J. Multipotent Mesenchymal Stem Cell Treatment for Discogenic Low Back Pain and Disc Degeneration. Stem Cells International 2016; Vol. 2016:1-13. Article ID 39083893. doi:10.1155/2016/3908389.

3. Kim KD. Stem Cells and Discogenic Low Back pain. Spine 2016; 41(75):S11-S12.

4. Elabd C, Centeno CJ, Schultz JR, et al. Intra-Discal Injection of Autologous, Hypoxic Cultured Bone Marrow-Derived Mesenchymal Stem Cells in Five Patients With Chronic Lower Back Pain: A Long-Term Safety and Feasibility Study. J Transl Med 2016; 14(253):1-9.

5. Pettine K, Suzuki R, Sand T, Murphy M. Treatment of Discogenic Back Pain with Autologous Bone Marrow Concentrate Injection with Minimum Two Year Follow-Up. International Orthopaedics (SICOT) 2016; 40:135-140.