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CME ARTICLE

The MILD Procedure: Is Minimally Invasive Laminectomy Decompression Better Than Sliced Bread?

Clifford Gevirtz, MD, MPH

Learning Objectives: After participating in this CME activity, the physician should be better able to:

1. Identify the indications for minimally invasive laminectomy decompression (MILD).
2. Assess the incidence of reported complications associated with MILD.
3. Evaluate the evidence of longer-term shortcomings of the procedure.

Lumbar spinal stenosis (LSS) is a common problem among an aging population. As the baby-boom generation ages into its 60s and beyond, physicians can expect to see large numbers of patients with symptoms related to spinal stenosis. Approximately 1 in 200 people in the United States over the age of 50 years has symptomatic LSS.[1]

The National Ambulatory Medical Care Survey (NAMCS) first determined the incidence of LSS in the US population.[2] NAMCS is an annual survey of 3000 general physicians conducted by the National Center for Health Statistics. The survey is intended to be representative of practicing, nongovernmental, office-based physicians in the United States. From 1989 to 1990, the diagnostic cluster for low back pain ranked fifth in frequency among categories and accounted for 2.8% of all patient visits. Of those visits, the frequency of LSS was approximately 25%.

The National Spine Network provides another estimate of the incidence of LSS.[3] In this study, the researchers prospectively collected data pertaining to 17,774 patients from 25 centers that treat back and neck problems. The average patient age was 47.5 years (standard deviation [SD] ±15.4 years; range, 17–98 years); 54.7% of patients were male; and 84.2% of patients were white. Among these patients, 13.1% were specifically diagnosed with

In This Issue

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spinal stenosis, 12.9% with age-related degenerative spondylosis, and 19.2% with herniated disks.

> Approximately 1 in 200 people in the United States over the age of 50 years has symptomatic lumbar spinal stenosis.

This article addresses some of the treatments available for spinal stenosis, including a new procedure, minimally invasive laminectomy decompression (MILD). (The *mild* procedure is a trademark of Vertos Medical Inc.) The practitioner will become familiar with the indications for the MILD procedure and the frequency of reported complications, and will be able to evaluate the evidence of its overall success or shortcomings.

Diagnosis of Lumbar Spinal Stenosis

The typical patient with LSS is an older man who presents with a history of neurogenic claudication symptoms verified through imaging studies (MRI or CT). For this typical patient, conservative measures have not alleviated symptoms satisfactorily.

Neurogenic claudication is triggered by axial-loading activities. Unlike intermittent or vascular claudication, neurogenic claudication is relieved by flexion and not by mere cessation of walking. The clinical symptoms of LSS result from a diminished cross-sectional area of the spinal canal secondary to direct compression of the nerve roots that comprise the cauda

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equina, reduction of venous outflow with nerve root ischemia, or some combination of the two.

The patient with a hypertrophied ligamentum flavum[4] that compromises the anteroposterior and lateral dimensions of the spinal canal, and who has failed conservative therapy, is the optimal candidate for the MILD procedure.

Conservative management usually starts with physical therapy, nonsteroidal anti-inflammatory medications and gabapentinoids (eg, gabapentin and pregabalin), physical therapy, and exercise. This is often followed by a series of epidural corticosteroid injections, but if these conservative measures fail, then surgical decompression and fusion is often the final resort.

> Unlike intermittent or vascular claudication, neurogenic claudication is relieved by flexion and not by mere cessation of walking.

The MILD Procedure

A less invasive approach is MILD, a minimally invasive alternative to open or endoscopic surgery for lumbar decompression in the treatment of LSS. MILD is performed using IV sedation or monitored anesthesia care and consists of partial removal of interlaminar bone (laminotomy) and partial excision (debulking) of the ipsilateral ligamentum flavum and fatty tissue from the posterior aspect of the lumbar spinal canal.

Decompression procedures primarily differ according to the size of the incision and guidance components. For example, a percutaneous approach is defined by a 5- to 10-mm surgical incision; an endoscopic approach requires a 15- to 20-mm incision, and a typical open laminotomy requires a 4- to 6-cm incision. The MILD procedure uses a 5.1-mm portal for a percutaneous approach. Continuous lateral oblique fluoroscopic image guidance with epiduralography is used throughout the procedure.[5] The average radiation dose received by patients has not been quantified in the published literature.

Methodology of the MILD Procedure

In LSS, the space within the spinal canal narrows, which leads to a gradual compression of nerves and ultimately symptomatic neurogenic claudication. The goal of surgical treatment of LSS is to achieve neural decompression adequate to provide relief from symptoms, while preserving, as much as possible, the anatomy, stability, and biomechanics of the lumbar spine.

Endoscopic and traditional open surgical treatment of LSS may require only a 1.5- to 6-cm incision, as mentioned previously, but those procedures often result in a wide laminectomy and significant undercutting of the medial facet with foraminotomy. This results in local tissue trauma, scarring, and potential postoperative spinal instability.[4]

The MILD procedure is a minimally invasive alternative to the standard laminotomy–laminectomy approach. Typically, MILD is performed using local infiltrated anesthesia and IV sedation to keep the patient comfortable and stationary.

As mentioned, the MILD procedure treats LSS by removing small portions of laminar bone and debulking the ligamentum flavum (Figure 1). This increases the space in the spinal canal (Figure 2) while minimizing trauma to the surrounding tissue and bony structures. The restoration of adequate space is demonstrated during the procedure with an oblique epidurogram that shows improved flow.

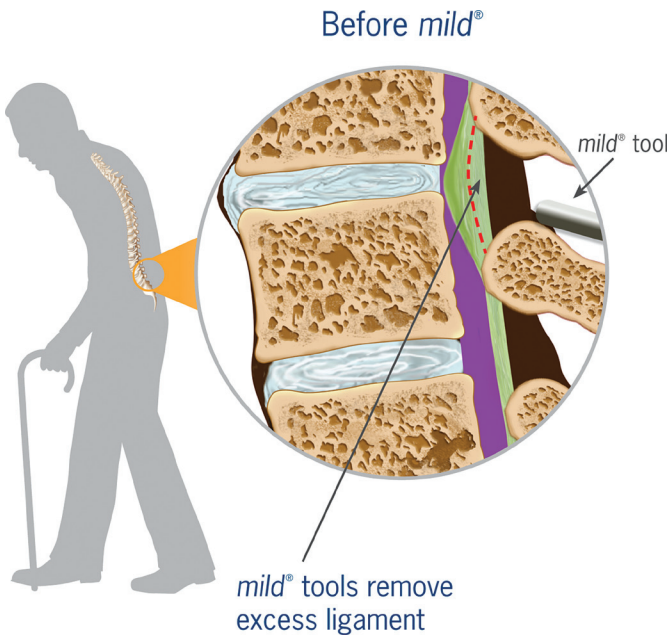

Figure 1. Illustration showing preoperative condition of laminar bone and ligamentum flavum. (Image courtesy of Vertos Medical Inc.)

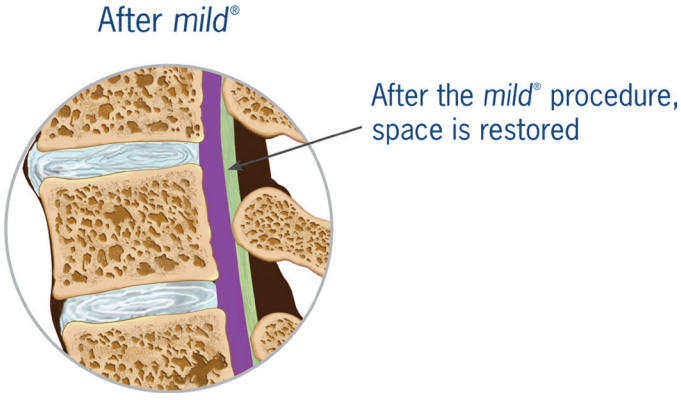

Figure 2. Illustration showing laminar bone and ligamentum flavum after MILD. (Image courtesy of Vertos Medical Inc.)

Figure 3. MILD surgical tray. (Image courtesy of Vertos Medical Inc.)

The surgical instruments used in the MILD procedure have built-in safety features, such as blunt tips to protect structures at the posterior approach, and special top-cutting surfaces for precision cutting at the desired angle. The MILD kit is for single-patient use and includes a portal stabilizer to minimize medial and lateral movement during the procedure, and an instrument-depth guide to assist in placement of the portal (Figure 3).

At the beginning of the procedure, the patient is placed in the prone position on a fluoroscopy-capable operating table, draped, and prepared in sterile fashion. Appropriate bolstering is used as needed.[5]

An epidurogram is then performed for the purpose of identifying the hypertrophic ligamentum flavum. Use of the contralateral oblique view presents the thickest cross-section of the lamina, providing optimal ligamentum-infolding imaging. Next, the interlaminar space is identified through fluoroscopic visualization.[5]

After the trajectory has been planned and the patient's skin marked, the MILD 6G portal and 7G trocar are inserted percutaneously. These devices are advanced along the desired trajectory under fluoroscopic guidance. Once positioned, the trocar is removed, and the access portal is left in the interlaminar space.[5]

The MILD bone sculptor rongeur is placed through the access portal to the lamina. The physician rotates this device, which precisely cuts and then removes small pieces of bone. Once sufficient access is obtained, the rongeur is removed, and the MILD tissue sculptor is advanced through the portal under the lamina into the dorsal aspect of the hypertrophic ligamentum flavum.[5]

Debulking of the ligamentum flavum is accomplished by removing the collagen-laden posterior portion of the ligament, while leaving the ventral fibers of the ligament intact. Improved contrast flow, which is the result of a reduction of infolding, along with a small amount of tissue removed, are clear indicators of the decompression endpoint on epidurogram.[5]

The procedure can be performed bilaterally and on multiple vertebral levels in one or more sessions. It should be noted that the angle of the cutting tip on the instrumentation requires a new incision and instrument insertion when the procedure is being performed bilaterally or at another level.[5]

Once adequate decompression has been achieved at the final operative level, the portal is removed and the wound typically closed using a sterile adhesive bandage. A suture typically is not required. Because there is minimal soft-tissue trauma, patients are usually observed for 2 hours after the procedure and subsequently discharged as clinically indicated. Patients are allowed to walk if they can tolerate it and instructed to increase activities slowly. No implants are left behind, and having had a previous MILD procedure does not impede future surgical interventions, should they become necessary.[5]

MILD Effectiveness

The MiDAS I (mild Decompression Alternative to Open Surgery) prospective clinical study[6] was conducted at 14 US spine specialist practices and designed to assess the safety and functional outcomes of MILD in the treatment of LSS.

Patient selection criteria for the MiDAS I study included prior failure of conservative therapy, a hypertrophic ligamentum flavum (>2.5 mm), and a reduced thecal sac cross-section. Patients were assessed according to a visual analog scale, Oswestry Disability Index, Zurich Claudication Questionnaire, and SF-12v2 Health Survey.

In all, 78 patients were treated, of whom 55 were older than 65 years. Twenty of the procedures were performed in an ambulatory surgical center, and 58 were performed at a hospital. Practitioners treated 51% of the patients at 2 levels, resulting in 115 total treated levels, for a total of 170 procedures with some levels treated bilaterally.[6]

There were no major device- or procedure-related complications in this patient cohort, with major complications defined as dural tears, nerve-root injury, hematomas, and infections.

At week 6 follow-up, there were significant improvements in all clinical outcomes: Visual analog scale pain score ($P < 0.0001$), Oswestry Disability Index functional mobility ($P < 0.0001$), Claudication Questionnaire pain and function ($P < 0.001$), and the SF-12v2 quality-of-life physical and mental component scores.

Similarly, Lingreen and Grider[7] conducted a retrospective review of 42 consecutive patients undergoing the MILD procedure. Patients ranged in age from 52 to 86 years, and all had failed prior conservative therapy for LSS. The majority of patients underwent 2 levels of bilateral decompression. There were no major adverse events. The most significant minor event was soreness lasting for a few days. No patient required admission for overnight observation.

MILD Safety

Given that the decompression component of the MILD procedure is similar to open laminotomy, the safety of the MILD

procedure emerges as the key unique outcome. As noted previously, neither Chopko and Caraway[6] nor Lingreen and Grider[7] reported major adverse events in a total of 120 patients. Furthermore, Deer et al[8] reported the safety data from a manual and electronic chart review for 90 additional patients treated by 14 physicians in 9 American states.[3] Again, there were no significant complications with the MILD procedure, including no reported incidents of dural puncture or tear, blood transfusion, nerve injury, epidural bleeding, hematoma, or infection.

None of the procedures was aborted. No patients required readmission to the hospital within 30 days of the MILD procedure in these studies. Of the 210 procedures published in the peer-reviewed literature, the reported incidence of major adverse events was zero, thus confirming the excellent safety record of the MILD procedure.

Deyo et al[8] recently reviewed the safety and effectiveness of the MILD procedure when indirectly compared with open or endoscopic laminectomy. The review was a retrospective cohort analysis of Medicare claims from 2002 to 2007 for patients undergoing surgery for spinal stenosis. Among the 21,474 patients undergoing open or endoscopic decompression only (ie, without fusion), there was a 2.1% incidence of medical complications and a 30-day mortality rate of 0.6%. The length of stay was 2.7 days, with 7.8% of patients rehospitalized within 30 days for any reason. These statistics compare favorably and imply a safety advantage to the MILD procedure.

Deer et al[8] concluded, "Using a minimally invasive lumbar decompression (MILD) for spinal stenosis, one can safely and effectively reduce pain, improve functionality, and minimally change spinal biomechanics and stability in LSS patients who have failed conservative treatment and who are not yet in need of, or who do not desire, more invasive open surgical decompression procedures."

A proper head-to-head trial would be to compare MILD with minimally invasive laminectomy and/or open laminectomy.

Procedure Setting

Although most commonly performed in the hospital outpatient setting, the MILD procedure can also be conducted safely and effectively in a freestanding ambulatory surgery center.[9] Its use in an office-based setting has not been reported. Because the patient is recovered after 2 hours of observation in a recovery room, and does not require overnight observation, MILD should be considered an outpatient procedure.[9]

Other Opinions of Efficacy

However, in contrast to reports of total success, Wilkinson and Fourney[10] reported that several of their patients who underwent MILD required further surgery after the formal study period ended.

A problem with the….MiDAS II trial is that there was no mention of the 17 patients who dropped out. It is unclear whether these patients went on to open laminectomy.

The *New York Times* noted some of the controversy in its September 5, 2012, article, "Clash Over a Spine Treatment." The article addressed a study of 10 patients who were followed up for 26 weeks after undergoing the MILD procedure. The article addresses the fact that many patients returned for surgery after the official follow-up period in the study ended—outside of the study protocol. A Canadian surgeon who had participated in the study continued to follow his patients beyond the 26 weeks and noticed many had pain return and needed surgery. Vertos accused him of violating the study agreement and protocol. There was a nasty chain of letters to the editor and responses back and forth. The manufacturer also complained to Fourney's academic institution, contending that he had violated the study protocol by continuing the study past the original period. From a scientific and ethical point of view, this charge is utter nonsense.

Ligamentum Flavum Has to Be Very Bulky

Mekhail et al[10] demonstrated that the ligamentum flavum contributes up to 85% of spinal canal stenosis. However, there is no way to tell how much ligamentum flavum contributes to the stenosis without the use of "dynamic" MRI. This study is limited, however, because there was no comparator group—and 50% of patients might do better anyway over time. A head-to-head trial should compare MILD with other minimally invasive procedures.

A problem with the multicenter study by Mekhail et al,[12] the MiDAS II trial, is that there was no mention of the 17 patients who dropped out. It is unclear whether these patients went on to open laminectomy. Other limitations include a lack of postoperative MRIs to document the actual degree of decompression. In addition, there is no mention of epidural corticosteroid injections or other interventions during the year of follow-up.

Some commentators[13] have suggested that MILD should be offered only to patients with symptomatic central stenosis when MRI clearly shows it is only or mostly caused by ligamentum flavum hypertrophy. Patients should be made aware that MILD will not help their back pain or their radicular symptoms.

In the *American Society of Regional Anesthesia Newsletter*, August 2011, Narouze[14] stated: "Although the MILD procedure seems to be very safe and efficacious in selected patients, it is premature to recommend its widespread use in patients suffering from lumbar spinal stenosis without well-controlled

studies comparing its outcomes with those of the more traditional open approaches. We also have to compare MILD with other minimally invasive laminectomies."

In a double-blind randomized prospective trial, Brown[15] compared MILD with epidural corticosteroid injection and pronounced MILD superior. This is not an appropriate comparison at all, however. Epidural corticosteroid injections do not resect any tissue and do not change structural issues. Rather, epidural corticosteroid injection decreases the inflammatory component of the pain. A proper head-to-head trial would be to compare MILD with minimally invasive laminectomy and/or open laminectomy.

According to the company's website, more than 15,000 MILD procedures have been performed. In all of these cases, according to the company, there is not one report of a dural tear or leak, infection, or hematoma. This is truly an extraordinary number of cases without a single wet tap. Indeed, this number far exceeds the expected complication rate by more than an order of magnitude (ie, in 15,000 cases, a wet tap rate of 1 in 1000 would have produced 15 cases). This raises some question of accuracy and veracity of the report.

Although the number of total procedures reported is 15,000, the lack of any complications raises questions of veracity.

Exclusion Criteria

Patients with the conditions listed below were excluded from study trials and, therefore, their treatment with MILD would not be evidence-based:

- Prior surgery at the intended treatment level;
- History of recent spinal fracture;
- Disabling back or leg pain from causes other than LSS;
- Significant/symptomatic facet hypertrophy;
- Bleeding disorders or current use of anticoagulation;
- Use of aspirin or nonsteroidal anti-inflammatory medications within 5 days of the proposed procedure;
- Epidural corticosteroid injection within 3 weeks of the proposed procedure;
- Dementia or inability to give an informed consent;
- Receiving worker's compensation; and
- Any patients in litigation or planning litigation about their back pain.

Conclusions

Like many new therapies, the MILD procedure appears to be an easy answer to the pain and disability of LSS. However, proper patient selection seems to be a major determinant in the success of the procedure. Patients with hypertrophy of the ligamentum flavum do best with the MILD approach. I also find it disturbing that not a single serious complication has been reported with this procedure. Not a single dural puncture? Not a single hematoma? Although the number of total procedures reported is 15,000, the lack of any complications raises questions of veracity. ■

References

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis Rheum.* 2008;58(1):26-35.
2. Hart LG, Deyo RA, Cherkin DC. Physician office visits for low back pain: frequency, clinical evaluation, and treatment patterns from a US national survey. *Spine*. 1995;20(1):11-19.
3. Fanuele JC, Birkmeyer NJ, Abdu WA, et al. The impact of spinal problems on the health status of patients: have we underestimated the effect? *Spine*. 2000;25(12):1509-1514.
4. Deer TR, Kapural L. New image-guided ultra-minimally invasive lumbar decompression method: the MILD procedure. *Pain Physician*. 2010;13:35-41.
5. Deer TR, Mekhail N, Lopez G, Amirdelfan K. Minimally Invasive Lumbar Decompression for Spinal Stenosis. *Journal of Neurosurgical Review*. 2011;1(S1):29-32.
6. Chopko B, Caraway DL. MiDAS I (mild Decompression Alternative to Open Surgery): a preliminary report of a prospective, multi-center clinical study. *Pain Physician*. 2010;13:369-378.
7. Lingreen R, Grider JS. Retrospective review of patient self-reported improvement and post-procedure findings for mild (minimally invasive lumbar decompression). *Pain Physician*. 2010;13:555-560.
8. Deer TR, Kim C, Bowman R, et al. Study of percutaneous lumbar decompression and treatment algorithm for patients suffering from neurogenic claudication. *Pain Physician*. 2012;15(6):451-460.
9. Deyo RA, Mirza SK, Martin BI, et al. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA*. 2010;303:1259-1265.
10. Wilkinson J, Fourney D. Failure of percutaneous remodeling of the ligamentum flavum and lamina for neurogenic claudication. *Neurosurgery*. 2012;71:86-92.
11. Mekhail N, Costandi S, Abraham B, et al. Functional and patient-reported outcomes in symptomatic lumbar spinal stenosis following percutaneous decompression. *Pain Practice*. 2012;12(6):417-425.
12. Chen H, Kelling J. MILD procedure for lumbar decompression: a review. *Pain Practice*. 2012.
13. Durkin B, Romeiser J, Shroyer ALW, et al. Report from a quality assurance program on patients undergoing the MILD procedure. *Pain Medicine*. 2013.
14. American Society of Regional Anesthesia and Pain Medicine. 10th Annual ASRA Pain Medicine Meeting and Workshop. www.asra.com/userfiles/ASRA_August_2011.pdf.
15. Brown LL. A double-blind, randomized, prospective study of epidural steroid injection vs. the mild® procedure in patients with symptomatic lumbar spinal stenosis. *Pain Practice*. 2012;12:333-341. doi:10.1111/j.1533-2500.2011.00518.x.

Prescription Opioid Use Increases Despite Nonmalignant Pain Prevalence Remaining Stable

Sonia Elabd, MA

Despite the prevalence of nonmalignant pain in the United States remaining stable at approximately 20% from 2000 to 2010, according to a study published in the October 2013 issue of *Medical Care*, the rate of prescribing opioids among all pain visits nearly doubled during that same period.[1]

The authors also reported that although the rate of opioid use increased by 73% during that decade, rates of prescribing nonopioid analgesics remained relatively the same. The study raises awareness of the trends in prescribing opioids and draws attention to some possible adverse consequences of the efforts to improve diagnosis and management of pain, as prescription drug abuse and deaths have also increased.

The study was conducted by researchers at the Johns Hopkins University Bloomberg School of Public Health in Baltimore, Maryland; the Mayo Clinic in Rochester, Minnesota; and Stanford University in Palo Alto, California.

The researchers analyzed the results of nearly 8 million office-based physician visit records from the 2000 to 2010 National Ambulatory Medical Care Survey, a national sample of visits to the emergency and outpatient departments of non-institutional general and short-stay hospitals. The study authors aimed to observe any trends in the diagnosis and management of nonmalignant pain in ambulatory settings and determine whether increases in the use of opioids corresponded with similar increases in the use of nonopioid analgesics.

"It was important to conduct this analysis given [that] efforts to improve the treatment of nonmalignant pain have coincided with escalating rates of prescription opioid use and abuse," said lead study author Matthew Daubresse, MHS, in an e-mail interview. Daubresse is a research data analyst with the Center for Drug Safety and Effectiveness at the Johns Hopkins Bloomberg School of Public Health.

The results of the analysis highlight several interesting findings. First, the prevalence of patient-reported pain did not change from 2000 to 2010, ranging between 17% and 19%, equal to about 20% of visits. However, providers' diagnoses of pain as a primary complaint increased by 50%.

Furthermore, the researchers also observed significant trends regarding prescribing opioids. In 2000, 11% of patient visits where pain was a primary symptom or diagnosis resulted in prescription of opioids. In 2010, 20% of visits were treated with an opioid, and about one-half were treated with any pain medicine.

Opioid use increased during the period studied, from 11.3% of visits to 19.6% (an increase of 73%), whereas rates of prescribing nonopioid drugs went up from 26% of visits to 29%.

Among all pain visits, prescription of opioids combined with nonsteroidal anti-inflammatory drugs increased by 39%, from 3.7% of visits to 5.2%.

When analyzing survey visits for new musculoskeletal pain, the researchers found more disparity between opioid prescriptions and nonopioid prescriptions. In 2000, 15.1% of visits resulted in opioid prescription, and by 2010, 24.4% of visits resulted in the patient received an opioid prescription. However, this trend did not occur for prescription of nonopioid medications for new musculoskeletal pain, which decreased from 38% of visits in 2000 to 29% of visits in 2010.

> We were surprised to discover prescriptions for nonopioid medications remained stable or declined.

Results Surprise Researchers

"We were surprised to discover prescriptions for nonopioid medications remained stable or declined, especially given no significant change in the proportion of doctor's office visits with pain or in the proportion of pain visits treated with pain relievers," said Daubresse. "We had expected to see an increase in nonopioid analgesic prescribing since there have been such remarkable increases in opioid use during the past decade."

The reasons for the increase in opioid prescriptions are not clear, but the authors believe that raising public awareness of pain may have had an important effect. National and international efforts, such as the American Pain Society's 1996 initiative, "pain as the fifth vital sign," that sought to address the underassessment and undertreatment of pain and improve clinician's identification and management of pain may have unintentionally resulted in clinicians more often prescribing opioids over other drugs.

Multiple Factors Each Played a Role

"We believe increased awareness of chronic pain as a public health problem prompted a variety of initiatives to improve the diagnosis and treatment of pain," said Daubresse. "Given that physician diagnoses of pain increased over the past decade and many of these initiatives coincided with the start of the opioid epidemic, we think it's likely that they had some influence on physician prescribing patterns. However, it's also important to acknowledge other potential factors, such as regulatory

changes at the federal level, promotional and lobbying activities of the pharmaceutical industry, and patient demand."

"Over-reliance on opioids has come at great costs and at the expense of many alternative, safer approaches," said G. Caleb Alexander, MD, MS, coauthor and associate professor of epidemiology and medicine at the Johns Hopkins Bloomberg School of Public Health, in an e-mail interview.

> Over-reliance on opioids has come at great costs and at the expense of many alternative, safer approaches.

According to a 2013 *Morbidity and Mortality Weekly Report* on overdoses of prescription opioids, in 2010, "enough opioid pain relievers were sold to medicate every adult in the United States with the equivalent of a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."

The report also stated that, from 1999 to 2010, deaths from opioid pain relievers increased 5-fold for women and 3.6 times among men.[2] In addition, in 2012, approximately 4.9 million individuals aged 12 years and more reported using pain relievers for nonmedical use, according to the 2012 Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health.[3]

More importantly, if the current trend in opioid prescription and use continues, there could be significant public health consequences.

"There is clear evidence from the Centers for Disease Control and Prevention that rates of sales, addiction, and death are highly correlated," said Alexander, the lead author of the study. "If current increases in prescribing continue, under current market and regulatory conditions, these data suggest that the morbidity and mortality associated with prescription opioids will similarly increase," he said.

Back to a Call for Balance

Accurately diagnosing and effectively managing patients' pain remains an important public health initiative; however, the authors advocate a balanced approach.

"Both clinicians and patients should recognize that there are dozens of pharmacologic and non-pharmacologic therapies that are available to treat chronic pain," said Alexander.

The authors emphasized the importance of considering nonopioid analgesics, including acetaminophen, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, muscle relaxants, and topical analgesics, and nonpharmacologic treatments. In the article, the authors wrote, "There is little evidence to support any greater safety or effectiveness of opioids over many of these alternative analgesics, particularly with respect to functional outcomes and longer term use."

On a national level, prescriptions of opioids may continue to disproportionately increase compared with nonopioid drugs unless broader changes in federal policy and regulations are made.

> The authors emphasized the importance of considering nonopioid analgesics.

"These findings demonstrate that policy-makers may need to re-evaluate regulations pertaining to narcotic analgesics to achieve a better balance between the risks and benefits of opioid and nonopioid analgesics," said Daubresse.

Multipronged approaches are now advocated, including stronger FDA regulation and Responsible Opioid Prescribing recommendations.

"There is no 'magic bullet' to solve the epidemic of opioid addiction and abuse," said Alexander.

"However, a good place to start would be to have stronger regulation by the Food and Drug Administration, such as the labeling changes recommended by Physicians for Responsible Opioid Prescribing (PROP), increase the use of public health approaches supported by the American Medical Association, American Public Health Association, and Office of National Drug Control Policy, such as naloxone distribution programs, and improve patient and provider education regarding the potential risks of prescription opioids, as well as the plentiful alternatives to them," he said.

Alexander stressed the importance of additional research on the safety and effectiveness of long-term opioid use for chronic nonmalignant pain.

"A variety of other questions also remain important yet unanswered," Alexander said. "For example, rigorous evaluations of the impact of prescription drug monitoring programs are important to conduct, as are mixed-methods evaluations of other approaches to reduce the epidemic of prescription opioid addiction and abuse." ■

References

1. Daubresse M, Chang H, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. *Med Care*. 2013;51:870-878.

2. CDC. Vital signs: overdoses of prescription opioid pain relievers and other drugs among women—United States, 1999–2010. *MMWR Morb Mort Week Rep.* 2013;62(26):537-542. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6226a3.htm.

3. Substance Abuse and Mental Health Services Administration (SAMHSA). *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: SAMHSA, 2013. http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm#ch2.

Use of Prescription Opioids May Contribute to Increased Risk of Depression

Sonia Elabd, MA

Results from a study published in the *Journal of General Internal Medicine*[1] suggest a possible relationship between the use of prescription opioids and the risk of developing major depression later.

> Until now, there had been no published studies investigating whether depression is a consequence of prescription opioid use.

Although opioids remain the mainstay of chronic pain management, incidences of abuse and death have continued to increase along with increased use of prescription opioids. The authors of the study point out the need for clinicians to have comprehensive knowledge of both the benefits and adverse effects of prescribing opioids not only to better manage patients' pain, but also to assess the possible individual risks of taking opioids long-term and at high doses.

Previous research studies have reported that opioid use in patients with non-cancer pain is linked to depression. In particular, several studies have shown that patients with depression may be more likely to start and continue to use opioids. However, until now, there had been no published studies investigating whether depression is a consequence of prescription opioid use for analgesia, or whether depression leads to prescription opioid use.

"From 1 to 5% of patients who initiate opioid analgesics report dysphoria as an acute side effect of treatment, suggesting adverse effects on mood could contribute to depression,"[1] wrote Jeffrey Scherrer, PhD, and lead author of this study. Scherrer is associate professor of family and community medicine at Saint Louis University School of Medicine and research assistant professor of psychiatry at Washington University School of Medicine.

"In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), depression that occurs as a result of opioid intoxication or withdrawal is denoted as an opioid-induced mood disorder. Whether routine medical use of opioid analgesics is associated with incident depression has not been studied,"[1] he wrote in the article.

The team of researchers from Saint Louis University School of Medicine, Washington University School of Medicine in Saint Louis, and Harvard Medical School analyzed the medical records of more than 175,000 individuals from the United States Department of Veterans Affairs to determine whether prescription opioid use is linked to increased risk of being diagnosed with depression later.

Nearly 50,000 individuals had no history of depression or opioid use within the last 2 years and were prescribed an opioid for non-cancer and non-HIV pain. Of these individuals, approximately 91% used an opioid for 1 to 89 days, 4% had 90 to 180 days of use, and 4.5% used opioids for 180 days or more.

The opioids prescribed included hydrocodone (41.2%), codeine (33%), oxycodone (23.6 %), morphine (0.9%), fentanyl (0.6%), meperidine (0.4%), hydromorphone (0.2%) and pentazocine (0.04%). Arthritis was the most common painful condition (77.5%) followed by back pain (60.2%), musculoskeletal pain (59.3%), neuropathy (26.0%), and headache (17.3%). Patients who used opioids for more than 90 days were more likely to have chronic pain diagnoses, with the exception of headache. Co-morbid conditions among the entire cohort included obesity (31.9%), nicotine dependence and/or personal history of smoking (37.8%) alcohol and/or drug abuse/dependence (20.1%), post-traumatic stress disorder (10.3%), and non-post-traumatic stress or anxiety disorder (7.7%).

> Patients who used opioids for 90 to 180 days had a 25% greater risk of depression.

Incidence of Depression Increased With Duration of Prescription Opioid Use

The incidence of depression was defined as the presence of a primary diagnosis of depression during at least 1 inpatient stay or 2 outpatient visits within a 12-month period that occurred after the initial baseline date. The authors found that the incidence of depression increased with the duration of prescription opioid use. During the 7-year follow-up period, patients who used opioids for 90 to 180 days had a 25% greater risk of depression.

Patients who used opioids for more than 180 days had a more than 50% increased risk. The incidence of depression among the 3 opioid-use groups was 17.7/1000 person years (PY) for 1 to 89 days of use, 23.8/1000 PY among patients

with 90 to 180 days of use, and 27.8/1000 PY for patients who used opioids for more than 180 days. In addition, patients who took opioids for longer than 180 days had a shorter time to diagnosis of depression compared with patients who took opioids for less time. Even after the researchers adjusted for chronic pain from conditions that included arthritis, back pain, headaches, musculoskeletal diseases, and neuropathies, the effects were still significant.

The researchers also studied the effects of morphine-equivalent dose on incidence of depression. At a dose of 38 mg morphine, the researchers observed an increase in incidence of depression. Therefore, defining "high daily dose" as at least 39 mg, and "low daily dose" as less than 39 mg, the investigators calculated the incidence of depression.

Regardless of the duration of prescription opioid use, patients who took a high daily dose of morphine had a significantly higher risk—in some cases, twice as high—of developing depression. Although the percentage of patients with depression among those receiving low daily dose remained relatively the same with duration of use, the percentage of patients using high daily dose increased from 9.3%, in those who used opioids for 89 days or less, to 13.1% in 90- to 180-day users, to 15.0% in patients who used the medication for more than 180 days. However, the authors note that these results should be viewed in perspective.

"These post-hoc analyses should be interpreted cautiously, because propensity scores were utilized to correct for duration of opioid exposure, but not for morphine equivalent dose,"[1] the authors wrote.

The study authors highlight the adverse consequences of opioid use and abuse and the increase in accidental drug overdoses and deaths caused by drug use and abuse.

"Our findings [show] that opioid use for more than 90 days significantly increases the risk of developing depression," the authors wrote.

The exact relationship between depression and opioid use is still unclear, but the authors propose that several factors, rather than a single factor, may be the cause.

The authors wrote, "The mechanisms by which opioids may contribute to the development of depression are unclear, but likely multifactorial. The possibilities include opioid-induced resetting of the brain 'reward pathway' to a higher threshold, resulting in the inability of natural rewards to generate pleasure and/or relief; kappa receptor overactivity associated with opiate discontinuation, with dysphoria and body aches occurring months and years after opioids are stopped; and via medical abnormalities associated with opiate use (e.g., adrenal, testosterone, and vitamin D deficiencies, glucose dysregulation) that may present as physical correlates of major depression. Whether collateral treatments can help to prevent or delay opioid-associated depression is a subject that merits further study."[1]

"Our data indicate that medical use of opioids for more than 90 days is more likely to promote than to relieve depression,"[1] wrote the authors in the published article. "That an opioid-associated risk of depression could be demonstrated in a sample at low risk of depression (given their advanced age and having no recent (24-month) history of depression) is noteworthy, and raises the possibility that some depression episodes may have been avoided had opioid therapy not been initiated or limited to less than 90 days."[1] ■

Reference

1. Scherrer JF, Svrakic DM, Freedland KE et al. Prescription opioid analgesics increase the risk of depression. *J Gen Intern Med.* 2013; Oct 29 [Epub ahead of print]. DOI: 10.1007/s11606-013-2648-1.

Topics in Pain Management CME Quiz

To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **January 31, 2015.** Only two entries will be considered for credit.

Online quiz instructions: To take the quiz online, **log on to your account at http://www.topicsinpainmanagement.com,** and click on the "CME" tab at the top of the page. Then click on "Access the CME activity for this newsletter," which will take you to the log-in page for **CME.lwwnewsletters.com.** Enter your ***username and password for this screen as follows***: Your ***CME username*** will be the letters LWW (case sensitive) followed by the 12-digit account number above your name on the paper answer form mailed with your issue. Your ***CME password*** will be **1234;** this password ***may not*** be changed. Follow the instructions on the site. You may print your official certificate ***immediately***. Please note: Lippincott CME Institute, Inc., ***will not*** mail certificates to online participants. **Online quizzes expire at 11:59 pm Pacific Standard Time on the due date.**

1. **Neurogenic claudication is triggered by axial loading activities, and unlike intermittent or vascular claudication, it is relieved by flexion and not by mere cessation of walking as in vascular claudication.**
   A. True
   B. False

2. **Approximately 1 in 200 people in the United States over the age of 50 years has symptomatic LSS.**
   A. True
   B. False

3. **If the conservative measures of physical therapy, nonsteroidal anti-inflammatory medications and gabapentinoids (eg, gabapentin and pregabalin), exercise, and epidural corticosteroid injections fail, then surgical decompression and fusion is often the final resort.**
   A. True
   B. False

4. **The restoration of adequate space to correct LSS is demonstrated during the MILD procedure with an oblique epidurogram that shows improved flow.**
   A. True
   B. False

5. **The MILD kit is only for single-patient use and includes a portal stabilizer, to minimize medial and lateral movement during the procedure, and an instrument-depth guide.**
   A. True
   B. False

6. **Wilkinson and Fourney reported that many of their patients who underwent MILD returned for surgery when they were followed up beyond the end of the study protocol.**
   A. True
   B. False

7. **The average radiation dose received by patients during the MILD procedure is extremely low and not worth measuring.**
   A. True
   B. False

8. **The MILD procedure can be conducted safely and effectively in an ambulatory surgery center, but use in an office-based setting has not been reported.**
   A. True
   B. False

9. **There have been no significant complications with the MILD procedure reported in the published studies, which includes no incidents of dural puncture or tear, blood transfusion, nerve injury, epidural bleeding, hematoma, or infections.**
   A. True
   B. False

10. **Some commentators have suggested that the MILD procedure should only be offered to patients with symptomatic central stenosis when MRI clearly shows it is only or mostly caused by ligamentum flavum hypertrophy.**
    A. True
    B. False

NEWS IN BRIEF

Compounding Pharmacy Recalls All Products After Adverse Event in California

Because of concerns about sterility and "out of an abundance of caution," Texas-based Abrams Royal Compounding Pharmacy issued a voluntary recall of all unexpired lots of sterile products that it had dispensed nationwide, according to a press release issued by the company and posted on the website of the FDA.[1]

The company issued the recall when a California woman experienced adverse effects after receiving an injection of a preparation from Abrams Royal.

The compounding pharmacy's website[2] carries a certification badge by the Pharmacy Compounding Accrediting Board, and refers to Abrams Royal, based in the Dallas area, as "one of the nation's largest and most innovative compounding pharmacies" that has "stayed true to our roots."

The recall involved all unexpired lots of sterile compounded products, including injectable medications, IVs, eye drops, pellet implants, nasal sprays, inhalation solutions, and eye ointments.

All recalled products have a label that includes Abrams Royal Pharmacy's name and phone number. Although not every label contains an expiration date, consumers can call the pharmacy and provide the lot number of any products in question, and a company representative will look up the expiration date.

"The recall was issued after a single, isolated report of an adverse event involving a patient in California who received a compounded medication from the pharmacy," the company's press release said. "Out of an abundance of caution, Abrams Royal is voluntarily recalling all sterile products within expiry. If there is microbial contamination in products intended to be sterile, patients are at risk for serious, potentially life-threatening infections."

The recalled products were distributed to health care facilities, physicians, and patients from June 17, 2013, through December 17, 2013.

Abrams Royal Pharmacy has begun notifying its customers by mail and is arranging for the return of all recalled medication.

Customers who have product, which is being recalled, should stop using it and contact the pharmacy to arrange for return of unused product. Consumers should contact their physician or health care provider if they have experienced any problems that may be related to taking or using these products. Adverse reactions may be reported to the FDA's MedWatch program.

To return a product or request assistance related to this recall, users should contact Abrams Royal at 214-349-8000, Monday through Friday, between 9 AM and 5 PM, central standard time.

Abrams Royal's pharmacists deeply regret the disruption that the voluntary recall and temporary suspension of its sterile compounding service have on the pharmacy's patients, but emphasized that safety is always their first concern.

This recall is being conducted with the knowledge of the FDA.

Those who wish to contact the FDA about the recall or the products can go to www.fda.gov/medwatch/report.htm. Mail should use postage-paid, pre-addressed Form FDA 3500, available at www.fda.gov/MedWatch/getforms.htm. The FDA's fax number is 800-FDA-0178.

References

1. FDA. Recall–Firm Press Release: Abrams Royal Pharmacy Issues Voluntary Nationwide Recall of All Lots of Unexpired Sterile Products Due to Lack of Sterility Assurance. December 18, 2013. http://www.fda.gov/Safety/Recalls/ucm379313.htm.
2. Abrams Royal Pharmacy. About us. https://arp-rx.com/about_us/.

Coming Soon:

- Ethical Challenges in Pain Medicine